Journal Pre-proof

Adhesion G protein-coupled receptors

Tobias Langenhan, Garret R. Anderson, Demet Araç, Gabriela Aust, Monserrat Avila-Zozaya, Sofie Morsing Bagger, Patrick Barth, Sandra Berndt, Stephen C. Blacklow, Beatriz Blanco-Redondo, Antony A. Boucard, James Bridges, Lara-Sophie Brodmerkel, Kathleen M. Caron, Yin Kwan Chung, 鍾炫坤, Andrew N. Dates, Virginea de Araujo Farias, Daniel Del Toro, Joseph G. Duman, Felix B. Engel, David M. Favara, Caroline J. Formstone, Chaoyu Fu, Alain Garcia De Las Bayonas, Anastasia Georgiadi, David E. Gloriam, Randy A. Hall, Jörg Hamann, Peter W. Hildebrand, Cheng-Chih Hsiao, Bill X. Huang, Jonathan A. Javitch, Hee-Yong Kim, 김희용, Robert J. Kittel, Gunnar Kleinau, Richard Leduc, Ines Liebscher, Hsi-Hsien Lin, Joshua Linnert, Marie-Gabrielle Ludwig, David C. Martinelli, Signe Mathiasen, Daniel Matúš, Mariam Melkumyan, Ana L. Moreno-Salinas, Jan Mulder, Michael A. Nash, Kasturi Pal, Daniel T. Pederick, Nicole A. Perry-Hauser, Xianhua Piao, Yu-Qi Ping, 平玉奇, Dimitris G. Placantonakis, Fabian Pohl, Simone Prömel, Mette M. Rosenkilde, Laurent Sabbagh, Richard C. Sando, Patrick Scheerer, Torsten Schöneberg, Elena Seiradake, Mareike Selcho, Florian Seufert, Abhishek K. Singh, Georgios Skiniotis, Katja Spiess, Norbert Sträter, David Strutt, Thomas C. Südhof, Jinpeng Sun, 孙金鹏, Gregory G. Tall, Doreen Thor, Douglas G. Tilley, Kimberley F. Tolias, Mario Vallon, Erwin G. Van Meir, Benoit Vanhollebeke, Giselle R. Wiggin, Uwe Wolfrum, Jie Yan, Nathan A. Zaidman, Yimin Zou, 邹益民, Nicole Scholz

PII: S0031-6997(26)00004-9

DOI: https://doi.org/10.1016/j.pharmr.2026.100116

Reference: PHARMR 100116

To appear in: *Pharmacological Reviews*

Received Date: 12 September 2025

Revised Date: 24 December 2025

Accepted Date: 9 January 2026

Please cite this article as: Langenhan T, Anderson GR, Araç D, Aust G, Avila-Zozaya M, Bagger SM, Barth P, Berndt S, Blacklow SC, Blanco-Redondo B, Boucard AA, Bridges J, Brodmerkel LS, Caron KM, Chung YK, Dates AN, de Araujo Farias V, Del Toro D, Duman JG, Engel FB, Favara DM, Formstone CJ, Fu C, De Las Bayonas AG, Georgiadi A, Gloriam DE, Hall RA, Hamann J, Hildebrand PW, Hsiao CC,

Huang BX, Javitch JA, Kim HY, Kittel RJ, Kleinau G, Leduc R, Liebscher I, Lin HH, Linnert J, Ludwig MG, Martinelli DC, Mathiasen S, Matúš D, Melkumyan M, Moreno-Salinas AL, Mulder J, Nash MA, Pal K, Pederick DT, Perry-Hauser NA, Piao X, Ping YQ, Placantonakis DG, Pohl F, Prömel S, Rosenkilde MM, Sabbagh L, Sando RC, Scheerer P, Schöneberg T, Seiradake E, Selcho M, Seufert F, Singh AK, Skiniotis G, Spiess K, Sträter N, Strutt D, Südhof TC, Sun J, Tall GG, Thor D, Tilley DG, Tolias KF, Vallon M, Van Meir EG, Vanhollebeke B, Wiggin GR, Wolfrum U, Yan J, Zaidman NA, Zou Y, Scholz N, Adhesion G protein-coupled receptors, *Pharmacological Reviews* (2026), doi: https://doi.org/10.1016/j.pharmr.2026.100116.

Title page

Article title: Adhesion G protein-coupled receptors

Author names:

Tobias Langenhan[1,2,3,*,#], Garret R. Anderson[4], Demet Araç[5], Gabriela Aust[6], Monserrat Avila-Zozaya[7], Sofie Morsing Bagger[8], Patrick Barth[9], Sandra Berndt[10,11], Stephen C. Blacklow[12], Beatriz Blanco-Redondo[1], Antony A. Boucard[13], James Bridges[14,15], Lara-Sophie Brodmerkel[1], Kathleen M. Caron[7], Yin Kwan Chung (鍾炫坤)[8], Andrew N. Dates[16], Virginea de Araujo Farias[17], Daniel Del Toro[18], Joseph G. Duman[19], Felix B. Engel[20], David M. Favara[21,22,23], Caroline J. Formstone[24], Chaoyu Fu[25], Alain Garcia De Las Bayonas[26,27], Anastasia Georgiadi[28], David E. Gloriam[29], Randy A. Hall[30], Jörg Hamann[31,32], Peter W. Hildebrand[33], Cheng-Chih Hsiao[31,32], Bill X. Huang[34], Jonathan A. Javitch[35,36], Hee-Yong Kim (김희용)[34], Robert J. Kittel[37], Gunnar Kleinau[38], Richard Leduc[39], Ines Liebscher[10,11], Hsi-Hsien Lin[40], Joshua Linnert[41], Marie-Gabrielle Ludwig[42], David C. Martinelli[43], Signe Mathiasen[8], Daniel Matúš[44], Mariam Melkumyan[34], Ana L. Moreno-Salinas[39], Jan Mulder[45,46], Michael A. Nash[47,48], Kasturi Pal[49], Daniel T. Pederick[50], Nicole A. Perry-Hauser[51], Xianhua Piao[52], Yu-Qi Ping (平玉奇)[53], Dimitris G. Placantonakis[54], Fabian Pohl[1], Simone Prömel[55], Mette M. Rosenkilde[8], Laurent Sabbagh[56], Richard C. Sando[57], Patrick Scheerer[38], Torsten Schöneberg[58,59], Elena Seiradake[60,61], Mareike Selcho[37], Florian Seufert[33], Abhishek K. Singh[20], Georgios Skiniotis[62], Katja Spiess[8,63], Norbert Sträter[64], David Strutt[65], Thomas C. Südhof[44], Jinpeng Sun (孙金鹏)[66], Gregory G. Tall[67], Doreen Thor[58], Douglas G. Tilley[68], Kimberley F. Tolias[19], Mario Vallon[69], Erwin G. Van Meir[17], Benoit Vanhollebeke[70,71], Giselle R. Wiggin[72], Uwe Wolfrum[41,73], Jie Yan[25], Nathan A. Zaidman[74], Yimin Zou (邹益民)[75], Nicole Scholz[1,*,#]

Affiliations:

[1]Rudolf Schönheimer Institute of Biochemistry, General Biochemistry, Medical Faculty, Leipzig University, Johannisallee 30, 04103 Leipzig, Germany

[2]Comprehensive Cancer Center Central Germany (CCCG), Leipzig, Germany

[3]Institute of Biology, Faculty of Life Sciences, Leipzig University, Leipzig, Germany

[4]Department of Molecular, Cell, and Systems Biology, University of California Riverside, Riverside, CA 92521, USA

[5]Department of Biochemistry and Molecular Biology, University of Chicago, Chicago, IL, USA

[6]Research Laboratories, Department of Orthopedics, Trauma and Plastic Surgery and Department of Visceral, Transplantation, Vascular and Thoracic Surgery, Medical Faculty, Leipzig University, Liebigstraße 19, 04103 Leipzig, Germany

[7]Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, 11 Mason Farm Road, Chapel Hill 27599 NC, USA

[8]Department of Biomedical Science, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3, 2200 Copenhagen N, Denmark

[9]Interfaculty Institute of Bioengineering, Lausanne, CH-1015 and Switzerland and Ludwig Institute for Cancer Research Lausanne, École Polytechnique Fédérale de Lausanne, Switzerland

[10]Rudolf Schönheimer Institute of Biochemistry, Signal Transduction, Medical Faculty, Leipzig University, Johannisallee 30, 04103 Leipzig, Germany

[11]Center for Biotechnology and Biomedicine, Department of Translational Drug Research and Signal Transduction, Leipzig University, 04103 Leipzig, Germany

[12]Blavatnik Institute, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, LHRRB201B, 45 Shattuck St. Boston, MA 02115, USA

[13]Department of Cell Biology, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (Cinvestav), México City C.P. 07360; Mexico

[14]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO, 80206, USA

[15]Department of Medicine, Division of Pulmonary Sciences and Critical Care, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045, USA

[16]Department of Psychiatry and Behavioral Sciences, University of California San Francisco, San Francisco, CA 94143, USA

[17]Laboratory of Molecular Neurooncology, Department of Neurosurgery, O'Neal Comprehensive Cancer Center, Heersink School of Medicine, University of Alabama at Birmingham, USA

[18]Department of Biomedical Sciences, Institute of Neurosciences, IDIBAPS, University of Barcelona, 08036 Barcelona, Spain

[19]Department of Neuroscience, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

[20]Experimental Renal and Cardiovascular Research, Department of Nephropathology, Institute of Pathology and Department of Cardiology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany

[21]Division of Structural Studies, MRC Laboratory of Molecular Biology, Francis Crick Avenue, Cambridge, UK

[22]Department of Oncology, University of Cambridge, Cambridge, UK

[23]Department of Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS, Foundation Trust, Cambridge, UK

[24]Department of Clinical, Pharmaceutical and Biological Sciences, University of Hertfordshire, Hatfield, UK

[25]National University of Singapore, Department of Physics and Mechanobiology Institute, Singapore, Singapore

[26]Department of Molecular and Cell Biology, University of California, Berkeley, CA, 94720, USA

[27]Howard Hughes Medical Institute, Chevy Chase, USA

[28]Head of Junior Group Endocrine Pharmacology, Institute for Diabetes and Cancer, Helmholtz Centre Munich, Ingolstädter Landstraße 1, 85764 Neuherberg, Germany and Deutsches Zentrum für Diabetesforschung, Neuherberg, Germany

[29]Department of Drug Design and Pharmacology, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark

[30]Department of Pharmacology and Chemical Biology, Emory University School of Medicine, Atlanta, GA, 30322, USA

[31]Department of Experimental Immunology, Amsterdam Institute of Immunology and Infectious Diseases, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, Netherlands

[32]Neuroimmunology Research Group, Netherlands Institute for Neuroscience, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands

[33]Leipzig University, Institute for Medical Physics and Biophysics, Medical Faculty, Leipzig, Germany

[34]Laboratory of Molecular Signaling, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD 20852, USA

[35]Departments of Psychiatry and Molecular Pharmacology and Therapeutics, Columbia University Vagelos College of Physicians and Surgeons, NY, New York, USA

[36]Division of Molecular Therapeutics, New York State Psychiatric Institute, NY, New York, USA

[37]Department of Animal Physiology, Institute of Biology, Faculty of Life Sciences, Leipzig University, Talstraße 33, 04103 Leipzig, Germany

[38]Charité − Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Institute of Medical Physics and Biophysics, Group Structural Biology of Cellular Signaling, Charitéplatz 1, 10117 Berlin, Germany

[39]Department of Pharmacology-Physiology, Université de Sherbrooke, Sherbrooke, QC J1H 5N4, Canada

[40]Department of Microbiology and Immunology, College of Medicine, Chang Gung University, 259 Wenhwa 1st Road, Kweishan District, Taoyuan City, 333, Taiwan

[41]Institute of Molecular Physiology (imP) Bio Centre 2, Johannes Gutenberg University Mainz, Hanns-Dieter-Hüsch-Weg 17, 55128 Mainz, Germany

[42]Novartis - Biomedical Research, Novartis Pharma AG, Fabrikstrasse 22-4, Novartis Campus, Basel 4056, Switzerland

[43]University of Connecticut Health, 263 Farmington Ave, MC 3401, Farmington, CT 06030-3401, USA

[44]Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Lorey Lokey Stem Cell Research Building (SIM1), 265 Campus Drive, Stanford, CA 94305, USA

[45]Department of Neuroscience, Karolinska Institute, Stockholm, Sweden

[46]Science for Life Laboratory, Department of Protein Science, KTH Royal Institute of Technology, Stockholm, Sweden

[47]Institute of Physical Chemistry, Department of Chemistry, University of Basel, Mattenstrasse 22, 4058 Basel, Switzerland

[48]Department of Biosystems Sciences and Engineering, ETH Zurich, 4056 Basel, Switzerland

[49]Department of Biology, Ashoka University, Sonipat 131029, India

[50]Department of Neuroscience, School of Medicine, Johns Hopkins University, 725 North Wolfe St., Baltimore, MD 21205, USA

[51]Centre for Translational Pharmacology, School of Molecular Biosciences, Advanced Research Centre, 11 Chapel Lane, University of Glasgow, Glasgow G11 6EW, Scotland, UK

[52]Weill Institute for Neuroscience, University of California San Francisco, 1651 4th Street, Floor 5, San Francisco, CA 94158, USA

[53]Medical Science and Technology Innovation Center, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, 250117, China

[54]Departments of Neurosurgery and Cell Biology, NYU Grossman School of Medicine, 530 First Avenue, Skirball 8R, New York, NY 10016, USA

[55]Institute of Cell Biology, Heinrich Heine University Düsseldorf, Universitätsstraße 1, 40225 Düsseldorf, Germany

[56]Domain Therapeutics, 7171 Frédérick-Banting St-Laurent, Québec, H4S 1Z9, Canada

[57]Department of Pharmacology, Vanderbilt Brain Institute, Vanderbilt University, 465 21st Avenue, MRB III BIO/SCI 7160A, Nashville, Tennessee 37232, USA

[58]Rudolf Schönheimer Institute of Biochemistry, Molecular Biochemistry, Medical Faculty, Leipzig University, Johannisallee 30, 04103 Leipzig, Germany

[59]University of Global Health Equity (UGHE), Kigali Heights, Plot 772, KG 7 Ave., 5th Floor, PO Box 6955 Kigali, Rwanda

[60]Department of Biochemistry, University of Oxford, South Parks Road, OX1 3QU, UK

[61]Kavli Institute for Nanoscience Discovery, University of Oxford, South Parks Road, OX1 3QU, UK

[62]Department of Structural Biology & Center of Excellence for Structural Cell Biology, St. Jude Children's Research Hospital, Memphis, TN, USA

[63]Department of Virology and Microbiological Preparedness, Statens Serum Institut, Copenhagen, Denmark

[64]Institute of Bioanalytical Chemistry, Center for Biotechnology and Biomedicine, Leipzig University, Deutscher Platz 5, 04103 Leipzig, Germany

[65]School of Biosciences, University of Sheffield, Firth Court, Sheffield, S10 2TN, UK

[66]Advanced Medical Research Institute, Meili Lake Translational Research Park, Cheeloo College of Medicine, Shandong University, Jinan, China

[67]Department of Pharmacology, University of Michigan Medical School, USA

[68]Department of Cardiovascular Sciences, Aging + Cardiovascular Discovery Center, Lewis Katz School of Medicine, Temple University, Philadelphia, PA 19140, USA

[69]Institute of Anatomy and Cell Biology, University of Würzburg, Koellikerstr. 6, 97070 Würzburg, Germany

[70]Laboratory of Neurovascular Signaling, Department of Molecular Biology, ULB Neuroscience Institute, Université libre de Bruxelles, Gosselies, Belgium

[71]WEL Research Institute, Wavre, Belgium

[72]Nxera Pharma UK Ltd., Steinmetz Building, Granta Park, Cambridge, CB21 6DG, UK

[73]Institute for Quantitative and Computational Biosciences (IQCB), Bio Centre 2, Johannes Gutenberg University Mainz, Hanns-Dieter-Hüsch-Weg 17, 55128 Mainz, Germany

[74]Department of Biochemistry and Molecular Biology, University of New Mexico School of Medicine, Albuquerque, New Mexico, USA

[75]Neurobiology Section, Biological Sciences Division, University of California, San Diego, La Jolla, CA 92093, USA

[*] Equal contribution

[#] Corresponding authors:

Tobias Langenhan, MD, DPhil (Oxon)

Rudolf Schönheimer Institute of Biochemistry

General Biochemistry, Medical Faculty, Leipzig University

Johannisallee 30, 04103 Leipzig, Germany

Tel. +49 341 9722100

Email: tobias.langenhan@gmail.com

Nicole Scholz, PhD

Rudolf Schönheimer Institute of Biochemistry

General Biochemistry, Medical Faculty, Leipzig University

Johannisallee 30, 04103 Leipzig, Germany

Tel. +49 341 9722100

Email: scholzlab@gmail.com

Number of text pages:

Number of tables: 2

Number of figures: 8

Number of references: 825

Number of words in the abstract: 139

Number of word in significance statement: 57

Table of contents

Title page 1
Table of contents 7
Abstract 10
Significance statement 10
Keywords 10
Abbreviations 11
I. Introduction 13
II. Receptor terminology 13
III. Generic residue numbering 14
IV. Structures of adhesion GPCRs 15
A. GAIN domains 15
B. Extracellular domains and ligand bound structures 16
C. 7TM domains 17
V. Autoproteolytic processing 19
VI. Alternative splicing and protein variants of adhesion GPCRs 20
VII. Subcellular trafficking, localisation and cellular functions of adhesion GPCRs 22
VIII. Anatomical and cellular distribution of human adhesion GPCR transcripts 24
IX. Interactions 25
A. Ligands (extracellular binding partners) 25
B. Intracellular binding partners (except G proteins, arrestins, Rac/Ras/Rho GTPases) 26
X. Receptor activation modes 27
A. TIA/*Stachel*-dependent signaling: dissociation model 27
B. TIA/*Stachel*-dependent signaling: non-dissociation model 28
C. TIA/*Stachel*-independent signaling 29
XI. Signaling routes 30
A. Cell-autonomous signaling 30
1. G proteins 30
2. Arrestins 31
3. Signaling pathways independent of G proteins and arrestins 31

4. Signaling with co-receptors 31
B. Non-cell autonomous signaling 32
XII. Physiology and pathophysiology 34
A. Organ systems 34
1. Nervous system - glia & neurons 34
2. Sensory systems 35
3. Vasculature 36
4. Lymphatic vessels 37
5. Skin 38
6. Heart 38
7. Lung 39
8. Musculoskeletal system 40
9. Immune system and spleen 40
10. Kidney 41
11. Pancreas 42
12. Metabolism, fat and liver 42
13. Gastrointestinal tract 43
14. Female reproductive system 44
15. Male reproductive system 45
B. Diseases 45
1. Cancer 45
2. Type II diabetes 48
3. Viral infection 48
4. Bacterial infections 48
5. Neurodevelopmental, neurodegenerative, and neuropsychiatric disorders 49
XIII. Adhesion GPCRs as drug targets 50
XIV. Phylogeny of adhesion GPCR and model organisms 52
A. Phylogenetic relationships of adhesion GPCR subfamilies and homologs 52
B. Model organisms for adhesion GPCR research 53
1. Choanoflagellates 53
2. Fruit fly (*Drosophila melanogaster*) 54
3. Roundworm (*Caenorhabditis elegans*) 55

4. Zebrafish (*Danio rerio*)....56
5. Chick (*Gallus gallus*)....57
6. Mouse (*Mus musculus*) and rat (*Rattus norvegicus*)....57
XV. Experimental technologies for adhesion GPCR interrogation....58
A. Molecular dynamics studies....58
B. Homology modelling....58
C. Acute receptor activation....59
D. Force assays....60
E. Receptor dissociation....62
XVI. Perspectives....63
Financial Support....64
Conflict of interest....65
Data availability....65
Acknowledgements....65
Author contributions....65
Declaration of generative AI and AI-assisted technologies in the writing process....66
Figure legends....67
Tables....71
Table 1....71
Table 2....84
References....90

Abstract

Adhesion G protein-coupled receptors (aGPCRs) constitute a structurally and functionally distinct group within the superfamily of GPCRs. In 2015, the International Union of Pharmacology invited the Adhesion GPCR Consortium to publish a comprehensive review about aGPCRs and to establish a unified nomenclature. Since then, substantial progress has been made in delineating the biological roles, molecular architecture, biochemical properties, expression profiles, ligand repertoire, and activation and signaling strategies of aGPCRs. Commensurate with these advances, their relevance to human pathophysiology has become increasingly evident. In a coordinated effort, the Adhesion GPCR Consortium has reviewed recent progress in the field and provides a comprehensive assessment of the current understanding of aGPCR biology here. This includes a focus on human and mammalian aGPCRs, their evolutionary origins, methodological approaches and model systems for their investigation, as well as emerging approaches for their therapeutic targeting.

Significance statement

Adhesion G protein-coupled receptors are versatile cell-surface proteins that integrate structural, biochemical, and physiological functions with major roles in health and disease. This review summarizes current knowledge of their molecular features, functions in diverse model systems, and emerging opportunities for therapeutic targeting, providing a comprehensive resource that connects basic biology with translational applications across multiple scientific disciplines.

Keywords

(up to 6)

Autoproteolysis

Cell adhesion

G protein-coupled receptors

Mechanobiology

Signaling

Abbreviations

1TM, single-pass transmembrane

7TM, seven-pass transmembrane

7TMD, seven-pass transmembrane domain

AA, amino acid

ADGR, ADhesion G protein-coupled Receptor

AFM, atomic force microscopy

AIS, adolescent idiopathic scoliosis

aGPCR, adhesion GPCR

AT1, alveolar type 1

AT2, alveolar type 2

BRET, bioluminescence energy transfer

CAM, chorio-allantoic membrane

CE, convergence and extension

CNS, central nervous system

COPD, chronic obstructive pulmonary disease

CRN, craniorachischisis

cryo-EM, cryogenic electron microscopy

CTF, C-terminal fragment

DHEA, dehydroepiandrosterone

ECL, extracellular loop

EGF, epidermal growth factor-like

EMT, epithelial to mesenchymal transition

EndMT, endothelial to mesenchymal transition

ENT, extracellular N-terminus

ER, endoplasmic reticulum

GAIN, GPCR autoproteolysis-inducing

GPCR, G protein-coupled receptor(s)

GPS, GPCR proteolysis site

GRKs, G-protein receptor kinases

GRN, generic residue numbering

hASMC, human airway smooth muscle cells

HIV, human immune deficiency virus

HormR, hormone receptor motif

ICL, intracellular loop

ICT, intracellular C-terminus

IPF, idiopathic pulmonary fibrosis

KO, knockout

KRT1, keratin 1

LEC, Lymphatic endothelial cells

MAGUK, membrane-associated guanylate kinase

MD, molecular dynamics

NK, natural killer

NRS, NTF release sensor

NTF, N-terminal fragment

PBM, PDZ-binding motif

PC1, polycystin-1

PCP, planar cell polarity

PKD1, polycystic kidney disease 1

PNS, peripheral nervous system

PR3, proteinase 3

PTK7, protein tyrosine kinase 7

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

SNPs, single nucleotide polymorphisms

TIA, tethered/intramolecular agonist

TLR, Toll-like receptor

TG2, transglutaminase-2

TMH, transmembrane helix

Treg, regulatory T

I. Introduction

Adhesion G protein-coupled receptors (aGPCRs) form a remarkable set of molecules within the superfamily of GPCR[1]. Ever since aGPCRs were recognized as a receptor family[2] and alternatively classified as B2 GPCRs[3], researchers across many scientific research fields have focused on elucidating their molecular architecture, biochemical features, pharmacological properties, physiological functions, and involvement in disease. This review summarizes the current state of knowledge on aGPCRs, covering a broad range of aspects relevant to the various scientific communities interested in these receptors.

In the following sections, we present an introduction to the general molecular, cellular, and physiological characteristics of all aGPCRs, with an emphasis on human and other mammalian family members. Furthermore, this review offers an overview of current efforts to elucidate the role of aGPCR dysfunction in various diseases and explores strategies for their pharmacological targeting. Finally, we provide a survey of the principal model organisms and experimental approaches currently employed in aGPCR research.

II. Receptor terminology

Similar to other GPCRs, the structural organization of aGPCRs can be topologically subdivided into three main regions: an extracellular N-terminus (ENT), a seven-transmembrane helix domain (7TMD) including extra- (ECL) and intracellular loops (ICLs), and an intracellular C-terminus (ICT) (Figs. 1 and 2)[1,4–6]. The ENTs of aGPCRs frequently contain a variety of protein domains commonly associated with adhesive functions (Fig. 3). This structural complexity can contribute to the unusually large size of many aGPCRs and underlies the substantial structural and functional diversity of this receptor class. While the ICTs of aGPCRs can also be very large, no annotated domains have been identified to date. Nevertheless, ICTs can facilitate interactions for example through PDZ-binding motifs (PBMs) to PDZ domains of scaffold proteins[7].

The GPCR autoproteolysis-inducing (GAIN) domain is the only extracellular structural element consistently found across nearly all aGPCRs[8] (Figs. 1A and 2A), with the exception of Eutherian A1 orthologs[9]. Located just outside the membrane, the GAIN domain of many but not all aGPCRs[10] can mediate receptor autoproteolysis at its intra-domain GPCR proteolysis site (GPS)[8,11], resulting in the cleavage of many, albeit not all, aGPCRs into N-terminal (NTF) and C-terminal (CTF) fragments (Fig. 4). These fragments remain non-covalently associated at the cell surface[12–14], where they can dissociate spontaneously and in response to ligand binding combined with mechanical stimuli. The structural entity of the GAIN domain-cleaved aGPCRs may be termed NTF-CTF complex rather than NTF-CTF dimers or heterodimers to avoid confusion with GPCRs that form functional oligomeric assemblies of more than one receptor molecule, e.g., $GABA_B$ or metabotropic glutamate receptors[15].

The NTFs of GAIN domain-cleaved aGPCRs comprise various extracellular domains including the larger part of the cleaved GAIN domain (Fig. 3), whereas the CTF includes the

C-terminal β-strand of the GAIN domain, the linker connecting the GAIN domain and 7TMD, the full 7TMD (Fig. 4), and the complete ICT. The segment corresponding to the last β-strand of the GAIN domain, which forms the N-terminus of the CTF, can undergo structural changes to engage directly with its own 7TMD and activate the receptor. Accordingly, this segment is referred to as a tethered or intramolecular agonist, also known as the *Stachel* (German for '*stinger*'; Fig. 2A). The *Stachel* sequence of aGPCRs does not represent a separate 'tethered' ligand but an integral segment of each receptor's polypeptide chain. Peptide mapping established its hydrophobic core as sufficient for receptor activation, yet unlike covalently bound chromophores (e.g., retinal in opsins) the *Stachel* is encoded, synthesized and retained within the same chain[16,17]. Consequently, the *Stachel* functions as an intramolecular agonist and may also be termed as such[10]. In the course of this review the agonist is referred to by the compound abbreviation TIA (tethered/intramolecular agonist) or by the term *Stachel*.

The stretch of amino acid (AA) residues linking the extracellular domains N-terminal to the GPS motif was historically denominated as a 'Stalk'[18,19]. It was later shown that the 'Stalk' and 'GPS motif' are constituent sequences of the GAIN domain[8]. Thus, the term 'Stalk' has become superfluous and its use should be discontinued[20]. Of note, the coordinates of the 'Stalk' region are distinct from the TIA, which immediately follows C-terminal to the GPS[10].

Since the adoption of the revised nomenclature system for aGPCRs in 2015 by the Adhesion GPCR Consortium, NC-IUPHAR, and HGNC, the updated gene/protein names using the ADGR (ADhesion G protein-coupled Receptor) prefix have been successfully integrated into scientific communication[1]. We suggest using these new names alongside their traditional synonyms, for example, 'ADGRB1/BAI1' or 'ADGRL3/Latrophilin-3', at least at the first mention in a publication. Once introduced, shorthand versions of the receptor names (e.g., B1 or L3) may be used, as conducted throughout this review.

III. Generic residue numbering

Generic residue numbering (GRN) schemes enable the comparison of corresponding AA residue positions in homologous proteins within or between species. The common principles for generating GRNs are based on either (i) identifying the most highly conserved AA positions in aligned protein sequences, which allows for assigning reference residues, or (ii) structural alignments (superimpositions) that consider secondary or even tertiary structures within conserved folds to define corresponding AA positions. Such comparisons can be critical to infer function, establish structure-function relationships across diverse datasets (e.g., conserved sequence motifs, structural interactions, pharmacologically and pathologically relevant mutations), or to facilitate a more consistent understanding of evolution.

Most GPCRs, including aGPCRs, share an archetypal 7TMD (Fig. 4) with an ENT and an ICT. The complex, often multi-domain structure of the aGPCR ENT varies across receptor subtypes, even within the same receptor group (Figs. 1, 3). As a result, a common GRN scheme for the N-termini of different aGPCR groups is not feasible. Furthermore, multiple transcript variants of individual members[21] add further complexity to the numbering system. This also applies to

the GAIN domain, found in 31 human aGPCRs (not considering *E4* due to its pseudogene status). The protein sequences of the GAIN domain vary substantially among aGPCR members, making reliable sequence alignment for assigning reference residues extremely difficult[9,10].

The *Stachel* core sequence and the GPS motif comprise the first highly conserved extracellular AA sequences directly adjacent to transmembrane helix (TMH) 1. The *Stachel* core has been observed as a β-strand bound within GAIN domain or ENT structures (Fig. 2A), but adopts an α-helical structure within the 7TMD in active state-like CTF structures (Fig. 2B). A recent sequence-based numbering approach focused on this conserved extracellular *Stachel* core sequence[16,17] and identified a leucine (L0.50) within the TxFxxLM core motif as the most highly conserved residue[10]. Here, "0" indicates the CTF region, while highly conserved TMH residues are denoted by the respective helix number (1, 2, etc.) combined with the ".50" designation (e.g., L1.50), allowing for up- or down-counting of adjacent residues. This scheme is an adaptation of the Ballesteros-Weinstein numbering system for class A GPCR[22].

Due to the high sequence variability of the GAIN domain, an alternative GRN scheme was developed based on the structural comparison of 14,435 vertebrate GAIN domain models[9]. This analysis revealed a secondary structure consensus of six α-helices (H1–H6) in the more structurally variable subdomain A (Fig. 2A), where some aGPCR subfamilies, e.g., D and G, show heterogeneity ranging from two to six α-helices. In the more conserved subdomain B, fourteen β-strands (S1–S14) were defined, with the GPS motif individually indexed (Fig. 2A). In this GRN scheme, the *Stachel* is designated as S14 (strand 14 of subdomain B), with its most highly conserved residue LS14.50 (equivalent to L0.50) located in the *Stachel* core.

For the 7TMD, the Wootten numbering scheme[23] was originally developed for the secretin receptor-like family (class B1 GPCRs) based on sequence conservation analyses, and was later also applied to aGPCRs (class B2 GPCRs) (Fig. 2C). This scheme was subsequently extended to include ICL1, ECL2, and helix 8 (H8), and the TMH1-7 numbering was revised to incorporate structural data that account for helix bulges or constrictions[24,25]. These GRNs were integrated into the GPCR database (GPCRdb), alongside the GAIN GRN scheme[9,26,27].

Importantly, phylogenetic analyses revealed that secretin-like receptors evolved from aGPCRs[28–30]. Consequently, a unified GRN scheme for most of the CTF region (*Stachel*–7TMD–intracellular helix 8), based on high sequence conservation across both aGPCR and secretin-like receptors, was recently proposed[31] (Fig. 2C). This provides a standardized framework for residue comparison across diverse receptor groups and members.

IV. Structures of adhesion GPCRs

A. GAIN domains

Crystal structure analyses of the GAIN domains of human B3 and rat L1[8] showed that the previously identified GPS motif[11], which comprises roughly 40-60 residues and includes

several highly conserved residues[32], is located at the C-terminus of a larger fold comprising approximately 320 residues and two subdomains (Figs. 3, 4).

The N-terminal subdomain A consists of up to six α-helices, with five of them forming a roughly parallel bundle, while a shorter helix 5 typically sits perpendicular to the others like a lid on top. Subdomain A is sometimes short through the lack of several α-helices (see Chapter III; Fig. 4A), for example in mouse G1[33], human G3[34], or human E5[35].

The core fold of the C-terminal subdomain B consists of a twisted β-sandwich including eleven β-strands in two antiparallel β-sheets. Additionally, short α-helices or β-strands may be found within flexible loop regions. Two highly conserved disulfide bridges stabilize subdomain B, both anchoring with one end close to the expected cleavage site (CxCxHL|T).

The cleavage site itself (referred to as GPS) is located within a sharply bent loop right before the last β-strand, which corresponds to the *Stachel*[16,17]; Fig. 4A). The GPS is flanked by two flexible regions, dubbed Flap 1 and Flap 2, which influence solvent accessibility and exposure of the GPS[14]. Structures of human F1[36], G3[34], L3[37], mouse G1[33], zebrafish G6[38], and rat L1[8] in the cleaved state demonstrated that the *Stachel* remains tightly bound within the GAIN domain fold after self-cleavage. The GAIN domains of human B2[39], B3[8], and a cleavage-deficient mutant of E5[35] were observed in an uncleaved state. To date no receptor has been structurally characterized in both a pre-cleavage and cleaved state.

B. Extracellular domains and ligand bound structures

Adhesion GPCRs exhibit diverse architectures of the ENTs that are critical for their unique activation mechanisms and functional specificity. While the membrane-proximal GAIN domain is present in most and the hormone receptor motif (HormR) domain in many aGPCRs, a diverse set of more N-terminal domains form a plethora of structures and interaction surfaces for binding partners of each individual aGPCR. Recent studies using mainly X-ray crystallography and single-particle cryogenic electron microscopy (cryo-EM) have begun to uncover the structural diversity of these domains and their complexes. While each structure appears unique, there are commonalities in how aGPCRs use their ENTs to recognise ligands (Table 1).

A recurring feature is a multidomain architecture in which several individually folded domains are attached to one another via linkers. Another emerging feature is their ability to form higher-order receptor complexes (Fig. 3A), or signaling hubs, that bring together multiple copies of the receptor and/or multiple ligands in a context-specific way.

ADGRL are exemplary with regards to these features. First described as receptors for the α-component of the black widow spider toxin 'latrotoxin'[40–42], they are now known to bind different endogenous ligands such as Fibronectin leucine-rich transmembrane protein (FLRT)[43] and Teneurins[44], using distinct binding domains (Fig. 3A). Structures suggest the formation of large signaling hubs that involve three or more proteins[45–50]. B1 and B3 require glycans - C-mannosylated tryptophan and O-fucosylated threonine residues in their thrombospondin domains - to bind to its ligands, the reticulon-4 receptors (Fig. 3B)[51,52]. The extended CUB

domain[53,54] (also referred to as atypical CUB domain[55]) of B3 (Fig. 1A) interacts with its ligand, complement component 1q-like 3 (C1ql3)[56–58], Ca^{2+}-dependently in a 3:3 stoichiometry[55]. This hexameric subunit displays an unusual atomic interface architecture that differs from a previously resolved C1q domain-receptor co-structure[59], and may get further joined into higher order complexes, e.g. a 36-meric super-complex[55]. Crystal structures of E5 in complex with CD55[60] and of E2[61] showed that the 3 epidermal growth factor (EGF) domains of E5 have a stable conformation for a trans-interaction with three short consensus repeat domains of CD55 in an antiparallel orientation (Fig. 3C). However, in many cases the individual domains of the ENT are connected by flexible linkers. An extreme example is G4, which contains a ~2,000 AA long glycosylated, flexible region between the N-terminal pentraxin domain and the SEA-HormR-GAIN domains (Fig. 3D)[62].

Important insights were gained with the full ENT structures of G6 (Fig. 3E), C1 (Fig. 3F) and G1 (Fig. 3G), which demonstrated that the extracellular domains display varying, isoform-dependent conformations that range from "compact/closed" to "extended/open-like" and dictate conformation-dependent downstream signaling. In some examples, the most distal, N-terminal domain is positioned near the transmembrane region, where it has a regulatory role in signaling[33,38,63,64]. Contrasting with larger aGPCRs is G3, which contains a minimal GAIN domain and just a short helical extension in the ENT[34].

Taken together, these results underscore the complexity of aGPCR signaling and the critical roles of their extracellular regions in receptor interaction, function and regulation.

C. 7TM domains

The N-termini of self-cleaved aGPCR CTFs are ~20-25 AAs long segments that extend extracellularly from TMH1. In cleaved but non-dissociated aGPCR NTF-CTF complexes, these CTF sequences are buried in a β-strand configuration within the NTF GAIN domain core (Fig. 4A). After NTF-CTF dissociation, the 7 AA long N-terminus of the CTF is liberated and becomes the TIA activating the CTF and drive G protein signaling, suggesting that the agonists binds intramolecularly to a 7TMD orthosteric site[16,17] (Fig. 4B).

Cryo-EM structures of TIA-activated G1 and L3 in complex with $G\alpha_{13}$[65] and D1, F1, G2, G4, and G5 in complex with $G\alpha_s$[66–68] revealed a shared hook-like, partial α-helical TIA pose that occupied a common orthosteric binding site within the core of the 7TMD bundle (Fig. 4B). The TIA consensus sequence TxFxxLM contacts multiple TMH spans and residues from ECL2[20,69].

In TIA-activated aGPCR-G protein complexes, the conserved toggle switch residue W6.53 directly engages the TIA to mediate receptor activation. As demonstrated for E5, W6.53 exhibited a marked rotational shift upon receptor activation, transitioning between inactive and active states[35]. Unlike class A and canonical class B GPCRs, which depend on conserved activation motifs (e.g., PIF, NPxxY, and DRY), aGPCRs lack these canonical sequences. Instead, activated aGPCRs show TMH6-TMH7 breaks or kinks like class B1 GPCR. Notably, the class B1 helix-unwinding residues G6.50/G7.50 are conserved in many aGPCRs, indicating they are a common feature of TIA-mediated aGPCR activation.

In the glucocorticoid-bound G3 complex, the receptor adopts a 7TMD architecture distinct from that of TIA-activated aGPCRs[70]. The glucocorticoid interacts with W6.53 to support receptor activation. One unconventional feature of the G3/GPR97-$G\alpha_o$ complex structure is the palmitoylation of the mini-$G\alpha_o$ C-terminus, which is inserted deeply into the 7TMD core. This modification is crucial for cortisol-induced coupling of G3 to $G\alpha_o$. However, it remains unclear whether this modification is present in native $G\alpha_o$.

Apo structures of E5 and G2 exhibit inactive- and active-state conformations, respectively[35,71]. The active-state G2 conformation is indistinguishable for the apo or dehydroepiandrosterone (DHEA)-bound forms indicating that it is stabilized by the bound $G\alpha_s$ and nanobody 35, as G2 can be activated by its TIA[72]. E5 exhibits an inactive, compact 7TMD conformation with pronounced inward shifts of the extracellular ends of TMH6 and TMH7, creating a constrained orthosteric pocket shielded by ECL hydrophobic residues, W685 and F760. The GAIN domain stabilizes an auto-inhibited state through direct interactions with ECL1 and 2, while the TIA remains sequestered within the hydrophobic core of the GAIN domain, preventing its interaction with the 7TMD core. A conserved "triad tethering motif" (W545-Y683-F760) forms a tight hydrophobic interaction to lock the inactive E5 conformation. Understanding whether these features are common to other apo-aGPCRs requires more structural investigations.

Critical synopsis and outlook: Structural insights into aGPCRs have fundamentally strengthened earlier concepts of TIA-dependent receptor activation and have enabled the delineation of 7TMD features that distinguish aGPCRs from other GPCR families. Not least, recent structural biology studies revealed the unexpected finding that steroids can bind to and activate aGPCRs by occupying positions that overlap with the canonical TIA-binding site. In the near future, it will be of prime interest to determine whether TIA- and steroid-mediated agonism are mutually exclusive or cooperative modes of receptor activation, how these modes relate to the receptors' perception of mechanical stimuli, and under which physiological conditions they occur individually or in concert.

The GAIN domain will likewise continue to attract structural attention. To date, only a single GAIN–7TMD co-structure has been solved, and many more are needed to understand the central role this domain plays in aGPCR signaling behavior. In particular, studies addressing the steric relationship and potential contacts between the GAIN domain and the 7TMD are still lacking. Similarly, the dynamic behavior of the GAIN domain under mechanical stimulation remains ill-defined, and approaches such as FRET imaging, NMR, and double electron–electron resonance (DEER) spectroscopy are in high demand to resolve structural transitions of the domain during receptor activation, signaling, and rest.

Structural work has also made major strides in uncovering how individual aGPCRs can engage multiple ligands, which has been a central conundrum in the field for a long time. A complex picture is emerging in which aGPCRs act as membrane-embedded hubs that integrate diverse extracellular cues—sometimes cooperative, sometimes mutually exclusive, into coherent cellular decisions. Frequently, however, this combinatorial logic remains unresolved. Subsequent work must therefore focus on how the structures of aGPCR–ligand complexes can illuminate cellular responses in the presence of more than one ligand for a given receptor. Cryo-electron tomography of intact aGPCR–ligand complexes at endogenous expression sites

within their native tissue context remains elusive, but will ultimately be required to complement—and in parts correct—our current understanding derived largely from studies of isolated domains or receptor fragments.

V. Autoproteolytic processing

Autoproteolytic cleavage at the GPS is a defining feature of many aGPCRs[73–75]. Prior to the discovery of the GAIN domain[8], a region of approximately 40-60 AAs, which is characterized by four conserved Cys, two invariant Tyr residues, and a consensus tripeptide cleavage sequence, had been dubbed the 'GPS motif'[13,32,76,77]. The GPS proteolytic reaction typically occurs at a three AA His(P-2)-Leu/Ile(P-1)-Ser/Thr(P+1) sequence within the GAIN domain (Fig. 2A)[11,77]. Deglycosylation and pulse-chase experiments suggest that this autoproteolytic process likely takes place in the endoplasmic reticulum (ER) during receptor biosynthesis[11,32,78–80]. Subsequent studies have demonstrated that early *N*-glycosylation plays a crucial role in regulating the efficiency of GPS proteolysis, highlighting the stringently controlled nature of receptor cleavage[80–82]. Recent advances have further uncovered key structural determinants and molecular interactions surrounding the GPS, which are essential for ensuring the completion of the autoproteolytic reaction[39,83]. Further, translational formation of the 7TMD and distance of the GAIN domain to the inner leaflet of the ER membrane enhances GAIN domain cleavage efficiency, probably by localizing the nascent GAIN domain in proximity to components of the *N*-glycosylation machinery required for correct domain folding and ER exit[80] (see also Chapter VIII).

GAIN domain autoproteolysis dissects the receptor into an NTF and a CTF, which remain tightly bound as a non-covalent complex at the cell surface[12–14] (Fig. 2A). Notably, the NTF of some aGPCRs such as L3 are in part spontaneously shed at the GPS[84], while the NTFs of other aGPCRs such as B1 and A2 are cleaved by proteinases at non-GPS locations releasing different fragments that can mediate non-cell autonomous functions[85–88].

Further analysis of crystal, cryo-EM and AlphaFold structures of various aGPCRs has highlighted the functional significance of the GAIN domain as an evolutionarily conserved protein fold, consisting of subdomains A and B (Fig. 2), necessary and sufficient for receptor autoproteolysis at the GPS[8,83,89]. The first reported structures analyzed GAIN domains of L1 and B3[8], which contain a long subdomain A built of six α-helices. Later studies showed that GAIN domains with a significantly shorter subdomain A, containing only 2-3 α-helices, are able to auto-proteolyze as well (see Chapters III, IV-A), e.g., G1[33], G3[34] and E5[35]. Hence, while the structure of subdomain B appears largely conserved across the aGPCR family, subdomain A exhibits much higher structural variability that is still compatible with GAIN domain autoproteolysis. These structural insights also enhanced the understanding of the molecular basis of *Stachel*-mediated aGPCR activation[65–68] and the role of aGPCRs as metabotropic mechanosensitive receptors[90–94] (see Chapters X and XV.D).

Interestingly, several non-aGPCR cell surface proteins, including the sea urchin sperm receptors for egg jelly and polycystic kidney disease 1(PKD1)-like proteins, also contain a

GAIN domain and undergo autoproteolysis[89,95–97]. These findings indicate a broader functional role for GPS cleavage in receptor biology[9]. As a result, specific point mutations in the GAIN domain that impact receptor structural stability and proteolysis have been associated with a range of unique genetic pathological disorders[94,98–101]. Overall, GAIN domain-mediated autoproteolytic processing is a vital post-translational modification that ensures the correct structural organization and functionalization of many aGPCRs.

Critical synopsis and outlook: Autoproteolytic processing of aGPCRs has been studied intensively. The remarkable evolutionary conservation of the GAIN domain and its autoproteolytic capacity underscores the substantial contribution this mechanism has made to the fitness of multicellular organisms. Nonetheless, many questions concerning the process itself, its cell biological role, and its physiological consequences remain unresolved. For example, is the steric flexibility of the GAIN domain a prerequisite for, or a consequence of, its self-cleavage? Are there extrinsic factors that cells can deploy to promote or inhibit receptor autoprocessing? Moreover, if the autoproteolytic step serves as a checkpoint for ER exit, what mechanisms does the ER use to assess whether cleavage of a given receptor molecule has taken place? Addressing these questions will be essential to extend our understanding of why many aGPCRs undergo autoproteolysis, whereas others do not.

VI. Alternative splicing and protein variants of adhesion GPCRs

Adhesion GPCRs are encoded by large genes with extended exon-intron structures that facilitate extensive transcript variation through alternative promoter usage and splicing events[12,21,102–105]. This genomic complexity enables the generation of multiple mRNA variants from a single gene, which can change the cell expression specificity and/or the open reading frame, potentially resulting in protein variants with distinct structural and functional properties.

Many aGPCRs and their transcript variants are expressed in a tissue-specific manner (Fig. 5). For instance, certain variants are predominantly found in neural tissues, whereas others are more common in immune cells[33,104]. This selective expression suggests that different protein forms may be adapted to meet cell-type specific needs. Beyond tissue specificity, spliceosomal reprogramming of aGPCR transcripts was also shown to occur within the same tissue or cell in a stimulus-dependent manner[106]. A striking example of this comes from the postsynaptic receptor L3, whose ability to promote synapse formation in the hippocampus[107] relies on two convergent pathways Gαs-mediated signalling and the assembly of postsynaptic scaffold condensates, both of which are governed by activity-dependent alternative splicing of L3[106]. Further, alternative splicing of the L homolog Cirl in *Drosophila* generates both canonical 7TMD-containing and atypical 7TMD-lacking proteins, whose co-expression enables G protein signalling and the discrimination between different mechanical stimulus intensities in sensory neurons[108].

While the identity of the specific factors guiding these processes remain unknown, these data unveil an intrinsic potential for cell autonomous modulation of aGPCR splicing events, which can sustain tissue/cell plasticity throughout development. Comparative analyses across species have revealed that transcript variants are conserved, suggesting that their functional significance may be evolutionarily conserved[21,104].

Alternative splicing can lead to considerable modifications in receptor structure. Variations may include the differential inclusion or exclusion of extracellular domains, segments of the 7TMD or ICT[21,104,109]. Such differences can influence key aspects of receptor function, including ligand binding affinity, receptor activation, and the modulation of downstream signaling pathways[109–112] (Fig. 6). Experimental studies have verified the existence of multiple aGPCR protein isoforms, exhibiting unique signalling properties and protein interaction profiles[106,108–113]. A well-established example of the latter is E5 and its ligand CD55 in the immune system. The E5 ENT exists in three different layouts containing between three to five EGF-like repeats, each of which is characterized by a different binding affinity to CD55[12,103,114] (Fig. 3C). Further, a prominent protein variant of L3 that excludes an element with inhibitory influence on transsynaptic interactions diminished $Ca_V1.4$ calcium channel activity, profoundly disrupted synaptic release by cone photoreceptor cells, and resulted in synaptic transmission deficits[115]. The L ortholog in *Drosophila*, Cirl, is alternatively spliced, giving rise to structurally disparate protein variants that act in concert to control mechanosensitive bandwidth in peripheral neurons[108]. In *C. elegans*, variants comprising only the ENT of L/LAT-1 and therefore lacking a functional 7TMD are present and could mediate 7TMD-independent function of the protein in the reproductive system in a non-cell autonomous manner[116] (Fig. 6C). G1 has multiple variants, and experiments with transgenic mice showed that the S4 variant is dispensable for cortical development and central nervous system (CNS) myelination but essential for microglia-mediated synaptic pruning[117]. Use of alternative promoters is another way to generate protein diversity and differential regulation. For example, the *B1* gene has an alternative promoter in the distal portion of intron 17 that drives the synthesis of shorter B1 isoforms lacking the ENT and resembling the ICT obtained after autoproteolytic cleavage at the GPS but with variable N-termini that can include new AAs[105]. These findings highlight the functional heterogeneity within the aGPCR class and illustrate how structural differences arising from alternative splicing can determine specific cellular outcomes.

The impact of natural, disease-causing mutations further emphasizes the importance of alternative splicing. Mutations located in exons common to all splice variants generally lead to a broad loss of receptor function, whereas mutations confined to alternatively-spliced regions may selectively impair individual isoforms[21]. One such example is provided in the C terminus of C1, which varies in length and sequence. Here, a $P^{2983}A$ mutation leads to faulty protein trafficking and is associated with neural tube defect[118]. Yet, $P^{2983}A$ is located in the variable C terminus of C1 and warrants thorough investigation of its pathogenicity. Such differential effect may account for tissue-specific disease manifestations and underscores the necessity of considering the splicing landscape when investigating the molecular basis of aGPCR-related disorders. The presence of multiple splice variants also carries significant experimental implications. When generating transgenic animal models or developing antibodies, it is crucial to consider the full spectrum of aGPCR variants to avoid misinterpretation of experimental

results. Furthermore, specifying the exact transcript variant used in functional or structural analyses is essential for ensuring reproducibility and for accurately correlating observed phenotypes with specific protein isoforms.

In summary, alternative promoter usage and alternative splicing are fundamental mechanisms that contribute to the structural and functional diversity of aGPCRs, thereby influencing receptor activity in both physiological regulation and pathology.

Critical synopsis and outlook: Motivated by the complex genomic architecture of many aGPCR loci, analyses of their splicing repertoires have begun to reveal a fascinating versatility in their gene products. This diversity ranges from subtle structural variations—some with critical consequences for receptor signaling—to major alterations that generate products no longer conforming to a canonical GPCR architecture. Thus far, only a few studies have traced individual splice forms through to their protein products and examined their occurrence and physiological functions in animal models, yet these have already uncovered intriguing roles in aGPCR activity. Many more such in-depth structure–function analyses will be required to understand how a cell chooses to express a particular splice form or a subset of splice forms of an aGPCR gene, and to what end.

VII. Subcellular trafficking, localisation and cellular functions of adhesion GPCRs

Adhesion GPCRs mediate cell-cell or cell-matrix interactions, thus requiring proper trafficking to the plasma membrane[107,119–121]. Anterograde trafficking guiding aGPCRs to the plasma membrane follows the ER-Golgi route, with the ENT acquiring *N*-glycosylation and mucin-type O-glycans[122–125]. Experiments with L1, E2 and D1 have shown that the GAIN domain undergoes autoproteolysis in the ER[11–13,32,80,122,124].

Our understanding of molecular cues directing aGPCR intracellular trafficking has largely been provided by mutational analyses. Mutagenesis of G1 with disease-relevant point mutations, including in the GAIN domain, unveiled disruption of its anterograde transport and accumulation in the ER[99,100,126,127]. However, mutations affecting self-cleavage within or in the immediate vicinity of the GPS in E2, E5 and D1 did not alter the receptors' principal ability to be trafficked to the plasma membrane, but rather the extent of protein exiting the ER[14,80,124,128]. In addition, also uncleaved subpopulations of cleavage-competent receptors were observed to be trapped in the ER, potentially due to their yet incomplete or improper GAIN domain folding[80,124]. These observations suggest that correct protein folding, but not GPS cleavage, is necessary for anterograde trafficking of aGPCR to the plasma membrane. GPS cleavage may act as a folding indicator before ER exit, but is not absolutely required for it. However, the importance of autoproteolytic cleavage for these phenomena may vary among aGPCRs[8,32,80,129].

N-glycosylation is an important determinant of aGPCR self-cleavage, maturation and trafficking[80–82]. Mutating *N*-glycosylation sites in the E2 NTF produced variable effects on

plasma membrane localization of the receptor[125], while pharmacologic inhibition of glycosylation or glycosylation-incompetent mutants impaired autoproteolysis of E2[80] or E5[81]. Further, *N*-glycosylation within the G6 NTF was shown to affect ER exit, while GPS cleavage was dispensable for membrane trafficking[82].

Retrograde trafficking of aGPCRs from the plasma membrane can occur spontaneously or upon ligand binding, as exemplified by L1, whose NTF and CTF undergo internalization into distinct endocytic organelles[122,130], some identified as early endosomes[131]. Studies with G2 suggest that arrestin-dependent endocytosis of its CTF is prominent upon dissociation from the NTF[132]. In contrast, A3 undergoes endocytosis via an arrestin-independent, clathrin-mediated mechanism[133].

V1, the largest aGPCR, is an interesting example of the wide variety of cellular functions mediated by a single receptor. V1 is found in the microvilli-like stereocilia of the mechanosensory hair cells in the inner ear and at the cilium of the photoreceptor cells of the retina and forms adhesion complexes with other molecules associated with Usher syndrome[134]. These depend on the formation of fibrous links between neighboring membranes by its exceptionally long ENT. V1 is targeted to the base of primary cilia by its interaction with a cytoplasmic chaperonin complex consisting of T-complex protein 1 (TCP-1) ring complex/chaperonin-containing TCP-1 chaperonins and the Bardet-Biedl syndrome chaperonin-like proteins[135,136]. V1 was also described as a metabotropic mechanoreceptor in focal adhesions controlling cell shape and motility[137,138]. Furthermore, V1 is a component of specialized mitochondria-associated ER membranes , where it is involved in Ca^{2+} release from the ER and its uptake into mitochondria, thus regulating cellular Ca^{2+} homeostasis[139]. Finally, V1 can inhibit the autophagy process at different steps[140].

Critical synopsis and outlook: In recent years, several connections have emerged between the post-translational processing of aGPCRs and their intracellular localisation, helping to bridge gaps in our understanding of aGPCR self-cleavage, glycosylation, and subcellular trafficking. For a few receptors, a basic understanding of their distribution within specific cell types has begun to take shape. However, it remains striking that for many aGPCRs, their proposed roles in sensing adhesive or mechanical cues are not yet supported by direct evidence of their localisation to the subcellular sites where such cues are encountered. This includes a broader lack of studies addressing the colocalisation of aGPCRs with their cognate ligands. A coordinated effort will be needed to address this substantial deficit in our understanding of aGPCR biology. Emerging technologies - such as advanced super-resolution microscopy, next-generation protein-labelling approaches including genetic code expansion and click chemistry, and the continuous development of highly specific binders (antibodies, nanobodies, monobodies) - promise to accelerate this progress. Together, these tools will be essential for determining the precise localisation of aGPCRs at their native expression sites within cells.

VIII. Anatomical and cellular distribution of human adhesion GPCR transcripts

Mammalian genomes contain a collective of 33 aGPCR loci, but the count in individual species varies[1,31,141] (Fig. 7). For example, as the mouse genome encodes 31 aGPCRs, as orthologs of *E2* and *E3* are lacking[142–144], and because *D2* is considered a pseudogene[31], only 30 aGPCR genes are likely to produce functional receptor proteins in the mouse. Of the 33 human aGPCR loci, *E4* and *F2* are currently annotated as pseudogenes. While some studies reported that these loci generate transcripts that encode truncated proteins[145] or are transcriptionally inactive (Fig. 5), respectively, other studies detected expression of *E4* and *F2* transcripts[21]. Until it is conclusively demonstrated that these transcripts fail to produce functional proteins and that the loss of *E4* or *F2* has no phenotypic consequences, their gene status remains unresolved.

Fig. 5 summarizes single-cell RNA sequencing data across 31 human tissues and bulk RNA sequencing of blood samples for all aGPCRs. It is unlikely that any of the approximately 200 cell types in the human body completely lacks aGPCR expression. In Fig. 5, the complex data are visually simplified by grouping cells with similar or overlapping functions, even if they originate from different organs. For example, serous secretory epithelial cells are found in the exocrine pancreas, as well as in salivary and mammary glands. These cells may not share the same embryonic origin. Interestingly, the presence of an aGPCR in a specific cell layer of one organ often corresponds to its presence in the same cell layer of another organ. For instance, *F4* is found in the epidermis, the squamous (cornified) epithelium of the skin[146], and is likely also present in organs or cavities lined by squamous (non-cornified) epithelium.

Some aGPCR transcripts are omnipresent in various functionally distinct cell types. The most prevalent examples are *E5* and *G1*. *E5* is predominantly expressed in immune cells, but also at moderate levels in smooth muscle[147], skeletal muscle[148], and lung epithelial cells. The presence of *G1*, first shown in circulating natural killer (NK)[149] and cytotoxic T cells[150], has been confirmed for many (secreting) epithelial cells, as well as microglia and astrocytes[151].

On the other hand, there are more selective aGPCRs expressed in only a few cell types. This applies to *E1-E3*, *G3*, and *G5*, all expressed by immune cells[152]. Furthermore, *D2* and *F3* are restricted to spermatids and spermatids/glial cells, respectively, whereas *G4* is a specific marker of intestinal enteroendocrine/enterochromaffin and Paneth cells. No transcripts encoding *F2*, which shares notable sequence homology with *F4*, were found in any tissue in the current analysis.

While cellular expression patterns of aGPCRs are becoming increasingly elucidated, there are cell types, such as osteocytes in bone and chondrocytes in cartilage, that are difficult to isolate for RNA sequencing, leaving knowledge lagging behind[153]. Moreover, most of these transcriptomic data still require validation at the protein level. One reason for the gaps in our knowledge about protein expression is the lack of thoroughly evaluated antibodies for most aGPCRs. Exceptions are antibodies targeting members of the E, G and L subfamilies. Generating a comprehensive set of tools for detecting aGPCRs at the protein level would benefit from a community effort, which includes rigorous quality controls such as cells

expressing ectopically tagged aGPCRs and CRISPR-generated aGPCR-deficient cell lines[151,154]. Another reason is the structural complexity of aGPCRs due to extensive alternative transcription[21], splicing[104] and posttranslational modification. These processes result in cell type- and context-specific expression of isoforms (e.g., E2 and E5)[155], protein truncation (e.g. by proteolytic cleavage within or outside the GPS)[74], and glycosylation (e.g. E5)[147,156].

Critical synopsis and outlook: Modern single-cell sequencing technologies have enormously widened the grasp of cellular expression patterns for aGPCRs. However, as with the demanding transition from splice- to isoform-level repertoires, single-cell protein expression studies that extend transcriptional information to the translational landscape are still lagging behind. Such analyses are urgently needed to establish where – and ideally at isoform-specific resolution - individual aGPCRs execute their functions.

IX. Interactions

A. Ligands (extracellular binding partners)

As bona fide adhesion molecules, aGPCRs participate in both heterophilic and homophilic protein-protein interactions that stabilize cell-cell or cell-matrix contacts, while also allosterically regulating receptor signaling. Interactions with extracellular ligands are mediated by subfamily-specific aGPCR domains and the GAIN domain located in the ENT (Table 1, Fig. 3). Efforts to identify extracellular ligands have been carried out in the cellular and tissue context in which individual aGPCRs are expressed. These efforts aim to shed light on a plethora of physiological processes involving a wide range of receptor-ligand pairs. Early work on the immunological response led to E5 being among the first deorphanized aGPCR[157]. Meanwhile, the neurotropism of an exogenous toxin would lead to its pairing with L1[13,158]. Subsequent studies on tissue development revealed that thus far only members of subfamilies C[159,160] and V[161,162] engage homophilically as adhesive aGPCR pairs. These observations highlight the potential of aGPCRs to participate in diverse types of ligand interactions[44,163,164].

The molecular basis for this ligand diversity resides in the presence of distinct domains, many with adhesive functions, organized into separate modules in different aGPCR subfamilies (Figs. 1, 3). For example, G subfamily members interact with cell surface antigens, phospholipids, extracellular matrix (ECM) molecules, steroid hormones or small molecule ligands through structurally distinct N-terminal adhesion modules (Fig. 3D,E,G) or within their transmembrane domains[71,121,165–173]. Interaction patterns are prone to further diversification as adhesion modules can accommodate many ligands at once[107], be modified by alternative splicing to regulate ligand binding[111,121] or stabilize interactions occurring *in trans* (across cells) (Fig. 3A-D) as well as *in cis* (within the same cell) configurations[130,174,175] (Fig. 3).

Transcending their mere adhesion role, a growing number of aGPCRs is shown to utilize their ligand interactions to initiate signaling through both G protein-coupled mechanisms [91,110,176–178] and G protein-independent pathways[179]. These advances have facilitated the identification of ligands with both positive and negative allosteric effects on aGPCR signaling[177,180].

Emerging from these studies is a pattern of wide physiological relevance, wherein a given aGPCR can engage with distinct cellular contexts to regulate cell-specific functions (Fig. 5). For example, F5 binding with its ligand sFNDC4 in adipose tissue contributes to glucose uptake[181], while in the lung, its interaction with the Sp-D ligand regulates surfactant homeostasis[182–184]. However, more than 30 % of vertebrate aGPCRs still lack assigned ligands including members of the V subfamily, whose ligand-pairing remains elusive despite or because it harbors the largest ENT among all aGPCRs[137]. Future efforts focusing on ligand discovery are likely to enhance our understanding of aGPCR functions.

B. Intracellular binding partners (except G proteins, arrestins, Rac/Ras/Rho GTPases)

Many aGPCRs bind to PDZ (Post-synaptic density protein 95 /Disc large tumor suppressor/Zona occludens 1) scaffold proteins via their cytoplasmic C-termini. Notably, nearly half of the 33 mammalian aGPCRs possess a PBM - typically the last C-terminal 4-5 AAs of the C-terminus - that can specifically dock into the binding pocket of target PDZ domains[185]. These protein-protein interactions (PPI) can influence receptor signaling, link receptors to the cytoskeleton, and/or influence the subcellular localization of both the receptors and their PDZ partners (Fig. 6A). For example, mechanical force-induced phosphorylation of E5 in its PBM alters the intracellular binding of E5 to the F-actin cytoskeleton[186].

Several aGPCR interactions with PDZ proteins have been reported. For example, L and B receptors are targeted to the post-synaptic membrane of neurons by binding to PDZ domains of the Shank (SH3 and multiple ankyrin repeat domains) and MAGUK (membrane-associated guanylate kinase) proteins[187–189]. In sensory cells, V1 is integrated into adhesion complexes by binding to the PDZ proteins harmonin, whirlin, and PDZD7, as well as to other proteins related to the Usher syndrome[135,185,190,191]. In non-neuronal cells, the MAGUK protein DLG1 interacts with A2, A3, and E5[186,192,193]. A2, A3 and C1 interact with the PDZ protein Dishevelled to modulate WNT signaling[194–196] (Fig. 6B). A2 was also found to interact with MAGI3 and DLG4237.

Regarding non-PDZ-mediated PPIs, E5 binds to β-catenin independently of the WNT pathway[197]. B1, B3 and A2 interact with the ELMO/DOCK180 complex regulating the F-actin cytoskeleton via RAC[198–202]. Additionally, the tetraspanin CD81 binds to G1 inhibiting NK cell activation[203].

Systematic affinity proteomic screens have validated known protein-protein interactions and have identified numerous novel putative interacting partners for A1-3, B1-3, D1, E5, L2, and V1[7,164,204]. These protein-protein interactions were associated with synapses, focal adhesions[137], mitochondria, the ER, ER-plasma membrane bridges[204], mitochondria-associated ER membranes[139], autophagosomes[140], the γ-secretase complex, nuclear-cytoplasmic shuttling, and primary cilia. At primary cilia, V1 was found to bind to CCT molecules of the TRiC-chaperonin complex and chaperonin-like Bardet-Biedl syndrome proteins[135,136]. V1 also binds to the Sigma-1 receptor and ACSL4 in mitochondria-associated ER membranes and controls

Ca^{2+} flux from the ER[139], while suppression of D1 signaling by ESYT1, a Ca^{2+}-dependent ER-plasma membrane molecular bridge, is abrogated by Ca^{2+} elevation[204].

Critical synopsis and outlook: Recent work has uncovered a strikingly diverse interaction landscape for aGPCRs, spanning extracellular ligands and intracellular binding partners. Extracellularly, aGPCRs engage heterophilic and homophilic partners through subfamily-specific adhesion modules and the GAIN domain, enabling both adhesive functions and allosteric regulation of signaling. The breadth of identified ligands - from ECM proteins and cell-surface antigens to steroid hormones and small molecules - highlights the modularity and contextual adaptability of their ENT architecture. Yet, more than one-third of vertebrate aGPCRs remain orphan receptors, illustrating persistent gaps in ligand discovery and tissue-specific mapping. Intracellularly, many aGPCRs harbor PDZ-binding motifs that link them to synaptic scaffolds, cytoskeletal networks, and polarity complexes, while additional non-PDZ interactions connect them to pathways controlling actin remodeling, organellar crosstalk, autophagy, and Ca^{2+} flux. Proteomic screens have further expanded this repertoire, revealing associations with mitochondria, ER–plasma membrane bridges, focal adhesions, and primary cilia. Looking ahead, a central challenge will be to mechanistically integrate these diverse interactions into unified models of aGPCR function. Key priorities include systematic ligand discovery, structural elucidation of receptor–partner complexes, and resolving how context-dependent extracellular and intracellular interactions converge to shape signaling bias. Such efforts will be essential for unlocking the pharmacological potential of this receptor family.

X. Receptor activation modes

A. TIA/*Stachel*-dependent signaling: dissociation model

Autoproteolytic cleavage of aGPCRs, first observed for E5[12] and L1[13], results in the presentation of stable NTF-CTF receptor complexes at the cell surface and is essential for the subsequent dissociation capacity of receptor fragments[11,14] (Fig. 6). Self-cleavage is essential for the function of many aGPCRs. This is exemplified, for example, by a mouse strain carrying a cleavage-deficient F5 point mutant knock-in as it displayed the same phenotype of pulmonary surfactant oversecretion as *F5* knock-out (KO) animals[205]. Engineered NTF deletions of G1 and B2 (i.e. CTF-only) had elevated signaling[206–208]. Numerous studies reporting enhanced constitutive activity of expressed CTF-only receptors support these findings, e.g. refs. [16,17,206–209]. The observation of receptor NTF-CTF complex dissociation via NTF release sensors (NRSs) of endogenously expressed aGPCRs in *Drosophila* demonstrated NTF-CTF separation *in vivo*[93]. Recovery of isolated aGPCR NTF from tissues and cells further corroborated NTF-CTF complex dissociation models of aGPCRs[210,211]. Additionally, chaotropic salt was used to dissociate NTFs from CTFs in overexpressed aGPCR membrane preparations leading to robust receptor and G protein activation[17,212].

These observations along with structural insights revealing the autoproteolytic mechanism of the GAIN domain[8], have led multiple groups to propose a model for the enhanced activity of

isolated aGPCR-CTFs. In this model, the residual extracellular N-terminus of the CTF is masked by NTF structural elements in intact NTF-CTF complexes; upon fragment dissociation, the CTF N-terminus is decrypted and binds intramolecularly to an orthosteric site within the CTF, serving as a TIA (Figs. 4B, 6A). A series of complementary studies with G1, G2, G5, G6, D1, F1 and L3 support this TIA hypothesis[17,72,113,212–214]. Furthermore, multiple structural analyses have demonstrated the commonality of TIA binding to aGPCR/G protein complexes (reviewed in[20,69]) and are described in detail in Chapter IV.

Acute activation of aGPCRs by exogenous proteases at engineered cleavage sites positioned N-terminal to the TIA of L3[215] and D1[124] helped confirm the model. A follow-up study found that TIA-mediated signaling of L3 required NTF dissociation and that ~5 % of the receptor population spontaneously sheds its NTF, potentially accounting for the majority of basal activity[84] (Fig. 6A). This parallels a study in which D1 was activated by an NTF-specific antibody in a cleavage-dependent manner; presumably, the antibody promoted partial NTF dissociation[216]. Modes of TIA-dependent and independent aGPCR activation mechanisms have been reviewed extensively[217,218] (Fig. 6A). A recent profiling study of TIA-dependent signaling and trafficking of human aGPCRs supported the TIA activation model for most receptors including those above[209]. However, despite strong TIA sequence conservation across the entire receptor panel, not all aGPCRs exhibited TIA-dependent signaling (Fig. 6A) , which correlated with AlphaFold predictions identifying receptors unlikely to exhibit TIA-binding to the CTF[209].

B. TIA/*Stachel*-dependent signaling: non-dissociation model

In addition to the dissociation-dependent activation of aGPCRs, findings conflicting with this activation scenario have also been reported. Several *in vitro* and *in vivo* studies have indicated that receptor self-cleavage is not essential for signaling or cell autonomous functions of certain aGPCRs supporting a model in which NTF release is not required to induce aGPCR activation via the TIA (Fig. 6A). However, not all reports dissected basal receptor activities from TIA-mediated stimulation.

For example, a study in *C. elegans* indicated that a cleavage-deficient mutant of LAT-1/L can rescue phenotypic defects similar to the cleavable receptor[219]. However, its metabotropic signaling activity was not examined at the time, and since the TIA sequence had not yet been described, its necessity for receptor function was not assessed. Its metabotropic signaling activity was discovered thereafter, and its TIA sequence identified[220]. Similarly, basal activities of cleavage-deficient mutants of D1[221], G1[222], and G2[223] were not significantly affected in all examined pathways. However, a contribution of the TIA to these signals was not directly tested. Of note, when dissecting the contribution of self-cleavage from agonism it is important to consider that the most C-terminal AA of the HL/T cleavage triad overlaps with the N-terminus of the TIA. A study in *D. melanogaster* actively addressed this by creating H>A (-2) and T>A (+1) alleles of the L homolog Cirl, showing that disruption of the internal agonist (T>A) failed to rescue the receptor function, while lack of cleavage showed wildtype results[92]. Additional support for cleavage-independent and thus non-dissociative aGPCR activation via the TIA sequence comes from uncleavable G5 and D1 receptors, which can be activated by mechanical

forces in an TIA-dependent manner[66,113]. However, conflicting reports exist for both examples[212,216], and studies frequently differ in their observations regarding self-cleavability of aGPCRs[113,216,224].

C. TIA/*Stachel*-independent signaling

While the TIA is clearly important for activation of signaling by several aGPCRs, it is not universally important (Fig. 6A). For example, deletion or mutation of the TIA has little impact on G protein-mediated signaling by B1[222], C1 or C3[225], whereas parallel studies revealed signaling by G1[222] and C2[225] to be heavily TIA-dependent. Similarly, mutation of the TIA was found to have no effect on stimulation of full-length G1 by an activating antibody[226], even though TIA exposure is essential for signaling by the isolated G1 CTF region[17,222]. These observations demonstrate that the importance of the TIA for signaling varies by receptor as well as by mode of activation.

Consistent with these findings, a recent comprehensive analysis of G protein-mediated signaling by the CTF regions of all human aGPCRs revealed TIA-dependent signaling in approximately half the receptors[209]. In contrast, the signaling activities of the other aGPCRs examined in this study appeared to be TIA-independent. Intriguingly, AlphaFold models of the isolated CTF correlated strongly with the TIA-dependence of signaling for each receptor, with intramolecularly bound TIA sequences predictive of TIA-dependent signaling[209].

Two distinct views have emerged regarding TIA-independent aGPCR signaling. First, for some aGPCRs there may be additional points of contact between the NTF and CTF beyond those by which the NTF sequesters the TIA. These interactions may enable the NTF to influence CTF conformation, consistent with recent cryo-EM studies on L3 showing that the GAIN domain exhibits conformational coupling with the 7TMD region[37]. Second, TIA-independent signaling could be indicative of tonic signaling capabilities by certain 7TMD, which could feasibly underlie long-lasting actions of particular aGPCRs, such as control of PCP by C1-3[227,228] or conventional dendritic cell type 2 positioning in the spleen by E5[91]. In this model, an important role of the NTF may be to guide the subcellular targeting of the CTF to ensure that TIA-independent signaling occurs in the right location.

Critical synopsis and outlook: How aGPCRs become activated has naturally been one of the most intensely studied questions in the field. The demonstration of tethered agonism more than a decade ago catalyzed research on individual aGPCR functions across pharmacological, structural, and physiological levels. Together with the discoveries of receptor dissociation through autoproteolytic processing and the mechanosensitivity of many aGPCRs, the role of the TIA in receptor signaling has remained a central focus of investigation. Despite substantial progress—supported by structural studies elucidating the conformation of the TIA bound to the 7TMD—several observations remain incompatible with the most parsimonious model of TIA-dependent activation via receptor dissociation. Chief among these is the finding that non-autoproteolyzed aGPCRs can nevertheless signal in a TIA-dependent manner. In addition, convincingly TIA-independent signaling events have been documented, raising the question of whether these distinct signaling modes can be mediated by the same receptor protein and under

which conditions aGPCRs may become biased toward one mode or another. A critical and systematic dissection of these phenomena is therefore warranted to reconcile these disparate mechanistic models and to define the principles that govern aGPCR activation.

XI. Signaling routes

A. Cell-autonomous signaling

1. G proteins

G proteins are the primary transducers of most GPCR-driven cellular responses (Fig. 6A). Receptors bind G proteins and catalyze nucleotide exchange, enabling interaction with various secondary effectors to propagate intracellular responses[229,230].

Evidence linking aGPCRs with G protein-mediated signaling was derived from affinity chromatography and immunoprecipitation studies, which revealed interactions between G proteins and L1[42] and G1[170]. Subsequently, regulation of Ca^{2+} mobilization and RhoA activation, indicative of G protein signaling, were observed downstream of L1[44] and G1[231], respectively. Mice lacking G1 or collagen III exhibit similar cerebral cortex defects as animals with neuronal Gα12/13 KOs[165,232–234], suggesting a link between collagen binding to G1 and G12/13 signaling. A diversity of G protein coupling partners has since been indicated for multiple aGPCRs[16,17,72,106,108,113,132,186,189,212,215,221,235–240].

Biochemical studies showed that the TIA of aGPCR mediate receptor activation and stimulation of G protein GTPγS binding[16,17]. This approach helped identify many other aGPCR-G protein coupling interactions[65,212,215].

A large-scale profiling study used G protein conformational biosensors and signaling assays downstream of G protein activation to define the TIA-dependent coupling patterns of the human aGPCR family in a single system[209]. This identified a preference for signaling through the $G\alpha_{12/13}$ subfamily, which activates RhoGEF to control cytoskeletal dynamics, thereby influencing cell migration, contractility, shape, and adhesion[241–243]. All these biological activities align well with the role of aGPCRs as mechanoreceptors.

The concordance of receptor and G protein KO phenotypes[91,220], the stimulation of aGPCR signaling by synthetic peptide agonists[211,244], and the disruption of secondary messenger pathways upon receptor deletion or mutation[106,108,220,245,246] have collectively confirmed several aGPCR-G protein signaling axes *in vivo*. Specific G protein signaling pathways have also been linked to various aGPCR-driven human disease states[247–249]. However, the physiological significance of other biochemically identified aGPCR-G protein interactions remains to be investigated.

2. Arrestins

Arrestins are cytosolic proteins that facilitate the desensitization and internalization of activated and phosphorylated GPCRs. Receptor phosphorylation by GRKs (G protein receptor kinases) (Fig. 6A) creates a phosphorylation pattern of serine or threonine residues, which directs arrestin interactions and function. In addition to turning off G protein-mediated signaling, recruitment of arrestins to GPCRs can result in the initiation of signaling cascades by scaffolding and activating effectors proteins like ERK1/2 or JNK3[250,251].

Regarding arrestin interactions with aGPCRs, the CTF of G1[208,222], B1[189,222], B2[247] and G2[132] have been shown to robustly co-immunoprecipitate with arrestins. In the case of G2, arrestin binding can facilitate complex formation with CFTR[240]. In bioluminescence energy transfer (BRET)-based studies, both F5[244] and L3[215] have shown to recruit arrestins in an activity-dependent manner.

Recently, comprehensive BRET assays were performed with all human aGPCR CTF constructs to determine potential arrestin interactions[209]. In these studies, TIA/*Stachel*-dependent recruitment of arrestins was observed for E1, E3, F1, F4, and G7. Similarly, recent screening using a cumate-inducible Tango-Trio assay revealed arrestin binding to A1, A3, F1, G1, G2, and G5[252]. Further work in this area is likely to reveal many more examples of aGPCR regulation and signaling mediated by arrestin recruitment.

3. Signaling pathways independent of G proteins and arrestins

Beyond their best-characterized G protein and arrestin pathways, aGPCRs signal through non-canonical mechanisms that utilize intracellular scaffolds and ectodomain-assembled receptor complexes (Fig. 6A). For example, subfamily B members control Rho-GTPase signaling and cytoskeletal remodeling by interacting with Rho-GTPase regulatory proteins (GEFs/activators and GAPs/inhibitors) via their large ICTs. B1 and B3 are associated with the ELMO/Dock180 Rac1-GEF complex to drive Rac1-dependent phagocytosis, myoblast fusion, and neuronal morphogenesis[200–202,253,254], though the expression of B1 in macrophages remains debated[154]. In neurons, B1 recruits the Par3/Tiam1 Rac1-GEF complex to synapses to promote Rac1-dependent dendritic spine and excitatory synapse development[119,255], and later engages the Rac1-GAP/RhoA-GEF Bcr to switch signaling towards RhoA-dependent dendrite growth arrest[256]. Additionally, B1 ICL1 interacts with the E3 ubiquitin ligase MDM2, preventing MDM2-mediated PSD95 and p53 degradation and impacting synaptic plasticity and medulloblastoma tumorigenesis[257,258]. These findings highlight ICT-dependent effectors as aGPCR signal transducers beyond G proteins and arrestins.

4. Signaling with co-receptors

Adhesion GPCRs interact with various co-receptors to regulate intrinsic G protein signaling or extrinsic signaling through associated receptors (Fig. 6B). These interactions are crucial for diverse physiological processes, including vascular development, neural functions, and immune responses.

E5 was the first aGPCR shown to heterodimerize with another receptor, the lysophosphatidic acid (LPS) receptor 1, leading to amplified LPA-dependent RHO and extracellular signal-regulated kinase activation[259,260].

A2 forms complexes with the WNT co-receptors RECK, FZD, and LRP5/6, regulating WNT7A/B-specific β-catenin signaling in brain endothelial cells, crucial for angiogenesis in the developing CNS and for blood-brain barrier integrity[179,196,261–265] (Fig. 6B).

B1 and B3 interact with RTN4/NoGo receptors regulating neuronal development[51,52].

The cadherin-like C subfamily regulates epithelial PCP and synaptogenesis by forming asymmetrical cell-cell contacts[266,267]. The C-VANGL complex on one cell interacts with the C-FZD complex on the adjacent cell. Notably, A and C subfamily members may not always signal through G proteins[209], while C receptors can couple to G proteins[225].

D1 interacts with protein tyrosine kinase 7 (PTK7) on neighboring cells, which positively regulates D1 signaling and requires both NTF interactions and cleavage at the GPS[178]. These findings shed light on the role of D1 in physiological processes and pathological conditions, such as glioblastoma and other malignancies[268–270].

G1 interacts with CD81 in resting NK cells, inhibiting NK effector functions[203]. Cross-linking of the G1 NTF by anti-G1 mAbs leads to dissociation of the G1-CD81 complex, activating NK cells. G3/GPR97 is a critical component of the PR3-CD177-G3-PAR2-CD16b complex on neutrophils, promoting enzymatic activity of membrane PR3 to cleave PAR2 thus orchestrating PAR2-induced neutrophil activation[34]. Thus, ENT-mediated aGPCR-GPCR complexes represent another signaling mechanism by which aGPCRs regulate diverse cell-type-specific functions.

In *Drosophila*, the L homolog Cirl is expressed as both a conventional 7TM receptor and a single-pass transmembrane (1TM) variant. These Cirl isoforms appear to heterodimerize (7TM-1TM) via ENT-driven interactions, forming a complex that signals through $G\alpha_o$ proteins to enable physiological mechanosensing in sensory neurons[108]. Aside from other long-known extracellular interactions[271], mammalian L1 associates with CNTN6 in cultured neurons, inhibiting pro-apoptotic signaling[175].

B. Non-cell autonomous signaling

Non-cell autonomy refers to the ability of a gene to influence a phenotype, behavior or response in cells other than those expressing its gene products (Fig. 6C). An illustrative example of non-cell autonomy is the action of a hormone that is secreted by a gland cell that acts on neighboring (paracrine) or distant target cells (endocrine). Non-cell autonomous signals can also be transmitted contact-dependently (juxtacrine), where the sending cell is in direct contact with the receiving cell, e.g. via interacting membrane proteins (Fig. 6C). The structure of aGPCRs lends itself to non-cell autonomous signaling as NTF or other ENT fragment shedding through mechanical forces or proteases can liberate signals from receptor molecules that impact adjacent neighboring or distant cells. Also the formation of aGPCR-ligand complexes between cell neighbors can underlie the non-cell autonomy of aGPCR signals[5,6,89] (Fig. 6C). Therefore,

for this form of signaling the terms 'N terminus-only', '7TM-independent' or '*trans*-signaling' are sometimes used[86].

For example, shed ENT fragments of E5 and the vasculostatins released from B1 ENTs impact angiogenesis[272]. Released extracellular fragments of A2[273] and B1[274] fragments may control endothelial cell survival by engaging with integrins and/or CD36[275].

The ENT of L4 promotes epithelial–mesenchymal transition in myofibroblast-like cells and enhances angiogenesis. It is speculated that the NTF is released upon epithelial damage in endothelial extracellular vesicles and aids endothelial sprouting[276].

L3 is expressed in postsynaptic horizontal cell dendrites in the mouse retina and controls synaptic release from presynaptic cone photoreceptor cells[106], although it is unclear whether the NTF of L3 needs to be released for that effect or remains in the mature NTF-CTF receptor complex.

Furthermore, it has been reported that the NTF of G6 can be secreted and bind to cardiomyocytes[246]. In addition, loss of G6-NTF results in defective compact-wall myocardium in zebrafish[277]. Based on these data, G6 appears to be expressed exclusively in the endocardium in the heart, non-cell autonomously regulates cardiomyocyte behavior and is required for proper heart development.

In *Drosophila*, the aGPCR Mayo is expressed in the midgut, where it regulates the generation of enterocytes by affecting cell lineage decisions. Genetic removal of *mayo*, however, also causes a drastic increase in cardiac pacing, a site where no Mayo expression is observed, through the dysregulation of potassium levels in the hemolymph by an unknown mechanism[278].

The Toll-like receptor (TLR) Toll-8/Tollo controls the number of neurons in the cortex of *D. melanogaster* by stimulation of asymmetric neuroblast divisions. This activity is suppressed by the L homolog Cirl, which is expressed in neighboring cortex glial cells, from where it releases its NTF that acts as an inhibiting modulator of the Toll-like receptor Tollo/Toll-8[93]. A similar interaction between Cirl and Toll-8 *in trans* is employed to control asymmetric myosin-II polarisation at cell-cell boundaries during embryogenesis and tissue morphogenesis in the fly[279]. Structural, functional and expression studies in *C. elegans* further support the interaction between subfamily L aGPCRs and TLR[280].

Also in *C. elegans* it was shown that the LAT-1 ENT directly interacts with a ligand of the DSL (Delta, Serrate, LAG-2) family, thereby modulating the Notch pathway in a non-cell autonomous fashion[281]. This interaction occurs on the same cell, the signal, however, is relayed to the opposing cell via the Notch receptor. It remains unclear whether the LAT-1 NTF is released in this context as non-cell autonomy can also emerge from direct interactions of the ENT of an aGPCR with surface-mounted partners without NTF release. For instance, a membrane-bound LAT-1 NTF is sufficient to modulate fertility by controlling sperm guidance, ovulation, and germ cell apoptosis in a non-cell autonomous manner[116,219]. The receptor further controls neuronal morphogenesis solely by its NTF[282]. Another example is the expression of B1 or B3 on glial cells or neurons, which can mediate interaction with RTN4/NoGo receptors on adjacent neurons[51] controlling neural network activity[52].

The C ortholog Flamingo is required for correct photoreceptor axon targeting in the fly's retina in a non-cell autonomous fashion[283], an effect that was also observed for the nematode homolog *fmi-1* in neuronal pathfinding[284].

Critical synopsis and outlook: The complex and expanding repertoire of signaling routes in which aGPCRs are embedded is undoubtedly one of the most fascinating - and most consequential - considerations for their prospects as pharmacological targets, a goal that remains unmet to date. Their potential druggability has both benefited from and been complicated by this functional versatility. Insights into the involvement of aGPCRs in multiple signaling pathways and complexes, and even their ability to act as ligands rather than solely as receptors, have broadened the landscape of potential sites for pharmacological intervention through small molecules or biologicals. At the same time, identifying modulators that selectively interfere with only one of several receptor signaling routes may prove particularly challenging.

XII. Physiology and pathophysiology

A. Organ systems

With this chapter we provide a dataset on the anatomical and cellular distribution of all human aGPCR transcripts (Chapter VIII, Fig. 5).

1. Nervous system - glia & neurons

In vertebrate nervous system development, neural tube closure, the fusion of neural folds at the midline that gives rise to the brain, spinal cord, and neural crest cells, occurs first, followed by neuronal birth and the migration of newborn neurons. Adhesion GPCRs play essential roles in each step, and consequently their dysfunction is associated with neurological diseases. C1 is required for neural tube closure in mice[285]. G1 regulates the birth and placement of cortical neurons. Loss-of-function mutations in G1 elicit bilateral frontoparietal polymicrogyria, a devastating human brain malformation[286,287], characterized by neuronal over-migration, ectopias on the brain surface, and myelination deficits[286,288]. G1 binds collagen III presented in the pial basement membrane[165] to initiate the proper stop signal. Similarly, subfamily L aGPCRs also direct neuronal migration using contact repulsion through binding to Teneurins and FLRT[49] (Fig. 3A). Following migration, neurons extend axons and dendrites (regulated by subfamily B[52,256] and C[289] members) and identify their partners in neural circuits. L2 facilitates hippocampal partner finding through spatially restricted expression and interaction with Teneurin-3, mediating axonal repulsion from incorrect targets[290] through G protein signaling[291].

Synaptogenesis follows brain patterning. Adhesion GPCRs of the L, B, and C subfamilies regulate dendritic spine and synapse formation throughout the CNS, including the hippocampus, cerebellum, cortex, olfactory bulb, and neuromuscular

junction[56,107,120,255,257,267,292–302]. Intriguingly, these receptors may contribute to a molecular code that specifies distinct synapse types, e.g. L1 is implicated in inhibitory synapses, L2/3 in excitatory inputs[107,120,292] and B3 in the formation of climbing fiber but not parallel fibers[295,296]. Recently described ADGRL-containing transsynaptic adhesion complexes regulated by alternative splicing are required for synapse assembly[106,107,303,304]. In some cases, lipid metabolites appear to regulate synaptogenesis through F1, which promotes neurite growth and synaptogenesis by binding to its ligand N-docosahexaenoylethanolamine[177,305].

Myelination is largely postnatal, involving oligodendrocytes (in the CNS) and Schwann cells (in the peripheral nervous system [PNS]) wrapping hydrophobic membranes around axons, enabling saltatory transmission of action potentials and providing trophic support. G1 functions cell autonomously in oligodendrocyte development and CNS myelination. Its loss-of-function yields CNS myelin deficits in zebrafish[306], mice[307], and humans[286,308]. G1 interaction with microglia-derived transglutaminase acts in this process[309]. V1 regulates myelination by means of MAG protein stability in myelin-forming cells of the auditory pathway[310]. In the PNS, G1 regulates myelin formation and maintenance through RhoA and the scaffold plectin[311]. G6 is indispensable in Schwann cell development and PNS myelination[312–314]. Its binding to collagen IV and laminin-211 initiates a $G\alpha_s$/cAMP signal to instruct myelin wrapping[245,315].

Adhesion GPCR research in glial function is nascent and an area of expected growth. Microglia regulate interneuron development[316], synaptic pruning[121], and protective response to amyloid deposition[317] through G1. Astrocytes actively regulate synaptic function by forming tripartite synapses with pre- and postsynaptic terminals. Many aGPCRs are present in astrocytes[318,319] and could serve as receptors enabling astrocytic sentinel functions at synapses. For example, astrocytic V1 controls glutamate homeostasis[320] and its dysfunction may be linked to epilepsy[321].

Collectively, these findings establish aGPCRs as essential stage-specific regulators of nervous system development, from neural tube closure through neurogenesis, migration, synaptogenesis, and myelination, whose disruption drives human neurological disease.

2. Sensory systems

Members of the aGPCR family are involved in both the development and physiology of sensory systems. Pathogenic variants of V1 are causative of defects in the auditory and visual systems that are clinically recognized as USH2C, a subtype of human Usher syndrome, the most common form of hereditary deaf-blindness[322,323]. USH2C is related to dysfunctions in the sensory cells of the inner ear and eye, where the extraordinarily long ENT of V1 forms fiber links. V1 establishes the ankle-links between neighboring stereocilia, which are essential for the correct hair bundle development of mechanosensory hair cells[324] and it forms fibers that stabilize the ciliary pocket of the light-sensitive photoreceptors[134]. Relatedly, the *D. melanogaster* ADGRL homolog Cirl contributes to the formation and function of photo- and mechanosensory organs[92,108,325,326], and the C homolog Flamingo partakes in visual system development[283,327,328]. Consistent with subfamily L role in synaptogenesis[44,106,271], Cirl was identified as a player in synaptic assembly of photoreceptor cells (R8 axons)[326]. Interestingly,

L3 controls synaptic release from cone photoreceptors on horizontal cells in mice non-cell autonomously[115] (Fig. 6C).

In the PNS, the subfamily L aGPCR Cirl is important for the physiology of mechanosensory neurons[92,325], providing the initial *in vivo* characterization of an aGPCR as metabotropic mechanosensor[329]. Expressed in chordotonal organs of *D. melanogaster*, Cirl sensitizes mechanosensory neurons for the stimulation by proprioceptive, auditory and tactile stimuli by acting upstream of mechanosensitive transient receptor potential channels [325] (Fig. 8). Further investigations demonstrated that Cirl modulates responses to innocuous and noxious mechanical stimuli in opposing directions. By sensitizing low-threshold mechanoreceptors and dampening high-threshold nociceptors, Cirl facilitates the separation of mechanosensory signals carrying different physiological information[90]. Moreover, the antinociceptive action of Cirl suggests a possible target for peripheral analgesic therapy[90]. Recent work showed that interaction of different Cirl isoforms enables the discrimination between distinct mechanical stimulus intensities through a $G\alpha_o$/cAMP-dependent signaling route[108].

Also vertebrate aGPCRs serve as critical components in mechanoceptive sensory organs, where they link mechanical force stimulation to ion channel function and intracellular signaling. Equilibrioception, the sense of balance, relies on rapid mechanoelectrical transduction (MET) in vestibular hair cells. L2, expressed at the apical surface of utricular hair cells, is required for normal vestibular function in mice[330]. Loss of L2 impairs balance behavior and abolishes MET currents independent of tip links. L2 conveys sensitivity to force stimuli to hair cells by enhancing the open probability of the ion channel TMC1, thereby driving glutamate release and calcium signaling[330]. D1 serves in a similar function as a key force sensor in utricular hair cells[331]. D1 converts mechanical stimuli into altered intracellular cAMP signaling via $G\alpha_i$ signaling, which in turn regulates plasma membrane excitability and is coupled to CNGA3 ion channel activity in a subset of hair cells. Reconstitution experiments and structural analyses confirmed the D1-mediated mechanotransduction pathway[331].

3. Vasculature

The formation of new blood vessels through sprouting angiogenesis is a highly coordinated and multistep collective cell migration event. aGPCRs regulate angiogenesis at various key steps. Endothelial cell-enriched G6 promotes angiogenesis in a cell autonomous manner by stimulating VEGFR2 transcription[332] or by interacting with and enhancing LRP1 expression[333]. The stimulation of endothelial cell proliferation or survival contributes to the angiogenic functions of G6 and A2[273,332,333]. In contrast, promotion of endothelial cell migration via small GTPase activation (Fig. 6A), which results in the modulation of cellular adhesion, filopodia, or lamellipodia, seems to constitute a more generic pro-angiogenic function of aGPCRs. Pro-migratory aGPCRs include E5 which regulates expression of the Rho GTPase Cdc42[334], via its soluble NTF that acts as a chemoattractant for endothelial cells through integrin receptors[272]. Similarly, G3 and A2 activate endothelial cell migration by acting on the small GTPases Rac, RhoA, or Cdc42[199,335,336]. Rac in turn upregulates A2 expression during capillary-like network formation[337]. A link between A2 and Cdc42 has also been detected in pericytes[338]. By contrast, L4 promotes angiogenesis without affecting endothelial cell migration, instead participating in

VEGF/Notch-dependent tip cell specification[339,340]. A2, an essential receptor for brain vascularization[336,341,342], also acts specifically in tip cells[179] by regulating the WNT/β-catenin-dependent expression of MMP25[343].

Reflecting their pleiotropic functions in the physiological angiogenic cascade, aGPCRs also affect tumor vascularization. L4[339,344] and A2[345,346] are enriched in tumor endothelial cells and their genetic inactivation reduces tumor growth and vessel density. G1, E2, and E5 expression in tumor cells stimulates tumor angiogenesis by increasing intra-tumoral levels of key angiogenic molecules like VEGF and MMP9[207,347]. By contrast, B1, B2, and B3 act as antiangiogenic and antitumorigenic factors, at least in part through their NTF, with the NTF of B1 termed vasculostatin[85,88,274,348,349] (Fig. 6C).

The vascular functions of aGPCRs extend beyond the regulation of angiogenesis. F5 has been implicated in patterning the retinal vasculature[350] and genetically interacts with L4 to shape the aortic arch arteries and the cardiac outflow tract, functions that may not be endothelial-autonomous[351]. F5 and L2 contribute to flow and fluid shear stress mechanotransduction[352,353]. C1 controls lymphatic endothelial cell movements during valve formation by inhibiting the maturation of adherens junctions[354]. L2, A2, and G6 contribute to the control of vascular permeability[355], the latter two especially at the blood-brain barrier[333,355,356]. L4 overexpression triggers endothelial-mesenchymal transition, linked to an increase in chemokine and cytokine expression[357], while its silencing markedly affects endothelial metabolism[358].

4. Lymphatic vessels

The lymphatic vasculature plays key roles in interstitial fluid balance, immune surveillance, and lipid absorption. Lymphatic endothelial cells (LEC) exhibit unique mechanosensitive properties and specialized cell-cell junctions, enabling them to adapt their permeability and regulate lymph flow[359–361]. These features, along with their ‘puzzle’ morphology, make LEC an attractive model for exploring the function of aGPCRs. To date, C1 and G3 have been studied in human lymphatics[335,354,362–366]. C1 regulates lymphatic valve formation through endothelial cell rearrangements and junction maturation via VE-cadherin stabilization[354]. In disease, C1 is implicated in hereditary lymphedema, a lymphatic vascular disorder characterized by chronic swelling[362,366]. However, the effects of C1 lymphedema-associated genetic variants on receptor function remain unclear. Similarly, G3 regulates cytoskeletal organization, cellular adhesion, junctional integrity, and migration of LECs via activity modulation of the small GTPases Cdc42 and RhoA[335]. Other aGPCRs, including A2, L4, G1, E5, and F5, are abundantly expressed in human LEC[335,367,368] (Fig. 5). However, their specific functions in lymphatic biology remain unexplored.

Given the critical role of aGPCRs in other conditions such as cancer metastasis and obesity, where lymphatic dysfunction is implicated[248,369], exploring the role of aGPCRs in lymphatics will have broad implications.

5. Skin

Human single cell RNAsequencing (scRNA-seq) data show moderate levels of C1, C2, F4, G1, L1, L2, and V1 in basal and suprabasal keratinocytes that form the epidermis, the squamous (cornified) epithelium of the skin (Fig. 5). These transcripts are also present in squamous (uncornified) epithelial cells covering other organs, such as the oral cavity, tongue, esophagus, and vagina. Among these, only F4 has been confirmed at the protein level in human[146]. A few basal, and all suprabasal, uncornified keratinocytes express F4. In psoriatic skin, F4 expression is diminished, suggesting its involvement in epidermal differentiation. Deletion of F4 reduced the number of keratinocyte layers in organotypic cocultures and abolished expression of keratin 1 (KRT1). Endogenous F4 exhibits unexpected close intracellular co-localization with KRT1[146]. In mice, not only F4 is present in the skin and other squamous cornified epithelia, but also F2[370], suggesting specific functions in these epithelia. Notably, F2 is completely missing in humans (Fig. 5). Members of the AC subfamily are, among others, expressed in a wide range of epithelia in human and mouse, where especially C1 controls the establishment of epithelial PCP[371], a process that polarizes epithelial cells within the plane of a tissue. For instance, mammalian C1 is responsible for the coordinated alignment of hair follicles across the skin surface[159].

6. Heart

Adhesion GPCRs are expressed in the heart during development (F5[351], G6[246,372,373], L2[374,375], L4[351]) and adulthood (F5[351], G6[246,372], L2[375], L4[351]; G1[376,377]) in endocardial cells (G6[246], F5[351], L4[351]), vascular endothelial cells (F5[351], L4[351]), cardiomyocytes (G1[376,377], L2[374,375]), and cardiac cushions (L2[374]) (Fig. 5).

KO studies have demonstrated their relevance. Analysis of global *L2*^{KO} mice, which are embryonic lethal, and *L2*-knockdown in chicken and stem cells indicates that L2 specifies cardiac lineage commitment[378,379] and controls endothelial-to-mesenchymal transition within cardiac cushions[374]. Postnatally-induced cardiomyocyte-specific *L2*-KO caused dilated cardiomyopathy, serious arrhythmia and death, which could be rescued with p38-MAPK activators[380]. Similarly, global G6 deletion is embryonic lethal, causing a thinned ventricular wall, hypotrabeculation, bradycardia, arrhythmia, abnormal mitochondria, and/or circulatory failure[246,373,381]. Recent data suggest these phenotypes may be secondary to placental defects[381], however another study reported normal placenta[373], and data in zebrafish (no placenta) showed G6 is required for trabeculation[246,277]. Increased perinatal lethality, ventricular septum defects and/or malformed large vessels[351] have been reported for global double *L4/F5* double KO, which alone cause no or a mild phenotype[382]. Surprisingly, similar to G6[381], endothelial-specific deletion of *L4/F5* did not cause a heart phenotype. These data indicate that aGPCRs in different cardiac cell types play important roles for heart development, but more work is required to resolve current controversies.

Studies also emphasize the importance of aGPCRs in adulthood. Cardiomyocyte-specific *G1*-KO and global *L4*-KO each caused little to no cardiac phenotype in unstressed hearts but an accelerated cardiac dysfunction upon chronic pressure overload[377,383]. Cardiomyocyte-specific

G1-KO mice displayed increased LV dilation and heart weight with no increase in wall thickness indicating impaired hypertrophy, although cardiomyocyte cross-sectional area was only slightly and not significantly decreased. Impaired hypertrophy would be in line with previous reports that *G1*-KO/knockdown[384,385] or PCBP2-mediated G1-mRNA degradation[385] attenuated induced hypertrophy in skeletal muscle or neonatal cardiomyocytes. In contrast, $L4^{KO}$ mice displayed increased pressure overload-induced LV wall thickness, fibrosis, and ccsa[383]. Collectively, there remains uncertainty about which signaling pathways and cellular behaviors are controlled by aGPCRs in the heart.

7. Lung

Transcripts of 12 aGPCR genes (*L1, L2, E5, A3, C1, C2, D1, F1, F5, G1, G6, V1*) are expressed in specialized epithelial cells throughout the respiratory tract including ciliated cells, basal respiratory cells, club cells, ionocytes, alveolar type 1 (AT1) and alveolar type 2 (AT2) cells (Fig. 5). However, a role for most of these receptors in lung function has not been reported. F5 is the most abundantly expressed aGPCR in AT1 and AT2 cells and several research groups generated loss-of-function mice to determine its role *in vivo*. The most striking phenotype in $F5^{KO}$ mice was a marked accumulation of pulmonary surfactant in the distal lung[182–184], resulting in progressive immune cell-mediated alveolar simplification[182,382,386–388]. Mechanistically, AT2 cell-specific F5 expression regulates surfactant secretion and uptake in AT2 cells via $G\alpha_{q/11}$ signaling[205,387]. Co-immunoprecipitation studies identified surfactant protein D as a putative F5 ligand[182], however, functional ligand-dependent receptor activation studies have not been reported.

Several aGPCRs have emerged as hits from unbiased screening approaches and genome-wide association studies in chronic lung diseases. For example, in idiopathic pulmonary fibrosis, E5 has been proposed as a marker for quiescent fibroblasts[389] and reduced G1 expression was observed in fibroblasts cultured from IPF patients[390]. In chronic obstructive pulmonary disease (COPD), single nucleotide polymorphisms (SNPs) in the *G6* locus have been reproducibly associated with reduced lung function, a pathological hallmark of tissue destruction in COPD[391–394]. In addition, decreased lung G6 expression in COPD patients supports a common SNP as being causal for disease[392]. In the context of idiopathic pulmonary arterial hypertension, G6 expression was increased in human airway smooth muscle cells (hASMC)[395] and novel SNPs suggest potential causal variants affecting G6 expression and/or function[396]. Furthermore, TIA-mediated activation of G6 in hASMC suggested a role in cell proliferation and airway remodeling[396]. Finally, *G6* knockdown in iPSC-derived human AT2 cells alters cellular responses to injury, demonstrating a role for this receptor in post-injury epithelial cell repair in the distal lung[397].

In summary, future studies are necessary to elucidate the function of many aGPCR family members expressed pulmonary epithelial and other respiratory tract cell types including fibroblasts, endothelial cells, and smooth muscle cells.

8. Musculoskeletal system

The musculoskeletal system, comprising bones, muscles, tendons, and joints, is essential for structural support, movement, and metabolism. Dysfunctions in this system can lead to conditions such as osteoporosis, muscle atrophy, and arthritis. aGPCRs have emerged as key regulators of musculoskeletal function, influencing development, repair, and mechanotransduction[398].

Genetic studies link *D1* and *G6* to human height, weight, and skeletal frame size[1,399,400]. Notably, G6 maintains growth plate homeostasis via the PTHrP/IHH pathway, with mutations implicated in adolescent idiopathic scoliosis (AIS)[401–405]. Similarly, D1 acts as a membrane receptor for androgens, activating the $G\alpha_s$/cAMP/PKA pathway to enhance muscle strength and growth. The development of the selective androgen analogs such as AP503, targeting D1 without binding nuclear androgen receptors, offers a promising treatment for muscle atrophy with minimal side effects, broadening the scope of androgen therapy[270]. D1 has recently been identified as a regulator of bone formation acting simultaneously on osteoblasts and osteoclasts. The receptor is activated by mechanical forces and interaction with its ligand PTK7[153,406].

Beyond these roles, G1 plays a significant role in protein synthesis and muscle hypertrophy. Its function is driven by PGC-1α4 or mechanical loading, which activates the $G\alpha_{12/13}$ pathway[384]. Interestingly, G1 expression is upregulated during early differentiation of human cultured myoblasts. Although G1-deficient myoblasts show impaired fusion *in vitro*, $G1^{KO}$ mice exhibit no overt phenotype, suggesting that compensatory mechanisms may mitigate its loss during muscle development[407]. Further, B1 and B3 promote myoblast fusion. B1 promotes myoblast fusion by recognizing phosphatidylserine on apoptotic cells through its thrombospondin repeats, initiating the ELMO/Dock180/Rac1 pathway[254]. Similarly, B3 interacts with ELMO to activate Rac1 (Fig. 6A), driving embryonic myoblast fusion processes[201].

Other aGPCRs also contribute to musculoskeletal function. E5 deletion results in abnormal sarcoplasmic reticulum structure, although skeletal muscle function remains unaffected, indicative of its impact on structure rather than function[148]. Meanwhile, V1 has been identified as a regulator of bone density in humans and mice, linking it to osteoporosis susceptibility[408].

Collectively, these findings solidify the role of aGPCRs as mechanosensors and signaling hubs in the musculoskeletal system, with significant implications for treating conditions like AIS, osteoporosis, and muscle degeneration.

9. Immune system and spleen

The immune system-associated aGPCRs are primarily clustered in two subfamilies, E and G (Fig. 5). Notably, several E and G receptors exhibit restricted expression within specific immune cell populations, making them selective biomarkers for distinct immune cell subsets[152]. For example, E1 (F4/80) serves as a well-established marker for mouse tissue macrophages, while E1 was identified as a specific marker for human eosinophils[409–411]. Individual aGPCRs are key markers of human mature polymorphonuclear granulocytes (E3)

and pan-cytotoxic lymphocytes as well as microglia (G1)[150,412,413]. Furthermore, aGPCRs have unique pathophysiological roles in regulating innate and adaptive immune responses, owing to their dual functions in cell adhesion and signaling[414]. Thus, myeloid-restricted aGPCRs, such as E2 and G3, are involved in necrotic-like cell recognition and specific activation of protease-activated receptor 2, respectively, leading to inflammatory activation of macrophages and neutrophils[34,239,415]. G1 is a NK-cell inhibitory receptor that suppresses cellular cytotoxicity, cytokine production and cell migration[150,203,416]. E5-deficient mice exhibited mild granulocytosis and enhanced antibacterial activity, whereas E1 was found to promote regulatory T (Treg) cell-mediated peripheral immune tolerance[417,418].

Compelling evidence supporting the role of aGPCRs as metabotropic mechanosensors has initially emerged from studies on immune aGPCRs. The E2^{C492Y} missense mutation, altering the GAIN domain of the receptor (Fig. 4), results in a less stable receptor complex that readily releases its NTF upon vibratory stimulation in the presence of its ligand, triggering excessive histamine release by mast cells to cause a rare dermal allergic disorder known as vibratory urticaria[94]. Similarly, E5 functions as a shear stress-dependent mechanosensor on leukocytes by interacting with CD55[419] (Fig. 3C). Notably, E5-mediated mechanosensing of CD55 on red blood cells is crucial for maintaining proper compartmentalization, homeostasis, and adaptive immune functions of type-2 conventional dendritic cells and marginal zone B cells in the spleen[91,420]. Likewise, G1 plays a critical role in platelet shape change during hemostasis by acting as a specific collagen receptor that responds to shear forces in blood circulation[211].

In addition, some aGPCRs are expressed in several differentiation stages of hematopoietic stem and progenitor cells, suggesting their potential involvement in normal hematopoietic development and leukemogenesis[421–424]. Finally, immune aGPCRs, including G1, E2, and E5, are implicated in various (patho)physiological processes and immunological disorders, highlighting their role in immune (dys)function[425–428]. For instance, E2 is temporarily upregulated on neutrophils in the posttraumatic course[428,429], and its expression is higher on neutrophils from sepsis compared to non-infectious patients with a systemic inflammatory response syndrome[427]. In conclusion, specific aGPCRs are actively involved in modulating diverse immune responses, with a crucial contribution to immune dysfunction and disorders.

10.Kidney

Numerous aGPCRs are expressed in the murine metanephric kidney in a variety of cell types (Fig. 5), including glomerular endothelial cells (F5[430], G1[431,432], G3[433], possibly L4[351,434]), mesangial cells (G3[433]), parietal epithelial cells (G6[435]), and podocytes (A2[436], C1: embryo[437], G3[433]) as well as cells of the proximal tubules (B1[438], C1[437], G1[151], G3[433]), distal tubules (B1[438], G1[151]), collecting ducts (C1: embryo[437], F5[439,440], G6[372,435], G3[434], F1[434]) and renal pelvis/urothelium (F1[370,441], G6[372,435]). This expression pattern has in part also been observed in zebrafish[442] and humans[443] (F1[441], G1[151], G6[435]).

Transcriptomic and proteomic data suggest another seven aGPCRs to be expressed in the murine nephron[444]. Notably, polycystin-1 (PC1), the protein product of the *PKD1* gene whose mutation causes autosomal dominant Polycystic Kidney Disease, can be regarded as an atypical

aGPCR[89,445] containing a GAIN domain and being responsive to a TIA[446,447] (Figs. 4, 6A). A variety of kidney diseases are associated with altered expression levels or patterns of a number of aGPCRs[443] (A2[436], G1[432], G3[433], G6[448]). While these descriptive data indicate that aGPCRs play an important role in kidney development and physiology, our understanding of their relevance is limited. C1 is the best-characterized aGPCR in kidney development with *C1*^{KO} mice exhibiting uretric bud branching defects, growth retardation, dilated cortical tubules, and mitotic spindle misorientation[449]. Adult global *F5*^{KO} exhibit impaired function with compromised basement membrane composition and morphological defects in the glomeruli[430]. Kidney-specific *F5*^{KO} have a significantly reduced urine pH, attributable to an increased V-ATPase accumulation[439]. Combined *F5;L4*^{DKO} results in ~50% perinatal lethality. Alive-born *F5;L4*^{DKO} mice exhibit loss of endothelial fenestration and fusion of podocyte foot processes resulting in proteinuria, uremia, and death at four weeks[351]. Yet, endothelial-specific *F5;L4*^{DKO} animals display no renal defects. Also, global *F1*^{KO} do not result in overt defects[370]. Finally, it has been shown that deletion of aGPCRs can be protective (G3: acute kidney injury[433], hypertensive nephropathy[450]; G1: diabetes[432]) or detrimental (A2: diabetes[436]) in kidney disease.

11.Pancreas

Adhesion GPCRs are increasingly recognized as regulators of glucose metabolism, acting at multiple levels including pancreatic islets, insulin-sensitive tissues, and local inflammatory environments. In human pancreatic islets, expression of several aGPCRs - such as *A2, A3, B3, C2, C3, E5, F1, F4, F5, G1, L1, L2,* and *L4* - has been reported[451,452] (Fig. 5). Their roles range from pancreatic development to insulin secretion. For instance, G1 enhances β-cell mitochondrial function and insulin release via collagen III-mediated ECM sensing, though its deletion does not impair glucose tolerance in mice[453–455]. L1 and L3 exert opposing effects on insulin secretion[112], while B3, via C1ql3 activation, suppresses insulin secretion by lowering cAMP levels[456].

12.Metabolism, fat and liver

Activation and signaling of aGPCRs changes the physiological function of adipocytes, hepatocytes, and myocytes, thereby influencing whole-body energy homeostasis. Indeed, it has been demonstrated that more than one-third of aGPCRs are among the most abundantly expressed GPCR in white adipose tissue[457]. Several members, namely A2, A3, D1, G1, G2, G6, L2, and F5, are involved in preadipocyte differentiation into mature adipocytes[457–460]. Besides, aGPCRs can also directly influence adipocyte function: G2 activation increases lipolysis[457] and modulates insulin-stimulated glucose uptake[457]. Regulation of insulin sensitivity has also been found for F5[181,458].

Additionally, aGPCRs can affect the thermogenic program as documented for B3[461], and specifically impact adipocytes as observed for A3, which is highly expressed in human adipocytes and murine brown fat. A3 knockdown in mice reduces uncoupling protein 1 and other thermogenic markers and exacerbates obesity, whereas A3 overexpression induces beige

adipocyte biogenesis and increases energy expenditure, improving metabolic homeostasis[462]. G2 expression is upregulated when brown adipose undergoes 'whitening' suggesting it negatively regulates brown/beige fat thermogenic capacity[463]. In a KO mouse model, it was shown that B3 reduces thermogenesis, however, it is still uncertain if this is mediated by its adipocyte-specific function[461].

Differential expression of several aGPCRs in the liver has been reported in hepatocytes (*A3, G6, G7, G8, F5, L2, L4*) and cholangiocytes (*A3, E5, G1, G2, G6, F1, L2*)[464] (Fig. 5), yet their functions remain incompletely understood. Emerging evidence links them to liver metabolism and injury. As such, F5 affects lipid metabolism[458] and ferroptosis in sepsis-induced liver injury[465]. Further, its deletion alleviates sepsis- and acetaminophen-induced liver injury[466]. F1 regulates hepatic lipid metabolism[467] and its absence mitigates steatosis and fibrosis in mice[468]. C2 affects LDL cholesterol levels[469] and lipid accumulation via modulation of reactive oxygen species[470]. G1 sensing of 17α-hydroxypregnenolone protects against ferroptosis-induced liver injury[471].

Taken together, these findings highlight critical roles for aGPCRs in metabolism and energy homeostasis.

13. Gastrointestinal tract

A closer examination of the human scRNA-seq data for aGPCRs (Fig. 5) reveals that several aGPCRs (*A3, E5, G1, G4, G6,* and *G7*) exhibit moderate expression across various (glandular) epithelial cell types in the gastrointestinal tract. Additionally, qRT-PCR analysis of 12 rat gastrointestinal segments identified 28 aGPCRs, some of which displayed restricted expression patterns along the gastrointestinal tract axis, likely associated with specific gut functions[472]. Similarly, an analysis of four mouse gastrointestinal canal subsegments detected low-abundance aGPCRs, with *B1-3* localized in the muscle-myenteric nerve layer and *G4* found in the duodenal, jejunal, and ileal mucosa[473].

Several aGPCRs are specifically expressed in specialized cell-types of the epithelial layer. Human E5 localizes at adherens junctions, interacting with β-catenin[197], though it is located intracellularly in colorectal cancer[474]. Human G1 colocalizes with pepsinogen at the gastric gland base and may support colonic stem cell expansion[151,475]. Mouse G2 has been reported to be selectively expressed in mature chemosensory cells[476], while human G4 is enriched in enterochromaffin and neuroendocrine carcinoma cells, serving as a potential biomarker[477]. Furthermore, G4 pentraxin-domain facilitated receptor homodimerization has been suggested to be critical to endogenous activation although its function remains unknown[62] (Fig. 3D).

In gastrointestinal tract development, the aGPCR Mayo of *D. melanogaster* shows midgut hyperplasia, hyperkalemia and tachycardia[278]. In mice, overexpression of E5 causes a dose-dependent megaintestine with normal microscopic morphology, providing a model for postnatal intestinal growth[478]. Expression of E5 and B1 in the colon was found to similarly protect mice from dextrane sulfate sodium -induced colitis, but likely via different mechanisms[479]. G7, found predominantly in intestinal epithelial cells in mice and humans, may aid in nutrient absorption[480].

While the cellular distribution in the gastrointestinal tract of certain aGPCRs has been recently characterized and offers insight into their roles in (patho)physiological processes, several receptors like A3 and G6 remain largely uncharacterized, highlighting the need for a comprehensive investigation of their protein expression patterns and gastrointestinal tract function.

14.Female reproductive system

Congenital abnormalities of the female reproductive tract affect 10 % of women, often with severe consequences[481]. aGPCRs are crucial in the development of these tissues, aiding in cell positioning and organization[482,483]. They facilitate cell-ECM interactions, essential for tissue integrity and function. Additionally, aGPCRs are involved in developmental signaling pathways, including the WNT signaling pathways, which regulate tissue morphogenesis and differentiation[93,484–488].

The *C. elegans* L homolog LAT-1 is important for the hermaphrodite nematode ovulation, sperm guidance and germ cell apoptosis, through a trans mechanism independent of its CTF[116,281] (Fig. 6C).

In mice, half of *A3*-deficient females fail to develop a vaginal opening during puberty; correspondingly, A3 is expressed in the female urogenital system, with the highest prepubertal expression and with a rapid drop after sexual maturation[482]. *A3* deficiency impairs estradiol-dependent vaginal canalization by unbalancing apoptotic regulators, potentially driven by the PCP WNT pathway[482], an established pathway for A3[164,192,193,195,489–492]. Aligned with the idea that A subfamily members interact with the WNT pathway is the finding that reduced post-pubertal A3 expression coincides with upregulated A2 expression – also active in WNT pathway signaling – in the female reproductive tract[482]. Curiously, also G protein-dependent signaling (Fig. 6A), although weak, was recently described for A3[489].

Birds display high expression of G1 and its ligand, collagen III, in the Müllerian duct, which gives rise to the fallopian tubes, uterus, and upper vagina in human females, and the oviducts in the chick[483] (Fig. 7). Knockdown of *G1* results in truncated ducts, suggesting a central role of G1 in the developmental elongation process, potentially via PAX2 signaling[483]. Intriguingly, G1 also modulates cellular β-catenin levels and regulates the canonical WNT pathway, possibly via its ligand transglutaminase-2 (TG2)[493].

G2 and G6 are both linked to uterus and placental development during pregnancy[381,494]. G2 regulates the decidualization of endometrial stromal cells during implantation and early gestation, likely involving the PI3K/Akt/mTOR signaling pathway[495]. For G6, G protein signaling by progesterone promotes breast cancer[496] and likely also female reproductive system development. Likewise, D1, expressed in the murine oviduct, regulates ductal fluid flow and embryo transit, possibly via Plxdc2[497].

aGPCRs involved in female reproduction have also been linked to male fertility, for example A3[498], G1[499] and G2[500], supporting their fundamental roles in development.

15.Male reproductive system

aGPCRs involved in the male reproductive tract are A2[240240] A3[498498]. G2 is highly expressed in the male reproductive system, primarily localized in the efferent ducts and proximal epididymis[501,502]. G2 plays a critical role in sperm maturation. *G2*^{KO} mice exhibit reduced sperm count or motility, and morphological abnormalities (such as head defects)[503], while also causing downregulation of genes related to sperm maturation in the epididymis (including cystatin, lipocalins, β-defensins, Adam28, Crisp1, and Enpp2)[500]. G2 couples with the anion channel CFTR (cystic fibrosis transmembrane conductance regulator) in a $G\alpha_q$-dependent manner to regulate Cl^- and pH homeostasis. The G2-$G\alpha_q$ signaling axis maintains the baseline outward rectifying current of CFTR, which is essential for fluid reabsorption and sperm maturation. G2, CFTR, β-arrestin1, and $G\alpha_q$ form a supercomplex localized to the apical membrane of non-ciliated cells, acting as a regional signaling hub to regulate fluid reabsorption and ion homeostasis[240] (Fig. 6A,B).

Clinical studies have identified various *G2* mutations (such as *p.Glu516Ter, p.Leu668ArgfsTer21*, *p.Arg814Ter,* and *p.Lys818Ter*) associated with male infertility and closely linked to congenital bilateral absence of the vas deferens. These mutations result in the deletion or truncation of the seven-transmembrane domain, disrupting the coupling of G2 with downstream $G\alpha_q$/$G\alpha_s$ proteins and β-arrestins[504–506] (Fig. 6A).

L2 interacts with its ligand LRG1 to ameliorate vascular and neurological abnormalities and restore diabetic erectile function[507].

B. Diseases

Adhesion GPCR are recognized in numerous disease contexts through their contributions to monogenic diseases, complex pathologies including cancer, diabetes, and neurological disorders, as well as as target structures for viral components.

1. Cancer

E5 was the first aGPCR reported to be regulated during tumorigenesis[508]. Over the past decades, many more aGPCRs have been implicated in cancer. Members of all nine aGPCR subfamilies are now considered to partake in tumorigenesis and/or the tumor microenvironment, influencing cancer growth and metastasis. Somatic mutations in aGPCRs have been detected in multiple cancers, but whether they drive or accompany tumorigenesis remains unclear. Alterations in aGPCR expression and/or signaling can contribute to key oncogenic processes (cancer hallmarks), such as tumor cell growth (proliferation and survival), motility and spread (migration, invasion, and metastasis), access to vasculature (vascular cooption, angiogenesis, vasculogenesis), tumor-promoting inflammation (immune cell recruitment), immune escape, and therapeutic resistance. Below is a non-exhaustive selection of key examples of aGPCR involvement in cancer:

Tumor progression and growth

Adhesion GPCRs can either suppress or promote tumor growth depending on their expression level and signaling context. Several studies have profiled the aGPCR expression in individual malignancies and assessed their prognostic impact[509–515].

For example, G1 is overexpressed in acute myeloid leukemia, colorectal, and prostate cancers and sustains *in vivo* tumor growth, invasion, and/or therapeutic resistance[516]. Conversely, the interaction of G1 with its ECM ligand, TG2, blocks the growth and metastasis of melanoma[166] and exerts tumor-suppressive functions in glioma[517].

Similarly, F1 in $HER2^+$ breast cancer promotes tumorigenesis but switches to a tumor-suppressive role upon interacting with laminin-111, leading to decreased receptor signaling, tumor cell senescence, increased HER2 expression and enhanced sensitivity to anti-HER2 therapies[180].

D1, a $G\alpha_s$-coupled aGPCR known to be regulated by ESYT1 in a Ca^{2+}-dependent manner, is allosterically activated by its ligand PTK7 to promote glioblastoma growth and brain invasion[178,204,268,518,519]. D1 has also been implicated in a few other malignancies, including lung and gastric adenocarcinoma, and leukemia[513,520–522], although its exact function in those settings has not been clearly determined.

Several members of the E subfamily, most notably E5, have also been implicated in a plethora of malignancies, where they contribute to cancer stem cell maintenance, tumor cell migration, invasion, apoptosis, proliferation, and response to therapy[510,523–547].

A2 was shown to regulate glioblastoma proliferation through effects on mitotic assembly and progression[548]. A3 was identified as a marker of stem cells in breast tissue, which are greatly expanded upon oncogenic transformation[549].

B family members are transcriptionally downregulated or frequently mutated in various cancers, including brain, breast, and lung, suggesting a tumor-suppressive role[549–553]. In brain malignancies, B1 undergoes epigenetic silencing, and reactivating its expression inhibits tumor cell proliferation, angiogenesis and tumor growth *in vivo*, further supporting its tumor-suppressive function[258,554].

Tumor cell migration/invasion and metastasis

Many aGPCRs, such as E1, E2, E5, L1, and G1, mediate ECM interactions and/or promote Epithelial to Mesenchymal Transition (EMT)[259,541,555–569], whilst L4 is associated with endothelial to mesenchymal transition (EndMT)[357]. By triggering changes in cell adhesion and motility, these receptors enable cancer cells to adopt invasive mesenchymal-like properties, promoting metastasis.

A2 expressed on pericyte-like cells derived from lung adenocarcinoma stem cells enables them to initiate brain metastases through trans-endothelial migration[556]. This effect of A2 is mediated by its ability to act as a WNT co-receptor, thus promoting canonical WNT7/b-catenin signaling[261,556,570].

L1-3, whose expression is induced by nuclear androgen receptor signaling, promote prostate cancer growth[571]. A similar effect is noted for L3 in urothelial cancer[572]. Cancer-linked mutations affecting the L3 GAIN domain impair its adhesion functions and $G\alpha_{13}$ signaling, leading to altered cell motility and cytoskeletal organization that may contribute to tumor progression[573]. L3 knockdown reduces bladder cancer cell migration[574].

G1 localizes to the leading edge of glioblastomas, supporting cell adhesion and invasive behavior of tumor cells[575]. G1 also promotes hepatocellular carcinoma metastasis[426,573]. L4 promotes migration in glioblastoma, colorectal cancer, retinoblastoma and neuroblastoma[576–579].

C1 promotes migration in ovarian cancer[580], whilst C3 knockdown in lung adenocarcinoma[581] and neuroendocrine prostate cancer[582] suppresses migration.

Immune evasion

Several aGPCRs are expressed in immune lineages of the tumor microenvironment. Members of the E subfamily (E1, E2, E3 and E5) can modulate the immune microenvironment by influencing immune cell infiltration to the tumor site and controlling the function of tumor-associated immune cells[510,531,583–587].

L4 overexpression in breast cancer cells is linked to an immunosuppressive tumor environment, marked by fewer cytotoxic T cells and more M2-like macrophages[588].

G1 is upregulated in exhausted, tumor-reactive T cells in cholangiocarcinoma, renal cell carcinoma, lung cancer and the bone marrow in AML[589–593], suggesting a broader role in immune suppression.

B3 regulates F-actin in T cells, reducing traction force and impairing cytotoxicity in melanoma and colorectal cancer[594]. These receptors may promote immune evasion by recruiting immune suppressor cells to the tumor or by inhibiting anti-tumor immune responses.

Angiogenesis

Some aGPCRs, including L4[339,340,595] and G1[516], are involved in tumor angiogenesis. By stimulating the tumor's ability to form blood vessels, aGPCRs directly contribute to cancer progression and are potential therapeutic targets.

The angiogenic actions of aGPCRs can be exploited therapeutically. For example, the use of anti-L4 antibodies or scFVs in glioblastoma xenografts normalizes tumor vessels and improves survival in comparison to untreated controls or those treated with anti-VEGF antibody (Bevacizumab) alone[596,597]. G1 can inhibit VEGF-induced angiogenesis in melanoma[207], while B1 acts as a negative regulator of angiogenesis through N-terminal cleavage events that releases vasculostatins[88]. In addition, E2 and E5 may also play a role in regulating tumor angiogenesis[347]. Finally, A2 expressed on tumor endothelial cells is necessary for VEGF-induced tumor angiogenesis[346].

2. Type II diabetes

Adhesion GPCRs regulate systemic insulin sensitivity through actions in adipose tissue and muscle. F5 mediates insulin-sensitizing effects of the hepatokine FNDC4 in adipose tissue. Its deletion impairs adipokine release and promotes systemic insulin resistance[181,458]. A3, activated by the flavonoid hesperetin, also contributes to improved insulin sensitivity in adipose tissue[462]. While aGPCRs are highly expressed in myoblasts, their function in skeletal muscle insulin sensitivity remains unexplored.

Importantly, aGPCRs also influence diabetes pathophysiology through immune–metabolic crosstalk. G3 expression in adipose tissue macrophages promotes proinflammatory signaling; its deletion dampens macrophage activation and reduces obesity-induced adipose inflammation[598]. These findings collectively point to aGPCRs as context-dependent regulators of insulin secretion, sensitivity, and inflammation - key elements in diabetes development and progression.

3. Viral infection

Viruses either encode GPCRs (viral vGPCRs)[599,600] or exploit host GPCRs[601] to manipulate cellular processes and enhance their control over the host environment. In response, hosts continually adapt their GPCRs to counter these viral strategies. Consequently, it is not surprising that viruses regulate or interact with aGPCRs given their crucial roles in cell signaling[218], maintaining host physical barriers[159,333,602–604] and immune surveillance[60,152,414,416,605,606].

During severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, several aGPCRs are implicated. Bioinformatic analysis revealed an interaction between the SARS-CoV-2 spike subunit and L4 mRNA levels, which are consistently downregulated in infected cells[607]. Additionally, D1 and G6 are upregulated in SARS-CoV-2 infected epithelial cell models. Targeted downregulation of these receptors reduces the release of free virus particles[607].

Adhesion GPCRs also play a role in latent viral infections. G1 is upregulated in human immune deficiency virus (HIV)-positive $CD4^+$ T-cells[608] and in cytomegalovirus-positive $CD8^+$ T-cells[150]. Viruses also directly interact with aGPCRs, e.g. binding of the mumps virus small hydrophobic protein to A3 triggering epithelial barrier dysfunction[609,610].

Studying interactions between viral proteins and aGPCRs is key for developing antiviral therapies and understanding viral pathogenesis. Despite being an emerging field, the few interactions discovered so far suggest that much remains to be uncovered.

4. Bacterial infections

B1 recognizes phosphatidylserine on the surface of apoptotic cells and bacteria, promoting their engulfment by macrophages and other phagocytes through the activation of downstream signaling pathways[200,611]. B2 and B3, are implicated in modulating immune responses[606,612,613]

and cellular interactions during pathogen clearance[614–617]. Together, these receptors contribute to efficient immune surveillance and removal of infectious agents, enhancing host defense mechanisms.

5. Neurodevelopmental, neurodegenerative, and neuropsychiatric disorders

B receptors play critical roles in brain development and synaptic architecture. B1 is essential for dendritic spine formation and excitatory synaptogenesis, and its absence in mice leads to social deficits, reduced brain weight, increased neuronal apoptosis, and heightened susceptibility to seizures; phenotypes relevant to autism spectrum disorder (ASD) and epilepsy[224,618]. Additionally, B1 interacts with autism-linked proteins such as neuroligin 1 and IRSp53, and ASD-relevant B1 variants have been reported in patients[618]. Decreased B1 expression is observed in the substantia nigra of Parkinson's disease patients as well as the substantia nigra and striatum of Parkinson's disease animal models[619], correlating with dopaminergic neuron loss. B2 is implicated in mood regulation and emotional behavior[620]. *B2*^{KO} mice exhibit antidepressant-like behavior[619,621]. Variants in B3, including polymorphism and copy number variations, are linked to schizophrenia-related disorganization[622,623], addiction[624], epilepsy and bipolar disorder[625]. Mice lacking full-length B3 have reduced brain and body weights, augmented energy expenditure and deficits in social interaction[461,626].

Recent insights into the genetic basis of craniorachischisis, a severe neural tube defect characterized by complete failure of neural tube closure have identified several potentially pathogenic variants in components that govern PCP establishment and maintenance including C1[118]. Functional studies revealed that although these variants did not disrupt known protein-protein interactions, they significantly impaired proper subcellular localization caused by reduced protein expression and defective plasma membrane trafficking, mechanisms consistent with phenotypes observed in analogous mouse mutants[627].

G1 has verified roles in spermatogonia[499], skeletal muscle[384,499] and brain development[286], CNS myelination[306,307], and hemostasis[211]. Mutations in G1 cause bilateral frontoparietal polymicrogyria, a recessive cortical malformation disorder characterized by severe developmental issues, intellectual disability, and seizures[286,288]. In adults, *G1* mRNA levels are upregulated in patients who respond to antidepressant treatment[628,629]. Reduced *G1* expression is linked to suicide, potentially due to a *G1* splice variant affecting synaptic pruning[117,630].

L3 is the most studied latrophilin homolog in neuropsychiatric disorders. Variants are primarily linked to childhood ADHD[631,632], but also connected to autism spectrum disorder[631–633] and substance use disorder[634]. L2 variants are associated with microcephaly with severely reduced sulcation and rhombencephalosynapsis[635], and with cocaine use disorder[636]. *L1* haploinsufficiency has been linked to intellectual disability and developmental delay in a small cohort of ten individuals[294], and to developmental and epileptic encephalopathy[637]. Pathogenic variants in V1 cause human Usher syndrome type 2 (USH2C), a common form of combined deaf-blindness[638]. V1 mouse models suffer from progressive deafness and show increased susceptibility to audiogenic seizures[639]. Recent studies have linked heterozygous

variation in V1 to various forms of epilepsy in humans[640,641]. In the CNS, defects in V1 cause alterations in myelination[310] and dysfunctions in hippocampal astrocytes[320].

Critical synopsis and outlook: The extensive repertoire of aGPCRs in model organisms and humans has been complemented by a tremendous increase in our understanding of the physiological functions these receptors support. A unifying theme across many recent findings is the role of aGPCRs as mechanosensors in diverse organ systems and cellular contexts. Given their unusual molecular architecture and the autoproteolytic processing characteristic of many family members, mechanical stimuli are natural physiological inputs for aGPCR activation. Importantly, such cues appear to be essential for multiple developmental programmes during and after embryogenesis. It is therefore unsurprising that germline and somatic mutations in aGPCR loci are associated with, and in some cases causal for, human developmental disorders and cancers. Future research must decipher the specific contributions of impaired aGPCR signaling to individual pathological conditions, both to understand disease mechanisms and to identify opportunities where therapeutic targeting of these receptors may benefit patients. The systematic delineation of defined signaling pathways, activating conditions, and expression patterns of individual aGPCR homologs will greatly enhance and likely accelerate this emerging translational branch of aGPCR research in the years ahead.

XIII. Adhesion GPCRs as drug targets

Adhesion GPCRs are emerging as promising drug targets because they integrate mechanical and chemical signals, control key physiological processes and are involved in several pathologies. The identification of pharmacological actuators of individual aGPCR functions is an urgent need to fully exploit their immense therapeutic potential.

ADGRA

A3 signaling can induce adipose thermogenesis, and the proposed A3 agonistic ligand hesperetin may represent an obesity treatment[462]. Engineered WNT ligands, designed as specific A2/Reck agonists enable blood-brain barrier repair in neurological disorders[356] (Fig. 6B).

ADGRB

Herpes simplex-derived oncolytic viruses engineered to express the B1 NTF-derived vasculostatin proteolytic fragment had potent anti-angiogenic and tumor-suppressive effects in brain cancer models[642–645]. Additionally, small molecules inhibiting the epigenetic reader MBD2 and the writer EZH2 target B1 gene epigenetic silencing and present a promising strategy to restore B1 expression and its tumor-suppressive functions[258,646].

ADGRD

A role for D1 in glioblastoma progression is supported by several studies. The identification of PTK7 as an allosteric modulator of D1, along with the development of antibodies targeting the D1 NTF, provides impetus to investigate these as potential therapeutic modalities[178,216]. D1 was also implicated as a receptor for the androgen 5α-DHT in muscle cells, where its action to raise cAMP levels was proposed to enhance muscle strengthening. A small molecule D1 activator, AP503, may serve as a drug lead for its beneficial actions with limited side effects[270].

ADGRE

Monoclonal antibody 1B2 directed against E5 proved efficacious in a mouse model of experimental arthritis and was proposed to work by neutralizing E5 through a combination of receptor internalization and induced NTF shedding[647]. However, later in-depth analyses of its mode of action *in vivo* revealed that the antibody depletes granulocytes in mice under conditions of acute inflammation via a Fc receptor-dependent mechanism[648]. An antibody-drug conjugate against E5 demonstrated efficacious killing of human glioblastoma cells, in which E5 plays a tumorigenic role[510]. Moreover, an afucosylated monoclonal antibody to E1 efficiently depletes eosinophilic granulocytes[411]. E2 may regulate serum factor H-related protein FHR1-related antibody-associated vasculitis[415], and E2 genetic variants are associated with vibratory urticaria[94]. Immune targeting E2[424] or E5[547,649] with engineered T cells expressing chimeric antigen receptors are promising novel pharmacotherapeutic tools capitalizing on the specific cellular expression patterns of aGPCRs that may prove useful in the future.

ADGRF

Synaptamide is an endogenous lipid that binds to the F1 GAIN domain and reduces LPS-induced inflammation in mice. It elevates cAMP levels in cultured microglia and suppresses proinflammatory cytokine levels, suggesting that F1 activation by synaptamide holds therapeutic potential to ameliorate brain and peripheral tissue inflammation[650].

ADGRG

G1 has varied roles in physiology and cancer progression. Small molecule antagonists, the partial agonist 3-α-DOG, and modulatory antibodies target the receptor. Pharmacological studies indicate that the small molecules occupy the orthosteric site in lieu of the TIA[173,651,652], and exhibit selectivity for G subfamily members[171,212]. Individual G1 antibodies inhibited glioma cell migration[653] and promoted RhoA signaling in breast cancer cells[654]. A G1-targeted antibody-drug conjugate proved efficacious in colorectal cancer cell models[655].

G6 is involved in axon myelination. *In vivo* phenotypic screening of small molecules was performed to correct mutant G6 Zebrafish Schwann cell development, otic and myelination defects and lead to the identification of potential agonists that are undergoing further

characterization[171,172,656]. G2/CFTR signaling is required for sperm maturation, representing a potential therapeutic target for male infertility[240].

ADGRL

L2 may play a role in equilibrioception and represents a potential therapeutic target for balance disorders such as vertigo. A small molecule termed D11 was reported to block the c-mesenchymal-to-epithelial transition mediated by L2-TMC1, thereby avoiding side effects associated with traditional vestibular suppressants[330].

Critical synopsis and outlook: The current landscape of drug-targeting strategies for aGPCRs remains limited and fragmented, reflecting our still emerging understanding of receptor- and ortholog-specific working principles. This immaturity is further compounded by the intersection of multiple input modalities - adhesive ligands, mechanical forces, and steroid hormones - that aGPCRs are capable of integrating or distinguishing. Only once we understand in molecular detail how an individual receptor parses these diverse cues, and which structural elements enable or bias one mode of activation over another, can a focused and rational development of pharmacological agents truly begin. A major challenge lies in identifying intervention points that selectively modulate defined signaling routes without perturbing others, a task complicated by the multifunctional nature of aGPCRs. Structural elucidation of ligand-binding sites, mechanosensitive receptor states, and allosteric interfaces will therefore be indispensable. In parallel, systematic pathway deconvolution and isoform-resolved expression studies will help reveal which signaling outputs are most physiologically or pathologically relevant, thereby guiding where pharmacological precision is needed most. As these mechanistic foundations solidify, new opportunities will emerge for designing small molecules, allosteric modulators, or engineered biologicals that can intervene with unprecedented selectivity. Ultimately, the maturation of our conceptual and structural understanding of aGPCR signaling will transform the currently fragmented therapeutic landscape into a more coherent framework for targeted drug discovery.

XIV. Phylogeny of adhesion GPCR and model organisms

A. Phylogenetic relationships of adhesion GPCR subfamilies and homologs

aGPCRs have been present in Metazoa for at least 750 million years[657] and are classified into nine families (A, B, C, D, E, F, G, L, V) based on the phylogenetic relationships of their 7TMD[1] (Fig. 7). This classification, however, has been challenged by recent studies, which highlight

ambiguities in the hierarchical organization of GPCRs and call for a revised system based on phylogenetically supported levels[30,31].

Notably, the Secretin-like receptor class is now considered to have evolved from aGPCRs, most likely from the D subfamily[28–31]. The evolutionary conservation of aGPCRs is evident, as at least one member of each family has a fish ortholog, indicating that all aGPCR families were already present by the Silurian period, approximately 419 million years ago. In vertebrates, no additional independent aGPCR families have been identified beyond the known nine, and sequences with a one-to-one orthology to human aGPCRs exist in at least one species from each major mammalian lineage (Monotremata, Marsupialia, and Eutheria), suggesting that the full aGPCR repertoire was already established before the rise of mammals over 178 million years ago[31].

However, despite this conservation, aGPCRs exhibit notable gene losses, duplications, and expansions across different taxa. For example, *F3* and *E5* are absent in birds, while multiple paralogs of certain aGPCRs, such as *E2*, exist in species like felids, marmots, and artiodactyls[31,658]. These variations reflect the genomic plasticity of aGPCRs, influenced by whole-genome duplications and local gene duplication events. Such dynamics have led to neo-functionalization or sub-functionalization of gene duplicates, which must be considered when studying aGPCR function in model organisms, as their roles may differ significantly from those in humans.

B. Model organisms for adhesion GPCR research

Research with animal models is a foundation of aGPCR research and has promoted insights into many of the physiological roles that are currently attributed to them[217,218,659–661]. In the following section, the main model species currently in use and their individual utility for questions pertaining to aGPCRs are introduced.

1. Choanoflagellates

As the closest living relatives of animals, choanoflagellates provide a window into the early evolution of GPCRs, and aGPCRs in particular[662,663]. Systematic analyses of GPCR repertoires in 23 choanoflagellate species, including *Salpingoeca rosetta*, have revealed that aGPCRs constitute the largest GPCR family in most choanoflagellates, with up to 41 aGPCRs predicted in some species[28,664–666]. Interestingly, the abundance and diversity of protein domains in the NTFs of choanoflagellate aGPCRs rival those found in metazoans, suggesting that the number of aGPCRs likely increased and their protein domain architectures diversified in the stem lineage leading to both metazoans and choanoflagellates.

Eighteen of the 19 choanoflagellate aGPCR subfamilies detected appear to have diversified independently from metazoan aGPCRs, with the exception of the V subfamily[28]. Nonetheless, choanoflagellate and metazoan aGPCRs share key structural features in the form of the HormR/GAIN/7TMD layout along with additional extracellular domains[666]. Thus, the HormR/GAIN/7TMD and diversity of other NTF domains evolved before the divergence of

choanoflagellates and metazoans and were, therefore, foundational to the subsequent evolution of metazoan aGPCRs.

Future efforts to reconstruct the premetazoan functions of aGPCRs will benefit from the study of aGPCR functions and regulation in phylogenetically relevant organisms, including choanoflagellates and diverse early branching animals.

2. Fruit fly (*Drosophila melanogaster*)

The aGPCR family in *D. melanogaster* contains five homologs allocated to subfamilies ADGRA (Remoulade), ADGRC (Flamingo/Starry night), ADGRL/A (Cirl) and one group equally evolutionarily related to all known aGPCR subfamilies termed ADGRX (Mayo, Ketchup)[30].

***Remoulade/CG15744 (remo*).** The predicted ENT of Remo is structurally homologous to that of vertebrate A2 (Fig. 1A). Notably, its irregular GPS ($H^{-2}R^{-1}T^{+1}$) suggests it is not self-cleavable[93]. Structure predictions of the *remo* gene product indicate coiled-coil elements in its ICR. Unlike A2, Remo lacks a C-terminal PBM. Recent observations have connected Remo signal transduction to Rac1, a member of the Rho family of small GTPases, and axon growth guidance in the central nervous system of the fly[667]. It is unclear whether Remo can also work akin to A2 as a WNT co-receptor in complex with RECK, Frizzled and Lrp5/6 (Fig. 6B).

***Flamingo/Starry night/CG11895 (Fmi* or *Stan*)** shares the same basic domain structure of ADGRC homologs consisting of cadherin repeats, an EGF-LamG region, HormR, GAIN domain and 7TMDs, and a long intracellular domain[160,668] (Fig. 1A). It is most extensively characterised for its function in the 'core' PCP pathway, controlling the orientation of epithelial structures such as hairs, bristles and the ommatidial units of the compound eye[160,668,669]. Here, Fmi interacts homophilically at cell-cell contacts, binding asymmetrically with the Frizzled 7TMD receptor in one cell and the Stbm/Vang 4TM protein in the opposing cell, thus apparently acting as both ligand and receptor for itself[160,266,670–673]. Flamingo also functions extensively in *Drosophila* peripheral and central nervous system development. This includes dendritic patterning[674,675], photoreceptor target selection in the brain[327,676] and mushroom body development[677–679]. Notably, both cell autonomous functions involving unidentified ligands[675,680] and homophilic functions involving Fmi-Fmi binding[283,680] have been reported. Moreover, while these functions appear to be independent of planar polarity pathway function[327,675], in several contexts planar polarity proteins also appear to act together with Fmi in the nervous system[678,679,681,682].

Cirl/CG8639. Similar to other ADGRL homologs, Cirl contains an extracellular RBL, HormR and GAIN domains but lacks an OLF domain[325] (Fig. 1A). Deletion of Cirl results in a broad reduction in mechanosensitivity of larvae including tactile sensitivity to gentle touch, auditory, proprioceptive and nocifensive stimuli[90,92,108,325]. This is explained by the expression of Cirl in dendrites and cilia of chordotonal neurons[92,683], which serve as the main mechanosensory nerve cells in insects, and nociceptive nerve cells[90]. In addition, Cirl is required for setting the number of neurons generated during central brain neurogenesis, where the aGPCR functions together with the Toll-like receptor Tollo/Toll-8[93]. For this function as a metabotropic mechanosensor

Cirl self-cleavage is necessary[93], while its mechanosensory role in the periphery does not require GAIN domain-mediated receptor autoproteolysis[90,92]. The Cirl-Tollo interaction is also required for the planar cell polarization of contractile cell-cell contacts in embryonic ectoderm[279]. In the visual system Cirl appears to affect activity-dependent synaptic assembly[326].

Mayo/CG11318 and ***Ketchup/CG15556 (ktch)***. Mayo and Ketchup are minimalist aGPCRs whose structure predictions only indicate the presence of GAIN and 7TM domains in each[30]. Both proteins contain a canonical GPS and are self-proteolysed[93,278]. Mayo is expressed in the epithelia of the midgut and anal plate of third instar larvae[684]. Genetic removal of *mayo* impacts enterocyte proliferation in the larval midgut, leading to a non-cell autonomous increase in potassium concentration in the hemolymph, which results in tachycardia[278]. Ketchup is expressed in the proventriculus of the gastrointestinal canal and Malpighian tubules, which function as the kidney equivalent in insects[684]. Ketchup's function in these organs, which regulate ion and water homeostasis, is unknown at the present time.

3. Roundworm (*Caenorhabditis elegans*)

In the nematode *C. elegans*, three aGPCRs exist: the L homologs LAT-1 and LAT-2, and the C homolog FMI-1.

Like its mammalian homologs (Fig. 1A), LAT-1 plays a role in the neuronal system of *C. elegans*. Here, it is essential for neuronal morphogenesis, affecting sensory structures such as the male sensory rays and head sensilla. Consistent with this, the absence of LAT-1 leads to defective male copulation behavior[282]. Beyond its neuronal role, LAT-1 regulates anterior-posterior division plane orientations in the early embryo via $G\alpha_s$ signaling[220,484] and contributes to fertility by modulating sperm guidance, ovulation, and germ cell apoptosis[116,219]. Further, LAT-1 modulates Notch signaling in the stem cell niche of the *C. elegans* gonad via direct interaction with the DSL ligand, thereby regulating germ cell proliferation to ensure the correct number of germ cells[281].

LAT-2, in contrast, remains less understood. Expression analyses revealed its presence in the pharyngeal primordium during embryogenesis and later in the pharynx and excretory system, suggesting roles in feeding and waste regulation[484].

Unlike in other species, a role of FMI-1 in PCP has not been described in *C. elegans* yet. The receptor is involved in neuronal circuit formation by controlling axon growth and pioneer-dependent axon navigation independently of PCP pathways[284,685,686]. It also regulates dendrite self-avoidance by antagonizing the PCP component VANG-1/van Gogh[687]. Additionally, FMI-1 has been linked to body size regulation and ECM composition, together with other PCP components[688].

4. Zebrafish (*Danio rerio*)

The zebrafish aGPCR repertoire contains close to 60 members that represent homologs of 24 of the mammalian 33 aGPCRs[442] (Fig. 1A). Missing homologs are restricted to subfamilies E, F, and G, which also exhibit zebrafish-specific expansions. These expansions, combined with the genome-wide duplication event that occurred within the teleost lineage, explain the larger number of zebrafish aGPCRs. Many true orthologs of human aGPCRs exist in zebrafish, making this model organism powerful to study their function.

L2 has been found to mediate shear stress mechanotransduction[353] and control vascular permeability in zebrafish endothelial cells[355]. CRISPR-Cas9 mutants and morphants of L3.1 (*lphn3*), the ortholog of L3, have been used to investigate its role in attention-deficit/hyperactivity and other externalizing disorders, revealing altered dopaminergic neuron distributions, hyperactive motor phenotypes, potential new therapeutic targets, and therapeutic and metabolic effects of existing and emerging drugs[689–697].

The zebrafish paralogs of C1 (*adgrc1a* and *b*) regulate convergence and extension (CE) and epiboly movements during gastrulation[698,699], as well as tissue homeostasis and aging phenotypes in adults[699]. Besides its role in CE[699], C2 controls facial motor neuron migration in the developing hindbrain[700]. C3 is required for the development of GABA and acoustic startle circuits in the inner retina[701] and hindbrain[702].

Zebrafish A2 has been investigated for its role in promoting WNT/β-catenin signaling during brain angiogenesis and dorsal root ganglia formation, contributing to the identification of its co-receptor Reck[179], the delineation of its mechanism in WNT ligand-specific signaling[196,263], the identification of highly specific pathway agonists[356] and its downstream angiogenic effector[343] (Fig. 6B). The closely related A3 was found to regulate PCP during zebrafish VE movements by binding Dishevelled[195], an interaction shared with zebrafish A2[196].

The role of G1 in oligodendrocyte development and peripheral myelination was revealed by the analysis of zebrafish G1 mutants[306,311]. Microglial-derived transglutaminase 2 was identified as a relevant ligand for A1 during CNS myelination, a finding supported by somatic gene disruptions in zebrafish[309]. Morpholino knockdown studies further implicated this receptor in the formation of hematopoietic stem cells[703], a process that could be compensated by the ectopic expression of G3[421].

Forward genetic screens in zebrafish revealed the essential role of G6 in PNS myelination[312]. Additional roles of this receptor in zebrafish include spine ossification[401], cardiac trabeculation[246], and inner ear morphogenesis[704]. The zebrafish model also contributed to elucidating the context-dependent mechanisms of G6 signaling, defining its ligands, and identifying potential small-molecule agonists and posttranscriptional regulators[16,171,172,245,246,315,656,705,706].

Zebrafish V1 models have been generated for the analysis of V1 functions and disease mechanisms associated with mutations in V1[707–709]. The *adgrv1*^{rmc22} zebrafish is the first *V1* mutant model for Usher syndrome type 2C that displays an early retinal dysfunction which can be used as outcome measures in the evaluation of therapeutic strategies[708].

5. Chick (*Gallus gallus*)

In the chick embryo (avian) model for developmental biology studies, the ability to fenestrate the eggshell provides ease of access to the embryo and enables temporal manipulation of live embryo development. Thus, changes can be made to tissue position through grafting[710], gene expression[710,711] and cell signaling pathways[712]. Overall, the chick model has contributed knowledge of C1 function in key gastrulation events[713] as well as in neural tube closure mechanisms[194]. The rich vascular network of the chick embryo chorio-allantoic membrane (CAM) also provides a unique assay system[714], offering efficient screening for anti-angiogenic drugs[715,716] as well as for studying cancer biology[347,717,718]. A sterile environment can be easily maintained following tumour cell inoculation *in vivo*, and since the avian immune system is not mature until day 15 post-gestation, immune rejection of xenografted cells is prevented. Indeed, a CAM assay-based drug screen recently identified Dub as an angiogenesis inhibitor for breast cancer, which acts via regulation of B1[719].

6. Mouse (*Mus musculus*) and rat (*Rattus norvegicus*)

Mice and rats offer several advantages for studying the complex roles of aGPCRs, including their genetic similarity to humans, the wide availability of genetic models, and their relevance to humans. The average protein identity between human and mouse aGPCRs is approximately 81 %, with a minimum of 60 % (G4) and a maximum of 98.5 % (L1).

Due to the large exon-intron structure and numerous splice variants of aGPCRs[104], rodent KO models require careful design. Global KO of several aGPCRs, such as *A2*, *F5*, and *G6*, leads to severe phenotypes including embryonic lethality[336,341], surfactant accumulation[182–184], and perinatal death[313,373]. In such cases, tissue-specific KO models can uncover more subtle receptor functions. Indeed, except for an $L3^{KO}$ rat model[720,721], most $aGPCR^{KOs}$ were generated in mice and use Cre-loxP systems for tissue-specific or temporally controlled receptor deletions (Table 2).

Some studies have used knock-in models to introduce tags (e.g., GFP, mCherry, HA, Myc) to facilitate receptor visualization in live cells or tissues[107,120,292]. This is especially valuable given the challenges in developing antibodies for aGPCRs.

In addition to null models, disease mouse models help investigate how mutations disrupt protein function and cellular processes. For example, the human *Y6244fsX1* mutation in *V1*, a key component of the ankle-link complex essential for cochlear hair cell development, was modeled in *V1 Y6236fsX1* mice. These mice recapitulated Usher syndrome type 2, demonstrating the relevance of mutant mice for studying disease mechanisms[638]. Notably, no humanized aGPCR rodent models exist, suggesting a promising area for future research.

Critical synopsis and outlook: Evolutionary analyses of aGPCRs have both supported and propelled research into their underlying working principles. The recent discovery of a broad aGPCR repertoire in unicellular species at the brink of multicellularity underscores the importance of their molecular design in mediating cell-cell communication, likely by enabling

the exchange of adhesive and mechanical cues within cell communities. Looking back into the evolutionary history of aGPCRs will continue to guide the recognition - and experimental interrogation, in both invertebrate and vertebrate models - of functional features that have remained conserved for at least 600 million years. Studies of the co-evolution of extracellular aGPCR ligand-binding domains and their cognate ligands have not yet been widely initiated, even though this line of inquiry may reveal the determinants of receptor-ligand specificity and thereby inform strategies for selectively modulating aGPCR function pharmacologically. Moreover, deciphering the evolutionary logic by which extracellular domains and ligands co-adapted to enable the diverse mechanochemical signaling modes characteristic of aGPCRs may offer important insights into how receptor architectures became tailored to the environmental and biomechanical properties of their cellular expression sites across different organisms, organs, and tissues.

XV. Experimental technologies for adhesion GPCR interrogation

A. Molecular dynamics studies

Studies of how aGPCR proteins behave and move using Molecular Dynamic (MD) simulations have mainly focused on the GAIN domain (Fig. 4) and have uncovered two dynamic regions near the GPS, termed flap 1 and flap 2[14] (Fig. 8). Expanding on this perspective, MD simulations supported investigations into the GPS cleavage mechanism, validating the presence of a T-shaped π-π interaction of the catalytic triad histidine as a key determinant of GPS cleavage competence in the GAIN domain[39]. In a biophysical study on CTF-NTF dissociation at the GAIN domain using single-molecule atomic force spectroscopy, MD was used to investigate GAIN mechanical stability and force propagation determinants of G1 mechanosensing[722,723].

With the characterization of 7TMD structures of several aGPCRs, future MD investigations are bound to uncover dynamics of *Stachel*-binding and *Stachel*-dependent signal transduction (Fig. 6), as well as using first GAIN/7TMD complexes[35,37] to investigate the dynamic continuum of *Stachel* release off the GAIN domain and transition into the 7TMD binding pocket (Fig. 4).

B. Homology modelling

Homology modeling serves as a critical computational tool for resolving aGPCR structures by leveraging conserved TMH frameworks from known homologous templates to predict the three-dimensional conformations of target receptors[724]. Its core workflow encompasses template selection, backbone mapping of transmembrane regions, side-chain optimization, and loop modeling, supplemented by MD simulations to refine dynamic conformations, such as the outward movement of the TMH6 in activated states[725,726].

However, traditional homology modeling faces limitations in accuracy due to challenges including template scarcity for aGPCRs and deviations in side-chain orientations within ligand-binding pockets. Deep learning-based protein structure prediction has emerged as a powerful technique for resolving the conformations of membrane proteins, including GPCR. Recent advances in deep learning models, such as AlphaFold and RoseTTAFold, have surpassed the accuracy limitations of traditional homology modeling, achieving near-experimental resolution for full-sequence structure prediction[727,728].These approaches primarily rely on multiple sequence alignments and co-evolutionary analysis, utilizing neural networks to learn spatial constraints and contact maps between residues, thereby inferring protein folding patterns[729]. For highly flexible membrane proteins like aGPCRs, deep learning enables precise prediction of transmembrane helix topology. However, challenges remain in loop modeling, conformational dynamics, and fine-grained predictions of ligand-binding pockets[730].

C. Acute receptor activation

Acute activation strategies have enabled investigation of the intracellular signaling activity of aGPCRs *in vitro* and are emerging as tools to study aGPCR functions *in vivo* (Fig. 8). Two main approaches, one relying on addition of ligands (Table 1), and the other on controlled exposure of the *Stachel*, have been explored.

Addition of soluble small molecules[173,177,235,270,496,651,656] or synthetic peptides derived from the *Stachel* sequence[16,17,68,72,113,205,212,220,238,661], combined with measurements of G protein activation, GTP turnover, or second messenger regulation, has been used to interrogate aGPCR signaling in a manner analogous to classical GPCR agonists (Fig. 6A). However, ligand specificity and solubility remain a challenge in these approaches.

For four aGPCRs (G1, G6, D1 and L3) naturally occurring adhesive ligands (derived from the ECM or membrane anchored) have also been shown to induce second messenger regulation upon acute presentation as purified proteins in solution[165,315,731], or when presented on coated substrates or through cell mixing[178,249,497]. Antibodies binding the NTF of G6 and D1 have been shown to induce cAMP production[216,732]. In future assay development, testing the impact of adhesive ligands in a more physiological setting, for example in a 3D matrix or in co-culture, while simultaneously applying an acute stimulus such as mechanical stress, will be informative. This can be supported by acute membrane anchoring of secreted ligand forms by exploiting genetic code expansion technology combined with biorthogonal integration of unnatural amino acids within the ligand. When expressed in co-culture with cognate receptor-expressing cells, such acute membrane ligand fixation can aid in investigating adhesion-dependent aGPCR activation[733].

Signaling profiling, which systematically screens the four main G protein pathways and directly measures G protein coupling, is now possible through strategies that acutely expose the *Stachel*, thereby circumventing ligand solubility issues. One of the first approaches used urea to dissociate the NTF and expose the *Stachel* [17].

In recent years, the strategy of engineering a protease site N-terminal to the *Stachel* to acutely trigger its exposure upon protease addition[84,124,209,215,225,734–736] has paved the way for using live

cell BRET readouts to monitor direct G protein activation and downstream effector interactions (Fig. 6A,B).

D. Force assays

A wide range of aGPCRs are involved in mechanotransduction, i.e., the conversion of mechanical forces into biochemically and physiologically actionable information[217,329,419,737,738]. Experimental approaches to define forces that are transmitted between aGPCRs and their adhesive ligands (Table 1) during mechanical stimulation, which affect individual aGPCR during signal transduction, and influence cellular responses to aGPCR activation, are a rapidly emerging area in aGPCR research (Fig. 8). These efforts are essential for determining the specific role of a given aGPCR within the distinct phases of mechanotransduction: mechanotransmission, the transfer of forces to and between molecules and cells; mechanosensation, the detection of such forces by conformational changes within membrane proteins; and mechanoresponse[739], the cellular signaling reaction triggered by this molecular level of force detection. However, for many aGPCRs and their observed functions, these roles have yet to be clearly defined.

Techniques that enable direct application of force to receptors while simultaneously measuring intracellular signaling will pave the way for directly linking GAIN domain force load to GPCR signaling output. One such method combines optical tweezers and confocal microscopy, using a highly focused laser beam to manipulate (hold, pull, or push) living cells mechanically[740,741], while simultaneously monitoring fluorescent signals. This approach leverages reporters that detect G protein recruitment, cAMP production[742], calcium mobilization[743] or Rho kinase activity[744] downstream of aGPCR activation (Figs. 6, 8).

Magnetic tweezers apply physiologically relevant force-loading rates (~pN/s) to measure conformational changes and GAIN domain dissociation of aGPCRs[745,746] (Figs. 4, 6, 8). Recent studies show that the GAIN B subdomain of self-cleaved receptors such as G1, L1 and L3 undergoes partial unfolding at low forces before dissociating at 10–20 pN. Similar partial unfolding was also observed in non-cleavable B3. These findings reveal conserved mechanical responses of the GAIN B subdomain across aGPCR subfamilies.

Single-molecule atomic force microscopy (AFM) is a valuable tool for characterizing mechanical properties of individual protein domains and protein-protein interactions[747], and has been used extensively for studying GPCR[748] (Fig. 8). However, its application to aGPCRs is more limited, with only a single report documenting GAIN-*Stachel* dissociation forces for isolated GAIN domains lacking the 7TMD in a range of ~ 95-160 pN at loading rates of 2,000-20,000 pN/sec[722].

The activation of G6 through its endogenous ligands laminin 211 and collagen IV in combination with pulling or pushing forces were studied using AFM with a coated cantilever[732]. A fluorescent cAMP sensor enabled measurement of this second messenger at the single cell level, revealing distinct activation modes for these ligands.

A high-throughput mechanical stimulation assay utilizing a magnetic tweezer system, integrated with a GPCR biosensor platform, was developed to examine the mechanosensitivity of selected aGPCRs[330]. In these assays, HEK293 cells expressing N-terminal Flag-tagged aGPCR and G protein BRET probes were incubated with paramagnetic beads, which were coated with anti-Flag M2 antibody. Forces were applied to the receptor-bound magnetic beads, enabling a real-time detection of force-induced G protein activation via a G protein dissociation BRET assay (Fig. 8). Using this method, five aGPCRs, D1, G6, L2, L3 and V1, were found to trigger $G\alpha_s$ or $G\alpha_i$ signaling in response to force stimulation. The platform's versatility extends to endogenous aGPCR studies by leveraging the magnetic beads coated with antibodies specifically recognizing the extracellular regions of the target receptors[330]. The force-induced changes in secondary messengers, such as cAMP and Ca^{2+}, or other cellular signals could also be quantified.

Vibration and shaking of heterologous cell cultures expressing aGPCRs G6[245], D1[66] and G5[113] have also been used to study the impact of broad mechanical forces on receptor activity (Fig. 8).

Physiological force-dependency of cellular aGPCR functions were first observed in flies[325] and mice[384]. Increased G1 expression was shown to modulate skeletal muscle hypertrophy as a target in a transcriptional cascade active during exercise. Similarly, anabolic effects of G1 on skeletal muscle mass *in vivo* were achieved through wheel-running and muscle overload by stretching[384]. Through direct sensory neuronal stimulation via Piezo-actuated glass probes operated between 100-1,500 Hz showed Cirl-dependent suppression of cAMP levels using a transgenic EPAC sensor[92,749]. Via electrophysiological recordings of proprioceptive neurons, Cirl-dependent maintenance of neuronal current amplitudes and frequency were demonstrated, which underlie mechanical stimulus-instructed organ functions and behaviours such as hearing, tactile perception, animal movement, and nociception[90,92,108,325]. Additional technical efforts provided transgenic sensors to investigate physiological ligand- and force-dependent receptor dissociation as observed in proprioceptive neurons during joint motion or central brain neurogenesis[93,683], collectively placing Cirl within the processes of mechanotransmission and -sensing.

Recently, similar physiological approaches demonstrated the mechanosensing contribution of L2[330] and D1[331] to equilibrioception in mice. A fluid jet system was used to directly apply mechanical stimuli to the cell surface of hair cells[750]. When integrated with BRET-based biosensors (Fig. 8), this system confirmed the mechanosensitivity of selected aGPCRs identified by a magnetic tweezer assay. Furthermore, the fluid jet system has been utilized to explore the physiological roles of aGPCR in the inner ear hair cells. Specifically, activation of L2 by the fluid jet stimulation increases intracellular Ca^{2+} levels and promotes glutamate secretion in mouse vestibular hair cells, a response that is severely impaired in L2-deficient hair cells[330,750]. Therefore, this multimodal methodology bridges molecular-scale force application with systems-level physiological outputs, offering high resolution for dissecting aGPCR roles in mechanobiology.

E. Receptor dissociation

In most aGPCRs, the GAIN domain is autoproteolytically active, although, for any given aGPCR, self-cleavage may be contextual depending on cell type[8,81,231,751] or other factors such as receptor glycosylation[81]. The autoproteolytic cleavage of aGPCRs and thus receptor dissociation can be suppressed by point mutations immediately adjacent to the GPS[11], or within the intra-domain environment of the cleavage site[39]. For example, mutations of a highly conserved histidine at the -2 position of the GPS abolishes cleavage and dissociation[11,16,205,219,221,325].

Detecting NTF-CTF dissociation events (Figs. 4, 6), especially at high spatial and/or temporal resolution, is important for understanding aGPCR function, but technically challenging. A biochemical approach used to characterize aGPCR dissociation involves affinity purification/immunoprecipitation of receptors using NTF- or CTF-specific antibodies or epitope tags to assess whether the two fragments remain non-covalently bound or have dissociated. As was demonstrated for D1 using this approach and subcellular fractionation[124], cleavage occurs in the ER, but the NTF and CTF remain non-covalently bound until they reach the plasma membrane. Once localized at the plasma membrane dissociation can take place.

A recent advance is the development of an NTF release sensor (NRS) system, which enables transcriptional detection and quantification of NTF dissociation from any given aGPCR in cell culture, and at cellular resolution, also *in vivo*[93,683] (Fig. 8). Its utility was demonstrated using NRS reporters for the *Drosophila* receptors Cirl, Mayo and Ketchup. In particular, analysis of Cirl-NTF release conditions in the developing brain revealed important biological functions of Cirl dissociation at the interface between glial and neural progenitor cells[93].

Critical synopsis and outlook: The adaptation of emerging technologies for the study of molecular, cellular, physiological and pathophysiological aspects has significantly improved the analyses of aGPCR properties. Specific focus is currently warranted to emulate the native environment, in which aGPCR natively receive and respond to their adequate stimuli, in in vitro assays. This requires different approaches than the pharmacological and cell biological analyses of non-aGPCRs and is hampered by the lack of detailed information on the ligand spectrum of individual homologs, the properties of mechanical stimuli they are activated by, and the potential crosstalk with other agonistic conditions such as steroid agonists. To complete our knowledge on these determinants of aGPCR signals, an increasing number of biophysical approaches, such as the ones pioneered for the investigation of motor proteins, adhesion molecules and other mechanoresponsive molecules, are required and need to be adapted to aGPCR questions. Also structural studies that aim at characterising full-length aGPCR in their native tissue environment including cryo-ET analyses, and molecular modelling techniques to grasp the dynamics of aGPCR systems without and with interactors are needed from here on out to continue the successful characterisation of aGPCR-dependent signals.

XVI. Perspectives

The decade that has passed since the last comprehensive review on aGPCRs published in this journal[1] has witnessed tremendous scientific progress across all aspects of these receptors, including their structure, signaling, biochemistry, and the diverse cell, tissue, and organ functions they regulate, and the consequences of their dysfunction. This progress has been driven by the concerted efforts of the international research community dedicated to aGPCRs, as represented by the Adhesion GPCR Consortium (https://www.adhesiongpcr.org). This collaborative network has played a pivotal role in advancing methodological innovations, standardizing aGPCR nomenclature to ensure precise communication, and fostering interdisciplinary dialogue among structural and cellular biologists, pharmacologists, biochemists, physiologists, geneticists, and clinicians. As a result, our mechanistic understanding of aGPCR activation and signaling paradigms has advanced significantly, laying the foundation for a more comprehensive understanding of aGPCR function and paving the way for novel therapeutic approaches targeting these complex receptors. Yet many fundamental questions remain unanswered, new scientific challenges are emerging, and the technological toolbox for aGPCR research remains incomplete. Major knowledge gaps include endogenous receptor expression patterns, receptor-specific ligands, context-dependent signaling pathways, isoform-specific functions, and the integration of aGPCR functions within broader cellular and physiological networks. Technological advances, including the development of specific antibodies, protocols for the application of mechanical stimuli, and assays to read and quantify their mechanoresponses, are highly sought after. Addressing these scientific and technological challenges will require sustained collaboration, further technological advances in structural and functional assays, both in silico, *in vitro* and *in vivo*, development of fragment- and isoform-specific antibodies, and the translation of basic discoveries into clinically relevant strategies. Considering the remarkable achievements to date, aGPCR research stands well-positioned to capitalize on these insights, deepen our biological understanding, and ultimately harness the therapeutic potential of aGPCRs in a wide range of diseases in which they play critical roles. We look forward with great anticipation to the advances and insights that the coming decade of aGPCR research will bring.

Financial Support

This work was supported by the Deutsche Forschungsgesellschaft (DFG) to Langenhan (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, project 542631574); Aust (FOR 2149 project number 246212759, project 432108769); Blanco-Redondo (DFG project number 574945774); Bridges (R01HL177550); Engel (FOR 2149 project number 246212759 and EN453/15-1 project number 522261482); Georgiadi (project 450149205-TRR333/1 (BATenergy) (project P03)); Hamann (FOR 2149 project number 246212759); Hildebrand (CRC1423 project number 421152132, subprojects C01, Z04); Kittel (KFO 5001 project number 426503586); Kleinau (EXC 311 2008/1 (UniSysCat)—390540038 (Research Unit E)); Liebscher (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, subproject B05; Prömel (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, subproject C04); Scheerer (CRC1423, project number 421152132, subproject A01, A05, Z03 and EXC 311 2008/1 (UniSysCat)—390540038 (Research Unit E)); Scholz (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, subproject B06); Schöneberg (FOR 2149 project number 246212759 and CRC 1423 project number 421152132); Sträter (FOR 2149 project number 246212759 and CRC 1423 project number 421152132, project 542631574); Vallon (project number 440925599); Wolfrum (FOR 2149 project number 246212759); the National Institutes of Health (NIH) to Caron and Avila-Zozaya (HD060860); Blacklow (2R35CA220340, 1R01CA272484 and 1R01AI172846); Duman (R01-CA283569 and R01-MH137505); Hall (R21-NS133638 and R21-NS142860); Sando (00MH117235 and DP2MH1401324); Tall (R35 GM149539); Tilley (HL134608); Tolias (MH137505 and 2RF1NS062829); Van Meir (NS117666 and NS144449); Zaidman (R00DK127215); the Wellcome Trust to Del Toro and Seiradake (226647/Z/22/Z); Strutt (210630/Z/18/Z and 305132/Z/23/Z); the Novo Nordisk Foundation to Chung (NNF23OC008432); Gloriam (NNF23OC0082561); the European Research Council (ERC) to Del Toro and Seiradake (Synergy grant SUNRISE: 101167188); Vanhollebeke (Ctrl-BBB 865176); the Federal Ministry of Research, Technology and Space (BMFTR) to Scholz (03VP11220); Langenhan (03VP11220); the NWO to Hamann (Gravitation Program 024.006.009); FRFS-WELBIO (CR-2017S-05R) to Vanhollebeke; the Secretaría de Educación, Ciencia, Tecnología e Innovación de la Ciudad de México to Boucard (SECTEI/165/2023; CONAHCYT PN2017-4687, CB221568, INFRA302758); Mitacs accelerate program IT29484 to Moreno-Salinas; the National Research Foundation (NRF) Singapore to Yan (MID-SIZED GRANT (MSG)(NRF-MSG-2023-0001)); the German Academic Exchange Service (DAAD) to Singh (reference number 91897195); the Alfred Sloan Foundation to Sando; the Leipzig University, Faculty of Medicine to Blanco-Redondo (Junior research grant); the Foundation Fighting Blindness (FFB) to Wolfrum (PPA-0717-0719-RAD); the Independent Research Fund Denmark to Mathiasen (Sapere Aude 1054-00086B) and (NNF23OC0081901); the National Science and Technology Council (NSTC), Taiwan to Lin (NSTC-113-2320-B-182-009); the University of California, Howard Hughes Medical Institute to Garcia De Las Bayonas; the Cancer Research UK (CRUK) and UK Research and Innovation (UKRI) to Favara; and the Deutsche Herzstiftung e.V., Manfred Roth Stiftung, and Research Foundation Medicine at the University Clinic Erlangen to Engel.

Conflict of interest

D.G.P. holds patents on the therapeutic targeting of ADGRE5 and ADGRD1 in GBM; M.G.L. is an employee of Novartis Pharma AG; L.S. is an employee of Domain Therapeutics; E.V.M. is co-founder, CSO and shareholder of OncoSpherix, LLC.; G.W. is Employee of and shareholder in Nxera Pharma UK Limited; N.S. and T.L. are co-inventors of a pending patent covering NTF release sensors for aGPCRs (WO/2022/063915; priority application: EP 3974535; applicant: Leipzig University). D.E.G. is a part-time employee and warrant-holder at Kvantify. B.V. is shareholder and founder of NeuVasQ Biotechnologies. S.C.B. is on the board of directors for the non-profit Revson Foundation and non-profit Institute for Protein Innovation, is on the scientific advisory board for Erasca, Inc. and MPM Capital, is head of the scientific advisory board with equity in Odyssey Therapeutics, and is a consultant for Scorpion Therapeutics.

Data availability

Transcriptome data on aGPCRs shown in Fig. 5 was extracted from the Human Protein Atlas (HPA) consortium.

Acknowledgements

We thank Ivana Henry, Cambridge, for her collaboration on the illustrations. We apologize to authors whose work was not referenced in this manuscript.

Author contributions

Langenhan and Scholz: conceptualization, supervision, writing, reviewing and editing, visualization, project administration, and funding acquisition.

Anderson, Araç, Aust, Avila-Zozaya, Bagger, Barth, Sandra Berndt, Blacklow, Blanco-Redondo, Boucard, Bridges, Brodmerkel, Caron, Chung (鍾, Dates, de Araujo Farias, Del Toro, Duman, Engel, Favara, Formstone, Fu, Garcia De Las Bayonas, Georgiadi, Gloriam, Hall, Hamann, Hildebrand, Hsiao, Huang, Javitch, Kim, Kittel, Kleinau, Leduc, Liebscher, Lin, Linnert, Ludwig, Martinelli, Mathiasen, Matúš, Melkumyan, Moreno-Salinas, Mulder, Nash, Pal, Pederick, Perry-Hauser, Piao, Ping, Placantonakis, Pohl, Prömel, Rosenkilde, Sabbagh, Sando, Scheerer, Schöneberg, Seiradake, Selcho, Seufert, Singh, Skiniotis, Spiess, Sträter, Strutt, Südhof, Sun, Tall, Thor, Tilley, Tolias, Vallon, Van Meir, Vanhollebeke, Wiggin, Wolfrum, Yan, Zaidman, and Zou: visualization, writing, review and editing.

Aust, Hamann, Hsiao, and Mulder: formal analysis.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Figure legends

Fig. 1. (A) Overview of human orthologs of the aGPCR family, their domain architecture and phylogenetic relationship[30]. Receptor names conform to current IUPHAR nomenclature[1]; previous names are given above in brackets. Domains are not drawn to scale, domain numbers per ortholog can vary depending on splice variant/isoform; the phylogenetic relationship is not shown for E4 due to its pseudogene status. NCBI's Conserved Domain Database[752] and Expasy PROSITE[753] were used to annotate domains. Additionally, models were generated using AlphaFold2[729] (except for V1) to corroborate the sequence-based with a structure-based approach. In case of a mismatch FoldSeek[754] was used to identify similar, known domains, based on its predicted structure. Where available (see Chapters IV.A and IV.B), known structures of aGPCR ENTs were used to verify predicted domains. Different types of Ig domains were assigned according to their specific topology[755]. A laminin EGF-like domain was predicted N-terminal to the GAIN domain of all C receptors, but was absent in the cryo-EM structure of ADGRC1[63] and thus omitted from the sketches. Legend: domain shapes only found in one subfamily are color-filled, domains found in more than one subfamily are left blank.

(B) Schematic depiction of receptor elements of aGPCR based either on their topology (left) applicable to non-cleaved and self-cleaved receptors, or on autoproteolysis (right) applicable to self-cleaved receptors only. Autoproteolyzed aGPCRs can exist as non-dissociated or dissociated non-covalent NTF-CTF complexes. TIA/Stachel is indicated in pink.

7TMD, heptahelical transmembrane domain; CA, cadherin; Calx-β, Na-Ca exchanger β; CTF, C-terminal fragment; CUB, complement C1r/C1s, Uegf, Bmp1; eCUB, extended complement C1r/C1s, Uegf, Bmp1; EGF, epidermal growth factor; ENT, extracellular N-terminus; EPTP, epitempin; GAIN, GPCR autoproteolysis-inducing; GPS, GPCR proteolysis site; HormR, hormone receptor motif; IgI-set, immunoglobulin I-set ; ICT, intracellular C-terminus; IgC1, immunoglobulin C1-set; LLR, leucine-rich repeat; NTF, N-terminal fragment; OLF, olfactomedin; PLL, Pentraxin/Laminin/neurexin/sex-hormone-binding-globulin-like; PM, plasma membrane; PTX, pentraxin; RBL/Lec, rhamnose-binding lectin/lectin; SEA, Sea urchin sperm protein, Enterokinase, Agrin; TIA, tethered/intramolecular agonist; TSR, thrombospondin repeat. See Chapter II.

Fig. 2. Generic residue numbering schemes for the GAIN domain and 7TMD of aGPCRs. Generic residue numbers indicate the position of a specific AA within a secondary structural element relative to the most conserved residue of the respective segment, which is assigned the number "X.50".

(A) The GAIN domain, located N-terminal to the 7TMD, is subdivided into subdomain A (yellow), which contains several α-helices (TMH1-TMH6), and subdomain B (blue), which consists of β-strands (S1–S14) and the GPS (red circles). S14 corresponds to the β-strand

formed by the *Stachel* core in its in-GAIN bound conformation[9]. Disordered regions connecting structural elements are labeled using the abbreviations of the adjacent segments, such as h3h4 or s2s3. The schemes in (A) represent structural models of aGPCR fragments determined through analysis of GAIN subdomain A (UniprotKB: A0A2Y9F628) and GAIN subdomain B (UniprotKB: A0A2I4CCH8).

(B) The 7TMD is composed of eight α-helices (TMH1-7 and helix 8), each with highly conserved AA residues characteristic of class B GPCRs[31], visualized at the CTF structure of F1 (PDB ID 7wu5). The TIA/*Stachel* core with the highly conserved L0.50 as part of the CTF can be bound as a helical segment in the 7TMD. The conserved ECL2 residues $C^{45.50}$ and V8.50 in the cytosolic helix 8 are included in supposed class B GRNs[10].

(C) Example of a comparison between different GPCR numbering schemes for TMH2.

See Chapter IV-A,C.

Fig. 3. Extracellular domains of aGPCRs and their interactions.

(A) Experimentally shown and predicted extracellular complex formations of L1-3 Lec and Olf domains (orange)[45–50,756].

(B) Interaction of the TSR3 domain of B1 with RTN4R. Mannose and fucose residues at the binding interface are shown as sticks.

(C) Crystal structure of the E5-CD55 complex.

(D) The G4 pentraxin domain forms a homodimer.

(E) The N-terminal CUB domain of the ENT of G6 interacts with the HormR-GAIN domains resulting in a compact ENT structure.

(F) CryoEM structure of CADH9-GAIN part (left) and crystal structures of the N-terminal cadherin domains 1-7 (right) of the C1 ENT.

(G) Crystal structure of the ENT of G1. A disulfide bridge (SS) links the PLL and GAIN domains.

See Chapter IV-B.

Fig. 4. Adhesion GPCR activation mediated by the TIA/*Stachel*. The illustration exemplifies the structural transition of an aGPCR from its inactive to active state using structures of E5[35]. (A) In the inactive conformation (PDB ID: 8IKJ), the TIA (in pink) is embedded in the GAIN domain as a buried β-strand. (B) Upon activation, the NTF dissociates from the CTF exposing the TIA. The TIA then inserts into the orthosteric binding pocket of the 7TMD through its N-terminal α-helical segment (PDB ID: 8IKL). See Chapter IV-C.

Fig. 5. Overview of gene expression of aGPCRs across human cell types obtained by single-cell RNA sequencing data from solid tissues and bulk RNA sequencing data from sorted blood collected by the Human Protein Atlas (HPA) consortium[757]. Note that (i) cell types are grouped primarily by function, not by tissue, (ii) ubiquitous cell types, such as endothelial cells lining vessels, appear only once, even though present in many tissues, (iii) organs contain various cell types and can appear in multiple categories (e.g., liver: hepatocytes and cholangiocytes under "specialized epithelial cells" and Kupffer cells under "immune cells"), (iv) hard-to-isolate cells, such as osteocytes and chondrocytes are not covered in this list, (v) enucleated cells/cell fragments, like red blood cells and platelets, are not included although they may express aGPCRs, (vi) data represent healthy adult tissues. nTPM (normalized transcripts per million) values represent the number of transcripts detected for a given gene. The size of the dot depends on the nTPM value (cut-off value of ≥ 4). Each data point represents gene expression and does not distinguish between transcript variants. *ADGRE4*[145,758] and *ADGRF2* are currently considered as pseudogenes in humans; however, transcripts originating from both loci have been reported[21]. See Chapters VIII and XII-A.

Fig. 6. Activation and signaling modes of aGPCRs.

(A) Central to the activation of many aGPCRs is the TIA/*Stachel* (in pink), but it is not necessarily a prerequisite for triggering aGPCR activity. Both TIA-dependent and TIA-independent activation modes have been reported. Ligand binding and/or mechanical force application can induce TIA-dependent aGPCR signaling in the intact NTF-CTF receptor complex (dissociation-independent TIA-dependent activation). Alternatively, the bipartite NTF-CTF complex can dissociate and trigger TIA-dependent metabotropic activity (dissociation-dependent TIA-dependent activation). Both scenarios can induce cell autonomous signaling in the aGPCR-expressing cell.

(B) Some receptors such as A2 function as part of a signalosome complex, where they not necessarily fulfil a metabotropic function but may be required for other aspects, e.g. for ligand recognition.

(C) aGPCRs can also relay non-cell autonomous signals via direct membrane-anchored aGPCR-ligand contact between neighboring cells, or by shedding ENT fragments including the NTF that affect the activity of distant cells.

See Chapters X and XI.

Fig. 7. Number of shared and private aGPCRs in vertebrate genomes. The dataset of human aGPCR genes (including the pseudogene *E4*) was used to extract the orthologous aGPCRs from all vertebrate classes using the webtool OrthoDB v11[759]. 87.9% of human aGPCRs are shared

within vertebrates as shown in the Venn diagram. The high number of fish aGPCR is mainly due to genome duplication in some ray-finned fish (*Actinopterygii*). Of note, the number of private fish, amphibian, reptile and bird aGPCRs is biased by the fact that only human aGPCRs were used to extract the orthologous sequences. Animal icons are examples. See Chapter III-A.

Fig. 8. Experimental technologies for aGPCR research. With the finding that aGPCRs are prone to detect adhesive ligands and mechanical stimuli the field has begun to explore and adapt existing technologies and establish new experimental strategies to mechanically activate aGPCRs and to capture the respective mechanoresponse. Some mechanical stimulation paradigms are shown including AFM, magnetic tweezers, acute application of sound stimuli, piezo element-driven pulling forces and shear stress. Sophisticated computer-based simulations in combination with crystal structures enables directed experimental strategies to investigate structural dynamics and conformational states of specific aGPCR domains. The NTF release sensor (NRS) is a transgenic system that converts the physical NTF separation into visible reporter gene signal and can thus provide quantitative spatiotemporal information of NTF release of a given aGPCR. Technologies such as mini Gs, cAMP and BRET assays have been used to track and quantify metabotropic activity of mechanically-stimulated aGPCRs. See Chapter XV.

Tables

Table 1

Table 1. Identity, level of evidence, effect and interface of known interaction partners of aGPCRs.

Receptor	Endogenous Ligands/Interactors	Exogenous Lig	Species / receptor	Identification/Isol Method	Tissue of or tissue/cell expression	Signaling pathways	Interaction interface	References
Subfamily A								
A2	Reck/Wnt7a/Wnt7b /Dishevelled-2		Mouse Zebrafish		Endothelium	β-catenin Cdc42		179,196,262,263,265,336, 570,760
A2	$\alpha_v\beta_3$ Integrin, α_5 Integrins		Human	Adhesion assay, affinity chromatography	Human umbilical vein endothelial cells (HUVEC)		ENT, HormR domain RGD motif	273
A2	Heparin		Human	ELISA	HUVEC cells		Unknown, but depends on the ionic strength of the environment (1M NaCl)	273
A2	Glycosaminoglycans (chondroitin sulfate A, heparan sulfate, dermatan sulfate)		Human	ELISA	HUVEC cells			273
A2	SDC1/SDC 2 (Syndecan)		Human	Cell-based genome-wide approach with CRISPR activation	HEK293 cells	-	-	51
A2	Discs large		Human	-	-	-	ICT, PDZ-binding motif(PBM)	193
Subfamily B								

B1	RTN4s/NoGo receptors (RTN4R, RTN4RL1, RTN4RL2)		Mouse, Human	Cell-based genome-wide approach with CRISPR activation, cell surface labeling assay, quantitative cell adhesion assay, binding affinity measurements surface plasmon resonance, pulldown, mass spectrometry	Neuron / glia, HEK293 cells	-	ENT, TSR3 domain (B1-RTN4R K_d = 26.8 nM, B1-RTN4RL1 Kd=9.6 nM, ENT, B1-RTN4RL2 K_d= 30 nM)	[51,52,761]
B1	Neuroligin 1		Mouse	Functional Assays, co-immunoprecipitation	Hippocampal neurons, HEK293 cells	-	ENT, Vasculostatin	[255]
B1	Phosphatidylserine		Mouse	Overlay binding assays phagocytosis assay (in vitro), engulfment assay (in vivo)	LR73 Chinese hamster ovary cells, J774 macrophages and NIH 3T3 cells) and primary cells (mouse astrocytes); apoptotic thymocytes injected into mouse peritoneum	ELMO1/Dock/Rac	ENT, TSR	[200]
B1	ATP11A			Co-immunoprecipitation assays	HEK293T cells	Reduces constitutive $G\alpha_{12/13}$ signaling	NTF	[762]
B1	Lipopolysaccharide		Mammalian	Biotin-streptavidin-phycoerythrin based flow cytometry	Macrophages	Rac/ELMO/Dock	ENT, TSRs	[253]

B1	Integrin $\alpha_v\beta_5$		Mouse	Immunoprecipitation of mouse brain lysate	HUVEC cells	-	ENT	[274]
B1	BAI-associated protein 2		Human	Y2H	-	-	Binding between AAs 1304 - 1584	[763]
B1	BAI-associated protein 3		Human	Co-immunoprecipitation	COS-7 cells	-	ICT	[764]
B2	GIP3 (glutaminase interacting protein)		Human	Human fetal brain cDNA library screened using a yeast two-hybrid assay, Circular Dichroism, Nuclear Magnetic Resonance spectroscopy	Human brain	$G\alpha_{16}$, NFAT pathway	ICT, C-terminal sequence RDGDFQTEV	[206,765]
B3	C1q-like proteins		Mouse	Affinity chromatography, Mass spectrometry, pulldown, proteomics	Mouse brain samples, HEK293 cells, C2C12 cells (muscle cell line)	-	ENT, eCUB, (C1ql-4) (K_d = 1–20 nM)	[53,56,295,766]
B3	RTN4R and RTN4RL1		Mouse	Cell surface labeling assays, quantitative cell adhesion assay, pulldown	HEK293 cells	-	ENT, TSR2 (B3-RTN4R with binding affinity of K_d=1.9 nM)	[52,761]
B3	Stabilin-2		Mouse, Chicken	Proteomics	purified BAI3 HEK293T cells and to affinity purify proteins from the supernatant of differentiating C2C12	Elmo proteins, β-Arrestin2	ENT	[766]

B3	Neuronal pentraxins (NPTX1/ NPTXR)		Mouse	Time-controlled cross-linking, Aggregation assay, Co-immunoprecipitation, mass spectrometry	mouse brain lysates, HEK293 cells		-	[53]
Subfamily C								
C1	ADGRC1 (homophilic trans interaction)		Mouse	Cell binding assay	HEK293 cells	-	ENT, cadherin repeats	[159]
C1	ADGRC2 (heterotypic trans interaction)		Mouse	Cell binding assay	HEK293 cells	-	ENT; cadherin repeats	[159]
C1	Vangl-2		Mouse	Fluorescence-based recruitment assay, co-immunoprecipitation	Cultured keratinocytes, HEK293T cells	-	-	[767,768]
C1	Frizzled-6		Mouse	Fluorescence-based recruitment assay	Cultured keratinocytes	-	-	[767]
C1	LRRK2		Mouse, Human	Co-immunoprecipitation, mass spectrometry	substantia nigra cells (SN4741), HEK293T cells	WNT/β-catenin pathway	-	[769]
C2	ADGRC2 (homophilic interaction)		Rat	Co-culture and aggregation assays, Calcium imaging	Cortex and hippocampal neurons, HEK293 cells	CaMKII, calcineurin, Ca^{2+} signaling	ENT, cadherin repeats	[159,289]
C2	ADGRC1 (homophilic trans interaction)			Cell binding assay	HEK293 cells	-	ENT, cadherin repeats	[159]

C3	ADGRC3 (homophilic trans interaction)		Rat	Cell binding assay, Co-IP (exogneous and brain lysate), aggregation assays, Calcium imaging	Cortex and hippocampal neurons, HEK293 cells	Ca^{2+} signaling	ENT, cadherin repeats	289,770
C3	Dystroglycan		Mouse	Live-cell binding assay, co-immunoprecipitation	COS-7 cells, HEK293 cells		ENT, LG1 domain	770
C3	Frizzled-3		Mouse	Co-immunoprecipitation	Brain extracts	-	-	267
C3	PSD-95		Mouse	Co-immunoprecipitation	Brain extracts	-	-	267
C3	SV2		Mouse	Co-immunoprecipitation	Brain extracts	-	-	267
Subfamily D								
D1	Protein Tyrosine Kinase 7 (Ptk7)		Human-patient derived, Mouse	Affinity co-purification, mass spectrometry	Patient-derived GBM cells, HEK293T cells	cAMP (specifically in trans), requires membrane anchoring	NTF	178,497
D1	5-hydrotestosterone		Mouse	cryoEM structure	HEK293 cells	$G\alpha_s$, cAMP-PKA	7TMD	270
D1	Plexin Domain-Containing Protein 2		Human	Library of single-transmembrane-spanning human cell surface receptors followed by interaction screening based on AVEXIS method	Expi293F cells	Increase in cAMP	ENT, PTX domain	497
D1	Methenolone		Mouse	cAMP screen, cryoEM structure	HEK293 cells	$G\alpha_s$, $G\alpha o$ cAMP-PKA	7TMD	270
D1		AP503		cryoEM structure	HEK293 cells	$G\alpha_s$, cAMP-PKA	7TMD	270

Subfamily E								
E2	Dermatan sulfate (chondroitin sulfate B)		Human	Cell-based ligand-binding assay	most cell surface, ECM	Mast cell degranulation (histamine release)	ENT, EGF-like domain 4	94,771
E2	FHR1		Human	RNA sequencing/Gene associated disease (GAD) analysis, direct protein-protein interaction assay	Complement system protein in blood	Inflammasome activation in monocytes	ENT	415
E3	unknown surface ligand		Human	Cell-based ligand-binding assay	macrophages and activated neutrophils	ND	ENT	772
E4	unknown surface ligand		Mouse	Cell-based ligand-binding assay	A20 mouse B-cell lymphoma cell line	ND	ENT, EGF-like domain 2	773
E5	CD55		Human/Mouse	Ab blocking assay/biochemical analysis	red blood cells, lymphocytes, etc.	induces $G\alpha_{13}$ signaling in cDC2 and marginal zone B cells in the spleen	ENT, EGF-like domains 1, 2, 5	91,102,157,420
E5	Dermatan sulfate		Human	Cell-based ligand-binding assay	most cell surface, ECM	ND	ENT, EGF-like domain 4	163,771
E5	α5β1, αvβ3 integrin		Human	Functional blocking Abs in cell attachment assay	HUVEC cells	enhances HUVEC chemotactic migration and angiogenic response	ENT, RGD motif	272
E5	CD90		Human	Cell adhesion assay/protein-cell binding assay	activated endothelial cells, Glioblastoma cells	ND	ENT, GAIN domain	510,774
E5	LPAR1		Human	Co-IP of tagged receptors, in situ proximity ligation assay	prostate cancer and thyroid cancer cells	increased Rho-ERK signaling	7TMD	259,260
E5	RIG-I		Mouse	Immunoprecipitation	HEK-293T or HeLa cells	Inhibition of IFN-I signaling	ICT	775

E5		gingipain K protease	Human	Multiplexed bioactivity screening of GPCRs, microbiome-GPCRome interactions	*Porphyromonas gingivalis*	Increased Tango reporter activity	ENT, cleavage at K290 residue	[776]
E5		SteD surface effector	Mouse	Pulldown, mass spectrometry, co-immunoprecipitation	MutuDCs (immortalized dendritic cells)	ubiquitination of a cytoplasmic lysine residue	CTF	[777]
E5	DLG1		Human	GST-Pulldown, proximity ligation assay	CD97-(over) expressing HT1080 cells; DLD1 cells		ICT, PBM	[186]
Subfamily F								
F1	N-docosahexaenoylethanolamine (synaptamide)		Mouse	pull down coupled to mass spectrometry	Mouse fetal brains or NSCs, HEK293	Gαs	ENT, GAIN domain	[177,305]
F1	occludin		Mouse	chemical crosslinking, affinity purification, and mass spectrometry	HEK293	ND	ND	[778]
F1	laminin-211		Human/Mouse	Cross-linking-aided IP coupled with mass spectrometry	BT474 and SKBR3 cells overexpressing Adgrf1	inhibition of $G\alpha_s$	ND	[180]
F5	surfactant protein D		Mouse	co-immunoprecipitation	HEK293T			[182]
F5	FNDC4		Mouse	fluorescent flow cytometry binding assay in live cells	immortalized pre adipocytes (imm. SVF) from inguinal WAT	$G\alpha_s$, increase in cAMP		[181]
Subfamily G								

G1	phosphatidylserine			flow cytometry, membrane lipid strips	Ba/F3 cells	ND	ENT, GAIN domain	[121]
G1	transglutaminase 2		Mouse, Human	radioimmunoprecipitation assay	lung, melanoma cells, keratinocytes	ROCK-dependent activation of ADAM17	ENT, STP region	[166,779]
G1	collagen III		Mouse	in vitro biotinylation/proteomics and MS	Meningeal Fibroblasts	RhoA activation	ENT, PLL domain	[165]
G1	laminin				HEK293T	together with TG2 increase in SRE luciferase		[167]
G1	L-phenylalanine		Human	High resolution mass spectrometry, NMR and coinjection analyses of the active fraction	supernatant of human gut bacteria	$G\alpha_s$-$G\alpha t$ and $G\alpha_s$-$G\alpha_o$ chimera-mediated increase in CRE-SEAP assay		[168]
G1	heparin		Mouse, Human	ELISA, pulldown	purified protein	induction of receptor shedding and increased cell adhesion but no identified increased signalling	ENT, AA 26-35	[169]
G1	progastrin		Human	Immunofluorescence staining and FACS analysis	Colo320 cells	ND	ND	[475]
G1	CD9, CD81		Human	mass spectrometry protein sequencing	NT2RA, HEK293 cells	scaffolding of $G\alpha 11$ and $G\alpha q$	ND	[170]
G1	Plectin		Mouse	unbiased mass-spectrometry screen, co-IP	P5 sciatic nerves	ND	NTF and CTF	[311]
G1		Antibody	mouse-human chimera	cell-based fluorescence binding assay	HEK293T	SRF increase	ENT, GAIN domain	[780]
G1		Monobody	Mouse		HEK293T	SRE luciferase inhibition	ENT	[33]

G1		small molecules incl. dihydromundulet one, 3-α-acetoxydihydrod eoxygedunin		in vitro substance screen	compound library	SRE luciferase activation		173,651,652
G2	Dehydroepiandroste rone		Mouse, Human	in vitro substance screen	compound library	increase in cAMP	7TMD	71
G2	Deoxycorticosteron		Mouse, Human	in vitro substance screen	compound library	decrease in cAMP	7TMD	71
G3	Cortisol, 11-deoxycortisol			in vitro substance screen	compound library	binding to receptor	7TMD	70
G3	L-phenylalanine		Human	High resolution mass spectrometry, NMR and coinjection analyses of the active fraction	supernatant of human gut bacteria	PRESTO Tango Assay activation		168
G3		Beclomethasone		in vitro substance screen	compound library	Go activation	7TMD	70,235
G3		Ezetimibe, Flunarizine, Zeranol		in vitro substance screen	compound library	ß-arrestin recruitment		781
G3		Compound 36, Compound 4		in vitro substance screen	compound library	$G\alpha_{13}$ activation	7TMD (assumed)	652
G5		Dihydromundulet one, 3-α-acetoxydihydrod eoxygedunin	HEK293T cells	in vitro substance screen	compound library	$G\alpha_{13}$ inhibition	7TMD (assumed)	173
G6	collagen IV		Zebrafish	co-immunoprecipitatio n	Sciatic nerve	increase in cAMP	ENT, CUB/Pentraxin	315
G6	collagen VI		Mouse	pull down coupled to mass spectrometry	Sciatic nerve	$G\alpha_i$, decrease in cAMP	ENT, GAIN domain	731

G6	laminin-211		Zebrafish, mouse	co-immunoprecipitation	Sciatic nerve	increase in cAMP when combined with mechanical forces	ENT, GAIN domain	[245,315]
G6	Prion protein		Zebrafish	co-immunoprecipitation	HEK293, SW10 cells	increase in cAMP	ENT (assumed)	[705]
G6	Progesterone, 17-hydroxyprogesterone		HEK293 cells, breast cancer cells	in vitro substance screen	compound library	$G\alpha_i$, decrease in cAMP	7TMD (assumed)	[496]
G6		Apomorphine	Zebrafish, COS7 cells	in vivo substance screen and in vitro verification	compound library	increase in cAMP	7TMD (assumed)	[656]
G6		multiple small molecules	Zebrafish	in vivo substance screen	compound library	ND		[172]
Subfamily L								
L1	Teneurin-2 (Lasso)		Rat	Affinity purification	brain lysates	cAMP decrease, Ca^{2+} increase	ENT, RBL/Lec domain	[44]
L1	FLRT1, 3		Rat	Affinity purification	brain lysates	cAMP increase/decrease	ENT, OLF domain	[43]
L1	Neurexin-1α, -1β, -2β, -3β		Rat	Cell binding assays	HEK293 cells	cAMP increase/decrease	ENT, OLF domain	[130]
L1	Contactin-6		Mouse	Affinity purification	Brain lysates and HEK293 cells	apoptosis	ENT	[175]
L1	Shank		Human, rat	Y2H, Co-IP	cDNA libraries of human brain, brain lysates		ICT	[187]
L1	TRIP8b		ND	Y2H SOS recruitment assay	cDNA library of rat brain		ICT	[782,783]
L1	glucose		Mouse	Affinity purification-LC/MS, ligand-receptor binding assays	Hypothalamic neurons, CHO cells	$G\alpha_i$/cAMP decrease	ND	[784]
L1		LK29, LK30, LK31	Human	Single-point protein ELISA, epitope mapping,			ENT, RBL/Lec domain	[785]

		(engineered synthetic binders)		Surface plasmon resonance				
L1		α-Latrotoxin		Cell-based Ca2+-uptake and neurotransmitter-release assays	Neurons	Massive neurotransmitter release	GAIN/TMH1 (residue 467–891)	[786]
L2	FLRT3		Rat	affinity chromatography, mass spectrometry,, co-immunoprecipitation	brain lysates, transfected heterologous cell lysates	Not determined (ND)	ENT	[43]
L2	Teneurin-2		Mouse	ligand-receptor binding via SPR	HEK293T		ENT, RBL/Lec domain	[787]
L2	Leucine-rich α-2-glycoprotein 1 (LRG1)		Mouse	Ligand-based receptor capture followed by LC–MS/M	HEK293T	increase in Lyn-PI3K-AKT-NF-κB p65 pathway		[507,788]
L3	FLRT1, 3		Rat	Affinity purification	brain lysates	Not determined (ND)	ENT	[43]
L3	FLRT2		Mouse	Crystal structure, co-immunoprecipotation, surface plasmon resonance	HEK293 cells, HeLa cells, cultured neurons	cell adhesion and repulsion	ENT, Lec/OLF domain	[48]
L3	UNC5D (only in ternary complex) with FLRT2		Mouse	Crystal structure, pulldown, mass spectrometry	HEK293 cells	cell adhesion	ENT, Lec/OLF domain	[48]
L3	FLRT3		Human	Crystal structure, cell aggregation assays	HEK293 cells	cell adhesion	ENT, OLF domain	[47]
L3	Teneurin-3		Rat	Co-immunoprecipotation	HEK293 cells	ND	ENT	[43]
L3		LK29, LK30, LK31	Human	Single-point protein ELISA,	-	SRE	ENT, RBL/Lec domain, breaks	[785]

		(engineered synthetic binders)		epitope mapping, Surface plasmon resonance			interaction between L3 with TEN2 but not FLRT3	
L3		LK12 (engineered synthetic binders)	Human	Single-point protein ELISA, epitope mapping, Surface plasmon resonance		SRE	ENT, Lec/Olf domain,	[785]
L4	ku80		Human		HUVEC cells	NFAT	ENT	[789]
L4	β-spectrin		Human		HUVEC cells	NFAT	ENT	[789]
Cirl	Toll-8/Tollo		*D. melanogaster*	Mass spectrometry, functional readouts	Lysates from *Drosophila* embryo and pupae	ND	ENT	[93,279]
HC110R	FMRFamide-like neuropeptides AF1, AF10, PF2		*H. contortus*	Surface plasmon resonance	-	ND	ENT	[790]
LAT-1	LAG-2 (DSL protein/Notch ligand)		*C. elegans*	BRET (in vitro) and BiFC (in vivo) assays	Somatic gonad, germ cell	ND	GAIN, RBL domain	[281]
Subfamily V								
V1	Harmonin		Mouse	GST-Pulldown, co-immunoprecipitation, yeast two-hybrid assays	COS-1 cells, bacterial lysates	ND	ICT, PBM	[190]
V1	Whirlin		Mouse	Glutathione S-transferase (GST) pull-down assays, yeast two-hybrid assays, immunoprecipitation assays	COS-1 cells, bacterial lysates	-	ICT, PBM	[191]

Table 2

Table 2. Currently available mouse models with associated publications from the Mouse Genome Informatics (MGI), International Mouse Strain Resource, and The Jackson Laboratory databases.

Receptor	Strain	Repository/Depositor	Description	Reference
ADGRA1	*Adgra1*$^{em1(IMPC)J}$	The Jackson Laboratory	Null/KO	791
	Adgra1$^{tm1b(EUCOMM)Hmgu}$	Helmholtz Zentrum Muenchen GmbH	Null/KO	791
ADGRA2	*Adgra2*$^{tm1.1Bstc}$	JAX 016881	Targeted (conditional ready); Exon 1 flanked by loxP sites for Cre-mediated excision	342
	Gpr124 null	Velocigene	Null/KO; Exons 3-13 targeted	341
ADGRA3	*Adgra3*$^{tm1.1(HBEGF,-cre/ERT2)Pac}$	JAX 068344	Tamoxifen-inducible; Exon 1 targeted for null/KO	549
	Adgra3^{tm1Lex}	Lexicon Pharmaceuticals	Null/KO	792
ADGRB1	*Adgrb1*$^{tm2a(EUCOMM)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	793
	Adgrb1$^{t-/-}$	Erwin G. Van Meir	Constitutive Null/Knockout of full-length isoform; Exon 2 targeted; short Bai1 isoforms remains expressed from the alternative promoter.	257
	Bai1$^{-/-}$	University of Virginia	Gene-trap mutation between exons 2 and 3.	479
ADGRB2	*Adgrb2*$^{tm1b(KOMP)Mbp}$	UC Davis	Null/KO	794
ADGRB3	*Adgrb3*$^{em1(IMPC)Bay}$	Baylor College of Medicine	Null/KO	791
	Bai3^{Flox}	Michisuke Yuzaki	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	295
	Adgrb3$^{\Delta 7/\Delta 7}$	Erwin G. Van Meir	Constitutive null/KO of full-length isoform; exon 10 targeted; short Bai3 isoforms remain expressed from the alternative promoter.	626

	Bai3$^{-/-}$	Sushant Bhatnagar	Constitutive null/KO of full length and short isoforms; exons 2 and 18 targeted.	461
	Adgrb3$^{Tn(sb\text{-}lacZ,GFP)PV449Jtak}$	Junji Takeda	Transposon insertion	795
ADGRC1	*Celsr1*^{ctb}	JAX 016111	Spontaneous null/KO; single G deletion results in a frameshift mutation	796
	Celsr1^{Crsh}		Single point mutation, D1040G	797
	Celsr1^{Scy}		Single point mutation, N1110K	798
	Celsr1$^{em1(IMPC)Mbp}$	IMPC UC Davis	Null/KO	791
	Celsr1^{KO}		Null/KO; Exons 26-29 targeted	799
ADGRC2	*Celsr2*^{tm1Dgen}	JAX 005779	Null/KO; Exon 23 targeted for insertion of bacterial lacZ	800
	Celsr2^{KO}		Null/KO; Exons 16-28 targeted	801
ADGRC3	*Celsr3*^{KO}		Null/KO; Exons 19-27 targeted	802
ADGRD1	*Adgrd1*$^{tm1a(EUCOMM)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	793,803
	Adgrd1$^{tm1b(EUCOMM)Wtsi}$	Wellcome Trust Sanger Institute	Null/KO	803
ADGRD2	*No current mouse models - ADGRD2 is a pseudogene in mice and is therefore non-functional*			
ADGRE1	*Adgre1*$^{tm1(cre)Kpf}$	Klaus Pfeffer	Targeted; endogenous coding sequence replaced with Cre and Neo	804
	Adgre1$^{tm1.1Mrl}$	Merck Research Laboratory	Targeted (conditional ready); Exon 16-17 flanked by loxP sites for Cre-mediated excision	805
ADGRE2	*No mouse orthologs*			
ADGRE3	*No mouse orthologs*			
ADGRE4	*Adgre4*$^{tm1b(EUCOMM)Hmgu}$	Helmholtz Zentrum Muenchen GmbH	Null/KO; target exon flanked by loxP sites for Cre-mediated excision, reporter tagged	791
ADGRE5	*Adgre5*^{tm1Dgen}	JAX 005788, Deltagen	Null/KO; Exons 2-5 targeted	806

	Adgre5^{tm1Kake}	Kathleen Kelly	Null/KO; Exons 2-12 replaced with PGKneo cassette	418
	Adgre5^{em2Cys}	Jason G. Cyster	Null/KO; Exons 2-3 targeted using CRISPR-Cas9 for intragenic deletion	91
ADGRF1	*Adgrf1*^{tm1Tcam}	Takeda Cambridge	Null/KO; Exon 12 targeted	370
	Adgrf1^{tm1Smoc}	Shanghai Model Organisms Center	Null/KO; Exons 11-13 targeted	468
	Adgrf1$^{tm1a(KOMP)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	793
ADGRF2	*Adgrf2*^{tm1Tcam}	Andreas P Russ/Takeda Pharmaceuticals	Null/KO; Exon 7 targeted	370
	Adgrf2^{em1Iwto}	Tsutomu Iwamoto	Null/KO; Exon 3 targeted	807
ADGRF3	*Adgrf3*$^{em1(IMPC)J}$	JAX 042379	Null/KO; Exon 8 targeted	791
	Adgrf3^{tm1Lex}	Lexicon Pharmaceuticals	Null/KO	792
	Adgrf3^{em1Kzt}	Keizo Tokuhiro	Null/KO; Exons 7-10 targeted	808
ADGRF4	*Adgrf4*^{tm1Tcam}	Takeda Cambridge	Null/KO; Exon 6 targeted	370
	Adgrf4$^{tm1a(KOMP)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	793
	Adgrf4$^{tm2a(EUCOMM)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	793
ADGRF5	*Adgrf5*$^{tm1.1Bstc}$	JAX 022505	Targeted (Conditional ready); Exon 2 targeted	183
	Adgrf5^{tm1Shiro}	Shigehisa Hirose	Null/KO; Exon 2 targeted	182
	Adgrf5$^{tm1.1Jpbs}$	James P Bridges	Targeted (Conditional ready); Exon 17 targeted for Flp-mediated recombination	184
	Adgrf5$^{tm1.2Jpbs}$	James P Bridges	Null/KO; Exon 17 targeted	184
	Adgrf5$^{tm1a(KOMP)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready)	793
	Adgrf5$^{tm1b(KOMP)Wtsi}$	Wellcome Trust Sanger Institute	Cre-excision of the tm1a allele	803

ADGRG1	*Adgrg1*^{tm1Lex}	Lexicon Pharmaceuticals	Null/KO; Exons 2-3 targeted	809
	Tg(Adgrg1-EGFP)HC35Gsat	Rockefeller University	Transgenic; EGFP reporter gene inserted at the initiating codon of the first coding exon	475
ADGRG2	*HE6*^{KO}		Null/KO; Exons 22-25 targeted	503
ADGRG3	*Adgrg3*^{tm1Fwa}	Frederick W Alt	Null/KO; Exons 2-8 targeted	810
	Adgrg3^{tm1Smoc}	Shanghai Model Organisms Center	Null/KO; Exons 1-2 targeted	598
ADGRG4	*Adgrg4*$^{em1(IMPC)J}$	JAX 051244	Null/KO; Exon 3 targeted	791
ADGRG5	*Adgrg5*^{tm1Lex}	Lexicon Pharmaceuticals	Null/KO	792
	Adgrg5$^{tm1a(EUCOMM)Wtsi}$	Wellcome Trust Sanger Institute	Targeted (Conditional ready); Exons targeted for Cre-mediated excision	793
	Adgrg5$^{tm1b(EUCOMM)Wtsi}$	Wellcome Trust Sanger Institute	Null/KO	791
ADGRG6	*Adgrg6*^{tm1Apr}	Andreas P Russ/Takeda Pharmaceuticals	Null/KO; Exon 18 targeted	373
	Adgrg6^{tm1Taki}	Tetsu Akiyama	Null/KO; Exon 2 targeted	246
	Adgrg6^{tm1Smoc}	Shanghai Model Organisms Center	Targeted (Conditional ready); Exon 2 targeted	811
	Adgrg6^{em1Jlp}	Jose Luis de la Pompa	Intragenic deletion of Exons 3 and 4 producing an N-terminal fragment lacking the CUB and PTX domains	381
	Adgrg6^{em2Jlp}	Jose Luis de la Pompa	Null/KO; Exon 7 targeted	381
	Adgrg6$^{tm1a(EUCOMM)Hmgu}$	Helmholtz Zentrum Muenchen GmbH	Targeted (Conditional ready)	372
	Gpr126$^{-/-}$	Lexicon Pharmaceuticals	Conditional ready	236
ADGRG7	*Adgrg7*^{tm1Wfro}	Wei-Fang Rong	Null/KO; Exons 10-12 targeted	480
	Adgrg7$^{tm1b(EUCOMM)Hmgu}$	Helmholtz Zentrum Muenchen GmbH	Null/KO	791
ADGRL1	*Adgrl1*^{tm1Sud}	JAX 006393	Null/KO; Exons 1-2 targeted	812

	Adgrl1$^{tm2.1Sud}$	JAX 035181	Null/KO; Myc-tagged mouse *ADGRL1* with floxed exon 2 for Cre-mediated excision	120
	Adgrl1$^{tm2c(EUCOMM)Hmgu}$	JAX 035185	Targeted (Conditional ready)	120
	Adgrl1^{-}		Null/KO; Exons 1-3 targeted	294
ADGRL2	*Lphn2*^{tm1Dgen}	HAR/EMMA	Null/KO	1,635
	Adgrl2^{tm1Sud}	JAX 023401	Targeted (Conditional ready) Contains Frt sites and a part of loxP sites for Cre-mediated excision or expression of an alternative transcript fused to mVenus	292
ADGRL3	*Adgrl3*^{tm1Sud}	JAX 026684	Conditional; Exon 6 flanked by loxP sites for Cre-mediated excision	293
	Adgrl3$^{Gt(S17-5H1)Sor}$	Texas A&M Institute for Genomic Medicine	Null/KO	813
	Adgrl3$^{tm1(KOMP)Vlcg}$	Velocigene	Null/KO	115
	Adgrl3$^{tm1.1(KOMP)Vlcg}$	Velocigene	Null/KO	803
ADGRL4	*Adgrl4*^{tm1Dgen}	DeltaGen, European Mouse Mutant Archive, HAR	Null/KO	383
	Adgrl4^{tm1Lex}	Lexicon Pharmaceuticals	Null/KO; Exons 4-6 targeted	792
	Adgrl4$^{em1(IMPC)Mbp}$	IMPC UC Davis	Null/KO	791
ADGRV1	*Adgrv1*^{tm1Pwh}	Perrin C White, JAX 009379	Null/KO; Exon 82 targeted	639
	Adgrv1^{tm1Msat}	Makoto Sato	Null/KO; Exons 2-4 targeted	814
	Adgrv1^{tm2Msat}	Makoto Sato	Null/KO; Exons 2-4 targeted, insertion of YFP	815
	Adgrv1$^{tm1.1(KOMP)Vlcg}$	Velocigene	Null/KO	803
	Adgrv1^{m1}		Spontaneous Null/KO; deletions in Exon 31 causes frameshift and premature stop codon	816

Adgrv1^{frings}	Spontaneous intragenic deletion; single nucleotide deletion that results in a nonsense mutation in Exon 27	817,818

References

1. Hamann J, Aust G, Araç D, et al. International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G Protein–Coupled Receptors. *Pharmacol Rev*. 2015;67(2):338-367. doi:10.1124/pr.114.009647
2. Fredriksson R, Lagerström MC, Lundin LG, Schiöth HB. The G-Protein-Coupled Receptors in the Human Genome Form Five Main Families. Phylogenetic Analysis, Paralogon Groups, and Fingerprints. *Mol Pharmacol*. 2003;63(6):1256-1272. doi:10.1124/mol.63.6.1256
3. Harmar AJ. Family-B G-protein-coupled receptors. *Genome Biol*. 2001;2(12):reviews3013.1. doi:10.1186/gb-2001-2-12-reviews3013
4. Lagerström MC, Schiöth HB. Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat Rev Drug Discov*. 2008;7(4):339-357. doi:10.1038/nrd2518
5. Langenhan T, Aust G, Hamann J. Sticky Signaling—Adhesion Class G Protein–Coupled Receptors Take the Stage. *Sci Signal*. 2013;6(276):re3. doi:10.1126/scisignal.2003825
6. Liebscher I, Schöneberg T, Prömel S. Progress in demystification of adhesion G protein-coupled receptors. *bchm*. 2013;394(8):937-950. doi:10.1515/hsz-2013-0109
7. Knapp B, Roedig J, Roedig H, et al. Affinity Proteomics Identifies Interaction Partners and Defines Novel Insights into the Function of the Adhesion GPCR VLGR1/ADGRV1. *Molecules*. 2022;27(10):3108. doi:10.3390/molecules27103108
8. Araç D, Boucard AA, Bolliger MF, et al. A novel evolutionarily conserved domain of cell-adhesion GPCRs mediates autoproteolysis. *EMBO J*. 2012;31(6):1364-1378. doi:10.1038/emboj.2012.26
9. Seufert F, Pérez-Hernández G, Pándy-Szekeres G, et al. *Gene*ric residue numbering of the GAIN domain of adhesion GPCRs. *Nat Commun*. 2025;16(1):246. doi:10.1038/s41467-024-55466-6
10. Kleinau G, Ali AH, Wiechert F, et al. Intramolecular activity regulation of adhesion GPCRs in light of recent structural and evolutionary information. *Pharmacol Res*. 2023;197:106971. doi:10.1016/j.phrs.2023.106971
11. Lin HH, Chang GW, Davies JQ, Stacey M, Harris J, Gordon S. Autocatalytic Cleavage of the EMR2 Receptor Occurs at a Conserved G Protein-coupled Receptor Proteolytic Site Motif*. *J Biol Chem*. 2004;279(30):31823-31832. doi:10.1074/jbc.m402974200
12. Gray JX, Haino M, Roth MJ, et al. CD97 is a processed, seven-transmembrane, heterodimeric receptor associated with inflammation. *J Immunol (Baltim, Md : 1950)*. 1996;157(12):5438-5447.
13. Krasnoperov VG, Bittner MA, Beavis R, et al. α-Latrotoxin Stimulates Exocytosis by the Interaction with a *Neurona*l G-Protein-Coupled Receptor. Neuron. 1997;18(6):925-937. doi:10.1016/s0896-6273(00)80332-3
14. Beliu G, Altrichter S, Guixà-González R, et al. Tethered agonist exposure in intact adhesion/class B2 GPCRs through intrinsic structural flexibility of the GAIN domain. *Mol Cell*. 2021;81(5):905-921.e5. doi:10.1016/j.molcel.2020.12.042

15. Ferré S, Casadó V, Devi LA, et al. G Protein–Coupled Receptor Oligomerization Revisited: Functional and Pharmacological Perspectives. Pharmacol Rev. 2014;66(2):413-434. doi:10.1124/pr.113.008052
16. Liebscher I, Schön J, Petersen SC, et al. A Tethered Agonist within the Ectodomain Activates the Adhesion G Protein-Coupled Receptors GPR126 and GPR133. *Cell Rep*. 2014;9(6):2018-2026. doi:10.1016/j.celrep.2014.11.036
17. Stoveken HM, Hajduczok AG, Xu L, Tall GG. Adhesion G protein-coupled receptors are activated by exposure of a cryptic tethered agonist. *Proc Natl Acad Sci*. 2015;112(19):6194-6199. doi:10.1073/pnas.1421785112
18. Stacey M, Lin HH, Gordon S, et al. LNB-TM7, a group of seven-transmembrane proteins related to family-B G-protein-coupled receptors. *Trends Biochem Sci*. 2000;25(6):284-289. doi:10.1016/s0968-0004(00)01583-8
19. Chang GW, Stacey M, Kwakkenbos MJ, Hamann J, Gordon S, Lin HH. Proteolytic cleavage of the EMR2 receptor requires both the extracellular stalk and the GPS motif. *Febs Lett*. 2003;547(1-3):145-150. doi:10.1016/s0014-5793(03)00695-1
20. Seufert F, Chung YK, Hildebrand PW, Langenhan T. 7TM domain structures of adhesion GPCRs: what's new and what's missing? Trends Biochem Sci. 2023;48(8):726-739. doi:10.1016/j.tibs.2023.05.007
21. Kuhn CK, Stenzel U, Berndt S, Liebscher I, Schöneberg T, Horn S. The repertoire and structure of adhesion GPCR transcript variants assembled from publicly available deep-sequenced human samples. *Nucleic Acids Res*. 2024;52(7):3823-3836. doi:10.1093/nar/gkae145
22. Ballesteros JA, Weinstein H. [19] Integrated methods for the construction of three-dimensional models and computational probing of structure-function relations in G protein-coupled receptors. In: Sealfon SC, ed. Vol 25. Methods in *Neuroscience*s. Elsevier; 1995:366-428. doi:10.1016/s1043-9471(05)80049-7
23. Wootten D, Simms J, Miller LJ, Christopoulos A, Sexton PM. Polar transmembrane interactions drive formation of ligand-specific and signal pathway-biased family B G protein-coupled receptor conformations. Proc Natl Acad Sci. 2013;110(13):5211-5216. doi:10.1073/pnas.1221585110
24. Nijmeijer S, Wolf S, Ernst OP, Graaf C de. Adhesion G Protein-coupled Receptors, Molecular, Physiological and Pharmacological Principles in Health and Disease. *Handb Exp Pharmacol*. 2016;234:43-66. doi:10.1007/978-3-319-41523-9_3
25. Isberg V, Graaf C de, Bortolato A, et al. Generic GPCR residue numbers – aligning topology maps while minding the gaps. *Trends Pharmacol Sci*. 2015;36(1):22-31. doi:10.1016/j.tips.2014.11.001
26. Isberg V, Vroling B, Kant R van der, Li K, Vriend G, Gloriam D. GPCRDB: an information system for G protein-coupled receptors. Nucleic Acids Res. 2014;42(D1):D422-D425. doi:10.1093/nar/gkt1255
27. Pándy-Szekeres G, Caroli J, Mamyrbekov A, et al. GPCRdb in 2023: state-specific structure models using AlphaFold2 and new ligand resources. Nucleic Acids Res. 2022;51(D1):D395-D402. doi:10.1093/nar/gkac1013
28. Nordström KJV, Lagerström MC, Wallér LMJ, Fredriksson R, Schiöth HB. The Secretin GPCRs Descended from the Family of Adhesion GPCRs. *Mol Biol Evol*. 2009;26(1):71-84.

doi:10.1093/molbev/msn228
29. Krishnan A, Dnyansagar R, Almén MS, et al. The GPCR repertoire in the demosponge Amphimedon queenslandica: insights into the GPCR system at the early divergence of animals. *BMC Evol Biol*. 2014;14(1):270. doi:10.1186/s12862-014-0270-4
30. Scholz N, Langenhan T, Schöneberg T. Revisiting the classification of adhesion GPCRs. *Ann N York Acad Sci*. 2019;1456(1):80-95. doi:10.1111/nyas.14192
31. Wittlake A, Prömel S, Schöneberg T. The Evolutionary History of Vertebrate Adhesion GPCRs and Its Implication on Their Classification. *Int J Mol Sci*. 2021;22(21):11803. doi:10.3390/ijms222111803
32. Krasnoperov V, Lu Y, Buryanovsky L, Neubert TA, Ichtchenko K, Petrenko AG. Post-translational Proteolytic Processing of the Calcium-independent Receptor of α-Latrotoxin (CIRL), a Natural Chimera of the Cell Adhesion Protein and the G Protein-coupled Receptor ROLE OF THE G PROTEIN-COUPLED RECEPTOR PROTEOLYSIS SITE (GPS) MOTIF*. J Biol Chem. 2002;277(48):46518-46526. doi:10.1074/jbc.m206415200
33. Salzman GS, Ackerman SD, Ding C, et al. Structural Basis for Regulation of GPR56/ADGRG1 by Its Alternatively Spliced Extracellular Domains. Neuron. 2016;91(6):1292-1304. doi:10.1016/j.neuron.2016.08.022
34. Chu TY, Zheng-Gérard C, Huang KY, et al. GPR97 triggers inflammatory processes in human neutrophils via a macromolecular complex upstream of PAR2 activation. Nat Commun. 2022;13(1):6385. doi:10.1038/s41467-022-34083-1
35. Mao C, Zhao RJ, Dong YJ, et al. Conformational transitions and activation of the adhesion receptor CD97. Mol Cell. 2024;84(3):570-583.e7. doi:10.1016/j.molcel.2023.12.020
36. Wang F, Wang Y, Qiu W, Zhang Q, Yang H, Song G. Crystal *Structure* of the Extracellular Domains of GPR110. *J Mol Biol*. 2023;435(6):167979. doi:10.1016/j.jmb.2023.167979
37. Kordon SP, Cechova K, Bandekar SJ, et al. Conformational coupling between extracellular and transmembrane domains modulates holo-adhesion GPCR function. Nat Commun. 2024;15(1):10545. doi:10.1038/s41467-024-54836-4
38. Leon K, Cunningham RL, Riback JA, et al. Structural basis for adhesion G protein-coupled receptor Gpr126 function. Nat Commun. 2020;11(1):194. doi:10.1038/s41467-019-14040-1
39. Pohl F, Seufert F, Chung YK, et al. Structural basis of GAIN domain autoproteolysis and cleavage-resistance in the adhesion G-protein coupled receptors. *bioRxiv*. Published online 2023:2023.03.12.532270. doi:10.1101/2023.03.12.532270
40. Davletov BA, Shamotienko OG, Lelianova VG, Grishin EV, Ushkaryov YA. Isolation and Biochemical Characterization of a Ca2+-independent α-Latrotoxin-binding Protein*. J Biol Chem. 1996;271(38):23239-23245. doi:10.1074/jbc.271.38.23239
41. Krasnoperov VG, Beavis R, Chepurny OG, Little AR, Plotnikov AN, Petrenko AG. The Calcium-Independent Receptor of α-Latrotoxin Is Not a Neurexin. *Biochem Biophys Res Commun*. 1996;227(3):868-875. doi:10.1006/bbrc.1996.1598
42. Lelianova VG, Davletov BA, Sterling A, et al. α-Latrotoxin Receptor, Latrophilin, Is a Novel Member of the Secretin Family of G Protein-coupled Receptors*. J Biol Chem. 1997;272(34):21504-21508. doi:10.1074/jbc.272.34.21504

43. O'Sullivan ML, de Wit J, Savas JN, et al. FLRT Proteins Are Endogenous Latrophilin Ligands and Regulate Excitatory Synapse *Development*. Neuron. 2012;73(5):903-910. doi:10.1016/j.neuron.2012.01.018
44. Silva JP, Lelianova VG, Ermolyuk YS, et al. Latrophilin 1 and its endogenous ligand Lasso/teneurin-2 form a high-affinity transsynaptic receptor pair with signaling capabilities. Proc Natl Acad Sci. 2011;108(29):12113-12118. doi:10.1073/pnas.1019434108
45. Jackson VA, del Toro D, Carrasquero M, et al. Structural Basis of Latrophilin-FLRT Interaction. Structure. 2015;23(4):774-781. doi:10.1016/j.str.2015.01.013
46. Ranaivoson FM, Liu Q, Martini F, et al. Structural and Mechanistic Insights into the Latrophilin3-FLRT3 Complex that Mediates Glutamatergic Synapse Development. Structure. 2015;23(9):1665-1677. doi:10.1016/j.str.2015.06.022
47. Lu YC, Nazarko OV, Sando R, et al. Structural Basis of Latrophilin-FLRT-UNC5 Interaction in Cell Adhesion. Structure. 2015;23(9):1678-1691. doi:10.1016/j.str.2015.06.024
48. Jackson VA, Mehmood S, Chavent M, et al. Super-complexes of adhesion GPCRs and neural guidance receptors. Nat Commun. 2016;7(1):11184. doi:10.1038/ncomms11184
49. Toro D del, Carrasquero-Ordaz MA, Chu A, et al. Structural Basis of Teneurin-Latrophilin Interaction in Repulsive Guidance of Migrating Neurons. Cell. 2019;180(2):323-339.e19. doi:10.1016/j.cell.2019.12.014
50. Li J, Xie Y, Cornelius S, et al. Alternative splicing controls teneurin-latrophilin interaction and synapse specificity by a shape-shifting mechanism. Nat Commun. 2020;11(1):2140. doi:10.1038/s41467-020-16029-7
51. Chong ZS, Ohnishi S, Yusa K, Wright GJ. Pooled extracellular receptor-ligand interaction screening using CRISPR activation. Genome Biol. 2018;19(1):205. doi:10.1186/s13059-018-1581-3
52. Wang J, Miao Y, Wicklein R, et al. RTN4/NoGo-receptor binding to BAI adhesion-GPCRs regulates neuronal development. Cell. 2021;184(24):5869-5885.e25. doi:10.1016/j.cell.2021.10.016
53. Sticco MJ, Palomino PAP, Lukacsovich D, et al. C1QL3 promotes cell-cell adhesion by mediating complex formation between ADGRB3/BAI3 and neuronal pentraxins. *FASEB J*. 2021;35(1):e21194. doi:10.1096/fj.202000351rr
54. Wei Z, Liao L, Han Y, et al. Structural basis of calcium-dependent C1ql/BAI assemblies in synaptic connectivity. Published online 2025. doi:10.21203/rs.3.rs-6014540/v1
55. Miao Y, Wang H, Jude KM, et al. Structure of the complex of C1q-like 3 protein with adhesion-GPCR BAI3. *Commun Biol*. 2025;8(1):693. doi:10.1038/s42003-025-08112-w
56. Bolliger MF, Martinelli DC, Südhof TC. The cell-adhesion G protein-coupled receptor BAI3 is a high-affinity receptor for C1q-like proteins. Proc Natl Acad Sci. 2011;108(6):2534-2539. doi:10.1073/pnas.1019577108
57. Ressl S, Vu BK, Vivona S, Martinelli DC, Südhof TC, Brunger AT. Structures of C1q-like Proteins Reveal Unique Features among the C1q/TNF Superfamily. Structure. 2015;23(4):688-699. doi:10.1016/j.str.2015.01.019
58. Martinelli DC, Chew KS, Rohlmann A, et al. Expression of C1ql3 in Discrete Neuronal Populations Controls Efferent Synapse Numbers and Diverse Behaviors. Neuron. 2016;91(5):1034-1051. doi:10.1016/j.neuron.2016.07.002
59. Elegheert J, Kakegawa W, Clay JE, et al. Structural basis for integration of GluD

receptors within synaptic organizer complexes. *Science*. 2016;353(6296):295-299. doi:10.1126/science.aae0104
60. Niu M, Xu S, Yang J, et al. Structural basis for CD97 recognition of the decay-accelerating factor CD55 suggests mechanosensitive activation of adhesion GPCRs. J Biol Chem. 2021;296:100776. doi:10.1016/j.jbc.2021.100776
61. Abbott RJM, Spendlove I, Roversi P, et al. Structural and Functional Characterization of a Novel T Cell Receptor Co-regulatory Protein Complex, CD97-CD55.
62. Kieslich B, Weiße RH, Brendler J, Ricken A, Schöneberg T, Sträter N. The dimerized pentraxin-like domain of the adhesion G protein–coupled receptor 112 (ADGRG4) suggests function in sensing mechanical forces. J Biol Chem. 2023;299(12):105356. doi:10.1016/j.jbc.2023.105356
63. Bandekar SJ, Garbett K, Kordon SP, et al. Structural basis for regulation of CELSR1 by a compact module in its extracellular region. Nat Commun. 2025;16(1):3972. doi:10.1038/s41467-025-59319-8
64. Dintzner E, Bandekar SJ, Leon K, Cechova K, Vafabakhsh R, Araç D. The far extracellular CUB domain of the adhesion GPCR ADGRG6/GPR126 is a key regulator of receptor signaling. bioRxiv. Published online 2024:2024.02.16.580607. doi:10.1101/2024.02.16.580607
65. Barros-Álvarez X, Nwokonko RM, Vizurraga A, et al. The tethered peptide activation mechanism of adhesion GPCRs. *Nature*. 2022;604(7907):757-762. doi:10.1038/s41586-022-04575-7
66. Ping YQ, Xiao P, Yang F, et al. Structural basis for the tethered peptide activation of adhesion GPCRs. Nature. 2022;604(7907):763-770. doi:10.1038/s41586-022-04619-y
67. Qu X, Qiu N, Wang M, et al. Structural basis of tethered agonism of the adhesion GPCRs ADGRD1 and ADGRF1. Nature. 2022;604(7907):779-785. doi:10.1038/s41586-022-04580-w
68. Xiao P, Guo S, Wen X, et al. Tethered peptide activation mechanism of the adhesion GPCRs ADGRG2 and ADGRG4. Nature. 2022;604(7907):771-778. doi:10.1038/s41586-022-04590-8
69. Gupta C, Bernadyn TF, Tall GG. Structural clarity is brought to adhesion G protein-coupled receptor tethered agonism. *Basic Clin Pharmacol Toxicol*. 2023;133(4):295-300. doi:10.1111/bcpt.13831
70. Ping YQ, Mao C, Xiao P, et al. Structures of the glucocorticoid-bound adhesion receptor GPR97–Go complex. Nature. 2021;589(7843):620-626. doi:10.1038/s41586-020-03083-w
71. Lin H, Xiao P, Bu RQ, et al. Structures of the ADGRG2–Gs complex in apo and ligand-bound forms. *Nat Chem Biol*. 2022;18(11):1196-1203. doi:10.1038/s41589-022-01084-6
72. Demberg LM, Rothemund S, Schöneberg T, Liebscher I. Identification of the tethered peptide agonist of the adhesion G protein-coupled receptor GPR64/ADGRG2. Biochem Biophys Res Commun. 2015;464(3):743-747. doi:10.1016/j.bbrc.2015.07.020
73. Tesmer JJG. A GAIN in understanding autoproteolytic G protein-coupled receptors and polycystic kidney disease proteins. EMBO J. 2012;31(6):1334-1335. doi:10.1038/emboj.2012.51
74. Nieberler M, Kittel RJ, Petrenko AG, Lin HH, Langenhan T. Adhesion G Protein-coupled Receptors, Molecular, Physiological and Pharmacological Principles in Health and Disease.

Handb Exp Pharmacol. 2016;234:83-109. doi:10.1007/978-3-319-41523-9_5
75. VanHook AM. GAINing Autoproteolytic Activity. Sci Signal. 2012;5(217):ec93-ec93. doi:10.1126/scisignal.2003072
76. Yona S, Lin HH, Siu WO, Gordon S, Stacey M. Adhesion-GPCRs: emerging roles for novel receptors. *Trends in biochemical sciences*. 2008;33(10):491-500. doi:10.1016/j.tibs.2008.07.005
77. Lin HH, Stacey M, Yona S, Chang GW. Adhesion-GPCRs, Structure to Function. *Adv Exp Med Biol*. 2010;706:49-58. doi:10.1007/978-1-4419-7913-1_4
78. Wei W, Hackmann K, Xu H, Germino G, Qian F. Characterization of cis-Autoproteolysis of Polycystin-1, the Product of Human Polycystic Kidney Disease 1 Gene*. J Biol Chem. 2007;282(30):21729-21737. doi:10.1074/jbc.m703218200
79. Abe J, Fukuzawa T, Hirose S. Cleavage of Ig-Hepta at a "SEA" Module and at a Conserved G Protein-coupled Receptor Proteolytic Site*. J Biol Chem. 2002;277(26):23391-23398. doi:10.1074/jbc.m110877200
80. Chung YK, Ihling CH, Zielke L, Mathiasen S, Sinz A, Langenhan T. Self-cleavage of the GAIN domain of adhesion G protein-coupled receptors requires multiple domain-extrinsic factors. Nat Commun. 2025;16(1):8736. doi:10.1038/s41467-025-64589-3
81. Hsiao CC, Cheng KF, Chen HY, et al. Site-specific N-glycosylation regulates the GPS auto-proteolysis of CD97. *FEBS Lett*. 2009;583(19):3285-3290. doi:10.1016/j.febslet.2009.09.001
82. Jayachandran A, Annadurai P, Upadhyay M, et al. Domain-specific N-glycosylation of the adhesion G-protein–coupled receptor ADGRG6 N-terminal fragment regulates trafficking, proteolytic processing, and signaling. *Mol Biol Cell*. 2025;36(8):ar101. doi:10.1091/mbc.e25-02-0060
83. Seufert F, Chung YK, Schick R, et al. Mechanistic insights into adhesion GPCR autoproteolysis by a multiscale computational approach. *Research Square*. Published online 2025. doi:10.21203/rs.3.rs-7121662/v1
84. Perry-Hauser NA, Rand JRD, Lee KH, Shi L, Javitch JA. N-terminal fragment shedding contributes to signaling of the full-length adhesion receptor ADGRL3. J Biol Chem. 2025;301(2):108174. doi:10.1016/j.jbc.2025.108174
85. Cork SM, Kaur B, Devi NS, et al. A proprotein convertase/MMP-14 proteolytic cascade releases a novel 40 kDa vasculostatin from tumor suppressor BAI1. *Oncogene*. 2012;31(50):5144-5152. doi:10.1038/onc.2012.1
86. Lehmann L, Groß VE, Behlendorf R, Prömel S. The N terminus-only function of adhesion GPCRs: emerging concepts. Trends Pharmacol Sci. 2025;46(3):231-248. doi:10.1016/j.tips.2025.01.004
87. Vallon M, Aubele P, Janssen KP, Essler M. Thrombin-induced shedding of tumour endothelial marker 5 and exposure of its RGD motif are regulated by cell-surface protein disulfide-isomerase. *Biochem J*. 2012;441(3):937-944. doi:10.1042/bj20111682
88. Kaur B, Brat DJ, Devi NS, Van Meir EG. Vasculostatin, a proteolytic fragment of *Brain Angiogenesis* Inhibitor 1, is an antiangiogenic and antitumorigenic factor. Oncogene. 2005;24(22):3632-3642. doi:10.1038/sj.onc.1208317
89. Prömel S, Langenhan T, Araç D. Matching structure with function: the GAIN domain of Adhesion-GPCR and PKD1-like proteins. Trends Pharmacol Sci. 2013;34(8):470-478.

doi:10.1016/j.tips.2013.06.002
90. Dannhäuser S, Lux TJ, Hu C, et al. Antinociceptive modulation by the adhesion GPCR CIRL promotes mechanosensory signal discrimination. *eLife*. 2020;9:e56738. doi:10.7554/elife.56738
91. Liu D, Duan L, Rodda LB, et al. CD97 promotes spleen dendritic cell homeostasis through the mechanosensing of red blood cells. Science. 2022;375(6581):eabi5965. doi:10.1126/science.abi5965
92. Scholz N, Guan C, Nieberler M, et al. Mechano-dependent signaling by Latrophilin/CIRL quenches cAMP in proprioceptive neurons. eLife. 2017;6:e28360. doi:10.7554/elife.28360
93. Scholz N, Dahse AK, Kemkemer M, et al. Molecular sensing of mechano- and ligand-dependent adhesion GPCR dissociation. Nature. 2023;615(7954):945-953. doi:10.1038/s41586-023-05802-5
94. Boyden SE, Desai A, Cruse G, et al. Vibratory Urticaria Associated with a Missense Variant in ADGRE2. *N Engl J Med*. 2016;374(7):656-663. doi:10.1056/nejmoa1500611
95. Yu S, Hackmann K, Gao J, et al. Essential role of cleavage of Polycystin-1 at G protein-coupled receptor proteolytic site for kidney tubular structure. *Proc National Acad Sci*. 2007;104(47):18688-18693. doi:10.1073/pnas.0708217104
96. Kurbegovic A, Kim H, Xu H, et al. Novel Functional Complexity of Polycystin-1 by GPS Cleavage In Vivo: Role in Polycystic Kidney Disease. *Mol Cell Biol*. 2014;34(17):3341-3353. doi:10.1128/mcb.00687-14
97. Mengerink KJ, Moy GW, Vacquier VD. suREJ3, a Polycystin-1 Protein, Is Cleaved at the GPS Domain and Localizes to the Acrosomal Region of Sea Urchin Sperm*. J Biol Chem. 2002;277(2):943-948. doi:10.1074/jbc.m109673200
98. Folts CJ, Giera S, Li T, Piao X. Adhesion G Protein-Coupled Receptors as Drug Targets for Neurological Diseases. Trends Pharmacol Sci. 2019;40(4):278-293. doi:10.1016/j.tips.2019.02.003
99. Chiang NY, Hsiao CC, Huang YS, et al. Disease-associated GPR56 Mutations Cause Bilateral Frontoparietal Polymicrogyria via Multiple Mechanisms*. J Biol Chem. 2011;286(16):14215-14225. doi:10.1074/jbc.m110.183830
100. Jin Z, Tietjen I, Bu L, et al. Disease-associated mutations affect GPR56 protein trafficking and cell surface expression. *Hum Mol Genet*. 2007;16(16):1972-1985. doi:10.1093/hmg/ddm144
101. Trudel M, Yao Q, Qian F. The Role of G-Protein-Coupled Receptor Proteolysis Site Cleavage of Polycystin-1 in Renal Physiology and Polycystic Kidney Disease. *Cells*. 2016;5(1):3. doi:10.3390/cells5010003
102. Hamann J, Stortelers C, Kiss-Toth E, Vogel B, Eichler W, Lier RAW van. Characterization of the CD55 (DAF)-binding site on the seven-span transmembrane receptor CD97. *Eur J Immunol*. 1998;28(5):1701-1707. doi:10.1002/(sici)1521-4141(199805)28:05<1701::aid-immu1701>3.0.co;2-2
103. Lin HH, Stacey M, Saxby C, et al. Molecular Analysis of the Epidermal Growth Factor-like Short Consensus Repeat Domain-mediated Protein-Protein Interactions DISSECTION OF THE CD97-CD55 COMPLEX*. J Biol Chem. 2001;276(26):24160-24169. doi:10.1074/jbc.m101770200
104. Knierim AB, Röthe J, Çakir MV, et al. Genetic basis of functional variability in

adhesion G protein-coupled receptors. *Sci Rep*. 2019;9(1):11036. doi:10.1038/s41598-019-46265-x
105. Parag RR, Yamamoto T, Saito K, Zhu D, Yang L, Van Meir EG. Novel Isoforms of Adhesion G Protein-Coupled Receptor B1 (ADGRB1/BAI1) Generated from an Alternative Promoter in Intron 17. *Mol Neurobiol*. 2025;62(1):900-917. doi:10.1007/s12035-024-04293-3
106. Wang S, DeLeon C, Sun W, Quake SR, Roth BL, Südhof TC. Alternative splicing of latrophilin-3 controls synapse formation. Nature. 2024;626(7997):128-135. doi:10.1038/s41586-023-06913-9
107. Sando R, Jiang X, Südhof TC. Latrophilin GPCRs direct synapse specificity by coincident binding of FLRTs and teneurins. Science. 2019;363(6429):eaav7969. doi:10.1126/science.aav7969
108. Bormann A, Körner MB, Dahse AK, et al. Intron retention of an adhesion GPCR generates 1TM isoforms required for 7TM-GPCR function. Cell Rep. 2025;44(1):115078. doi:10.1016/j.celrep.2024.115078
109. Garbett K, Zheng C, Drube J, Hoffmann C, Gurevich VV, Sando RC. Cytoplasmic tail composition modulates the G protein and arrestin-3 signaling bias of the adhesion GPCR LPHN2. bioRxiv. Published online 2025:2025.07.04.663222. doi:10.1101/2025.07.04.663222
110. Ovando-Zambrano J, Arias-Montaño J, Boucard AA. Alternative splicing event modifying ADGRL1/latrophilin-1 cytoplasmic tail promotes both opposing and dual cAMP signaling pathways. Ann N York Acad Sci. 2019;1456(1):168-185. doi:10.1111/nyas.14198
111. Boucard AA, Maxeiner S, Südhof TC. Latrophilins Function as
doi:10.1016/j.celrep.2019.01.040
113. Wilde C, Fischer L, Lede V, et al. The constitutive activity of the adhesion GPCR GPR114/ADGRG5 is mediated by its tethered agonist. FASEB J. 2016;30(2):666-673. doi:10.1096/fj.15-276220
114. Hamann J, Eichler W, Hamann D, et al. Expression cloning and chromosomHeterophilic Cell-adhesion Molecules by Binding to Teneurins REGULATION BY ALTERNATIVE SPLICING*. J Biol Chem. 2014;289(1):387-402. doi:10.1074/jbc.m113.504779
112. Röthe J, Thor D, Winkler J, et al. Involvement of the Adhesion GPCRs Latrophilins in the Regulation of Insulin Release. Cell Rep. 2019;26(6):1573-1584.e5. al mapping of the leukocyte activation antigen CD97, a new seven-span transmembrane molecule of the secretion receptor superfamily with an unusual extracellular domain. J Immunol (Baltim, Md : 1950). 1995;155(4):1942-1950.
115. Wang Y, Cao Y, Hays CL, et al. Adhesion GPCR Latrophilin 3 regulates synaptic function of cone photoreceptors in a trans-synaptic manner. Proc Natl Acad Sci. 2021;118(45):e2106694118. doi:10.1073/pnas.2106694118
116. Matúš D, Post WB, Groß VE, et al. The N terminus-only (trans) function of the adhesion G protein-coupled receptor latrophilin-1 controls multiple processes in reproduction of Caenorhabditis elegans. *G3: Genes, Genomes, Genet*. 2024;14(11):jkae206. doi:10.1093/g3journal/jkae206
117. Li T, Luo R, Schmidt R, et al. GPR56 S4 variant is required for microglia-mediated synaptic pruning. *Glia*. 2023;71(3):560-570. doi:10.1002/glia.24293

118. Robinson A, Escuin S, Doudney K, et al. Mutations in the planar cell polarity genes CELSR1 and SCRIB are associated with the severe neural tube defect craniorachischisis. *Hum Mutat*. 2012;33(2):440-447. doi:10.1002/humu.21662
119. Duman JG, Tzeng CP, Tu YK, et al. The Adhesion-GPCR BAI1 Regulates Synaptogenesis by Controlling the Recruitment of the Par3/Tiam1 Polarity Complex to Synaptic Sites. *J Neurosci*. 2013;33(16):6964-6978. doi:10.1523/jneurosci.3978-12.2013
120. Matúš D, Lopez JM, Sando RC, Südhof TC. Essential Role of Latrophilin-1 Adhesion GPCR Nanoclusters in Inhibitory Synapses. J Neurosci. 2024;44(23):e1978232024. doi:10.1523/jneurosci.1978-23.2024
121. Li T, Chiou B, Gilman CK, et al. A splicing isoform of GPR56 mediates microglial synaptic refinement via phosphatidylserine binding. EMBO J. 2020;39(16):EMBJ2019104136. doi:10.15252/embj.2019104136
122. Volynski KE, Silva J, Lelianova VG, Rahman MA, Hopkins C, Ushkaryov YA. Latrophilin fragments behave as independent proteins that associate and signal on binding of LTXN4C. EMBO J. 2004;23(22):4423-4433. doi:10.1038/sj.emboj.7600443
123. Malaker SA, Riley NM, Shon DJ, et al. Revealing the human mucinome. Nat Commun. 2022;13(1):3542. doi:10.1038/s41467-022-31062-4
124. Frenster JD, Stephan G, Ravn-Boess N, et al. Functional impact of intramolecular cleavage and dissociation of adhesion G protein–coupled receptor GPR133 (ADGRD1) on canonical signaling. J Biol Chem. 2021;296:100798. doi:10.1016/j.jbc.2021.100798
125. Huang YS, Chiang NY, Chang GW, Lin HH. Membrane-association of EMR2/ADGRE2-NTF is regulated by site-specific N-glycosylation. Sci Rep. 2018;8(1):4532. doi:10.1038/s41598-018-22849-x
126. Kishore A, Hall RA. Disease-associated extracellular loop mutations in the adhesion G protein-coupled receptor G1 (ADGRG1; GPR56) differentially regulate downstream signaling. J Biol Chem. 2017;292(23):9711-9720. doi:10.1074/jbc.m117.780551
127. Ke N, Ma H, Diedrich G, et al. Biochemical characterization of genetic mutations of GPR56 in patients with bilateral frontoparietal polymicrogyria (BFPP). *Biochemical and biophysical research communications*. 2008;366(2):314-320. doi:10.1016/j.bbrc.2007.11.071
128. Hsiao CC, Chen HY, Chang GW, Lin HH. GPS autoproteolysis is required for CD97 to up-regulate the expression of N-cadherin that promotes homotypic cell–cell aggregation. FEBS Lett. 2011;585(2):313-318. doi:10.1016/j.febslet.2010.12.005
129. Ojeda-Muñiz EY, Rodríguez-Hernández B, Correoso-Braña KG, Segura-Landa PL, Boucard AA. Biased signalling is structurally encoded as an autoproteolysis event in adhesion G protein-coupled receptor Latrophilin-3/ADGRL3. Basic Clin Pharmacol Toxicol. 2023;133(4):342-352. doi:10.1111/bcpt.13927
130. Boucard AA, Ko J, Südhof TC. High Affinity Neurexin Binding to Cell Adhesion G-protein-coupled Receptor CIRL1/Latrophilin-1 Produces an Intercellular Adhesion Complex*. J Biol Chem. 2012;287(12):9399-9413. doi:10.1074/jbc.m111.318659
131. Singh J, Elhabashy H, Muthukottiappan P, et al. Cross-linking of the endolysosomal system reveals potential flotillin structures and cargo. Nat Commun. 2022;13(1):6212. doi:10.1038/s41467-022-33951-0
132. Azimzadeh P, Talamantez-Lyburn SC, Chang KT, Inoue A, Balenga N. Spatial regulation of GPR64/ADGRG2 signaling by β-arrestins and GPCR kinases. Ann N York

Acad Sci. 2019;1456(1):26-43. doi:10.1111/nyas.14227
133. Spiess K, Bagger SO, Torz LJ, et al. Arrestin-independent constitutive endocytosis of GPR125/ADGRA3. Ann N York Acad Sci. 2019;1456(1):186-199. doi:10.1111/nyas.14263
134. Maerker T, Wijk E van, Overlack N, et al. A novel Usher protein network at the periciliary reloading point between molecular transport machineries in vertebrate photoreceptor cells. Hum Mol Genet. 2008;17(1):71-86. doi:10.1093/hmg/ddm285
135. Linnert J, Knapp B, Güler BE, Boldt K, Ueffing M, Wolfrum U. Usher syndrome proteins ADGRV1 (USH2C) and CIB2 (USH1J) interact and share a common interactome containing TRiC/CCT-BBS chaperonins. *Front Cell Dev Biol*. 2023;11:1199069. doi:10.3389/fcell.2023.1199069
136. Linnert J, Kusuluri DK, Güler BE, Patnaik SR, May-Simera HL, Wolfrum U. The BBS/CCT chaperonin complex ensures the localization of the adhesion G protein-coupled receptor ADGRV1 to the base of primary cilia. Front Cell Dev Biol. 2025;13:1520723. doi:10.3389/fcell.2025.1520723
137. Kusuluri DK, Güler BE, Knapp B, et al. Adhesion G protein-coupled receptor VLGR1/ADGRV1 regulates cell spreading and migration by mechanosensing at focal adhesions. *iScience*. 2021;24(4):102283. doi:10.1016/j.isci.2021.102283
138. Güler BE, Linnert J, Wolfrum U. Monitoring paxillin in astrocytes reveals the significance of the adhesion G protein coupled receptor VLGR1/ADGRV1 for focal adhesion assembly. Basic Clin Pharmacol Toxicol. 2023;133(4):301-312. doi:10.1111/bcpt.13860
139. Krzysko J, Maciag F, Mertens A, et al. The Adhesion GPCR VLGR1/ADGRV1 Regulates the Ca2+ Homeostasis at Mitochondria-Associated ER Membranes. Cells. 2022;11(18):2790. doi:10.3390/cells11182790
140. Linnert J, Güler BE, Krzysko J, Wolfrum U. The adhesion G protein-coupled receptor VLGR1/ADGRV1 controls autophagy. Basic Clin Pharmacol Toxicol. 2023;133(4):313-330. doi:10.1111/bcpt.13869
141. Krishnan A, Nijmeijer S, Graaf C de, Schiöth HB. Adhesion G Protein-coupled Receptors, Molecular, Physiological and Pharmacological Principles in Health and Disease. Handb Exp Pharmacol. 2016;234:15-41. doi:10.1007/978-3-319-41523-9_2
142. Bjarnadóttir TK, Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC, Schiöth HB. The human and mouse repertoire of the adhesion family of G-protein-coupled receptors. *Genomics*. 2004;84(1):23-33. doi:10.1016/j.ygeno.2003.12.004
143. Bjarnadóttir TK, Gloriam DE, Hellstrand SH, Kristiansson H, Fredriksson R, Schiöth HB. Comprehensive repertoire and phylogenetic analysis of the G protein-coupled receptors in human and mouse. Genomics. 2006;88(3):263-273. doi:10.1016/j.ygeno.2006.04.001
144. Haitina T, Olsson F, Stephansson O, et al. Expression profile of the entire family of Adhesion G protein-coupled receptors in mouse and rat. *BMC neuroscience*. 2008;9:43. doi:10.1186/1471-2202-9-43
145. Hamann J, Kwakkenbos MJ, Jong EC de, Heus H, Olsen AS, Lier RAW van. Inactivation of the EGF-TM7 receptor EMR4 after the Pan-Homo divergence. Eur J Immunol. 2003;33(5):1365-1371. doi:10.1002/eji.200323881
146. Winkler R, Quaas M, Glasmacher S, et al. The Adhesion G-Protein-Coupled Receptor GPR115/ADGRF4 Regulates Epidermal Differentiation and Associates with Cytoskeletal KRT1. Cells. 2022;11(19):3151. doi:10.3390/cells11193151

147. Aust G, Wandel E, Boltze C, et al. Diversity of CD97 in smooth muscle cells. *Cell Tissue Res*. 2006;324(1):139-147. doi:10.1007/s00441-005-0103-2
148. Zyryanova T, Schneider R, Adams V, et al. Skeletal Muscle Expression of the Adhesion-GPCR CD97: CD97 Deletion Induces an Abnormal Structure of the Sarcoplasmatic Reticulum but Does Not Impair Skeletal Muscle Function. *PLoS ONE*. 2014;9(6):e100513. doi:10.1371/journal.pone.0100513
149. Chiesa MD, Falco M, Parolini S, et al. GPR56 as a novel marker identifying the CD56dull CD16+ NK cell subset both in blood stream and in inflamed peripheral tissues. *Int Immunol*. 2010;22(2):91-100. doi:10.1093/intimm/dxp116
150. Peng YM, Garde MDB van de, Cheng KF, et al. Specific expression of GPR56 by human cytotoxic lymphocytes. *J Leukoc Biol*. 2011;90(4):735-740. doi:10.1189/jlb.0211092
151. Kaiser F, Morawski M, Krohn K, et al. Adhesion GPCR GPR56 Expression Profiling in Human Tissues. Cells. 2021;10(12):3557. doi:10.3390/cells10123557
152. Lin HH, Hsiao CC, Pabst C, Hébert J, Schöneberg T, Hamann J. Chapter Five Adhesion GPCRs in Regulating Immune Responses and Inflammation. *Adv Immunol*. 2017;136:163-201. doi:10.1016/bs.ai.2017.05.005
153. Lehmann J, Lin H, Zhang Z, et al. The mechanosensitive adhesion G protein-coupled receptor 133 (GPR133/ADGRD1) enhances bone formation. *Signal Transduct Target Ther*. 2025;10(1):199. doi:10.1038/s41392-025-02291-y
154. Hsiao CC, Poel M van der, Ham TJ van, Hamann J. Macrophages Do Not Express the Phagocytic Receptor BAI1/ADGRB1. *Front Immunol*. 2019;10:962. doi:10.3389/fimmu.2019.00962
155. Kwakkenbos MJ, Pouwels W, Matmati M, et al. Expression of the largest CD97 and EMR2 isoforms on leukocytes facilitates a specific interaction with chondroitin sulfate on B cells. *Journal of leukocyte biology*. 2005;77(1):112-119. doi:10.1189/jlb.0704402
156. Wobus M, Vogel B, Schmücking E, Hamann J, Aust G. N-glycosylation of CD97 within the EGF domains is crucial for epitope accessibility in normal and malignant cells as well as CD55 ligand binding. *International journal of cancer Journal international du cancer*. 2004;112(5):815-822. doi:10.1002/ijc.20483
157. Hamann J, Vogel B, Schijndel GM van, Lier RA van. The seven-span transmembrane receptor CD97 has a cellular ligand (CD55, DAF). *J Exp Medicine*. 1996;184(3):1185-1189. doi:10.1084/jem.184.3.1185
158. Südhof TC. α-LATROTOXIN AND ITS RECEPTORS: Neurexins and CIRL/Latrophilins. Neuroscience. 2001;24(1):933-962. doi:10.1146/annurev.neuro.24.1.933
159. Basta LP, Sil P, Jones RA, Little KA, Hayward-Lara G, Devenport D. Celsr1 and Celsr2 exhibit distinct adhesive interactions and contributions to planar cell polarity. Front Cell Dev Biol. 2023;10:1064907. doi:10.3389/fcell.2022.1064907
160. Usui T, Shima Y, Shimada Y, et al. Flamingo, a Seven-Pass Transmembrane Cadherin, Regulates Planar Cell Polarity under the Control of Frizzled. Cell. 1999;98(5):585-595. doi:10.1016/s0092-8674(00)80046-x
161. McGee J, Goodyear RJ, McMillan DR, et al. The Very Large G-Protein-Coupled Receptor VLGR1: A Component of the Ankle Link Complex Required for the Normal Development of Auditory Hair Bundles. J Neurosci. 2006;26(24):6543-6553. doi:10.1523/jneurosci.0693-06.2006

162. Sun JP, Li R, Ren HZ, Xu AT, Yu X, Xu ZG. The Very Large G Protein Coupled Receptor (Vlgr1) in Hair Cells. *J Mol Neurosci*. 2013;50(1):204-214. doi:10.1007/s12031-012-9911-5
163. Kop EN, Kwakkenbos MJ, Teske GJD, et al. Identification of the epidermal growth factor–TM7 receptor EMR2 and its ligand dermatan sulfate in rheumatoid synovial tissue. *Arthritis Rheum*. 2005;52(2):442-450. doi:10.1002/art.20788
164. Knapp B, Roedig J, Boldt K, et al. Affinity proteomics identifies novel functional modules related to adhesion GPCRs. Ann N York Acad Sci. 2019;1456(1):144-167. doi:10.1111/nyas.14220
165. Luo R, Jeong SJ, Jin Z, Strokes N, Li S, Piao X. G protein-coupled receptor 56 and collagen III, a receptor-ligand pair, regulates cortical development and lamination. Proc Natl Acad Sci. 2011;108(31):12925-12930. doi:10.1073/pnas.1104821108
166. Xu L, Begum S, Hearn JD, Hynes RO. GPR56, an atypical G protein-coupled receptor, binds tissue transglutaminase, TG2, and inhibits melanoma tumor growth and metastasis. Proc Natl Acad Sci. 2006;103(24):9023-9028. doi:10.1073/pnas.0602681103
167. Zhu B, Luo R, Jin P, et al. GAIN domain–mediated cleavage is required for activation of G protein–coupled receptor 56 (GPR56) by its natural ligands and a small-molecule agonist. J Biol Chem. 2019;294(50):19246-19254. doi:10.1074/jbc.ra119.008234
168. Chen H, Nwe PK, Yang Y, et al. A Forward Chemical Genetic Screen Reveals Gut Microbiota *Metabolites* That Modulate Host Physiology. Cell. 2019;177(5):1217-1231.e18. doi:10.1016/j.cell.2019.03.036
169. Chiang NY, Chang GW, Huang YS, et al. Heparin interacts with the adhesion GPCR GPR56, reduces receptor shedding, and promotes cell adhesion and motility. *J Cell Sci*. 2016;129(11):2156-2169. doi:10.1242/jcs.174458
170. Little KD, Hemler ME, Stipp CS. Dynamic Regulation of a GPCR-Tetraspanin-G Protein Complex on Intact Cells: Central Role of CD81 in Facilitating GPR56-Gαq/11 Association. Mol Biol Cell. 2004;15(5):2375-2387. doi:10.1091/mbc.e03-12-0886
171. Diamantopoulou E, Baxendale S, León A de la V de, et al. Identification of compounds that rescue otic and myelination defects in the zebrafish adgrg6 (gpr126) mutant. eLife. 2019;8:e44889. doi:10.7554/elife.44889
172. Asad A, Shahidan NO, León A de la V de, Wiggin GR, Whitfield TT, Baxendale S. A screen of pharmacologically active compounds to identify modulators of the Adgrg6/Gpr126 signalling pathway in zebrafish embryos. Basic Clin Pharmacol Toxicol. 2023;133(4):364-377. doi:10.1111/bcpt.13923
173. Stoveken HM, Bahr LL, Anders MW, Wojtovich AP, Smrcka AV, Tall GG. Dihydromunduletone Is a Small-Molecule Selective Adhesion G Protein–Coupled Receptor Antagonist. Mol Pharmacol. 2016;90(3):214-224. doi:10.1124/mol.116.104828
174. Li J, Shalev-Benami M, Sando R, et al. Structural Basis for Teneurin Function in Circuit-Wiring: A Toxin Motif at the Synapse. Cell. 2018;173(3):735-748.e15. doi:10.1016/j.cell.2018.03.036
175. Zuko A, Oguro-Ando A, Post H, et al. Association of Cell Adhesion Molecules Contactin-6 and Latrophilin-1 Regulates Neuronal Apoptosis. *Front Mol Neurosci*. 2016;9:143. doi:10.3389/fnmol.2016.00143
176. Cruz-Ortega JS, Boucard AA. Actin cytoskeleton remodeling defines a distinct cellular

function for adhesion G protein-coupled receptors ADGRL/latrophilins 1, 2 and 3. *Biol Open*. 2019;8(4):bio039826. doi:10.1242/bio.039826
177. Lee JW, Huang BX, Kwon H, et al. Orphan GPR110 (ADGRF1) targeted by N-docosahexaenoylethanolamine in development of neurons and cognitive function. Nat Commun. 2016;7(1):13123. doi:10.1038/ncomms13123
178. Frenster JD, Erdjument-Bromage H, Stephan G, et al. PTK7 is a positive allosteric modulator of GPR133 signaling in glioblastoma. Cell Rep. 2023;42(7):112679. doi:10.1016/j.celrep.2023.112679
179. Vanhollebeke B, Stone OA, Bostaille N, et al. Tip cell-specific requirement for an atypical Gpr124- and Reck-dependent Wnt/β-catenin pathway during brain angiogenesis. eLife. 2015;4:e06489. doi:10.7554/elife.06489
180. Abdulkareem NM, Bhat R, Castillo M, et al. Interactions between ADGRF1 (GPR110) and extracellular matrix proteins govern its effects on tumorigenesis in HER2-positive breast cancer. *Br J Pharmacol*. 2025;182(11):2524-2541. doi:10.1111/bph.17463
181. Georgiadi A, Lopez-Salazar V, Merahbi RE, et al. Orphan GPR116 mediates the insulin sensitizing effects of the hepatokine FNDC4 in adipose tissue. Nat Commun. 2021;12(1):2999. doi:10.1038/s41467-021-22579-1
182. Fukuzawa T, Ishida J, Kato A, et al. Lung Surfactant Levels are Regulated by Ig-Hepta/GPR116 by Monitoring Surfactant Protein D. PLoS ONE. 2013;8(7):e69451. doi:10.1371/journal.pone.0069451
183. Yang MY, Hilton MB, Seaman S, et al. Essential Regulation of Lung Surfactant Homeostasis by the Orphan G Protein-Coupled Receptor GPR116. Cell Rep. 2013;3(5):1457-1464. doi:10.1016/j.celrep.2013.04.019
184. Bridges JP, Ludwig MG, Mueller M, et al. Orphan G Protein–Coupled Receptor GPR116 Regulates Pulmonary Surfactant Pool Size. *Am J Respir Cell Mol Biol*. 2013;49(3):130522202035005. doi:10.1165/rcmb.2012-0439oc
185. Knapp B, Wolfrum U. Adhesion G Protein-coupled Receptors, Molecular, Physiological and Pharmacological Principles in Health and Disease. Handb Exp Pharmacol. 2016;234(10):147-178. doi:10.1007/978-3-319-41523-9_8
186. Hilbig D, Sittig D, Hoffmann F, et al. Mechano-Dependent Phosphorylation of the PDZ-Binding Motif of CD97/ADGRE5 Modulates Cellular Detachment. Cell Rep. 2018;24(8):1986-1995. doi:10.1016/j.celrep.2018.07.071
187. Kreienkamp HJ, Zitzer H, Gundelfinger ED, Richter D, Böckers TM. The Calcium-independent Receptor for α-Latrotoxin from Human and Rodent Brains Interacts with Members of the ProSAP/SSTRIP/Shank Family of Multidomain Proteins*. J Biol Chem. 2000;275(42):32387-32390. doi:10.1074/jbc.c000490200
188. Südhof TC. Signaling by latrophilin adhesion-GPCRs in synapse assembly. Neuroscience. 2025;575:150-161. doi:10.1016/j.neuroscience.2025.03.041
189. Stephenson JR, Paavola KJ, Schaefer SA, Kaur B, Van Meir EG, Hall RA. Brain-specific Angiogenesis Inhibitor-1 Signaling, Regulation, and Enrichment in the Postsynaptic Density*. J Biol Chem. 2013;288(31):22248-22256. doi:10.1074/jbc.m113.489757
190. Reiners J, Wijk E van, Märker T, et al. Scaffold protein harmonin (USH1C) provides molecular links between Usher syndrome type 1 and type 2. Hum Mol Genet. 2005;14(24):3933-3943. doi:10.1093/hmg/ddi417

191. Wijk E van, Zwaag B van der, Peters T, et al. The DFNB31 gene product whirlin connects to the Usher protein network in the cochlea and retina by direct association with USH2A and VLGR1. Hum Mol Genet. 2006;15(5):751-765. doi:10.1093/hmg/ddi490
192. Sakurai T, Kamakura S, Hayase J, Kohda A, Nakamura M, Sumimoto H. GPR125 (ADGRA3) is an autocleavable adhesion GPCR that traffics with Dlg1 to the basolateral membrane and regulates epithelial apicobasal polarity. J Biol Chem. 2022;298(10):102475. doi:10.1016/j.jbc.2022.102475
193. Yamamoto Y, Irie K, Asada M, Mino A, Mandai K, Takai Y. Direct binding of the human homologue of the Drosophila disc large tumor suppressor gene to seven-pass transmembrane proteins, tumor endothelial marker 5 (TEM5), and a novel TEM5-like protein. Oncogene. 2004;23(22):3889-3897. doi:10.1038/sj.onc.1207495
194. Nishimura T, Honda H, Takeichi M. Planar Cell Polarity Links Axes of Spatial Dynamics in Neural-Tube Closure. Cell. 2012;149(5):1084-1097. doi:10.1016/j.cell.2012.04.021
195. Li X, Roszko I, Sepich DS, et al. Gpr125 modulates Dishevelled distribution and planar cell polarity signaling. Development. 2013;140(14):3028-3039. doi:10.1242/dev.094839
196. Eubelen M, Bostaille N, Cabochette P, et al. A molecular mechanism for Wnt ligand-specific signaling. Science. 2018;361(6403):eaat1178. doi:10.1126/science.aat1178
197. Hilbig D, Dietrich N, Wandel E, et al. The Interaction of CD97/ADGRE5 With β-Catenin in Adherens Junctions Is Lost During Colorectal Carcinogenesis. *Front Oncol*. 2018;8:182. doi:10.3389/fonc.2018.00182
198. Weng Z, Situ C, Lin L, Wu Z, Zhu J, Zhang R. Structure of BAI1/ELMO2 complex reveals an action mechanism of adhesion GPCRs via ELMO family scaffolds. Nat Commun. 2019;10(1):51. doi:10.1038/s41467-018-07938-9
199. Hernández-Vásquez MN, Adame-García SR, Hamoud N, et al. Cell adhesion controlled by adhesion G protein–coupled receptor GPR124/ADGRA2 is mediated by a protein complex comprising intersectins and Elmo–Dock. J Biol Chem. 2017;292(29):12178-12191. doi:10.1074/jbc.m117.780304
200. Park D, Tosello-Trampont AC, Elliott MR, et al. BAI1 is an engulfment receptor for apoptotic cells upstream of the ELMO/Dock180/Rac module. Nature. 2007;450(7168):430-434. doi:10.1038/nature06329
201. Hamoud N, Tran V, Croteau LP, Kania A, Côté JF. G-protein coupled receptor BAI3 promotes myoblast fusion in vertebrates. Proc Natl Acad Sci. 2014;111(10):3745-3750. doi:10.1073/pnas.1313886111
202. Lanoue V, Usardi A, Sigoillot SM, et al. The adhesion-GPCR BAI3, a gene linked to psychiatric disorders, regulates dendrite morphogenesis in neurons. *Mol Psychiatry*. 2013;18(8):943-950. doi:10.1038/mp.2013.46
203. Chang GW, Hsiao CC, Peng YM, et al. The Adhesion G Protein-Coupled Receptor GPR56/ADGRG1 Is an Inhibitory Receptor on Human NK Cells. Cell Rep. 2016;15(8):1757-1770. doi:10.1016/j.celrep.2016.04.053
204. Stephan G, Haddock S, Wang S, et al. Modulation of GPR133 (ADGRD1) signaling by its intracellular interaction partner extended synaptotagmin 1. Cell Rep. 2024;43(5):114229. doi:10.1016/j.celrep.2024.114229
205. Bridges JP, Safina C, Pirard B, et al. Regulation of pulmonary surfactant by the adhesion

GPCR GPR116/ADGRF5 requires a tethered agonist-mediated activation mechanism. eLife. 2022;11:e69061. doi:10.7554/elife.69061
206. Okajima D, Kudo G, Yokota H. Brain-specific angiogenesis inhibitor 2 (BAI2) may be activated by proteolytic processing. *J Recept Signal Transduct*. 2010;30(3):143-153. doi:10.3109/10799891003671139
207. Yang L, Chen G, Mohanty S, et al. GPR56 Regulates VEGF Production and Angiogenesis during Melanoma Progression. *Cancer Res*. 2011;71(16):5558-5568. doi:10.1158/0008-5472.can-10-4543
208. Paavola KJ, Stephenson JR, Ritter SL, Alter SP, Hall RA. The N Terminus of the Adhesion G Protein-coupled Receptor GPR56 Controls Receptor Signaling Activity*. J Biol Chem. 2011;286(33):28914-28921. doi:10.1074/jbc.m111.247973
209. Dates AN, Jones DTD, Smith JS, et al. Heterogeneity of tethered agonist signaling in adhesion G protein-coupled receptors. *Cell Chem Biol*. 2024;31(8):1542-1553.e4. doi:10.1016/j.chembiol.2024.03.004
210. Silva JP, Ushkaryov YA. Adhesion-GPCRs, Structure to Function. Adv Exp Med Biol. 2010;706:59-75. doi:10.1007/978-1-4419-7913-1_5
211. Yeung J, Adili R, Stringham EN, et al. GPR56/ADGRG1 is a platelet collagen-responsive GPCR and hemostatic sensor of shear force. Proc Natl Acad Sci. 2020;117(45):28275-28286. doi:10.1073/pnas.2008921117
212. Bernadyn TF, Vizurraga A, Adhikari R, Kwarcinski F, Tall GG. GPR114/ADGRG5 is activated by its tethered peptide agonist because it is a cleaved adhesion GPCR. J Biol Chem. 2023;299(10):105223. doi:10.1016/j.jbc.2023.105223
213. Liebscher I, Schön J, Petersen SC, et al. A Tethered Agonist within the Ectodomain Activates the Adhesion G Protein-Coupled Receptors GPR126 and GPR133. Cell Rep. 2015;10(6):1021. doi:10.1016/j.celrep.2015.01.065
214. Qian Y, Ma Z, Liu C, et al. Structural insights into adhesion GPCR ADGRL3 activation and Gq, Gs, Gi, and G12 coupling. Mol Cell. 2022;82(22):4340-4352.e6. doi:10.1016/j.molcel.2022.10.009
215. Mathiasen S, Palmisano T, Perry NA, et al. G12/13 is activated by acute tethered agonist exposure in the adhesion GPCR ADGRL3. Nat Chem Biol. 2020;16(12):1343-1350. doi:10.1038/s41589-020-0617-7
216. Stephan G, Frenster JD, Liebscher I, Placantonakis DG. Activation of the adhesion G protein–coupled receptor GPR133 by antibodies targeting its N-terminus. J Biol Chem. 2022;298(6):101949. doi:10.1016/j.jbc.2022.101949
217. Vizurraga A, Adhikari R, Yeung J, Yu M, Tall GG. Mechanisms of adhesion G protein–coupled receptor activation. J Biol Chem. 2020;295(41):14065-14083. doi:10.1074/jbc.rev120.007423
218. Lala T, Hall RA. Adhesion G protein-coupled receptors: structure, signaling, physiology, and pathophysiology. *Physiol Rev*. 2022;102(4):1587-1624. doi:10.1152/physrev.00027.2021
219. Prömel S, Frickenhaus M, Hughes S, et al. The GPS Motif Is a Molecular Switch for Bimodal Activities of Adhesion Class G Protein-Coupled Receptors. Cell Rep. 2012;2(2):321-331. doi:10.1016/j.celrep.2012.06.015
220. Müller A, Winkler J, Fiedler F, et al. Oriented Cell Division in the C. elegans Embryo Is

Coordinated by G-Protein Signaling Dependent on the Adhesion GPCR LAT-1. Chisholm AD, ed. *PLoS Genet*. 2015;11(10):e1005624. doi:10.1371/journal.pgen.1005624
221. Bohnekamp J, Schöneberg T. Cell Adhesion Receptor GPR133 Couples to Gs Protein*. J Biol Chem. 2011;286(49):41912-41916. doi:10.1074/jbc.c111.265934
222. Kishore A, Purcell RH, Nassiri-Toosi Z, Hall RA. Stalk-dependent and Stalk-independent Signaling by the Adhesion G Protein-coupled Receptors GPR56 (ADGRG1) and BAI1 (ADGRB1)*. J Biol Chem. 2016;291(7):3385-3394. doi:10.1074/jbc.m115.689349
223. Peeters MC, Fokkelman M, Boogaard B, et al. The adhesion G protein-coupled receptor G2 (ADGRG2/GPR64) constitutively activates SRE and NFκB and is involved in cell adhesion and migration. *Cell Signal*. 2015;27(12):2579-2588. doi:10.1016/j.cellsig.2015.08.015
224. Duman JG, Tu YK, Tolias KF. Emerging Roles of BAI Adhesion-GPCRs in Synapse Development and Plasticity. *Neural Plast*. 2016;2016(1):8301737. doi:10.1155/2016/8301737
225. Bui DLH, Roach A, Li J, et al. The adhesion GPCRs CELSR1–3 and LPHN3 engage G proteins via distinct activation mechanisms. Cell Rep. 2023;42(6):112552. doi:10.1016/j.celrep.2023.112552
226. Salzman GS, Zhang S, Gupta A, Koide A, Koide S, Araç D. Stachel-independent modulation of GPR56/ADGRG1 signaling by synthetic ligands directed to its extracellular region. Proc Natl Acad Sci. 2017;114(38):10095-10100. doi:10.1073/pnas.1708810114
227. Tissir F, Goffinet AM. Chapter Nine Atypical Cadherins Celsr1–3 and Planar Cell Polarity in Vertebrates. *Prog Mol Biol Transl Sci*. 2013;116:193-214. doi:10.1016/b978-0-12-394311-8.00009-1
228. Langenhan T, Piao X, Monk KR. Adhesion G protein-coupled receptors in nervous system development and disease. *Nat Rev Neurosci*. 2016;17(9):550-561. doi:10.1038/nrn.2016.86
229. Syrovatkina V, Alegre KO, Dey R, Huang XY. Regulation, Signaling, and Physiological Functions of G-Proteins. J Mol Biol. 2016;428(19):3850-3868. doi:10.1016/j.jmb.2016.08.002
230. Gilman AG. G Proteins: Transducers of Receptor-Generated Signals. *Annu Rev Biochem*. 1987;56(1):615-649. doi:10.1146/annurev.bi.56.070187.003151
231. Iguchi T, Sakata K, Yoshizaki K, Tago K, Mizuno N, Itoh H. Orphan G Protein-coupled Receptor GPR56 Regulates Neural Progenitor Cell Migration via a Gα12/13 and Rho Pathway. J Biol Chem. 2008;283(21):14469-14478. doi:10.1074/jbc.m708919200
232. Li S, Jin Z, Koirala S, et al. GPR56 regulates pial basement membrane integrity and cortical lamination. *Journal of Neuroscience*. 2008;28(22):5817-5826. doi:10.1523/jneurosci.0853-08.2008
233. Jeong S, Luo R, Li S, Strokes N, Piao X. Characterization of G protein-coupled receptor 56 protein expression in the mouse developing neocortex. *J Comp Neurol*. 2012;520(13):2930-2940. doi:10.1002/cne.23076
234. Moers A, Nürnberg A, Goebbels S, Wettschureck N, Offermanns S. Gα12/Gα13 Deficiency Causes Localized Overmigration of Neurons in the Developing Cerebral and Cerebellar Cortices. Mol Cell Biol. 2008;28(5):1480-1488. doi:10.1128/mcb.00651-07
235. Gupte J, Swaminath G, Danao J, Tian H, Li Y, Wu X. Signaling property study of

adhesion G-protein-coupled receptors. FEBS Lett. 2012;586(8):1214-1219. doi:10.1016/j.febslet.2012.03.014
236. Mogha A, Benesh AE, Patra C, et al. Gpr126 Functions in Schwann Cells to Control Differentiation and Myelination via G-Protein Activation. J Neurosci. 2013;33(46):17976-17985. doi:10.1523/jneurosci.1809-13.2013
237. Hu QX, Dong JH, Du HB, et al. Constitutive Gαi Coupling Activity of Very Large G Protein-coupled Receptor 1 (VLGR1) and Its Regulation by PDZD7 Protein*. J Biol Chem. 2014;289(35):24215-24225. doi:10.1074/jbc.m114.549816
238. Demberg LM, Winkler J, Wilde C, et al. Activation of Adhesion G Protein-coupled Receptors AGONIST SPECIFICITY OF STACHEL SEQUENCE-DERIVED PEPTIDES*. J Biol Chem. 2017;292(11):4383-4394. doi:10.1074/jbc.m116.763656
239. Hsiao CC, Chu TY, Wu CJ, et al. The Adhesion G Protein-Coupled Receptor GPR97/ADGRG3 Is Expressed in Human Granulocytes and Triggers Antimicrobial Effector Functions. Front Immunol. 2018;9:2830. doi:10.3389/fimmu.2018.02830
240. Zhang DL, Sun YJ, Ma ML, et al. Gq activity- and β-arrestin-1 scaffolding-mediated ADGRG2/CFTR coupling are required for male fertility. eLife. 2018;7:e33432. doi:10.7554/elife.33432
241. Guo P, Tai Y, Wang M, et al. Gα12 and Gα13: Versatility in Physiology and Pathology. Front Cell Dev Biol. 2022;10:809425. doi:10.3389/fcell.2022.809425
242. Worzfeld T, Wettschureck N, Offermanns S. G12/G13-mediated signalling in mammalian physiology and disease. Trends Pharmacol Sci. 2008;29(11):582-589. doi:10.1016/j.tips.2008.08.002
243. Suzuki N, Hajicek N, Kozasa T. Regulation and Physiological Functions of G12/13-Mediated Signaling Pathways. *Neurosignals*. 2009;17(1):55-70. doi:10.1159/000186690
244. Sénéchal C, Fujita R, Jamet S, et al. The adhesion G-protein-coupled receptor Gpr116 is essential to maintain the skeletal muscle stem cell pool. Cell Rep. 2022;41(7):111645. doi:10.1016/j.celrep.2022.111645
245. Petersen SC, Luo R, Liebscher I, et al. The Adhesion GPCR GPR126 Has Distinct, Domain-Dependent Functions in Schwann Cell Development Mediated by Interaction with Laminin-211. Neuron. 2015;85(4):755-769. doi:10.1016/j.neuron.2014.12.057
246. Patra C, Amerongen MJ van, Ghosh S, et al. Organ-specific function of adhesion G protein-coupled receptor GPR126 is domain-dependent. Proc Natl Acad Sci. 2013;110(42):16898-16903. doi:10.1073/pnas.1304837110
247. Purcell RH, Toro C, Gahl WA, Hall RA. A disease-associated mutation in the adhesion GPCR BAI2 (ADGRB2) increases receptor signaling activity. Hum Mutat. 2017;38(12):1751-1760. doi:10.1002/humu.23336
248. Dietzsch AN, Al-Hasani H, Altschmied J, et al. Dysfunction of the adhesion G protein-coupled receptor latrophilin 1 (ADGRL1/LPHN1) increases the risk of obesity. Signal Transduct Target Ther. 2024;9(1):103. doi:10.1038/s41392-024-01810-7
249. Moreno-Salinas AL, Holleran BJ, Ojeda-Muñiz EY, et al. Convergent selective signaling impairment exposes the pathogenicity of latrophilin-3 missense variants linked to inheritable ADHD susceptibility. Mol Psychiatry. 2022;27(5):2425-2438. doi:10.1038/s41380-022-01537-3
250. McDonald PH, Chow CW, Miller WE, et al. β-Arrestin 2: A Receptor-Regulated MAPK

Scaffold for the Activation of JNK3. Science. 2000;290(5496):1574-1577. doi:10.1126/science.290.5496.1574
251. DeFea KA, Zalevsky J, Thoma MS, Déry O, Mullins RD, Bunnett NW. β-Arrestin–Dependent Endocytosis of Proteinase-Activated Receptor 2 Is Required for Intracellular Targeting of Activated Erk1/2. *J Cell Biol*. 2000;148(6):1267-1282. doi:10.1083/jcb.148.6.1267
252. Zeghal M, Laroche G, Freitas JD, Wang R, Giguère PM. Profiling of basal and ligand-dependent GPCR activities by means of a polyvalent cell-based high-throughput platform. Nat Commun. 2023;14(1):3684. doi:10.1038/s41467-023-39132-x
253. Das S, Owen KA, Ly KT, et al. Brain angiogenesis inhibitor 1 (BAI1) is a pattern recognition receptor that mediates macrophage binding and engulfment of Gram-negative bacteria. Proc Natl Acad Sci. 2011;108(5):2136-2141. doi:10.1073/pnas.1014775108
254. Hochreiter-Hufford AE, Lee CS, Kinchen JM, et al. Phosphatidylserine receptor BAI1 and apoptotic cells as new promoters of myoblast fusion. Nature. 2013;497(7448):263-267. doi:10.1038/nature12135
255. Tu YK, Duman JG, Tolias KF. The Adhesion-GPCR BAI1 Promotes Excitatory Synaptogenesis by Coordinating Bidirectional Trans-synaptic Signaling. J Neurosci. 2018;38(39):8388-8406. doi:10.1523/jneurosci.3461-17.2018
256. Duman JG, Mulherkar S, Tu YK, et al. The adhesion-GPCR BAI1 shapes dendritic arbors via Bcr-mediated RhoA activation causing late growth arrest. eLife. 2019;8:e47566. doi:10.7554/elife.47566
257. Zhu D, Li C, Swanson AM, et al. BAI1 regulates spatial learning and synaptic plasticity in the hippocampus. *J Clin Investig*. 2015;125(4):1497-1508. doi:10.1172/jci74603
258. Zhu D, Osuka S, Zhang Z, et al. BAI1 Suppresses Medulloblastoma Formation by Protecting p53 from Mdm2-Mediated Degradation. *Cancer Cell*. 2018;33(6):1004-1016.e5. doi:10.1016/j.ccell.2018.05.006
259. Ward Y, Lake R, Yin JJ, et al. LPA Receptor Heterodimerizes with CD97 to Amplify LPA-Initiated RHO-Dependent Signaling and Invasion in Prostate Cancer Cells. Cancer Res. 2011;71(23):7301-7311. doi:10.1158/0008-5472.can-11-2381
260. Ward Y, Lake R, Martin PL, et al. CD97 amplifies LPA receptor signaling and promotes thyroid cancer progression in a mouse model. Oncogene. 2013;32(22):2726-2738. doi:10.1038/onc.2012.301
261. Cho C, Smallwood PM, Nathans J. Reck and Gpr124 Are Essential Receptor Cofactors for Wnt7a/Wnt7b-Specific Signaling in Mammalian CNS Angiogenesis and *Blood*-Brain Barrier Regulation. Neuron. 2017;95(5):1056-1073.e5. doi:10.1016/j.neuron.2017.07.031
262. Vallon M, Yuki K, Nguyen TD, et al. A RECK-WNT7 Receptor-Ligand Interaction Enables Isoform-Specific Regulation of Wnt Bioavailability. Cell Rep. 2018;25(2):339-349.e9. doi:10.1016/j.celrep.2018.09.045
263. America M, Bostaille N, Eubelen M, Martin M, Stainier DYR, Vanhollebeke B. An integrated model for Gpr124 function in Wnt7a/b signaling among vertebrates. Cell Rep. 2022;39(9):110902. doi:10.1016/j.celrep.2022.110902
264. Yuki K, Vallon M, Ding J, et al. GPR124 regulates murine brain embryonic angiogenesis and BBB formation by an intracellular domain-independent mechanism. Development. 2024;151(11):dev202794. doi:10.1242/dev.202794

265. Heiden R, Hannig L, Kuo CJ, Ergün S, Braunger BM, Vallon M. WNT7A/B assemble a GPR124-RECK-LRP5/6 co-receptor complex to activate β-catenin signaling in brain endothelial cells. J Biol Chem. Published online 2025:110682. doi:10.1016/j.jbc.2025.110682
266. Chen WS, Antic D, Matis M, et al. Asymmetric Homotypic Interactions of the Atypical Cadherin Flamingo Mediate Intercellular Polarity Signaling. Cell. 2008;133(6):1093-1105. doi:10.1016/j.cell.2008.04.048
267. Thakar S, Wang L, Yu T, et al. Evidence for opposing roles of Celsr3 and Vangl2 in glutamatergic synapse formation. Proc Natl Acad Sci. 2017;114(4):E610-E618. doi:10.1073/pnas.1612062114
268. Bayin NS, Frenster JD, Kane JR, et al. GPR133 (ADGRD1), an adhesion G-protein-coupled receptor, is necessary for glioblastoma growth. *Oncogenesis*. 2016;5(10):e263-e263. doi:10.1038/oncsis.2016.63
269. Frenster JD, Inocencio JF, Xu Z, et al. GPR133 Promotes Glioblastoma Growth in Hypoxia. *Neurosurgery*. 2017;64(CN_suppl_1):177-181. doi:10.1093/neuros/nyx227
270. Yang Z, Ping YQ, Wang MW, et al. Identification, structure, and agonist design of an androgen membrane receptor. Cell. 2025;188(6):1589-1604.e24. doi:10.1016/j.cell.2025.01.006
271. Moreno-Salinas AL, Avila-Zozaya M, Ugalde-Silva P, Hernández-Guzmán DA, Missirlis F, Boucard AA. Latrophilins: A Neuro-Centric View of an Evolutionary Conserved Adhesion G Protein-Coupled Receptor Subfamily. *Front Neurosci*. 2019;13:700. doi:10.3389/fnins.2019.00700
272. Wang T, Ward Y, Tian L, et al. CD97, an adhesion receptor on inflammatory cells, stimulates angiogenesis through binding integrin counterreceptors on endothelial cells. Blood. 2005;105(7):2836-2844. doi:10.1182/blood-2004-07-2878
273. Vallon M, Essler M. Proteolytically Processed Soluble Tumor Endothelial Marker (TEM) 5 Mediates Endothelial Cell Survival during Angiogenesis by Linking Integrin αvβ3 to Glycosaminoglycans*. J Biol Chem. 2006;281(45):34179-34188. doi:10.1074/jbc.m605291200
274. Koh JT, Kook H, Kee HJ, et al. Extracellular fragment of brain-specific angiogenesis inhibitor 1 suppresses endothelial cell proliferation by blocking αvβ5 integrin. *Exp Cell Res*. 2004;294(1):172-184. doi:10.1016/j.yexcr.2003.11.008
275. Kaur B, Cork SM, Sandberg EM, et al. Vasculostatin Inhibits Intracranial Glioma Growth and Negatively Regulates In vivo Angiogenesis through a CD36-Dependent Mechanism. Cancer Res. 2009;69(3):1212-1220. doi:10.1158/0008-5472.can-08-1166
276. Sheldon H, Zhang W, Bridges E, et al. ELTD1 is present in extracellular vesicles derived from endothelial cells as a cleaved extracellular domain which induces in vivo angiogenesis. *J Extracell Biol*. 2022;1(8):e52. doi:10.1002/jex2.52
277. Srivastava S, Gunawan F, Gentile A, Petersen SC, Stainier DYR, Engel FB. Adgrg6/Gpr126 is required for myocardial Notch activity and N-cadherin localization to attain trabecular identity. bioRxiv. Published online 2022:2022.05.27.493401. doi:10.1101/2022.05.27.493401
278. Vieira Contreras F, Auger GM, Müller L, et al. The adhesion G-protein-coupled receptor mayo/CG11318 controls midgut development in Drosophila. Cell Rep. 2024;43(1):113640. doi:10.1016/j.celrep.2023.113640

279. Lavalou J, Mao Q, Harmansa S, et al. Formation of polarized contractile interfaces by self-organized Toll-8/Cirl GPCR asymmetry. *Dev Cell*. 2021;56(11):1574-1588.e7. doi:10.1016/j.devcel.2021.03.030
280. Carmona-Rosas G, Li J, Smith JJ, et al. Structural basis and functional roles for Toll-like receptor binding to Latrophilin in C. elegans development. *Nat Struct Mol Biol*. Published online 2025:1-14. doi:10.1038/s41594-025-01592-8
281. Post WB, Groß VE, Matúš D, et al. Notch activity is modulated by the aGPCR Latrophilin binding the DSL ligand in C. elegans. Nat Commun. 2025;16(1):6461. doi:10.1038/s41467-025-61730-0
282. Matúš D, Post WB, Horn S, Schöneberg T, Prömel S. Latrophilin-1 drives neuron morphogenesis and shapes chemo- and mechanosensation-dependent behavior in C. elegans via a trans function. Biochem Biophys Res Commun. 2022;589:152-158. doi:10.1016/j.bbrc.2021.12.006
283. Chen PL, Clandinin TR. The Cadherin Flamingo Mediates Level-Dependent Interactions that Guide Photoreceptor Target Choice in Drosophila. Neuron. 2008;58(1):26-33. doi:10.1016/j.neuron.2008.01.007
284. Najarro EH, Ackley BD. C. elegans fmi-1/flamingo and Wnt pathway components interact genetically to control the anteroposterior neurite growth of the VD GABAergic neurons. Dev Biol. 2013;377(1):224-235. doi:10.1016/j.ydbio.2013.01.014
285. Curtin JA, Quint E, Tsipouri V, et al. Mutation of Celsr1 Disrupts Planar Polarity of Inner Ear Hair Cells and Causes Severe Neural Tube Defects in the Mouse. *Curr Biol*. 2003;13(13):1129-1133. doi:10.1016/s0960-9822(03)00374-9
286. Piao X, Hill RS, Bodell A, et al. G Protein-Coupled Receptor-Dependent Development of Human Frontal Cortex. Science. 2004;303(5666):2033-2036. doi:10.1126/science.1092780
287. Bae BI, Tietjen I, Atabay KD, et al. Evolutionarily Dynamic Alternative Splicing of GPR56 Regulates Regional Cerebral Cortical Patterning. Science. 2014;343(6172):764-768. doi:10.1126/science.1244392
288. Bahi-Buisson N, Poirier K, Boddaert N, et al. GPR56-related bilateral frontoparietal polymicrogyria: further evidence for an overlap with the cobblestone complex. Brain. 2010;133(11):3194-3209. doi:10.1093/brain/awq259
289. Shima Y, Kawaguchi S ya, Kosaka K, et al. Opposing roles in neurite growth control by two seven-pass transmembrane cadherins. *Nat Neurosci*. 2007;10(8):963-969. doi:10.1038/nn1933
290. Pederick DT, Lui JH, Gingrich EC, et al. Reciprocal repulsions instruct the precise assembly of parallel hippocampal networks. Science. 2021;372(6546):1068-1073. doi:10.1126/science.abg1774
291. Pederick DT, Perry-Hauser NA, Meng H, He Z, Javitch JA, Luo L. Context-dependent requirement of G protein coupling for Latrophilin-2 in target selection of hippocampal axons. eLife. 2023;12:e83529. doi:10.7554/elife.83529
292. Anderson GR, Maxeiner S, Sando R, Tsetsenis T, Malenka RC, Südhof TC. Postsynaptic adhesion GPCR latrophilin-2 mediates target recognition in entorhinal-hippocampal synapse assembly. J Cell Biol. 2017;216(11):3831-3846. doi:10.1083/jcb.201703042
293. Zhang RS, Liakath-Ali K, Südhof TC. Latrophilin-2 and latrophilin-3 are redundantly

essential for parallel-fiber synapse function in cerebellum. eLife. 2020;9:e54443. doi:10.7554/elife.54443
294. Vitobello A, Mazel B, Lelianova VG, et al. ADGRL1 haploinsufficiency causes a variable spectrum of neurodevelopmental disorders in humans and alters synaptic activity and behavior in a mouse model. *Am J Hum Genet*. 2022;109(8):1436-1457. doi:10.1016/j.ajhg.2022.06.011
295. Kakegawa W, Mitakidis N, Miura E, et al. Anterograde C1ql1 Signaling Is Required in Order to Determine and Maintain a Single-Winner Climbing Fiber in the Mouse Cerebellum. Neuron. 2015;85(2):316-329. doi:10.1016/j.neuron.2014.12.020
296. Sigoillot SM, Iyer K, Binda F, et al. The Secreted Protein C1QL1 and Its Receptor BAI3 Control the Synaptic Connectivity of Excitatory Inputs Converging on Cerebellar Purkinje Cells. Cell Rep. 2015;10(5):820-832. doi:10.1016/j.celrep.2015.01.034
297. Aimi T, Matsuda K, Yuzaki M. C1ql1-Bai3 signaling is necessary for climbing fiber synapse formation in mature Purkinje cells in coordination with neuronal activity. *Mol Brain*. 2023;16(1):61. doi:10.1186/s13041-023-01048-4
298. Wang CY, Liu Z, Ng YH, Südhof TC. A Synaptic Circuit Required for Acquisition but Not Recall of Social Transmission of Food Preference. Neuron. 2020;107(1):144-157.e4. doi:10.1016/j.neuron.2020.04.004
299. Zhou Q, Qin J, Liang Y, et al. Celsr3 is required for Purkinje cell maturation and regulates cerebellar postsynaptic plasticity. iScience. 2021;24(7):102812. doi:10.1016/j.isci.2021.102812
300. Li C, Wei J an, Wang D, et al. Planar cell polarity protein Celsr2 maintains structural and functional integrity of adult cortical synapses. *Prog Neurobiol*. 2022;219:102352. doi:10.1016/j.pneurobio.2022.102352
301. Donohue JD, Amidon RF, Murphy TR, et al. Parahippocampal latrophilin-2 (ADGRL2) expression controls topographical presubiculum to entorhinal cortex circuit connectivity. Cell Rep. 2021;37(8):110031. doi:10.1016/j.celrep.2021.110031
302. Feng B, Freitas AE, Gorodetski L, et al. Planar cell polarity signaling components are a direct target of β-amyloid–associated degeneration of glutamatergic synapses. *Sci Adv*. 2021;7(34):eabh2307. doi:10.1126/sciadv.abh2307
303. Sando R, Südhof TC. Latrophilin GPCR signaling mediates synapse formation. eLife. 2021;10:e65717. doi:10.7554/elife.65717
304. Zhang X, Chen X, Matúš D, Südhof TC. Reconstitution of synaptic junctions orchestrated by teneurin-latrophilin complexes. Science. 2025;387(6731):322-329. doi:10.1126/science.adq3586
305. Huang BX, Hu X, Kwon HS, et al. Synaptamide activates the adhesion GPCR GPR110 (ADGRF1) through GAIN domain binding. Commun Biol. 2020;3(1):109. doi:10.1038/s42003-020-0831-6
306. Ackerman SD, Garcia C, Piao X, Gutmann DH, Monk KR. The adhesion GPCR Gpr56 regulates oligodendrocyte development via interactions with Gα12/13 and RhoA. Nat Commun. 2015;6(1):6122. doi:10.1038/ncomms7122
307. Giera S, Deng Y, Luo R, et al. The adhesion G protein-coupled receptor GPR56 is a cell-autonomous regulator of oligodendrocyte development. Nat Commun. 2015;6(1):6121. doi:10.1038/ncomms7121

308. Piao X, Chang BS, Bodell A, et al. Genotype–phenotype analysis of human frontoparietal polymicrogyria syndromes. *Ann Neurol*. 2005;58(5):680-687. doi:10.1002/ana.20616
309. Giera S, Luo R, Ying Y, et al. Microglial transglutaminase-2 drives myelination and myelin repair via GPR56/ADGRG1 in oligodendrocyte precursor cells. eLife. 2018;7:e33385. doi:10.7554/elife.33385
310. Shin D, Lin ST, Fu YH, Ptáček LJ. Very large G protein-coupled receptor 1 regulates myelin-associated glycoprotein via Gαs/Gαq-mediated protein kinases A/C. Proc Natl Acad Sci. 2013;110(47):19101-19106. doi:10.1073/pnas.1318501110
311. Ackerman SD, Luo R, Poitelon Y, et al. GPR56/ADGRG1 regulates development and maintenance of peripheral myelin. J Exp Med. 2018;215(3):941-961. doi:10.1084/jem.20161714
312. Monk KR, Naylor SG, Glenn TD, et al. A G Protein–Coupled Receptor Is Essential for Schwann Cells to Initiate Myelination. Science. 2009;325(5946):1402-1405. doi:10.1126/science.1173474
313. Monk KR, Oshima K, Jörs S, Heller S, Talbot WS. Gpr126 is essential for peripheral nerve development and myelination in mammals. Development. 2011;138(13):2673-2680. doi:10.1242/dev.062224
314. Mogha A, Harty BL, Carlin D, et al. Gpr126/Adgrg6 Has Schwann Cell Autonomous and Nonautonomous Functions in Peripheral Nerve Injury and Repair. J Neurosci. 2016;36(49):12351-12367. doi:10.1523/jneurosci.3854-15.2016
315. Paavola KJ, Sidik H, Zuchero JB, Eckart M, Talbot WS. Type IV collagen is an activating ligand for the adhesion G protein–coupled receptor GPR126. Sci Signal. 2014;7(338):ra76. doi:10.1126/scisignal.2005347
316. Yu D, Li T, Delpech JC, et al. Microglial GPR56 is the molecular target of maternal immune activation-induced parvalbumin-positive interneuron deficits. Sci Adv. 2022;8(18):eabm2545. doi:10.1126/sciadv.abm2545
317. Zhu B, Wangzhou A, Yu D, et al. Adhesion G protein-coupled receptor ADGRG1 promotes protective microglial response in Alzheimer's disease. bioRxiv. Published online 2024:2024.10.15.618329. doi:10.1101/2024.10.15.618329
318. Zhang Y, Chen K, Sloan SA, et al. An RNA-Sequencing Transcriptome and Splicing Database of Glia, Neurons, and Vascular Cells of the Cerebral Cortex. J Neurosci. 2014;34(36):11929-11947. doi:10.1523/jneurosci.1860-14.2014
319. Soto JS, Jami-Alahmadi Y, Chacon J, et al. Astrocyte–neuron subproteomes and obsessive–compulsive disorder mechanisms. Nature. 2023;616(7958):764-773. doi:10.1038/s41586-023-05927-7
320. Güler BE, Zorin M, Linnert J, Nagel-Wolfrum K, Wolfrum U. The adhesion GPCR ADGRV1 controls glutamate homeostasis in hippocampal astrocytes supporting neuron development: first insights into to pathophysiology of ADGRV1-associated epilepsy. bioRxiv. Published online 2024:2024.04.25.591120. doi:10.1101/2024.04.25.591120
321. Leng X, Zhang T, Guan Y, Tang M. Genotype and phenotype analysis of epilepsy caused by ADGRV1 mutations in Chinese children. *Seizure*. 2022;103:108-114. doi:10.1016/j.seizure.2022.11.005
322. Fuster-García C, García-Bohórquez B, Rodríguez-Muñoz A, et al. Usher Syndrome:

Genetics of a Human Ciliopathy. Int J Mol Sci. 2021;22(13):6723. doi:10.3390/ijms22136723
323. Reiners J, Nagel-Wolfrum K, Jürgens K, Märker T, Wolfrum U. Molecular basis of human Usher syndrome: Deciphering the meshes of the Usher protein network provides insights into the pathomechanisms of the Usher disease. *Exp Eye Res*. 2006;83(1):97-119. doi:10.1016/j.exer.2005.11.010
324. Lefèvre G, Michel V, Weil D, et al. A core cochlear phenotype in USH1 mouse mutants implicates fibrous links of the hair bundle in its cohesion, orientation and differential growth. Development. 2008;135(8):1427-1437. doi:10.1242/dev.012922
325. Scholz N, Gehring J, Guan C, et al. The Adhesion GPCR Latrophilin/CIRL Shapes Mechanosensation. Cell Rep. 2015;11(6):866-874. doi:10.1016/j.celrep.2015.04.008
326. Osaka J, Yasuda H, Watanuki Y, et al. Identification of genes regulating stimulus-dependent synaptic assembly in Drosophila using an automated synapse quantification system. *Genes Genet Syst*. 2022;97(6):297-309. doi:10.1266/ggs.22-00114
327. Lee RC, Clandinin TR, Lee CH, Chen PL, Meinertzhagen IA, Zipursky SL. The protocadherin Flamingo is required for axon target selection in the Drosophila visual system. Nat Neurosci. 2003;6(6):557-563. doi:10.1038/nn1063
328. Hakeda-Suzuki S, Berger-Müller S, Tomasi T, et al. Golden Goal collaborates with Flamingo in conferring synaptic-layer specificity in the visual system. Nat Neurosci. 2011;14(3):314-323. doi:10.1038/nn.2756
329. Scholz N, Monk KR, Kittel RJ, Langenhan T. Adhesion G Protein-coupled Receptors, Molecular, Physiological and Pharmacological Principles in Health and Disease. Handb Exp Pharmacol. 2016;234:221-247. doi:10.1007/978-3-319-41523-9_10
330. Yang Z, Zhou SH, Zhang QY, et al. A force-sensitive adhesion GPCR is required for equilibrioception. Cell Res. 2025;35(4):243-264. doi:10.1038/s41422-025-01075-x
331. Yang Z, Zhou SH, Wang MW, et al. Force sensing GPR133 is essential for normal balance and modulates vestibular hair cell membrane excitability via Gi signaling and CNGA3 coupling. bioRxiv. Published online 2023:2023.10.24.563882. doi:10.1101/2023.10.24.563882
332. Cui H, Wang Y, Huang H, et al. GPR126 Protein Regulates Developmental and Pathological Angiogenesis through Modulation of VEGFR2 Receptor Signaling*. J Biol Chem. 2014;289(50):34871-34885. doi:10.1074/jbc.m114.571000
333. Kakogiannos N, Scalise AA, Martini E, et al. GPR126 is a specifier of blood-brain barrier formation in the mouse central nervous system. J Clin Investig. 2024;134(15):e165368. doi:10.1172/jci165368
334. Zhao W, Wang Z, Sun Z, Wang S, Wu M, Zheng L. Lentivirus-mediated overexpression of CD97/ADGRE5 reverses dysregulated high glucose-induced endothelial cell migration. *Mol Med Rep*. 2017;15(5):3048-3054. doi:10.3892/mmr.2017.6417
335. Valtcheva N, Primorac A, Jurisic G, Hollmén M, Detmar M. The Orphan Adhesion G Protein-coupled Receptor GPR97 Regulates Migration of Lymphatic Endothelial Cells via the Small GTPases RhoA and Cdc42*. J Biol Chem. 2013;288(50):35736-35748. doi:10.1074/jbc.m113.512954
336. Kuhnert F, Mancuso MR, Shamloo A, et al. Essential Regulation of CNS Angiogenesis by the Orphan G Protein–Coupled Receptor GPR124. Science. 2010;330(6006):985-989.

doi:10.1126/science.1196554
337. Vallon M, Rohde F, Janssen KP, Essler M. Tumor endothelial marker 5 expression in endothelial cells during capillary morphogenesis is induced by the small GTPase Rac and mediates contact inhibition of cell proliferation. Exp Cell Res. 2010;316(3):412-421. doi:10.1016/j.yexcr.2009.10.013
338. Chen DY, Sun NH, Lu YP, et al. GPR124 facilitates pericyte polarization and migration by regulating the formation of filopodia during ischemic injury. *Theranostics*. 2019;9(20):5937-5955. doi:10.7150/thno.34168
339. Masiero M, Simões FC, Han HD, et al. A Core Human Primary Tumor Angiogenesis Signature Identifies the Endothelial Orphan Receptor ELTD1 as a Key Regulator of Angiogenesis. Cancer Cell. 2013;24(2):229-241. doi:10.1016/j.ccr.2013.06.004
340. Favara DM, Liebscher I, Jazayeri A, et al. Elevated expression of the adhesion GPCR ADGRL4/ELTD1 promotes endothelial sprouting angiogenesis without activating canonical GPCR signalling. Sci Rep. 2021;11(1):8870. doi:10.1038/s41598-021-85408-x
341. Anderson KD, Pan L, Yang X man, et al. Angiogenic sprouting into neural tissue requires Gpr124, an orphan G protein-coupled receptor. Proc Natl Acad Sci. 2011;108(7):2807-2812. doi:10.1073/pnas.1019761108
342. Cullen M, Elzarrad MK, Seaman S, et al. GPR124, an orphan G protein-coupled receptor, is required for CNS-specific vascularization and establishment of the blood–brain barrier. Proc Natl Acad Sci. 2011;108(14):5759-5764. doi:10.1073/pnas.1017192108
343. Schevenels G, Cabochette P, America M, et al. A brain-specific angiogenic mechanism enabled by tip cell specialization. Nature. 2024;628(8009):863-871. doi:10.1038/s41586-024-07283-6
344. Dieterich LC, Mellberg S, Langenkamp E, et al. Transcriptional profiling of human glioblastoma vessels indicates a key role of VEGF-A and TGFβ2 in vascular abnormalization. *J Pathol*. 2012;228(3):378-390. doi:10.1002/path.4072
345. Carson-Walter EB, Watkins DN, Nanda A, Vogelstein B, Kinzler KW, Croix BS. Cell surface tumor endothelial markers are conserved in mice and humans. Cancer Res. 2001;61(18):6649-6655.
346. Wang Y, Cho SG, Wu X, Siwko S, Liu M. G-Protein Coupled Receptor 124 (GPR124) in Endothelial Cells Regulates Vascular Endothelial Growth Factor (VEGF)-Induced Tumor Angiogenesis. *Curr Mol Med*. 2014;14(4):543-554. doi:10.2174/1566524014666140414205943
347. Tjong WY, Lin HH. The role of the RGD motif in CD97/ADGRE5-and EMR2/ADGRE2-modulated tumor angiogenesis. Biochem Biophys Res Commun. 2019;520(2):243-249. doi:10.1016/j.bbrc.2019.09.113
348. Kee HJ, Koh JT, Kim MY, et al. Expression of Brain-Specific Angiogenesis Inhibitor 2 (BAI2) in Normal and Ischemic Brain: Involvement of BAI2 in the Ischemia-Induced Brain Angiogenesis. *J Cereb Blood Flow Metab*. 2002;22(9):1054-1067. doi:10.1097/00004647-200209000-00003
349. Kee HJ, Ahn KY, Choi KC, et al. Expression of brain-specific angiogenesis inhibitor 3 (BAI3) in normal brain and implications for BAI3 in ischemia-induced brain angiogenesis and malignant glioma. 2004;569(1-3):307-316. doi:10.1016/j.febslet.2004.06.011
350. Niaudet C, Petkova M, Jung B, et al. Adgrf5 contributes to patterning of the endothelial

deep layer in retina. Angiogenesis. 2019;22(4):491-505. doi:10.1007/s10456-019-09674-0
351. Lu S, Liu S, Wietelmann A, et al. Developmental vascular remodeling defects and postnatal kidney failure in mice lacking Gpr116 (Adgrf5) and Eltd1 (Adgrl4). PLoS ONE. 2017;12(8):e0183166. doi:10.1371/journal.pone.0183166
352. Qiu D, Xu K, Chung N, et al. Identification and validation of G protein-coupled receptors modulating flow-dependent signaling pathways in vascular endothelial cells. *Front Mol Biosci*. 2023;10:1198079. doi:10.3389/fmolb.2023.1198079
353. Tanaka K, Chen M, Prendergast A, et al. Latrophilin-2 mediates fluid shear stress mechanotransduction at endothelial junctions. EMBO J. 2024;43(15):3175-3191. doi:10.1038/s44318-024-00142-0
354. Tatin F, Taddei A, Weston A, et al. Planar Cell Polarity Protein Celsr1 Regulates Endothelial Adherens Junctions and Directed Cell Rearrangements during Valve Morphogenesis. Dev Cell. 2013;26(1):31-44. doi:10.1016/j.devcel.2013.05.015
355. Camillo C, Facchinello N, Villari G, et al. LPHN2 inhibits vascular permeability by differential control of endothelial cell adhesion. J Cell Biol. 2021;220(11):e202006033. doi:10.1083/jcb.202006033
356. Martin M, Vermeiren S, Bostaille N, et al. Engineered Wnt ligands enable blood-brain barrier repair in neurological disorders. Science. 2022;375(6582):eabm4459. doi:10.1126/science.abm4459
357. Sheldon H, Alexander J, Bridges E, et al. ELTD1 Activation Induces an Endothelial-EMT Transition to a Myofibroblast Phenotype. Int J Mol Sci. 2021;22(20):11293. doi:10.3390/ijms222011293
358. Favara DM, Zois CE, Haider S, et al. ADGRL4/ELTD1 Silencing in Endothelial Cells Induces ACLY and SLC25A1 and Alters the Cellular Metabolic Profile. Metabolites. 2019;9(12):287. doi:10.3390/metabo9120287
359. Davis RB, Kechele DO, Blakeney ES, Pawlak JB, Caron KM. Lymphatic deletion of calcitonin receptor–like receptor exacerbates intestinal inflammation. *JCI Insight*. 2017;2(6):e92465. doi:10.1172/jci.insight.92465
360. Petrova TV, Koh GY. Organ-specific lymphatic vasculature: From development to pathophysiology. J Exp Med. 2018;215(1):35-49. doi:10.1084/jem.20171868
361. Schoofs H, Daubel N, Schnabellehner S, et al. Dynamic cytoskeletal regulation of cell shape supports resilience of lymphatic endothelium. Nature. 2025;641(8062):465-475. doi:10.1038/s41586-025-08724-6
362. Gonzalez-Garay ML, Aldrich MB, Rasmussen JC, et al. A novel mutation in CELSR1 is associated with hereditary lymphedema. *Vasc Cell*. 2016;8(1):1. doi:10.1186/s13221-016-0035-5
363. Erickson RP, Lai L, Mustacich DJ, Bernas MJ, Kuo PH, Witte MH. Sex-limited penetrance of lymphedema to females with CELSR1 haploinsufficiency: A second family. *Clin Genet*. 2019;96(5):478-482. doi:10.1111/cge.13622
364. Seo SH, Lee S, Park JK hyung, et al. Clinical staging and genetic profiling of Korean patients with primary lymphedema using targeted gene sequencing. Sci Rep. 2022;12(1):13591. doi:10.1038/s41598-022-17958-7
365. Rogerson D, Alkelai A, Giordano J, et al. Investigation into the genetics of fetal congenital lymphatic anomalies. *Prenat Diagn*. 2023;43(6):703-716. doi:10.1002/pd.6345

366. Xia S, Liu Z, Yan H, et al. Lymphedema complicated by protein-losing enteropathy with a 22q13.3 deletion and the potential role of CELSR1. Medicine. 2021;100(24):e26307. doi:10.1097/md.0000000000026307
367. Xu W, Nelson-Maney NP, Bálint L, et al. Orphan G-Protein Coupled Receptor GPRC5B Is Critical for Lymphatic Development. Int J Mol Sci. 2022;23(10):5712. doi:10.3390/ijms23105712
368. Manolis D, Hasan S, Maraveyas A, et al. Quantitative proteomics reveals CLR interactome in primary human cells. J Biol Chem. 2024;300(6):107399. doi:10.1016/j.jbc.2024.107399
369. Karakousi T, Mudianto T, Lund AW. Lymphatic vessels in the age of cancer immunotherapy. *Nat Rev Cancer*. 2024;24(6):363-381. doi:10.1038/s41568-024-00681-y
370. Prömel S, Waller-Evans H, Dixon J, et al. Characterization and functional study of a cluster of four highly conserved orphan adhesion-GPCR in mouse. *Dev Dyn*. 2012;241(10):1591-1602. doi:10.1002/dvdy.23841
371. Goffinet AM, Tissir F. Seven pass Cadherins CELSR1-3. *Semin Cell Dev Biol*. 2017;69:102-110. doi:10.1016/j.semcdb.2017.07.014
372. Musa G, Cazorla-Vázquez S, Amerongen MJ van, et al. Gpr126 (Adgrg6) is expressed in cell types known to be exposed to mechanical stimuli. Ann N York Acad Sci. 2019;1456(1):96-108. doi:10.1111/nyas.14135
373. Waller-Evans H, Prömel S, Langenhan T, et al. The Orphan Adhesion-GPCR GPR126 Is Required for Embryonic Development in the Mouse. PLoS ONE. 2010;5(11):e14047. doi:10.1371/journal.pone.0014047
374. Doyle SE, Scholz MJ, Greer KA, et al. Latrophilin-2 is a novel component of the epithelial-mesenchymal transition within the atrioventricular canal of the embryonic chicken heart. Dev Dyn. 2006;235(12):3213-3221. doi:10.1002/dvdy.20973
375. Lee CS, Cho HJ, Lee JW, et al. The G Protein-Coupled Receptor Latrophilin-2, A Marker for Heart Development, Induces Myocardial Repair After Infarction. *Stem Cells Transl Med*. 2022;11(3):332-342. doi:10.1093/stcltm/szab015
376. Liu M, Parker RMC, Darby K, et al. GPR56, a Novel Secretin-like Human G-Protein-Coupled Receptor Gene. Genomics. 1999;55(3):296-305. doi:10.1006/geno.1998.5644
377. Einspahr J, Xu H, Roy R, et al. Loss of cardiomyocyte-specific adhesion G-protein-coupled receptor G1 (ADGRG1/GPR56) promotes pressure overload-induced heart failure. *Biosci Rep*. 2024;44(9):BSR20240826. doi:10.1042/bsr20240826
378. Lee CS, Cho HJ, Lee JW, et al. Identification of Latrophilin-2 as a Novel Cell-Surface Marker for the Cardiomyogenic Lineage and Its Functional Significance in Heart Development. *Circulation*. 2019;139(25):2910-2912. doi:10.1161/circulationaha.119.040826
379. Lee CS, Cho HJ, Lee JW, Son H, Chai J, Kim HS. Adhesion GPCR Latrophilin-2 Specifies Cardiac Lineage Commitment through CDK5, Src, and P38MAPK. *Stem Cell Rep*. 2021;16(4):868-882. doi:10.1016/j.stemcr.2021.03.003
380. Kang M, Lee CS, Son H, et al. Latrophilin-2 Deletion in Cardiomyocyte Disrupts Cell Junction, Leading to D-CMP. *Circ Res*. 2024;135(11):1098-1115. doi:10.1161/circresaha.124.324670
381. Torregrosa-Carrión R, Piñeiro-Sabarís R, Siguero-Álvarez M, et al. Adhesion G protein–coupled receptor Gpr126/Adgrg6 is essential for placental development. Sci Adv.

2021;7(46):eabj5445. doi:10.1126/sciadv.abj5445
382. Niaudet C, Hofmann JJ, Mäe MA, et al. Gpr116 Receptor Regulates Distinctive Functions in Pneumocytes and Vascular Endothelium. PLoS ONE. 2015;10(9):e0137949. doi:10.1371/journal.pone.0137949
383. Xiao J, Jiang H, Zhang R, et al. Augmented Cardiac Hypertrophy in Response to Pressure Overload in Mice Lacking ELTD1. PLoS ONE. 2012;7(5):e35779. doi:10.1371/journal.pone.0035779
384. White JP, Wrann CD, Rao RR, et al. G protein-coupled receptor 56 regulates mechanical overload-induced muscle hypertrophy. Proc Natl Acad Sci. 2014;111(44):15756-15761. doi:10.1073/pnas.1417898111
385. Zhang Y, Si Y, Ma N, Mei J. The RNA-binding protein PCBP2 inhibits Ang II-induced hypertrophy of cardiomyocytes though promoting GPR56 mRNA degeneration. Biochem Biophys Res Commun. 2015;464(3):679-684. doi:10.1016/j.bbrc.2015.06.139
386. Ariestanti DM, Ando H, Hirose S, Nakamura N. Targeted Disruption of Ig-Hepta/Gpr116 Causes Emphysema-like Symptoms That Are Associated with Alveolar Macrophage Activation*. J Biol Chem. 2015;290(17):11032-11040. doi:10.1074/jbc.m115.648311
387. Brown K, Filuta A, Ludwig MG, et al. Epithelial Gpr116 regulates pulmonary alveolar homeostasis via Gq/11 signaling. JCI Insight. 2017;2(11):e93700. doi:10.1172/jci.insight.93700
388. Kubo F, Ariestanti DM, Oki S, et al. Loss of the adhesion G-protein coupled receptor ADGRF5 in mice induces airway inflammation and the expression of CCL2 in lung endothelial cells. *Respir Res*. 2019;20(1):11. doi:10.1186/s12931-019-0973-6
389. Heinzelmann K, Lehmann M, Gerckens M, et al. Cell-surface phenotyping identifies CD36 and CD97 as novel markers of fibroblast quiescence in lung fibrosis. *Am J Physiol-Lung Cell Mol Physiol*. 2018;315(5):L682-L696. doi:10.1152/ajplung.00439.2017
390. Yang J, Wang Z, Leng D, et al. G protein-coupled receptor 56 regulates matrix production and motility of lung fibroblasts. *Exp Biol Med*. 2014;239(6):686-696. doi:10.1177/1535370214529395
391. Sakornsakolpat P, Prokopenko D, Lamontagne M, et al. Genetic landscape of chronic obstructive pulmonary disease identifies heterogeneous cell-type and phenotype associations. *Nat Genet*. 2019;51(3):494-505. doi:10.1038/s41588-018-0342-2
392. Terzikhan N, Sun F, Verhamme FM, et al. Heritability and genome-wide association study of diffusing capacity of the lung. *Eur Respir J*. 2018;52(3):1800647. doi:10.1183/13993003.00647-2018
393. Shrine N, Izquierdo AG, Chen J, et al. Multi-ancestry genome-wide association analyses improve resolution of genes and pathways influencing lung function and chronic obstructive pulmonary disease risk. Nat Genet. 2023;55(3):410-422. doi:10.1038/s41588-023-01314-0
394. Shrine N, Guyatt AL, Erzurumluoglu AM, et al. New genetic signals for lung function highlight pathways and chronic obstructive pulmonary disease associations across multiple ancestries. Nat Genet. 2019;51(3):481-493. doi:10.1038/s41588-018-0321-7
395. Gorr MW, Sriram K, Muthusamy A, Insel PA. Transcriptomic analysis of pulmonary artery smooth muscle cells identifies new potential therapeutic targets for idiopathic pulmonary arterial hypertension. Br J Pharmacol. 2020;177(15):3505-3518.

doi:10.1111/bph.15074
396. Hall RJ, O'Loughlin J, Billington CK, Thakker D, Hall IP, Sayers I. Functional genomics of GPR126 in airway smooth muscle and bronchial epithelial cells. FASEB J. 2021;35(7):e21300. doi:10.1096/fj.202002073r
397. Werder RB, Berthiaume KA, Merritt C, et al. The COPD GWAS gene ADGRG6 instructs function and injury response in human iPSC-derived type II alveolar epithelial cells. Am J Hum Genet. 2023;110(10):1735-1749. doi:10.1016/j.ajhg.2023.08.017
398. Sreepada A, Tiwari M, Pal K. Adhesion G protein-coupled receptor gluing action guides tissue development and disease. *J Mol Med*. 2022;100(10):1355-1372. doi:10.1007/s00109-022-02240-0
399. Chan YF, Jones FC, McConnell E, Bryk J, Bünger L, Tautz D. Parallel Selection Mapping Using Artificially Selected Mice Reveals Body Weight Control Loci. Curr Biol. 2012;22(9):794-800. doi:10.1016/j.cub.2012.03.011
400. Kim JJ, Park YM, Baik KH, et al. Exome sequencing and subsequent association studies identify five amino acid-altering variants influencing human height. Hum Genet. 2012;131(3):471-478. doi:10.1007/s00439-011-1096-4
401. Kou I, Takahashi Y, Johnson TA, et al. Genetic variants in GPR126 are associated with adolescent idiopathic scoliosis. Nat Genet. 2013;45(6):676-679. doi:10.1038/ng.2639
402. Liu Z, Hussien AA, Wang Y, et al. An adhesion G protein-coupled receptor is required in cartilaginous and dense connective tissues to maintain spine alignment. eLife. 2021;10:e67781. doi:10.7554/elife.67781
403. Karner CM, Long F, Solnica-Krezel L, Monk KR, Gray RS. Gpr126/Adgrg6 deletion in cartilage models idiopathic scoliosis and pectus excavatum in mice. Hum Mol Genet. 2015;24(15):4365-4373. doi:10.1093/hmg/ddv170
404. Soranzo N, Rivadeneira F, Chinappen-Horsley U, et al. Meta-Analysis of Genome-Wide Scans for Human Adult Stature Identifies Novel Loci and Associations with Measures of Skeletal Frame Size. PLoS Genet. 2009;5(4):e1000445. doi:10.1371/journal.pgen.1000445
405. Bian F, Hansen V, Feng HC, et al. The G protein-coupled receptor ADGRG6 maintains mouse growth plate homeostasis through IHH signaling. *J Bone Miner Res*. 2024;39(11):1644-1658. doi:10.1093/jbmr/zjae144
406. He L, Zhang Q, You Y, et al. Exogenous activation of the adhesion GPCR ADGRD1/GPR133 protects against bone loss by negatively regulating osteoclastogenesis. Sci Adv. 2025;11(28):eads3829. doi:10.1126/sciadv.ads3829
407. Wu MP, Doyle JR, Barry B, et al. G-protein coupled receptor 56 promotes myoblast fusion through serum response factor- and nuclear factor of activated T-cell-mediated signalling but is not essential for muscle development in vivo. *FEBS J*. 2013;280(23):6097-6113. doi:10.1111/febs.12529
408. Urano T, Shiraki M, Yagi H, et al. GPR98/Gpr98 Gene Is Involved in the Regulation of Human and Mouse Bone Mineral Density. *J Clin Endocrinol Metab*. 2012;97(4):E565-E574. doi:10.1210/jc.2011-2393
409. Austyn JM, Gordon S. F4/80, a monoclonal antibody directed specifically against the mouse macrophage. Eur J Immunol. 1981;11(10):805-815. doi:10.1002/eji.1830111013
410. Hamann J, Koning N, Pouwels W, et al. EMR1, the human homolog of F4/80, is an eosinophil-specific receptor. *European journal of immunology*. 2007;37(10):2797-2802.

doi:10.1002/eji.200737553
411. Legrand F, Tomasevic N, Simakova O, et al. The eosinophil surface receptor epidermal growth factor–like module containing mucin-like hormone receptor 1 (EMR1): A novel therapeutic target for eosinophilic disorders. *J Allergy Clin Immunol*. 2014;133(5):1439-1447.e8. doi:10.1016/j.jaci.2013.11.041
412. Matmati M, Pouwels W, Bruggen R van, et al. The human EGF-TM7 receptor EMR3 is a marker for mature granulocytes. Journal of leukocyte biology. 2007;81(2):440-448. doi:10.1189/jlb.0406276
413. Poel M van der, Ulas T, Mizee MR, et al. Transcriptional profiling of human microglia reveals grey–white matter heterogeneity and multiple sclerosis-associated changes. Nat Commun. 2019;10(1):1139. doi:10.1038/s41467-019-08976-7
414. Tseng WY, Stacey M, Lin HH. Role of Adhesion G Protein-Coupled Receptors in Immune Dysfunction and Disorder. Int J Mol Sci. 2023;24(6):5499. doi:10.3390/ijms24065499
415. Irmscher S, Brix SR, Zipfel SLH, et al. Serum FHR1 binding to necrotic-type cells activates monocytic inflammasome and marks necrotic sites in vasculopathies. Nat Commun. 2019;10(1):2961. doi:10.1038/s41467-019-10766-0
416. Palacios D, Majhi RK, Szabo EK, et al. The G Protein–Coupled Receptor GPR56 Is an Inhibitory Checkpoint for NK Cell Migration. J Immunol. 2024;213(9):1349-1357. doi:10.4049/jimmunol.2400228
417. Lin HH, Faunce DE, Stacey M, et al. The macrophage F4/80 receptor is required for the induction of antigen-specific efferent regulatory T cells in peripheral tolerance. *The Journal of experimental medicine*. 2005;201(10):1615-1625. doi:10.1084/jem.20042307
418. Wang T, Tian L, Haino M, et al. Improved Antibacterial Host Defense and Altered Peripheral Granulocyte Homeostasis in Mice Lacking the Adhesion Class G Protein Receptor CD97. *Infect Immun*. 2006;75(3):1144-1153. doi:10.1128/iai.00869-06
419. Karpus ON, Veninga H, Hoek RM, et al. Shear Stress–Dependent Downregulation of the Adhesion-G Protein–Coupled Receptor CD97 on Circulating Leukocytes upon Contact with Its Ligand CD55. J Immunol. 2013;190(7):3740-3748. doi:10.4049/jimmunol.1202192
420. Liu D, Winer BY, Chou MY, et al. Dynamic encounters with red blood cells trigger splenic marginal zone B cell retention and function. *Nat Immunol*. 2024;25(1):142-154. doi:10.1038/s41590-023-01690-z
421. Maglitto A, Mariani SA, Pater E de, et al. Unexpected redundancy of Gpr56 and Gpr97 during hematopoietic cell development and differentiation. *Blood Adv*. 2021;5(3):829-842. doi:10.1182/bloodadvances.2020003693
422. Pabst C, Bergeron A, Lavallée VP, et al. GPR56 identifies primary human acute myeloid leukemia cells with high repopulating potential in vivo. Blood. 2016;127(16):2018-2027. doi:10.1182/blood-2015-11-683649
423. Martin GH, Roy N, Chakraborty S, et al. CD97 is a critical regulator of acute myeloid leukemia stem cell function. J Exp Med. 2019;216(10):2362-2377. doi:10.1084/jem.20190598
424. Haubner S, Mansilla-Soto J, Nataraj S, et al. Cooperative CAR targeting to selectively eliminate AML and minimize escape. Cancer Cell. 2023;41(11):1871-1891.e6. doi:10.1016/j.ccell.2023.09.010

425. Tseng WY, Wu YJJ, Yang TY, et al. High levels of soluble GPR56/ADGRG1 are associated with positive rheumatoid factor and elevated tumor necrosis factor in patients with rheumatoid arthritis. *J Microbiol, Immunol Infect*. 2017;51(4):485-491. doi:10.1016/j.jmii.2016.11.010
426. Luo Y, Lu J, Lei Z, et al. GPR56 facilitates hepatocellular carcinoma metastasis by promoting the TGF-β signaling pathway. *Cell Death Dis*. 2024;15(10):715. doi:10.1038/s41419-024-07095-6
427. Lewis SM, Treacher DF, Edgeworth J, et al. Expression of CD11c and EMR2 on neutrophils: potential diagnostic biomarkers for sepsis and systemic inflammation. *Clin Exp Immunol*. 2015;182(2):184-194. doi:10.1111/cei.12679
428. Zheng L, Rang M, Fuchs C, et al. The Posttraumatic Increase of the Adhesion GPCR EMR2/ADGRE2 on Circulating Neutrophils Is Not Related to Injury Severity. Cells. 2023;12(22):2657. doi:10.3390/cells12222657
429. Zheng L, Fuchs C, Kleber C, Osterhoff G, Aust G. Long-lasting changes in circulating dendritic cell and monocyte subsets, and altered expression of EMR2, CD97 and EMR3 on these cells in the posttraumatic course. *Clin Transl Immunol*. 2025;14(6):e70040. doi:10.1002/cti2.70040
430. Nagase M, Ando H, Beppu Y, et al. Glomerular Endothelial Cell Receptor Adhesion G-Protein–Coupled Receptor F5 (ADGRF5) and the Integrity of the Glomerular Filtration Barrier. *J Am Soc Nephrol*. 2024;35(10):1366-1380. doi:10.1681/asn.0000000000000427
431. Fu J, Wei C, Zhang W, et al. Gene expression profiles of glomerular endothelial cells support their role in the glomerulopathy of diabetic mice. *Kidney Int*. 2018;94(2):326-345. doi:10.1016/j.kint.2018.02.028
432. Wu J, Wang Z, Cai M, et al. GPR56 Promotes Diabetic Kidney Disease Through eNOS Regulation in Glomerular Endothelial Cells. *Diabetes*. 2023;72(11):1652-1663. doi:10.2337/db23-0124
433. Fang W, Wang Z, Li Q, et al. Gpr97 Exacerbates AKI by Mediating Sema3A Signaling. J Am Soc Nephrol. 2018;29(5):1475-1489. doi:10.1681/asn.2017080932
434. Steichen H, Xue J, Zaidman NA. Identification and localization of adhesion G protein-coupled receptor expression in the murine kidney. *Am J Physiol-Ren Physiol*. 2025;329(1):F11-F19. doi:10.1152/ajprenal.00134.2025
435. Cazorla-Vázquez S, Kösters P, Bertz S, et al. Adhesion GPCR Gpr126 (Adgrg6) Expression Profiling in Zebrafish, Mouse, and Human Kidney. Cells. 2023;12(15):1988. doi:10.3390/cells12151988
436. Li Y, Duan Y, Chu Q, et al. G-protein coupled receptor GPR124 protects against podocyte senescence and injury in diabetic kidney disease. Kidney Int. 2025;107(4):652-665. doi:10.1016/j.kint.2024.12.013
437. Yates LL, Papakrivopoulou J, Long DA, et al. The planar cell polarity gene Vangl2 is required for mammalian kidney-branching morphogenesis and glomerular maturation. Hum Mol Genet. 2010;19(23):4663-4676. doi:10.1093/hmg/ddq397
438. Izutsu T, Konda R, Sugimura J, Iwasaki K, Fujioka T. Brain-Specific Angiogenesis Inhibitor 1 is a Putative Factor for Inhibition of Neovascular Formation in Renal Cell Carcinoma. *J Urol*. 2011;185(6):2353-2358. doi:10.1016/j.juro.2011.02.019
439. Zaidman NA, Tomilin VN, Khayyat NH, et al. Adhesion-GPCR Gpr116 (ADGRF5)

expression inhibits renal acid secretion. Proc Natl Acad Sci. 2020;117(42):26470-26481. doi:10.1073/pnas.2007620117
440. Abe J, Suzuki H, Notoya M, Yamamoto T, Hirose S. Ig-Hepta, a Novel Member of the G Protein-coupled Hepta-helical Receptor (GPCR) Family That Has Immunoglobulin-like Repeats in a Long N-terminal Extracellular Domain and Defines a New Subfamily of GPCRs*. J Biol Chem. 1999;274(28):19957-19964. doi:10.1074/jbc.274.28.19957
441. Lum AM, Wang BB, Beck-Engeser GB, Li L, Channa N, Wabl M. Orphan receptor GPR110, an oncogene overexpressed in lung and prostate cancer. *BMC Cancer*. 2010;10(1):40. doi:10.1186/1471-2407-10-40
442. Harty BL, Krishnan A, Sanchez NE, Schiöth HB, Monk KR. Defining the gene repertoire and spatiotemporal expression profiles of adhesion G protein-coupled receptors in zebrafish. *BMC Genom*. 2015;16(1):62. doi:10.1186/s12864-015-1296-8
443. Cazorla-Vázquez S, Engel FB. Adhesion GPCRs in Kidney Development and Disease. Front Cell Dev Biol. 2018;6:9. doi:10.3389/fcell.2018.00009
444. Poll BG, Chen L, Chou CL, Raghuram V, Knepper MA. Landscape of GPCR expression along the mouse nephron. Am J Physiol-Ren Physiol. 2021;321(1):F50-F68. doi:10.1152/ajprenal.00077.2021
445. Sussman CR, Wang X, Chebib FT, Torres VE. Modulation of polycystic kidney disease by G-protein coupled receptors and cyclic AMP signaling. Cell Signal. 2020;72:109649. doi:10.1016/j.cellsig.2020.109649
446. Pawnikar S, Magenheimer BS, Munoz EN, Maser RL, Miao Y. Mechanism of tethered agonist-mediated signaling by polycystin-1. Proc Natl Acad Sci. 2022;119(19):e2113786119. doi:10.1073/pnas.2113786119
447. Pawnikar S, Magenheimer BS, Joshi K, et al. Activation of polycystin-1 signaling by binding of stalk-derived peptide agonists. eLife. 2024;13:RP95992. doi:10.7554/elife.95992
448. Kösters P, Cazorla-Vázquez S, Krüger R, et al. Adhesion G Protein-Coupled Receptor Gpr126 (Adgrg6) Expression Profiling in Diseased Mouse, Rat, and Human Kidneys. Cells. 2024;13(10):874. doi:10.3390/cells13100874
449. Brzóska HŁ, d'Esposito AM, Kolatsi-Joannou M, et al. Planar cell polarity genes Celsr1 and Vangl2 are necessary for kidney growth, differentiation, and rostrocaudal patterning. Kidney Int. 2016;90(6):1274-1284. doi:10.1016/j.kint.2016.07.011
450. Wu J chao, Wang X jie, Zhu J han, et al. GPR97 deficiency ameliorates renal interstitial fibrosis in mouse hypertensive nephropathy. *Acta Pharmacol Sin*. 2023;44(6):1206-1216. doi:10.1038/s41401-022-01041-y
451. Amisten S, Salehi A, Rorsman P, Jones PM, Persaud SJ. An atlas and functional analysis of G-protein coupled receptors in human islets of Langerhans. *Pharmacol Ther*. 2013;139(3):359-391. doi:10.1016/j.pharmthera.2013.05.004
452. Kaczmarek I, Suchý T, Prömel S, Schöneberg T, Liebscher I, Thor D. The relevance of adhesion G protein-coupled receptors in metabolic functions. Biol Chem. 2022;403(2):195-209. doi:10.1515/hsz-2021-0146
453. Al-Amily IM, Sjögren M, Duner P, Tariq M, Wollheim CB, Salehi A. Ablation of GPR56 Causes β-Cell Dysfunction by ATP Loss through Mistargeting of Mitochondrial VDAC1 to the Plasma Membrane. *Biomolecules*. 2023;13(3):557. doi:10.3390/biom13030557

454. Dunér P, Al-Amily IM, Soni A, et al. Adhesion G Protein-Coupled Receptor G1 (ADGRG1/GPR56) and Pancreatic β-Cell Function. J Clin Endocrinol Metab. 2016;101(12):4637-4645. doi:10.1210/jc.2016-1884
455. Olaniru OE, Pingitore A, Giera S, et al. The adhesion receptor GPR56 is activated by extracellular matrix collagen III to improve β-cell function. *Cell Mol Life Sci*. 2018;75(21):4007-4019. doi:10.1007/s00018-018-2846-4
456. Gupta R, Nguyen DC, Schaid MD, et al. Complement 1q-like-3 protein inhibits insulin secretion from pancreatic β-cells via the cell adhesion G protein–coupled receptor BAI3. J Biol Chem. 2018;293(47):18086-18098. doi:10.1074/jbc.ra118.005403
457. Suchý T, Zieschang C, Popkova Y, et al. The repertoire of Adhesion G protein-coupled receptors in adipocytes and their functional relevance. *Int J Obes*. 2020;44(10):2124-2136. doi:10.1038/s41366-020-0570-2
458. Nie T, Hui X, Gao X, et al. Adipose tissue deletion of Gpr116 impairs insulin sensitivity through modulation of adipose function. FEBS Lett. 2012;586(20):3618-3625. doi:10.1016/j.febslet.2012.08.006
459. Hasan MA, Roy P, Dolan S, Martin PE, Patterson S, Bartholomew C. Adhesion G-protein coupled receptor 56 is required for 3T3-L1 adipogenesis. *J Cell Physiol*. 2020;235(2):1601-1614. doi:10.1002/jcp.29079
460. Ye C, Wang X, Lin J, et al. Systematical identification of regulatory GPCRs by single-cell trajectory inference reveals the role of ADGRD1 and GPR39 in adipogenesis. *Sci China Life Sci*. 2025;68(4):1057-1072. doi:10.1007/s11427-024-2732-8
461. Alsharif H, Latimer MN, Perez KC, et al. Loss of Brain Angiogenesis Inhibitor-3 (BAI3) G-Protein Coupled Receptor in Mice Regulates Adaptive Thermogenesis by Enhancing Energy Expenditure. Metabolites. 2023;13(6):711. doi:10.3390/metabo13060711
462. Zhao Z, Hu L, Song B, et al. Constitutively active receptor ADGRA3 signaling induces adipose thermogenesis. eLife. 2024;13:RP100205. doi:10.7554/elife.100205
463. Harms MJ, Ishibashi J, Wang W, et al. Prdm16 Is Required for the Maintenance of Brown Adipocyte Identity and Function in Adult Mice. *Cell Metab*. 2014;19(4):593-604. doi:10.1016/j.cmet.2014.03.007
464. Fagerberg L, Hallström BM, Oksvold P, et al. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteom : MCP*. 2013;13(2):397-406. doi:10.1074/mcp.m113.035600
465. Wang Y, Wang T, Xiang Q, et al. GPR116 promotes ferroptosis in sepsis-induced liver injury by suppressing system Xc–/GSH/GPX4. *Cell Biol Toxicol*. 2023;39(6):3015-3030. doi:10.1007/s10565-023-09815-8
466. Xiang Q, Li N, Zhang Y, Wang T, Wang Y, Bian J. GPR116 alleviates acetaminophen-induced liver injury in mice by inhibiting endoplasmic reticulum stress. Cell Mol Life Sci. 2024;81(1):299. doi:10.1007/s00018-024-05313-0
467. Wu M, Lo TH, Li L, et al. Amelioration of non-alcoholic fatty liver disease by targeting adhesion G protein-coupled receptor F1 (Adgrf1). eLife. 2023;12:e85131. doi:10.7554/elife.85131
468. Ma B, Zhu J, Tan J, et al. Gpr110 deficiency decelerates carcinogen-induced hepatocarcinogenesis via activation of the IL-6/STAT3 pathway. *Am J cancer Res*. 2017;7(3):433-447.

469. Kathiresan S, Melander O, Guiducci C, et al. Six new loci associated with blood low-density lipoprotein cholesterol, high-density lipoprotein cholesterol or triglycerides in humans. Nat Genet. 2008;40(2):189-197. doi:10.1038/ng.75
470. Tan J, Che Y, Liu Y, et al. CELSR2 deficiency suppresses lipid accumulation in hepatocyte by impairing the UPR and elevating ROS level. FASEB J. 2021;35(10):e21908. doi:10.1096/fj.202100786rr
471. Lin H, Ma C, Zhuang X, et al. Sensing steroid hormone 17α-hydroxypregnenolone by GPR56 enables protection from ferroptosis-induced liver injury. Cell Metab. 2024;36(11):2402-2418.e10. doi:10.1016/j.cmet.2024.09.007
472. Badiali L, Cedernaes J, Olszewski PK, Nylander O, Vergoni AV, Schiöth HB. Adhesion GPCRs are widely expressed throughout the subsections of the gastrointestinal tract. *BMC Gastroenterol*. 2012;12(1):134. doi:10.1186/1471-230x-12-134
473. Ito J, Ito M, Nambu H, et al. Anatomical and histological profiling of orphan G-protein-coupled receptor expression in gastrointestinal tract of C57BL/6J mice. Cell Tissue Res. 2009;338(2):257. doi:10.1007/s00441-009-0859-x
474. Becker S, Wandel E, Wobus M, et al. Overexpression of CD97 in Intestinal Epithelial Cells of Transgenic Mice Attenuates Colitis by Strengthening Adherens Junctions. PLoS ONE. 2010;5(1):e8507. doi:10.1371/journal.pone.0008507
475. Jin G, Sakitani K, Wang H, et al. The G-protein coupled receptor 56, expressed in colonic stem and cancer cells, binds progastrin to promote proliferation and carcinogenesis. *Oncotarget*. 2017;8(25):40606-40619. doi:10.18632/oncotarget.16506
476. Grunddal KV, Tonack S, Egerod KL, et al. Adhesion receptor ADGRG2/GPR64 is in the GI-tract selectively expressed in mature intestinal tuft cells. *Mol Metab*. 2021;51:101231. doi:10.1016/j.molmet.2021.101231
477. Leja J, Essaghir A, Essand M, et al. Novel markers for enterochromaffin cells and gastrointestinal neuroendocrine carcinomas. *Modern Pathol*. 2009;22(2):261-272. doi:10.1038/modpathol.2008.174
478. Hofmann F, Thalheim T, Rother K, et al. How to Obtain a Mega-Intestine with Normal Morphology: In Silico Modelling of Postnatal Intestinal Growth in a Cd97-Transgenic Mouse. Int J Mol Sci. 2021;22(14):7345. doi:10.3390/ijms22147345
479. Lee CS, Penberthy KK, Wheeler KM, et al. Boosting Apoptotic Cell Clearance by Colonic Epithelial Cells Attenuates Inflammation In Vivo. *Immunity*. 2016;44(4):807-820. doi:10.1016/j.immuni.2016.02.005
480. Ni YY, Chen Y, Lu SY, et al. Deletion of Gpr128 results in weight loss and increased intestinal contraction frequency. *World J Gastroenterol*. 2014;20(2):498-508. doi:10.3748/wjg.v20.i2.498
481. Acién M, Acién P. Female Genital Tract Congenital Malformations, Classification, Diagnosis and Management. Published online 2014:3-14. doi:10.1007/978-1-4471-5146-3_1
482. Kvam JM, Nybo ML, Torz L, et al. High incidence of imperforate vagina in ADGRA3-deficient mice. *BMC Biol*. 2024;22(1):77. doi:10.1186/s12915-024-01873-6
483. Roly ZY, Major AT, Fulcher A, Estermann M, Hirst CE, Smith C. Adhesion G-protein coupled receptor, GPR56, is required for Müllerian duct development in the chick. *J Endocrinol*. 2019;1(aop):395-413. doi:10.1530/joe-19-0419
484. Langenhan T, Prömel S, Mestek L, et al. Latrophilin signaling links anterior-posterior

tissue polarity and oriented cell divisions in the C. elegans embryo. Dev Cell. 2009;17(4):494-504. doi:10.1016/j.devcel.2009.08.008
485. vandenBerg AL, Sassoon DA. Non-canonical Wnt signaling regulates cell polarity in female reproductive tract development via van gogh-like 2. Development. 2009;136(9):1559-1570. doi:10.1242/dev.034066
486. Murata T, Ishitsuka Y, Karouji K, et al. β-cateninC429S mice exhibit sterility consequent to spatiotemporally sustained Wnt signalling in the internal genitalia. Sci Rep. 2014;4(1):6959. doi:10.1038/srep06959
487. Steinhart Z, Angers S. Wnt signaling in development and tissue homeostasis. Development. 2018;145(11):dev146589. doi:10.1242/dev.146589
488. St-Jean G, Boyer A, Zamberlam G, Godin P, Paquet M, Boerboom D. Targeted ablation of Wnt4 and Wnt5a in Müllerian duct mesenchyme impedes endometrial gland development and causes partial Müllerian agenesis. *Biol Reprod*. 2019;100(1):49-60. doi:10.1093/biolre/ioy160
489. Bagger SM, Schihada H, Walser ALS, et al. Complex G-protein signaling of the adhesion GPCR, ADGRA3. J Biol Chem. 2025;301(5):108441. doi:10.1016/j.jbc.2025.108441
490. Fu J, Yen T, Chen Y, et al. Involvement of Gpr125 in the myeloid sarcoma formation induced by cooperating MLL/AF10(OM-LZ) and oncogenic KRAS in a mouse bone marrow transplantation model. *Int J Cancer*. 2013;133(8):1792-1802. doi:10.1002/ijc.28195
491. James RG, Biechele TL, Conrad WH, et al. Bruton's Tyrosine Kinase Revealed as a Negative Regulator of Wnt–β-Catenin Signaling. Sci Signal. 2009;2(72):ra25. doi:10.1126/scisignal.2000230
492. Wu Y, Chen W, Gong L, Ke C, Wang H, Cai Y. Elevated G-Protein Receptor 125 (GPR125) Expression Predicts Good Outcomes in Colorectal Cancer and Inhibits Wnt/β-Catenin Signaling Pathway. *Méd Sci Monit : Int Méd J Exp Clin Res*. 2018;24:6608-6616. doi:10.12659/msm.910105
493. Ganesh RA, Venkataraman K, Sirdeshmukh R. GPR56 signaling pathway network and its dynamics in the mesenchymal transition of glioblastoma. *J Cell Commun Signal*. 2023;17(4):1527-1535. doi:10.1007/s12079-023-00792-5
494. Yoo JY, Ahn JI, Kim TH, et al. G-protein coupled receptor 64 is required for decidualization of endometrial stromal cells. Sci Rep. 2017;7(1):5021. doi:10.1038/s41598-017-05165-8
495. Shen H, Jin M, Gu S, Wu Y, Yang M, Hua X. CD97 Is Decreased in Preeclamptic Placentas and Promotes Human Trophoblast Invasion Through PI3K/Akt/mTOR Signaling Pathway. *Reprod Sci*. 2020;27(8):1553-1561. doi:10.1007/s43032-020-00183-w
496. An W, Lin H, Ma L, et al. Progesterone activates GPR126 to promote breast cancer development via the Gi pathway. Proc Natl Acad Sci. 2022;119(15):e2117004119. doi:10.1073/pnas.2117004119
497. Bianchi E, Sun Y, Almansa-Ordonez A, et al. Control of oviductal fluid flow by the G-protein coupled receptor Adgrd1 is essential for murine embryo transit. Nat Commun. 2021;12(1):1251. doi:10.1038/s41467-021-21512-w
498. Nybo ML, Kvam JM, Nielsen JE, et al. Loss of Adgra3 causes obstructive azoospermia with high penetrance in male mice. FASEB J. 2023;37(2):e22781.

doi:10.1096/fj.202200762rr
499. Chen G, Yang L, Begum S, Xu L. GPR56 is essential for testis development and male fertility in mice. Dev Dyn. 2010;239(12):3358-3367. doi:10.1002/dvdy.22468
500. Davies B, Behnen M, Cappallo-Obermann H, Spiess A, Theuring F, Kirchhoff C. Novel epididymis-specific mRNAs downregulated by HE6/Gpr64 receptor gene disruption. *Mol Reprod Dev*. 2007;74(5):539-553. doi:10.1002/mrd.20636
501. Kirchhoff C, Osterhoff C, Samalecos A. HE6/GPR64 adhesion receptor co-localizes with apical and subapical F-actin scaffold in male excurrent duct epithelia. *Reproduction*. 2008;136(2):235-245. doi:10.1530/rep-08-0078
502. Obermann H, Samalecos A, Osterhoff C, Schröder B, Heller R, Kirchhoff C. HE6, a two-subunit heptahelical receptor associated with apical membranes of efferent and epididymal duct epithelia. Mol Reprod Dev. 2003;64(1):13-26. doi:10.1002/mrd.10220
503. Davies B, Baumann C, Kirchhoff C, et al. Targeted Deletion of the Epididymal Receptor HE6 Results in Fluid Dysregulation and Male Infertility. Mol Cell Biol. 2004;24(19):8642-8648. doi:10.1128/mcb.24.19.8642-8648.2004
504. Khan MJ, Pollock N, Jiang H, et al. X-linked ADGRG2 mutation and obstructive azoospermia in a large Pakistani family. Sci Rep. 2018;8(1):16280. doi:10.1038/s41598-018-34262-5
505. Patat O, Pagin A, Siegfried A, et al. Truncating Mutations in the Adhesion G Protein-Coupled Receptor G2 Gene ADGRG2 Cause an X-Linked Congenital Bilateral Absence of Vas Deferens. Am J Hum Genet. 2016;99(2):437-442. doi:10.1016/j.ajhg.2016.06.012
506. Yuan P, Liang ZK, Liang H, et al. Expanding the phenotypic and genetic spectrum of Chinese patients with congenital absence of vas deferens bearing CFTR and ADGRG2 alleles. *Andrology*. 2019;7(3):329-340. doi:10.1111/andr.12592
507. Yin GN, Kim DK, Kang JI, et al. Latrophilin-2 is a novel receptor of LRG1 that rescues vascular and neurological abnormalities and restores diabetic erectile function. *Exp Mol Med*. 2022;54(5):626-638. doi:10.1038/s12276-022-00773-5
508. Aust G, Eichler W, Laue S, et al. CD97: a dedifferentiation marker in human thyroid carcinomas. Cancer Res. 1997;57(9):1798-1806.
509. Shi W, Xu C, Lei P, et al. A correlation study of adhesion G protein-coupled receptors as potential therapeutic targets for breast cancer. *Breast Cancer Res Treat*. 2024;207(2):417-434. doi:10.1007/s10549-024-07373-z
510. Ravn-Boess N, Roy N, Hattori T, et al. The expression profile and tumorigenic mechanisms of CD97 (ADGRE5) in glioblastoma render it a targetable vulnerability. Cell Rep. 2023;42(11):113374. doi:10.1016/j.celrep.2023.113374
511. Gad AA, Balenga N. The Emerging Role of Adhesion GPCRs in Cancer. *ACS Pharmacol Transl Sci*. 2020;3(1):29-42. doi:10.1021/acsptsci.9b00093
512. Yang J, Wu S, Alachkar H. Corrigendum to "Characterization of upregulated adhesion GPCRs in acute myeloid leukemia" [*Transl Res*. 2019 Oct:212:26-35. doi: 10.1016/j.trsl.2019.05.004. Epub 2019 May 17.]. Transl Res. 2025;275:62. doi:10.1016/j.trsl.2024.11.003
513. Yang J, Wu S, Alachkar H. Characterization of upregulated adhesion GPCRs in acute myeloid leukemia. Transl Res. 2019;212:26-35. doi:10.1016/j.trsl.2019.05.004
514. Stephan G, Ravn-Boess N, Placantonakis DG. Adhesion G protein-coupled receptors in

glioblastoma. *Neuro-Oncol Adv*. 2021;3(1):vdab046. doi:10.1093/noajnl/vdab046
515. Lei P, Wang H, Yu L, et al. A correlation study of adhesion G protein-coupled receptors as potential therapeutic targets in Uterine Corpus Endometrial cancer. *Int Immunopharmacol*. 2022;108:108743. doi:10.1016/j.intimp.2022.108743
516. Ng KF, Chen TC, Stacey M, Lin HH. Role of ADGRG1/GPR56 in Tumor Progression. Cells. 2021;10(12):3352. doi:10.3390/cells10123352
517. Moreno M, Pedrosa L, Paré L, et al. GPR56/ADGRG1 Inhibits Mesenchymal Differentiation and Radioresistance in Glioblastoma. Cell Rep. 2017;21(8):2183-2197. doi:10.1016/j.celrep.2017.10.083
518. Frenster JD, Kader M, Kamen S, et al. Expression profiling of the adhesion G protein-coupled receptor GPR133 (ADGRD1) in glioma subtypes. Neuro-Oncol Adv. 2020;2(1):vdaa053. doi:10.1093/noajnl/vdaa053
519. Zhang S, Zhang Y, Sun X. Targeting GPR133 via miR-106a-5p inhibits the proliferation, invasion, migration and epithelial-mesenchymal transition (EMT) of glioma cells. *Int J Neurosci*. 2024;134(9):991-1002. doi:10.1080/00207454.2023.2201873
520. Wu G, Zhai D, Xie J, et al. N6-methyladenosine (m6A) RNA modification of G protein-coupled receptor 133 increases proliferation of lung adenocarcinoma. *FEBS Open Bio*. 2022;12(3):571-581. doi:10.1002/2211-5463.13244
521. Zhou LL, Jiao Y, Chen HM, et al. Differentially expressed long noncoding RNAs and regulatory mechanism of LINC02407 in human gastric adenocarcinoma. World J Gastroenterol. 2019;25(39):5973-5990. doi:10.3748/wjg.v25.i39.5973
522. Lv M, Li X, Tian W, Yang H, Zhou B. ADGRD1 as a Potential Prognostic and Immunological Biomarker in Non-Small-Cell Lung Cancer. *BioMed Res Int*. 2022;2022(1):5699892. doi:10.1155/2022/5699892
523. Jaspars LH, Vos W, Aust G, Lier RAWV, Hamann J. Tissue distribution of the human CD97 EGF-TM7 receptor. *Tissue Antigens*. 2001;57(4):325-331. doi:10.1034/j.1399-0039.2001.057004325.x
524. Safaee M, Ivan ME, Oh MC, et al. The role of epidermal growth factor-like module containing mucin-like hormone receptor 2 in human cancers. *Oncol Rev*. 2013;8(1):242. doi:10.4081/oncol.2014.242
525. Tjong WY, Lin HH. The RGD motif is involved in CD97/ADGRE5-promoted cell adhesion and viability of HT1080 cells. Sci Rep. 2019;9(1):1517. doi:10.1038/s41598-018-38045-w
526. Hsiao CC, Keysselt K, Chen HY, et al. The Adhesion GPCR CD97/ADGRE5 inhibits apoptosis. *Int J Biochem Cell Biol*. 2015;65:197-208. doi:10.1016/j.biocel.2015.06.007
527. BUZATU IM, COSTACHI A, DOCEA AO, MANEA EV, ZLATIAN O. Research Progress of EMR2 Receptor Function in Glioma and its Potential Application as Therapeutic Target. *Curr Heal Sci J*. 2024;50(4):467-477. doi:10.12865/chsj.50.04.02
528. Safaee M, Fakurnejad S, Bloch O, et al. Proportional Upregulation of CD97 Isoforms in Glioblastoma and Glioblastoma-Derived Brain Tumor Initiating Cells. PLoS ONE. 2015;10(2):e0111532. doi:10.1371/journal.pone.0111532
529. Liu JK, Lubelski D, Schonberg DL, et al. Phage display discovery of novel molecular targets in glioblastoma-initiating cells. *Cell Death Differ*. 2014;21(8):1325-1339. doi:10.1038/cdd.2014.65

530. Safaee M, Clark AJ, Oh MC, et al. Overexpression of CD97 Confers an Invasive Phenotype in Glioblastoma Cells and Is Associated with Decreased Survival of Glioblastoma Patients. PLoS ONE. 2013;8(4):e62765. doi:10.1371/journal.pone.0062765
531. Yang R, Zhang W, Shang X, et al. Neutrophil-related genes predict prognosis and response to immune checkpoint inhibitors in bladder cancer. *Front Pharmacol*. 2022;13:1013672. doi:10.3389/fphar.2022.1013672
532. Feliciano A, Garcia-Mayea Y, Jubierre L, et al. miR-99a reveals two novel oncogenic proteins E2F2 and EMR2 and represses stemness in lung cancer. Cell Death Dis. 2017;8(10):e3141-e3141. doi:10.1038/cddis.2017.544
533. Davies JQ, Lin HH, Stacey M, et al. Leukocyte adhesion-GPCR EMR2 is aberrantly expressed in human breast carcinomas and is associated with patient survival. *Oncol Rep*. 2011;25(3):619-627. doi:10.3892/or.2010.1117
534. Mirkowska P, Hofmann A, Sedek L, et al. Leukemia surfaceome analysis reveals new disease-associated features. Blood. 2013;121(25):e149-e159. doi:10.1182/blood-2012-11-468702
535. Santorelli L, Capitoli G, Chinello C, et al. In-Depth Mapping of the Urinary N-Glycoproteome: Distinct Signatures of ccRCC-related Progression. *Cancers*. 2020;12(1):239. doi:10.3390/cancers12010239
536. Wu J, Lei L, Wang S, Gu D, Zhang J. Immunohistochemical Expression and Prognostic Value of CD97 and Its Ligand CD55 in Primary Gallbladder Carcinoma. BioMed Res Int. 2012;2012(1):587672. doi:10.1155/2012/587672
537. He Y, Wang W, Xu L, et al. Immunohistochemical Expression and Prognostic Significance of CD97 and its Ligand DAF in Human Cervical Squamous Cell Carcinoma. *Int J Gynecol Pathol*. 2015;34(5):473-479. doi:10.1097/pgp.0000000000000200
538. Mustafa T, Eckert A, Klonisch T, et al. Expression of the epidermal growth factor seven-transmembrane member CD97 correlates with grading and staging in human oral squamous cell carcinomas. *Cancer epidemiology, Biomark Prev : a Publ Am Assoc Cancer Res, cosponsored Am Soc Prev Oncol*. 2005;14(1):108-119.
539. Mustafa T, Klonisch T, Hombach-Klonisch S, et al. Expression of CD97 and CD55 in human medullary thyroid carcinomas. *Int J Oncol*. 2004;24(2):285-294.
540. Rutkowski MJ, Sughrue ME, Kane AJ, Kim JM, Bloch O, Parsa AT. Epidermal growth factor module-containing mucin-like receptor 2 is a newly identified adhesion G protein-coupled receptor associated with poor overall survival and an invasive phenotype in glioblastoma. *J Neuro-Oncol*. 2011;105(2):165-171. doi:10.1007/s11060-011-0576-7
541. Slepak TI, Guyot M, Walters W, Eichberg DG, Ivan ME. Dual role of the adhesion G-protein coupled receptor ADRGE5/CD97 in glioblastoma invasion and proliferation. J Biol Chem. 2023;299(9):105105. doi:10.1016/j.jbc.2023.105105
542. Zhang X, Zhang X, Yang Q, et al. Comprehensive analysis of ADGRE5 gene in human tumors: Clinical relevance, prognostic implications, and potential for personalized immunotherapy. *Heliyon*. 2024;10(6):e27459. doi:10.1016/j.heliyon.2024.e27459
543. Aust G, Steinert M, Schütz A, et al. CD97, but Not Its Closely Related EGF-TM7 Family Member EMR2, Is Expressed on Gastric, Pancreatic, and Esophageal Carcinomas. *Am J Clin Pathol*. 2002;118(5):699-707. doi:10.1309/a6ab-vf3f-7m88-c0ej
544. Steinert M, Wobus M, Boltze C, et al. Expression and regulation of CD97 in colorectal

carcinoma cell lines and tumor tissues. *The American journal of pathology*. 2002;161(5):1657-1667. doi:10.1016/s0002-9440(10)64443-4
545. Yin Y, Xu X, Tang J, et al. CD97 Promotes Tumor Aggressiveness Through the Traditional G Protein–Coupled Receptor–Mediated Signaling in Hepatocellular Carcinoma. *Hepatology*. 2018;68(5):1865-1878. doi:10.1002/hep.30068
546. Li C, Liu DR, Li GG, et al. CD97 promotes gastric cancer cell proliferation and invasion through exosome-mediated MAPK signaling pathway. World J Gastroenterol. 2015;21(20):6215-6228. doi:10.3748/wjg.v21.i20.6215
547. Zhou S, Lin W, Jin X, et al. CD97 maintains tumorigenicity of glioblastoma stem cells via mTORC2 signaling and is targeted by CAR Th9 cells. *Cell Rep Med*. 2024;5(12):101844. doi:10.1016/j.xcrm.2024.101844
548. Cherry AE, Vicente JJ, Xu C, et al. GPR124 regulates microtubule assembly, mitotic progression, and glioblastoma cell proliferation. Glia. 2019;67(8):1558-1570. doi:10.1002/glia.23628
549. Spina E, Simundza J, Incassati A, et al. Gpr125 is a unifying hallmark of multiple mammary progenitors coupled to tumor latency. Nat Commun. 2022;13(1):1421. doi:10.1038/s41467-022-28937-x
550. Kaur B, Brat DJ, Calkins CC, Van Meir EG. Brain Angiogenesis Inhibitor 1 Is Differentially Expressed in Normal Brain and Glioblastoma Independently of p53 Expression. *Am J Pathol*. 2003;162(1):19-27. doi:10.1016/s0002-9440(10)63794-7
551. Shiratsuchi T, Nishimori H, Ichise H, Nakamura Y, Tokino T. Cloning and characterization of BAI2 and BAI3, novel genes homologous to brain-specific angiogenesis inhibitor 1 (BAI1). *Cytogenet Genome Res*. 1997;79(1-2):103-108. doi:10.1159/000134693
552. Kan Z, Jaiswal BS, Stinson J, et al. Diverse somatic mutation patterns and pathway alterations in human cancers. Nature. 2010;466(7308):869-873. doi:10.1038/nature09208
553. Kee HJ, Ahn KY, Choi KC, et al. Expression of brain-specific angiogenesis inhibitor 3 (BAI3) in normal brain and implications for BAI3 in ischemia-induced brain angiogenesis and malignant glioma. FEBS Lett. 2004;569(1-3):307-316. doi:10.1016/j.febslet.2004.06.011
554. Zhu D, Hunter SB, Vertino PM, Van Meir EG. Overexpression of MBD2 in Glioblastoma Maintains Epigenetic Silencing and Inhibits the Antiangiogenic Function of the Tumor Suppressor Gene BAI1. Cancer Res. 2011;71(17):5859-5870. doi:10.1158/0008-5472.can-11-1157
555. Meng ZW, Zhang L, Cai XR, Wang X, She FF, Chen YL. Author Correction: IL-8 is a novel prometastatic chemokine in intrahepatic cholangiocarcinoma that induces CXCR2-PI3K/AKT signaling upon CD97 activation. Sci Rep. 2024;14(1):8478. doi:10.1038/s41598-024-58952-5
556. Huang Q, Liu L, Xiao D, et al. CD44+ lung cancer stem cell-derived pericyte-like cells cause brain metastases through GPR124-enhanced trans-endothelial migration. Cancer Cell. 2023;41(9):1621-1636.e8. doi:10.1016/j.ccell.2023.07.012
557. Hsiao C, Wang W, Kuo W, et al. CD97 inhibits cell migration in human fibrosarcoma cells by modulating TIMP-2/MT1- MMP/MMP-2 activity – role of GPS autoproteolysis and functional cooperation between the N- and C-terminal fragments. FEBS J. 2014;281(21):4878-4891. doi:10.1111/febs.13027
558. Wobus M, Huber O, Hamann J, Aust G. CD97 overexpression in tumor cells at the

invasion front in colorectal cancer (CC) is independently regulated of the canonical Wnt pathway. *Mol Carcinog*. 2006;45(11):881-886. doi:10.1002/mc.20262
559. Liu D, Li C, Trojanowicz B, et al. CD97 promotion of gastric carcinoma lymphatic metastasis is exosome dependent. *Gastric Cancer*. 2016;19(3):754-766. doi:10.1007/s10120-015-0523-y
560. Eichberg DG, Slepak TI, Pascoini AL, Komotar RJ, Ivan ME. Genetic manipulation of adhesion GPCR CD97/ADGRE5 modulates invasion in patient-derived glioma stem cells. J Neuro-Oncol. 2021;153(3):383-391. doi:10.1007/s11060-021-03778-8
561. Meng ZW, Zhang L, Cai XR, Wang X, She FF, Chen YL. IL-8 is a novel prometastatic chemokine in intrahepatic cholangiocarcinoma that induces CXCR2-PI3K/AKT signaling upon CD97 activation. Sci Rep. 2023;13(1):18711. doi:10.1038/s41598-023-45496-3
562. Galle J, Sittig D, Hanisch I, et al. Individual Cell-Based Models of Tumor-Environment Interactions Multiple Effects of CD97 on Tumor Invasion. Am J Pathol. 2006;169(5):1802-1811. doi:10.2353/ajpath.2006.060006
563. Chidambaram A, Fillmore HL, Meter TEV, Dumur CI, Broaddus WC. Novel report of expression and function of CD97 in malignant gliomas: correlation with Wilms tumor 1 expression and glioma cell invasiveness: Laboratory investigation. *J Neurosurg*. 2012;116(4):843-853. doi:10.3171/2011.11.jns111455
564. Ward Y, Lake R, Faraji F, et al. Platelets Promote Metastasis via Binding Tumor CD97 Leading to Bidirectional Signaling that Coordinates Transendothelial Migration. Cell Rep. 2018;23(3):808-822. doi:10.1016/j.celrep.2018.03.092
565. Garofano K, Rashid K, Smith M, et al. Prostate cancer cell-platelet bidirectional signaling promotes calcium mobilization, invasion and apoptotic resistance via distinct receptor-ligand pairs. Sci Rep. 2023;13(1):2864. doi:10.1038/s41598-023-29450-x
566. Liu Y, Chen L, Peng S, et al. The expression of CD97EGF and its ligand CD55 on marginal epithelium is related to higher stage and depth of tumor invasion of gastric carcinomas. Oncol Rep. 2005;14(6):1413-1420.
567. Ali H, Olsson L, Lindmark G, Hammarström ML, Hammarström S, Sitohy B. The myeloid cell biomarker EMR1 is ectopically expressed in colon cancer. *Tumor Biol*. 2021;43(1):209-223. doi:10.3233/tub-200082
568. Aust G, Zheng L, Quaas M. To Detach, Migrate, Adhere, and Metastasize: CD97/ADGRE5 in Cancer. Cells. 2022;11(9):1538. doi:10.3390/cells11091538
569. Akter R, Park R, Lee SK, et al. Upregulation of EMR1 (ADGRE1) by Tumor-Associated Macrophages Promotes Colon Cancer Progression by Activating the JAK2/STAT1,3 Signaling Pathway in Tumor Cells. Int J Mol Sci. 2024;25(8):4388. doi:10.3390/ijms25084388
570. Posokhova E, Shukla A, Seaman S, et al. GPR124 Functions as a WNT7-Specific Coactivator of Canonical β-Catenin Signaling. Cell Rep. 2015;10(2):123-130. doi:10.1016/j.celrep.2014.12.020
571. Teramoto Y, Najafi MAE, Matsukawa T, Sharma A, Goto T, Miyamoto H. Latrophilins as Downstream Effectors of Androgen Receptors including a Splice Variant, AR-V7, Induce Prostate Cancer Progression. Int J Mol Sci. 2024;25(13):7289. doi:10.3390/ijms25137289
572. Goto T, Yasui M, Teramoto Y, Nagata Y, Mizushima T, Miyamoto H. Latrophilin-3 as a downstream effector of the androgen receptor induces urothelial tumorigenesis. Mol

Carcinog. 2024;63(10):1847-1854. doi:10.1002/mc.23783
573. Avila-Zozaya M, Rodríguez-Hernández B, Monterrubio-Ledezma F, Cisneros B, Boucard AA. Thwarting of Lphn3 Functions in Cell Motility and Signaling by Cancer-Related GAIN Domain Somatic Mutations. Cells. 2022;11(12):1913. doi:10.3390/cells11121913
574. Goto T, Teramoto Y, Nagata Y, Miyamoto H. Latrophilin-3 as a downstream effector of the androgen receptor induces bladder cancer progression. *Discov Oncol*. 2024;15(1):440. doi:10.1007/s12672-024-01324-2
575. Shashidhar S, Lorente G, Nagavarapu U, et al. GPR56 is a GPCR that is overexpressed in gliomas and functions in tumor cell adhesion. Oncogene. 2005;24(10):1673-1682. doi:10.1038/sj.onc.1208395
576. Geng G, Zhang L, Yu Y, Guo X, Li Q, Ming M. ADGRL4 Promotes Cell Growth, Aggressiveness, EMT, and Angiogenesis in Neuroblastoma via Activation of ERK/STAT3 Pathway. Curr Mol Med. 2025;25(1):45-55. doi:10.2174/0115665240254765231117122210
577. Santiago JG, Burgos-Tirado N, Lafontaine DD, et al. Adhesion G protein-coupled receptor, ELTD1, is a potential therapeutic target for retinoblastoma migration and invasion. BMC Cancer. 2021;21(1):53. doi:10.1186/s12885-020-07768-3
578. Li J, Shen J, Wang Z, et al. ELTD1 facilitates glioma proliferation, migration and invasion by activating JAK/STAT3/HIF-1α signaling axis. Sci Rep. 2019;9(1):13904. doi:10.1038/s41598-019-50375-x
579. Sun J, Zhang Z, Chen J, Xue M, Pan X. ELTD1 promotes invasion and metastasis by activating MMP2 in colorectal cancer. *Int J Biol Sci*. 2021;17(12):3048-3058. doi:10.7150/ijbs.62293
580. Zuo J, Zheng A, Wang X, et al. Upregulation of CELSR1 expression promotes ovarian cancer cell proliferation, migration, and invasion. *Méd Oncol*. 2023;41(1):10. doi:10.1007/s12032-023-02232-1
581. Li Y, Zhu L, Hao R, Li Y, Zhao Q, Li S. Systematic expression analysis of the CELSR family reveals the importance of CELSR3 in human lung adenocarcinoma. *J Cell Mol Med*. 2021;25(9):4349-4362. doi:10.1111/jcmm.16497
582. Emmenis LV, Ku SY, Gayvert K, et al. The identification of CELSR3 and other potential cell surface targets in neuroendocrine prostate cancer. *Cancer Res Commun*. 2023;3(8):1447-1459. doi:10.1158/2767-9764.crc-22-0491
583. Li J, Meng Z, Cao Z, et al. ADGRE5-centered Tsurv model in T cells recognizes responders to neoadjuvant cancer immunotherapy. Front Immunol. 2024;15:1304183. doi:10.3389/fimmu.2024.1304183
584. Su Q, Li L, Li X, et al. CD97 serves as a novel biomarker of immune cell infiltration in hepatocellular carcinoma. *World J Surg Oncol*. 2022;20(1):382. doi:10.1186/s12957-022-02829-2
585. VOGL UM, ÖHLER L, RASIC M, FRISCHER JM, MODAK M, STÖCKL J. Evaluation of Prognostic Immune Signatures in Patients with Breast, Colorectal and Pancreatic Cancer Receiving Chemotherapy. *Anticancer Res*. 2017;37(4):1947-1955. doi:10.21873/anticanres.11535
586. Xiang S, Li J, Shen J, et al. Identification of Prognostic Genes in the Tumor Microenvironment of Hepatocellular Carcinoma. Front Immunol. 2021;12:653836.

doi:10.3389/fimmu.2021.653836
587. Yoon JW, Kim KM, Cho S, et al. Th1-poised naive CD4 T cell subpopulation reflects anti-tumor immunity and autoimmune disease. Nat Commun. 2025;16(1):1962. doi:10.1038/s41467-025-57237-3
588. Sheldon H, Bridges E, Silva I, et al. ADGRL4/ELTD1 expression in breast cancer cells induces vascular normalisation and immune suppression. *Mol Cancer Res*. 2021;19(11):molcanres.MCR-21-0171-A.2021. doi:10.1158/1541-7786.mcr-21-0171
589. Liu C, Liu T, Hu Y, et al. G Protein–Coupled Receptor 56 Characterizes CTLs and Reflects the Progression of Lung Cancer Patients. J Immunol. 2023;211(4):683-692. doi:10.4049/jimmunol.2101048
590. Mei Y, Liu Y, Liu W, et al. Identifying ADGRG1 as a specific marker for tumor-reactive T cells in acute myeloid leukemia. *Exp Hematol Oncol*. 2024;13(1):92. doi:10.1186/s40164-024-00560-0
591. Mathioudaki A, Wang X, Sedloev D, et al. The remission status of AML patients after allo-HCT is associated with a distinct single-cell bone marrow T-cell signature. Blood. 2024;143(13):1269-1281. doi:10.1182/blood.2023021815
592. Zheng C, Fass JN, Shih YP, et al. Transcriptomic profiles of neoantigen-reactive T cells in human gastrointestinal cancers. Cancer Cell. 2022;40(4):410-423.e7. doi:10.1016/j.ccell.2022.03.005
593. Jacquier A, Lambert T, Delattre JF, et al. Tumor infiltrating and peripheral CD4+ILT2+ T cells are a cytotoxic subset selectively inhibited by HLA-G in clear cell renal cell carcinoma patients. *Cancer Lett*. 2021;519:105-116. doi:10.1016/j.canlet.2021.06.018
594. Yang Y, Wen D, Lin F, et al. Suppression of non-muscle myosin II boosts T cell cytotoxicity against tumors. Sci Adv. 2024;10(44):eadp0631. doi:10.1126/sciadv.adp0631
595. Favara DM, Banham AH, Harris AL. A review of ELTD1, a pro-angiogenic adhesion GPCR. *Biochem Soc Trans*. 2014;42(6):1658-1664. doi:10.1042/bst20140216
596. Zalles M, Smith N, Saunders D, et al. A tale of two multi-focal therapies for glioblastoma: An antibody targeting ELTD1 and nitrone-based OKN-007. J Cell Mol Med. 2022;26(2):570-582. doi:10.1111/jcmm.17133
597. Zalles M, Smith N, Saunders D, et al. ELTD1 as a multi-focal target for malignant gliomas: preclinical studies. Neuro-Oncol Adv. 2021;3(1):vdab132. doi:10.1093/noajnl/vdab132
598. Shi J, Zhang X, Wang S, et al. Gpr97 is dispensable for metabolic syndrome but is involved in macrophage inflammation in high-fat diet-induced obesity in mice. Sci Rep. 2016;6(1):24649. doi:10.1038/srep24649
599. Rosenkilde MM, Tsutsumi N, Knerr JM, Kildedal DF, Garcia KC. Viral G Protein–Coupled Receptors Encoded by β- and γ-Herpesviruses. *Annu Rev Virol*. 2022;9(1):329-351. doi:10.1146/annurev-virology-100220-113942
600. Spiess K, Rosenkilde MM. G Protein-Coupled Receptor Genetics, Research and Methods in the Post-Genomic Era. *Methods Pharmacol Toxicol*. Published online 2013:45-65. doi:10.1007/978-1-62703-779-2_3
601. Dragic T, Litwin V, Allaway GP, et al. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. Nature. 1996;381(6584):667-673. doi:10.1038/381667a0
602. Chang J, Mancuso MR, Maier C, et al. Gpr124 is essential for blood–brain barrier

integrity in central nervous system disease. *Nat Med*. 2017;23(4):450-460. doi:10.1038/nm.4309
603. Pickering C, Hägglund M, Szmydynger-Chodobska J, et al. The Adhesion GPCR GPR125 is specifically expressed in the choroid plexus and is upregulated following brain injury. *Bmc Neurosci*. 2008;9(1):97. doi:10.1186/1471-2202-9-97
604. Karki P, Ke Y, Zhang C, et al. GPR68 Mediates Lung Endothelial Dysfunction Caused by Bacterial Inflammation and Tissue Acidification. Cells. 2024;13(24):2125. doi:10.3390/cells13242125
605. Nijmeijer S, Vischer HF, Leurs R. Adhesion GPCRs in immunology. *Biochem Pharmacol*. 2016;114:88-102. doi:10.1016/j.bcp.2016.04.013
606. Hamann J, Hsiao CC, Lee CS, Ravichandran KS, Lin HH. Adhesion G Protein-coupled Receptors, Molecular, Physiological and Pharmacological Principles in Health and Disease. Handb Exp Pharmacol. 2016;234(4):329-350. doi:10.1007/978-3-319-41523-9_15
607. Nahalka J. 1-L Transcription of SARS-CoV-2 Spike Protein S1 Subunit. Int J Mol Sci. 2024;25(8):4440. doi:10.3390/ijms25084440
608. Wanjalla CN, McDonnell WJ, Barnett L, et al. Adipose Tissue in Persons With HIV Is Enriched for CD4+ T Effector Memory and T Effector Memory RA+ Cells, Which Show Higher CD69 Expression and CD57, CX3CR1, GPR56 Co-expression With Increasing Glucose Intolerance. Front Immunol. 2019;10:408. doi:10.3389/fimmu.2019.00408
609. Woznik M, Rödner C, Lemon K, Rima B, Mankertz A, Finsterbusch T. Mumps virus small hydrophobic protein targets ataxin-1 ubiquitin-like interacting protein (ubiquilin 4). *J Gen Virol*. 2010;91(11):2773-2781. doi:10.1099/vir.0.024638-0
610. MARIE RM, KATJA S, TORZ PLJ, NYBO HML, KATRINE Q. SMALL HYDROPHOBIC PROTEIN DRUG CONJUGATES AND USES THEREOF. Published online 2024.
611. Elliott MR, Zheng S, Park D, et al. Unexpected requirement for ELMO1 in clearance of apoptotic germ cells in vivo. Nature. 2010;467(7313):333-337. doi:10.1038/nature09356
612. Penberthy KK, Ravichandran KS. Apoptotic cell recognition receptors and scavenger receptors. *Immunol Rev*. 2016;269(1):44-59. doi:10.1111/imr.12376
613. Mathema VB, Na-Bangchang K. Regulatory roles of brain-specific angiogenesis inhibitor 1(BAI1) protein in inflammation, tumorigenesis and phagocytosis: A brief review. *Crit Rev OncolHematol*. 2017;111:81-86. doi:10.1016/j.critrevonc.2017.01.006
614. Mazaheri F, Breus O, Durdu S, et al. Distinct roles for BAI1 and TIM-4 in the engulfment of dying neurons by microglia. Nat Commun. 2014;5(1):4046. doi:10.1038/ncomms5046
615. Das S, Sarkar A, Ryan KA, et al. Brain angiogenesis inhibitor 1 is expressed by gastric phagocytes during infection with Helicobacter pylori and mediates the recognition and engulfment of human apoptotic gastric epithelial cells. FASEB J. 2014;28(5):2214-2224. doi:10.1096/fj.13-243238
616. Morioka S, Kajioka D, Yamaoka Y, et al. Chimeric efferocytic receptors improve apoptotic cell clearance and alleviate inflammation. Cell. 2022;185(26):4887-4903.e17. doi:10.1016/j.cell.2022.11.029
617. Zhou X, Zhu D, Wu D, et al. Microneedle delivery of CAR-M-like engineered macrophages alleviates intervertebral disc degeneration through enhanced efferocytosis

capacity. Cell Rep Med. 2025;6(4):102079. doi:10.1016/j.xcrm.2025.102079
618. Shiu FH, Wong JC, Yamamoto T, et al. Mice lacking full length Adgrb1 (Bai1) exhibit social deficits, increased seizure susceptibility, and altered brain development. *Exp Neurol*. 2022;351:113994. doi:10.1016/j.expneurol.2022.113994
619. Choi JS, Bae WY, Nam S, Jeong JW. New Targets for Parkinson's Disease: Adhesion G Protein-Coupled Receptor B1 is Downregulated by AMP-Activated Protein Kinase Activation. *OMICS: A J Integr Biol*. 2018;22(7):493-501. doi:10.1089/omi.2018.0047
620. Moon SY, Shin SA, Oh YS, Park HH, Lee CS. Understanding the Role of the BAI Subfamily of Adhesion G Protein-Coupled Receptors (GPCRs) in Pathological and Physiological Conditions. Genes. 2018;9(12):597. doi:10.3390/genes9120597
621. Okajima D, Kudo G, Yokota H. Antidepressant-like behavior in brain-specific angiogenesis inhibitor 2-deficient mice. *J Physiol Sci*. 2011;61(1):47-54. doi:10.1007/s12576-010-0120-0
622. Liao HM, Chao YL, Huang AL, et al. Identification and characterization of three inherited genomic copy number variations associated with familial schizophrenia. *Schizophr Res*. 2012;139(1-3):229-236. doi:10.1016/j.schres.2012.05.015
623. DeRosse P, Lencz T, Burdick KE, Siris SG, Kane JM, Malhotra AK. The Genetics of Symptom-Based Phenotypes: Toward a Molecular Classification of Schizophrenia. *Schizophr Bull*. 2008;34(6):1047-1053. doi:10.1093/schbul/sbn076
624. Liu Q, Drgon T, Johnson C, Walther D, Hess J, Uhl GR. Addiction molecular genetics: 639,401 SNP whole genome association identifies many "cell adhesion" genes. *Am J Méd Genet Part B: Neuropsychiatr Genet*. 2006;141B(8):918-925. doi:10.1002/ajmg.b.30436
625. McCarthy MJ, Nievergelt CM, Kelsoe JR, Welsh DK. A Survey of Genomic Studies Supports Association of Circadian Clock Genes with Bipolar Disorder Spectrum Illnesses and Lithium Response. PLoS ONE. 2012;7(2):e32091. doi:10.1371/journal.pone.0032091
626. Shiu FH, Wong JC, Bhattacharya D, et al. Generation and initial characterization of mice lacking full-length BAI3 (ADGRB3) expression. Basic Clin Pharmacol Toxicol. 2023;133(4):353-363. doi:10.1111/bcpt.13917
627. Curtin JA, Quint E, Tsipouri V, et al. Mutation of Celsr1 Disrupts Planar Polarity of Inner Ear Hair Cells and Causes Severe Neural Tube Defects in the Mouse. Curr Biol. 2003;13(13):1129-1133. doi:10.1016/s0960-9822(03)00374-9
628. Belzeaux R, Gorgievski V, Fiori LM, et al. GPR56/ADGRG1 is associated with response to antidepressant treatment. Nat Commun. 2020;11(1):1635. doi:10.1038/s41467-020-15423-5
629. Qi W, Guan W. GPR56: A potential therapeutic target for neurological and psychiatric disorders. Biochem Pharmacol. 2024;226:116395. doi:10.1016/j.bcp.2024.116395
630. Lion M, Ibrahim EC, Caccomo-Garcia E, et al. A specific GPR56/ADGRG1 splicing isoform is associated with antidepressant response in major depressive disorder. *Eur Neuropsychopharmacol*. 2025;93:5-14. doi:10.1016/j.euroneuro.2025.01.001
631. Bruxel EM, Moreira-Maia CR, Akutagava-Martins GC, et al. Meta-analysis and systematic review of ADGRL3 (LPHN3) polymorphisms in ADHD susceptibility. Mol Psychiatry. 2021;26(6):2277-2285. doi:10.1038/s41380-020-0673-0
632. Domené S, Stanescu H, Wallis D, et al. Screening of human LPHN3 for variants with a potential impact on ADHD susceptibility. Am J Méd Genet Part B: Neuropsychiatr Genet.

2011;156(1):11-18. doi:10.1002/ajmg.b.31141
633. Kappel DB, Schuch JB, Rovaris DL, et al. ADGRL3 rs6551665 as a Common Vulnerability Factor Underlying Attention-Deficit/Hyperactivity Disorder and Autism Spectrum Disorder. *NeuroMolecular Med*. 2019;21(1):60-67. doi:10.1007/s12017-019-08525-x
634. Arcos-Burgos M, Vélez JI, Martinez AF, et al. ADGRL3 (LPHN3) variants predict substance use disorder. *Transl Psychiatry*. 2019;9(1):42. doi:10.1038/s41398-019-0396-7
635. Vezain M, Lecuyer M, Rubio M, et al. A de novo variant in ADGRL2 suggests a novel mechanism underlying the previously undescribed association of extreme microcephaly with severely reduced sulcation and rhombencephalosynapsis. *Acta Neuropathol Commun*. 2018;6(1):109. doi:10.1186/s40478-018-0610-5
636. Sun J, Kranzler HR, Gelernter J, Bi J. A genome-wide association study of cocaine use disorder accounting for phenotypic heterogeneity and gene–environment interaction. *J Psychiatry Neurosci*. 2020;45(1):34-44. doi:10.1503/jpn.180098
637. Lei W, Xiong Y, Shi Y, et al. ADGRL1 variants: From developmental and epileptic encephalopathy to genetic epilepsy with febrile seizures plus. *Dev Med Child Neurol*. 2025;67(1):119-125. doi:10.1111/dmcn.16005
638. Guan Y, Du H, Yang Z, et al. Deafness-Associated ADGRV1 Mutation Impairs USH2A Stability through Improper Phosphorylation of WHRN and WDSUB1 Recruitment. *Adv Sci*. 2023;10(16):2205993. doi:10.1002/advs.202205993
639. McMillan DR, White PC. Loss of the transmembrane and cytoplasmic domains of the very large G-protein-coupled receptor-1 (VLGR1 or Mass1) causes audiogenic seizures in mice. *Mol Cell Neurosci*. 2004;26(2):322-329. doi:10.1016/j.mcn.2004.02.005
640. Myers KA, Nasioulas S, Boys A, et al. ADGRV1 is implicated in myoclonic epilepsy. *Epilepsia*. 2018;59(2):381-388. doi:10.1111/epi.13980
641. Zhou P, Meng H, Liang X, et al. ADGRV1 Variants in Febrile Seizures/Epilepsy With Antecedent Febrile Seizures and Their Associations With Audio-Visual Abnormalities. Front Mol Neurosci. 2022;15:864074. doi:10.3389/fnmol.2022.864074
642. Nair M, Bolyard C, Lee TJ, Kaur B, Yoo JY. Therapeutic Application of Brain-Specific Angiogenesis Inhibitor 1 for Cancer Therapy. Cancers. 2021;13(14):3562. doi:10.3390/cancers13143562
643. Meisen WH, Dubin S, Sizemore ST, et al. Changes in BAI1 and Nestin Expression Are Prognostic Indicators for Survival and Metastases in Breast Cancer and Provide Opportunities for Dual Targeted Therapies. *Mol Cancer Ther*. 2015;14(1):307-314. doi:10.1158/1535-7163.mct-14-0659
644. Hardcastle J, Kurozumi K, Dmitrieva N, et al. Enhanced Antitumor Efficacy of Vasculostatin (Vstat120) Expressing Oncolytic HSV-1. *Mol Ther*. 2010;18(2):285-294. doi:10.1038/mt.2009.232
645. Bolyard C, Meisen WH, Banasavadi-Siddegowda Y, et al. BAI1 Orchestrates Macrophage Inflammatory Response to HSV Infection—Implications for Oncolytic Viral Therapy. *Clin Cancer Res*. 2016;23(7):1809-1819. doi:10.1158/1078-0432.ccr-16-1818
646. Zhang H, Zhu D, Zhang Z, et al. EZH2 targeting reduces medulloblastoma growth through epigenetic reactivation of the BAI1/p53 tumor suppressor pathway. Oncogene. 2020;39(5):1041-1048. doi:10.1038/s41388-019-1036-7

647. Groot DM de, Vogel G, Dulos J, et al. Therapeutic antibody targeting of CD97 in experimental arthritis: the role of antigen expression, shedding, and internalization on the pharmacokinetics of anti-CD97 monoclonal antibody 1B2. *Journal of immunology (Baltimore, Md : 1950)*. 2009;183(6):4127-4134. doi:10.4049/jimmunol.0901253
648. Veninga H, Groot DM de, McCloskey N, et al. CD97 antibody depletes granulocytes in mice under conditions of acute inflammation via a Fc receptor-dependent mechanism. J Leukoc Biol. 2011;89(3):413-421. doi:10.1189/jlb.0510280
649. Shang K, Huang D, Liu J, et al. CD97-directed CAR-T cells with enhanced persistence eradicate acute myeloid leukemia in diverse xenograft models. Cell Rep Med. Published online 2025:102148. doi:10.1016/j.xcrm.2025.102148
650. Park T, Chen H, Kim HY. GPR110 (ADGRF1) mediates anti-inflammatory effects of N-docosahexaenoylethanolamine. *J Neuroinflammation*. 2019;16(1):225. doi:10.1186/s12974-019-1621-2
651. Stoveken HM, Larsen SD, Smrcka AV, Tall GG. Gedunin- and Khivorin-Derivatives Are Small-Molecule Partial Agonists for Adhesion G Protein-Coupled Receptors GPR56/ADGRG1 and GPR114/ADGRG5. Mol Pharmacol. 2018;93(5):477-488. doi:10.1124/mol.117.111476
652. Vizurraga AL, Robertson MJ, Yu M, Skiniotis G, Tall GG. Hexahydroquinoline Derivatives Are Selective Agonists for the Adhesion G Protein-Coupled Receptor ADGRG1/GPR56. Mol Pharmacol. 2023;104(1):28-41. doi:10.1124/molpharm.123.000688
653. Ohta S, Sakaguchi S, Kobayashi Y, Mizuno N, Tago K, Itoh H. Agonistic Antibodies Reveal the Function of GPR56 in Human Glioma U87-MG Cells. *Biol Pharm Bull*. 2015;38(4):594. doi:10.1248/bpb.b14-00752
654. Jallouli R, Moreno-Salinas AL, Laniel A, et al. G protein selectivity profile of GPR56/ADGRG1 and its effect on downstream effectors. Cell Mol Life Sci. 2024;81(1):383. doi:10.1007/s00018-024-05416-8
655. Jacob J, Francisco LE, Chatterjee T, et al. An antibody–drug conjugate targeting GPR56 demonstrates efficacy in preclinical models of colorectal cancer. *Br J Cancer*. 2023;128(8):1592-1602. doi:10.1038/s41416-023-02192-3
656. Bradley EC, Cunningham RL, Wilde C, et al. In vivo identification of small molecules mediating Gpr126/Adgrg6 signaling during Schwann cell development. Ann N York Acad Sci. 2019;1456(1):44-63. doi:10.1111/nyas.14233
657. Erwin DH. Early metazoan life: divergence, environment and ecology. *Philos Trans R Soc B: Biol Sci*. 2015;370(1684):20150036. doi:10.1098/rstb.2015.0036
658. Schöneberg T. Modulating vertebrate physiology by genomic fine-tuning of GPCR functions. Physiol Rev. 2025;105(1):383-439. doi:10.1152/physrev.00017.2024
659. Langenhan T, Barr MM, Bruchas MR, et al. Model Organisms in G Protein–Coupled Receptor Research. Mol Pharmacol. 2015;88(3):596-603. doi:10.1124/mol.115.098764
660. Monk KR, Hamann J, Langenhan T, Nijmeijer S, Schöneberg T, Liebscher I. Adhesion G Protein–Coupled Receptors: From In Vitro Pharmacology to In Vivo Mechanisms. Mol Pharmacol. 2015;88(3):617-623. doi:10.1124/mol.115.098749
661. Liebscher I, Cevheroğlu O, Hsiao C, et al. A guide to adhesion GPCR research. FEBS J. 2022;289(24):7610-7630. doi:10.1111/febs.16258
662. Richter DJ, Fozouni P, Eisen MB, King N. Gene family innovation, conservation and

loss on the animal stem lineage. eLife. 2018;7:e34226. doi:10.7554/elife.34226
663. King N, Westbrook MJ, Young SL, et al. The genome of the choanoflagellate Monosiga brevicollis and the origin of metazoans. 2008;451(7180):783-788. doi:10.1038/nature06617
664. Krishnan A, Almén MS, Fredriksson R, Schiöth HB. The Origin of GPCRs: Identification of Mammalian like Rhodopsin, Adhesion, Glutamate and Frizzled GPCRs in Fungi. PLoS ONE. 2012;7(1):e29817. doi:10.1371/journal.pone.0029817
665. Mendoza A de, Sebé-Pedrós A, Ruiz-Trillo I. The Evolution of the GPCR Signaling System in Eukaryotes: Modularity, Conservation, and the Transition to Metazoan Multicellularity. *Genome Biol Evol*. 2014;6(3):606-619. doi:10.1093/gbe/evu038
666. Bayonas AGDL, King N. G protein-coupled receptor diversity and evolution in the closest living relatives of Metazoa. eLife. 2025;(14):RP107467. doi:10.7554/elife.107467.2
667. Yang X, Pan C, Ye M, et al. Drosophila adhesion GPCR Remoulade regulates axon growth, branching, and guidance by modulating Rac1 GTPase. *J Genet Genom*. 2024;51(4):458-461. doi:10.1016/j.jgg.2023.11.006
668. Chae J, Kim MJ, Goo JH, et al. The Drosophila tissue polarity gene starry night encodes a member of the protocadherin family. Development. 1999;126(23):5421-5429. doi:10.1242/dev.126.23.5421
669. Lu B, Usui T, Uemura T, Jan L, Jan YN. Flamingo controls the planar polarity of sensory bristles and asymmetric division of sensory organ precursors in Drosophila. Curr Biol. 1999;9(21):1247-S1. doi:10.1016/s0960-9822(99)80505-3
670. Strutt H, Warrington S, Madathil ACK, Langenhan T, Strutt D. Molecular symmetry breaking in the Frizzled-dependent planar polarity pathway. Curr Biol. 2023;33(24):5340-5354.e6. doi:10.1016/j.cub.2023.10.071
671. Strutt H, Strutt D. Differential Stability of Flamingo Protein Complexes Underlies the Establishment of Planar Polarity. Curr Biol. 2008;18(20):1555-1564. doi:10.1016/j.cub.2008.08.063
672. Lawrence PA, Casal J, Struhl G. Cell interactions and planar polarity in the abdominal epidermis of Drosophila. Development. 2004;131(19):4651-4664. doi:10.1242/dev.01351
673. Strutt D, Strutt H. Differential activities of the core planar polarity proteins during Drosophila wing patterning. *Developmental biology*. 2007;302(1):181-194. doi:10.1016/j.ydbio.2006.09.026
674. Gao FB, Brenman JE, Jan LY, Jan YN. Genes regulating dendritic outgrowth, branching, and routing in Drosophila. *Genes Dev*. 1999;13(19):2549-2561. doi:10.1101/gad.13.19.2549
675. Gao FB, Kohwi M, Brenman JE, Jan LY, Jan YN. Control of Dendritic Field Formation in Drosophila The Roles of Flamingo and Competition between Homologous Neurons. Neuron. 2000;28(1):91-101. doi:10.1016/s0896-6273(00)00088-x
676. Senti KA, Usui T, Boucke K, Greber U, Uemura T, Dickson BJ. Flamingo Regulates R8 Axon-Axon and Axon-Target Interactions in the Drosophila Visual System. Curr Biol. 2003;13(10):828-832. doi:10.1016/s0960-9822(03)00291-4
677. Reuter JE, Nardine TM, Penton A, et al. A mosaic genetic screen for genes necessary for Drosophila mushroom body neuronal morphogenesis. Development. 2003;130(6):1203-1213. doi:10.1242/dev.00319
678. Shimizu K, Sato M, Tabata T. The Wnt5/Planar Cell Polarity Pathway Regulates Axonal

Development of the Drosophila Mushroom Body Neuron. J Neurosci. 2011;31(13):4944-4954. doi:10.1523/jneurosci.0154-11.2011
679. Ng J. Wnt/PCP proteins regulate stereotyped axon branch extension in Drosophila. Development. 2011;139(1):165-177. doi:10.1242/dev.068668
680. Kimura H, Usui T, Tsubouchi A, Uemura T. Potential dual molecular interaction of the Drosophila 7-pass transmembrane cadherin Flamingo in dendritic morphogenesis. J Cell Sci. 2006;119(6):1118-1129. doi:10.1242/jcs.02832
681. Li X, Wang Y, Wang H, et al. Epithelia-derived wingless regulates dendrite directional growth of drosophila ddaE neuron through the Fz-Fmi-Dsh-Rac1 pathway. Mol Brain. 2016;9(1):46. doi:10.1186/s13041-016-0228-0
682. Matsubara D, Horiuchi S ya, Shimono K, Usui T, Uemura T. The seven-pass transmembrane cadherin Flamingo controls dendritic self-avoidance via its binding to a LIM domain protein, Espinas, in Drosophila sensory neurons. Genes Dev. 2011;25(18):1982-1996. doi:10.1101/gad.16531611
683. Buhlan M, Ljaschenko D, Scholz N, Langenhan T. Experimental modulation of physiological force application on leg joint neurons in intact Drosophila melanogaster. *Nat Protoc*. 2024;19(1):113-126. doi:10.1038/s41596-023-00907-7
684. Blanco-Redondo B, Langenhan T. Parallel Genomic Engineering of Two Drosophila Genes Using Orthogonal attB/attP Sites. G3: Genes, Genomes, Genet. 2018;8(9):3109-3118. doi:10.1534/g3.118.200565
685. Najarro EH, Wong L, Zhen M, et al. Caenorhabditis elegans Flamingo Cadherin fmi-1 Regulates GABAergic Neuronal Development. J Neurosci. 2012;32(12):4196-4211. doi:10.1523/jneurosci.3094-11.2012
686. Steimel A, Wong L, Najarro EH, Ackley BD, Garriga G, Hutter H. The Flamingo ortholog FMI-1 controls pioneer-dependent navigation of follower axons in C. elegans. Development. 2010;137(21):3663-3673. doi:10.1242/dev.054320
687. Hsu HW, Liao CP, Chiang YC, Syu RT, Pan CL. Caenorhabditis elegans Flamingo FMI-1 controls dendrite self-avoidance through F-actin assembly. Development. 2020;147(14):dev179168. doi:10.1242/dev.179168
688. Schön JL, Groß VE, Post WB, et al. The adhesion GPCR and PCP component flamingo (FMI-1) alters body size and regulates the composition of the extracellular matrix. *Matrix Biol*. 2024;128:1-10. doi:10.1016/j.matbio.2024.02.005
689. Lange M, Norton W, Coolen M, et al. The ADHD-susceptibility gene lphn3.1 modulates dopaminergic neuron formation and locomotor activity during zebrafish development. Mol Psychiatry. 2012;17(9):946-954. doi:10.1038/mp.2012.29
690. Lange M, Froc C, Grunwald H, Norton WHJ, Bally-Cuif L. Pharmacological analysis of zebrafish lphn3.1 morphant larvae suggests that saturated dopaminergic signaling could underlie the ADHD-like locomotor hyperactivity. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2018;84(Pt A):181-189. doi:10.1016/j.pnpbp.2018.02.010
691. Reuter I, Knaup S, Romanos M, Lesch KP, Drepper C, Lillesaar C. Developmental exposure to acetaminophen does not induce hyperactivity in zebrafish larvae. *J Neural Transm*. 2016;123(8):841-848. doi:10.1007/s00702-016-1556-z
692. Fontana BD, Reichmann F, Tilley CA, et al. adgrl3.1-deficient zebrafish show noradrenaline-mediated externalizing behaviors, and altered expression of externalizing

disorder-candidate genes, suggesting functional targets for treatment. Transl Psychiatry. 2023;13(1):304. doi:10.1038/s41398-023-02601-4
693. Þorsteinsson H, Baukmann HA, Sveinsdóttir HS, et al. Validation of L-type calcium channel blocker amlodipine as a novel ADHD treatment through cross-species analysis, drug-target Mendelian randomization, and clinical evidence from medical records. *Neuropsychopharmacology*. 2025;50(7):1145-1155. doi:10.1038/s41386-025-02062-x
694. Grzymala B, Þorsteinsson H, Halldórsdóttir DÞ, et al. Metabolomic and lipidomic profiling reveals convergent pathways in attention deficit hyperactivity disorder therapeutics: Insights from established and emerging treatments. *J Pharmacol Exp Ther*. 2025;392(4):103403. doi:10.1016/j.jpet.2025.103403
695. Fontana BD, Alnassar N, Norton WHJ, Parker MO. Social isolation intensifies adgrl3.1-related externalizing and internalizing behaviors in zebrafish. Prog Neuro-Psychopharmacol Biol Psychiatry. 2025;136:111193. doi:10.1016/j.pnpbp.2024.111193
696. Sveinsdóttir HS, Christensen C, Þorsteinsson H, et al. Novel non-stimulants rescue hyperactive phenotype in an adgrl3.1 mutant zebrafish model of ADHD. Neuropsychopharmacology. 2023;48(8):1155-1163. doi:10.1038/s41386-022-01505-z
697. Martinez AF, Abe Y, Hong S, et al. An Ultraconserved Brain-Specific Enhancer Within ADGRL3 (LPHN3) Underpins Attention-Deficit/Hyperactivity Disorder Susceptibility. Biol Psychiatry. 2016;80(12):943-954. doi:10.1016/j.biopsych.2016.06.026
698. Formstone CJ, Mason I. Combinatorial activity of Flamingo proteins directs convergence and extension within the early zebrafish embryo via the planar cell polarity pathway. Developmental biology. 2005;282(2):320-335. doi:10.1016/j.ydbio.2005.03.026
699. Carreira-Barbosa F, Kajita M, Kajita M, et al. Flamingo regulates epiboly and convergence/extension movements through cell cohesive and signalling functions during zebrafish gastrulation. Development. 2009;136(3):383-392. doi:10.1242/dev.026542
700. Wada H, Tanaka H, Nakayama S, Iwasaki M, Okamoto H. Frizzled3a and Celsr2 function in the neuroepithelium to regulate migration of facial motor neurons in the developing zebrafish hindbrain. 2006;133(23):4749-4759. doi:10.1242/dev.02665
701. Lewis A, Wilson N, Stearns G, Johnson N, Nelson R, Brockerhoff SE. Celsr3 Is Required for Normal Development of GABA Circuits in the Inner Retina. PLoS Genet. 2011;7(8):e1002239. doi:10.1371/journal.pgen.1002239
702. Meserve JH, Navarro MF, Ortiz EA, Granato M. Celsr3 drives development and connectivity of the acoustic startle hindbrain circuit. *PLOS Genet*. 2024;20(10):e1011415. doi:10.1371/journal.pgen.1011415
703. Kartalaei PS, Yamada-Inagawa T, Vink CS, et al. Whole-transcriptome analysis of endothelial to hematopoietic stem cell transition reveals a requirement for Gpr56 in HSC generation. J Exp Med. 2015;212(1):93-106. doi:10.1084/jem.20140767
704. Geng FS, Abbas L, Baxendale S, et al. Semicircular canal morphogenesis in the zebrafish inner ear requires the function of gpr126 (lauscher), an adhesion class G protein-coupled receptor gene. Development. 2013;140(21):4362-4374. doi:10.1242/dev.098061
705. Küffer A, Lakkaraju AKK, Mogha A, et al. The prion protein is an agonistic ligand of the G protein-coupled receptor Adgrg6. Nature. 2016;536(7617):464-468. doi:10.1038/nature19312
706. Musa G, Srivastava S, Petzold J, Cazorla-Vázquez S, Engel FB. miR-27a/b is a

posttranscriptional regulator of Gpr126 (Adgrg6). Ann N York Acad Sci. 2019;1456(1):109-121. doi:10.1111/nyas.14245
707. Ebermann I, Phillips JB, Liebau MC, et al. PDZD7 is a modifier of retinal disease and a contributor to digenic Usher syndrome. J Clin Investig. 2010;120(6):1812-1823. doi:10.1172/jci39715
708. Stemerdink M, Broekman S, Peters T, Kremer H, Vrieze E de, Wijk E van. Generation and Characterization of a Zebrafish Model for ADGRV1-Associated Retinal Dysfunction Using CRISPR/Cas9 Genome Editing Technology. Cells. 2023;12(12):1598. doi:10.3390/cells12121598
709. Xiao X, Zheng H, Xiong M, Chen X, Jiang L, Hu Y. Genotypic and phenotypic characteristics of ADGRV1 mutations in four children and functional validation in a zebrafish model. Gene. 2025;942:149246. doi:10.1016/j.gene.2025.149246
710. Rashidi H, Sottile V. The chick embryo: hatching a model for contemporary biomedical research. *BioEssays*. 2009;31(4):459-465. doi:10.1002/bies.200800168
711. Itasaki N, Bel-Vialar S, Krumlauf R. 'Shocking' developments in chick embryology: electroporation and in ovo gene expression. *Nat Cell Biol*. 1999;1(8):E203-E207. doi:10.1038/70231
712. Poopalasundaram S, Richardson J, Graham A. Key separable events in the remodelling of the pharyngeal arches. *J Anat*. 2023;243(1):100-109. doi:10.1111/joa.13850
713. Voiculescu O, Bertocchini F, Wolpert L, Keller RE, Stern CD. The amniote primitive streak is defined by epithelial cell intercalation before gastrulation. 2007;449(7165):1049-1052. doi:10.1038/nature06211
714. Ribatti D. The chick embryo chorioallantoic membrane (CAM). A multifaceted experimental model. *Mech Dev*. 2016;141:70-77. doi:10.1016/j.mod.2016.05.003
715. AS MN, Deshpande R, Kale VP, Bhonde RR, Datar SP. Establishment of an in ovo chick embryo yolk sac membrane (YSM) assay for pilot screening of potential angiogenic and anti-angiogenic agents. *Cell Biol Int*. 2018;42(11):1474-1483. doi:10.1002/cbin.11051
716. Öztürk AA, Kıyan HT. Treatment of oxidative stress-induced pain and inflammation with dexketoprofen trometamol loaded different molecular weight chitosan nanoparticles: Formulation, characterization and anti-inflammatory activity by using in vivo HET-CAM assay. *Microvasc Res*. 2020;128:103961. doi:10.1016/j.mvr.2019.103961
717. Patiño-Morales CC, Jaime-Cruz R, Ramírez-Fuentes TC, Villavicencio-Guzmán L, Salazar-García M. Technical Implications of the Chicken Embryo Chorioallantoic Membrane Assay to Elucidate Neuroblastoma Biology. Int J Mol Sci. 2023;24(19):14744. doi:10.3390/ijms241914744
718. Murphy JB, Rous P. THE BEHAVIOR OF CHICKEN SARCOMA IMPLANTED IN THE DEVELOPING EMBRYO. J Exp Med. 1912;15(2):119-132. doi:10.1084/jem.15.2.119
719. Cao J, Liu X, Yang Y, et al. Decylubiquinone suppresses breast cancer growth and metastasis by inhibiting angiogenesis via the ROS/p53/ BAI1 signaling pathway. Angiogenesis. 2020;23(3):325-338. doi:10.1007/s10456-020-09707-z
720. Regan SL, Hufgard JR, Pitzer EM, et al. Knockout of latrophilin-3 in Sprague-Dawley rats causes hyperactivity, hyper-reactivity, under-response to amphetamine, and disrupted dopamine markers. *Neurobiol Dis*. 2019;130:104494. doi:10.1016/j.nbd.2019.104494
721. Regan SL, Pitzer EM, Hufgard JR, Sugimoto C, Williams MT, Vorhees CV. A novel

role for the ADHD risk gene latrophilin-3 in learning and memory in Lphn3 knockout rats. Neurobiol Dis. 2021;158:105456. doi:10.1016/j.nbd.2021.105456
722. Dumas L, Marfoglia M, Yang B, et al. Uncovering and engineering the mechanical properties of the adhesion GPCR ADGRG1 GAIN domain. bioRxiv. Published online 2023:2023.04.05.535724. doi:10.1101/2023.04.05.535724
723. Marfoglia M, Guirardel L, Barth P. AlloPool: An Adaptive Graph Neural Network for Dynamic Allosteric Network Prediction in Protein Systems. bioRxiv. Published online 2024:2024.11.01.621466. doi:10.1101/2024.11.01.621466
724. Zhang Y, DeVries ME, Skolnick J. Structure Modeling of All Identified G Protein–Coupled Receptors in the Human Genome. *PLoS Comput Biol*. 2006;2(2):e13. doi:10.1371/journal.pcbi.0020013
725. Lebon G, Warne T, Edwards PC, et al. Agonist-bound adenosine A2A receptor structures reveal common features of GPCR activation. Nature. 2011;474(7352):521-525. doi:10.1038/nature10136
726. Brunskole I, Strasser A, Seifert R, Buschauer A. Role of the second and third extracellular loops of the histamine H4 receptor in receptor activation. *Naunyn-Schmiedeberg's Arch Pharmacol*. 2011;384(3):301. doi:10.1007/s00210-011-0673-3
727. Abramson J, Adler J, Dunger J, et al. Accurate structure prediction of biomolecular interactions with AlphaFold 3. Nature. 2024;630(8016):493-500. doi:10.1038/s41586-024-07487-w
728. Krishna R, Wang J, Ahern W, et al. Generalized biomolecular modeling and design with RoseTTAFold All-Atom. Science. 2024;384(6693):eadl2528. doi:10.1126/science.adl2528
729. Jumper J, Evans R, Pritzel A, et al. Highly accurate protein structure prediction with AlphaFold. Nature. 2021;596(7873):583-589. doi:10.1038/s41586-021-03819-2
730. He X heng, Li J rui, Shen S yi, Xu HE. AlphaFold3 versus experimental structures: assessment of the accuracy in ligand-bound G protein-coupled receptors. Acta Pharmacol Sin. 2025;46(4):1111-1122. doi:10.1038/s41401-024-01429-y
731. Wilde C, Chaudhry PM, Luo R, Simon KU, Piao X, Liebscher I. Collagen VI Is a Gi-Biased Ligand of the Adhesion GPCR GPR126/ADGRG6. Cells. 2023;12(11):1551. doi:10.3390/cells12111551
732. Mitgau J, Franke J, Schinner C, et al. The N Terminus of Adhesion G Protein–Coupled Receptor GPR126/ADGRG6 as Allosteric Force Integrator. Front Cell Dev Biol. 2022;10:873278. doi:10.3389/fcell.2022.873278
733. Streit M, Hemberger M, Häfner S, Knote F, Langenhan T, Beliu G. Optimized genetic code expansion technology for time-dependent induction of adhesion GPCR-ligand engagement. *Protein Sci*. 2023;32(4):e4614. doi:10.1002/pro.4614
734. Lizano E, Hayes JL, Willard FS. A synthetic method to assay adhesion-family G-protein coupled receptors. Determination of the G-protein coupling profile of ADGRG6(GPR126). Biochem Biophys Res Commun. 2020;534:317-322. doi:10.1016/j.bbrc.2020.11.086
735. Perry-Hauser NA, VanDyck MW, Lee KH, Shi L, Javitch JA. Disentangling autoproteolytic cleavage from tethered agonist–dependent activation of the adhesion receptor ADGRL3. J Biol Chem. 2022;298(12):102594. doi:10.1016/j.jbc.2022.102594
736. Garbett K, Tosun B, Lopez JM, Smith CM, Honkanen K, Sando RC. Synaptic Gα12/13 signaling establishes hippocampal PV inhibitory circuits. Proc Natl Acad Sci.

2024;121(52):e2407828121. doi:10.1073/pnas.2407828121
737. Wilde C, Mitgau J, Suchý T, Schöneberg T, Liebscher I. Translating the force—mechano-sensing GPCRs. *Am J Physiol-Cell Physiol*. 2022;322(6):C1047-C1060. doi:10.1152/ajpcell.00465.2021
738. Sun S, Wang W. Mechanosensitive adhesion G protein-coupled receptors: Insights from health and disease. *Genes Dis*. 2025;12(3):101267. doi:10.1016/j.gendis.2024.101267
739. Hoffman BD, Grashoff C, Schwartz MA. Dynamic molecular processes mediate cellular mechanotransduction. Nature. 2011;475(7356):316-323. doi:10.1038/nature10316
740. Arbore C, Perego L, Sergides M, Capitanio M. Probing force in living cells with optical tweezers: from single-molecule mechanics to cell mechanotransduction. *Biophys Rev*. 2019;11(5):765-782. doi:10.1007/s12551-019-00599-y
741. Català-Castro F, Schäffer E, Krieg M. Exploring cell and tissue mechanics with optical tweezers. J Cell Sci. 2022;135(15). doi:10.1242/jcs.259355
742. Klarenbeek J, Goedhart J, Batenburg A van, Groenewald D, Jalink K. Fourth-Generation Epac-Based FRET Sensors for cAMP Feature Exceptional Brightness, Photostability and Dynamic Range: Characterization of Dedicated Sensors for FLIM, for Ratiometry and with High Affinity. PLoS ONE. 2015;10(4):e0122513. doi:10.1371/journal.pone.0122513
743. Feng Y, Brazin KN, Kobayashi E, Mallis RJ, Reinherz EL, Lang MJ. Mechanosensing drives acuity of αβ T-cell recognition. Proc Natl Acad Sci. 2017;114(39):E8204-E8213. doi:10.1073/pnas.1703559114
744. Fritz RD, Letzelter M, Reimann A, et al. A Versatile Toolkit to Produce Sensitive FRET Biosensors to Visualize Signaling in Time and Space. Sci Signal. 2013;6(285):rs12. doi:10.1126/scisignal.2004135
745. Fu C, Huang W, Tang Q, et al. Unveiling Mechanical Activation: GAIN Domain Unfolding and Dissociation in Adhesion GPCRs. *Nano Lett*. 2023;23(20):9179-9186. doi:10.1021/acs.nanolett.3c01163
746. Zhong BL, Lee CE, Vachharajani VT, Bauer MS, Südhof TC, Dunn AR. Piconewton Forces Mediate GAIN Domain Dissociation of the Latrophilin-3 Adhesion GPCR. Nano Lett. 2023;23(20):9187-9194. doi:10.1021/acs.nanolett.3c03171
747. Yang B, Liu Z, Liu H, Nash MA. Next Generation Methods for Single-Molecule Force Spectroscopy on Polyproteins and Receptor-Ligand Complexes. Front Mol Biosci. 2020;7:85. doi:10.3389/fmolb.2020.00085
748. Zocher M, Bippes CA, Zhang C, Müller DJ. Single-molecule force spectroscopy of G-protein -coupled receptors. *Chem Soc Rev*. 2013;42(19):7801-7815. doi:10.1039/c3cs60085h
749. Nikolaev VO, Bünemann M, Hein L, Hannawacker A, Lohse MJ. Novel single chain cAMP sensors for receptor-induced signal propagation. *The Journal of biological chemistry*. 2004;279(36):37215-37218. doi:10.1074/jbc.c400302200
750. Caprara GA, Peng AW. Mechanotransduction in mammalian sensory hair cells. Mol Cell Neurosci. 2022;120:103706. doi:10.1016/j.mcn.2022.103706
751. Yang L yun, Liu X fang, Yang Y, et al. Biochemical features of the adhesion G protein-coupled receptor CD97 related to its auto-proteolysis and HeLa cell attachment activities. Acta Pharmacol Sin. 2017;38(1):56-68. doi:10.1038/aps.2016.89
752. Wang J, Chitsaz F, Derbyshire MK, et al. The conserved domain database in 2023. Nucleic Acids Res. 2022;51(D1):D384-D388. doi:10.1093/nar/gkac1096

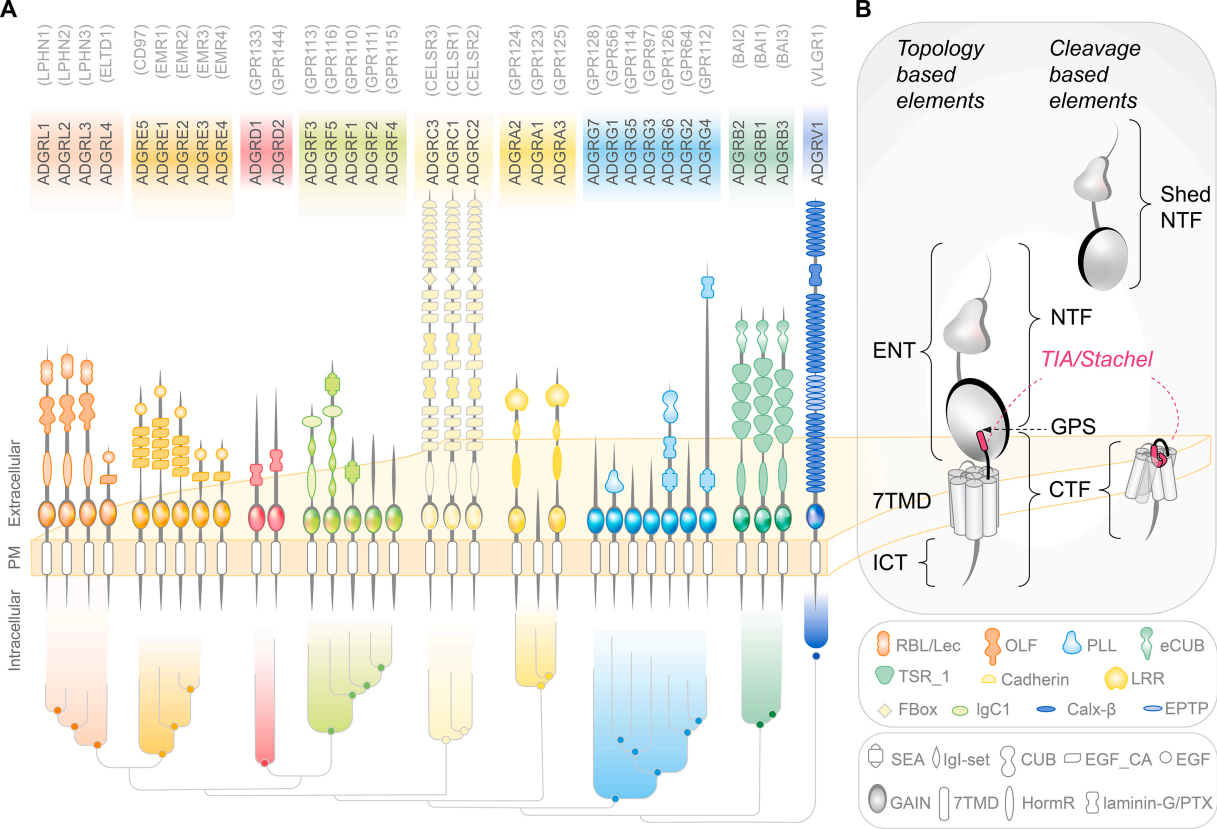
753. Sigrist CJA, Castro E de, Cerutti L, et al. New and continuing developments at PROSITE. Nucleic Acids Res. 2012;41(D1):D344-D347. doi:10.1093/nar/gks1067
754. Kempen M van, Kim SS, Tumescheit C, et al. Fast and accurate protein structure search with Foldseek. *Nat Biotechnol*. 2024;42(2):243-246. doi:10.1038/s41587-023-01773-0
755. Tawfeeq C, Wang J, Khaniya U, et al. IgStrand: A universal residue numbering scheme for the immunoglobulin-fold (Ig-fold) to study Ig-proteomes and Ig-interactomes. *PLOS Comput Biol*. 2025;21(4):e1012813. doi:10.1371/journal.pcbi.1012813
756. Seiradake E, del Toro D, Nagel D, et al. FLRT Structure: Balancing Repulsion and Cell Adhesion in Cortical and Vascular Development. Neuron. 2014;84(2):370-385. doi:10.1016/j.neuron.2014.10.008
757. Uhlén M, Fagerberg L, Hallström BM, et al. Tissue-based map of the human proteome. Science. 2015;347(6220):1260419. doi:10.1126/science.1260419
758. Caminschi I, Vandenabeele S, Sofi M, et al. Gene structure and transcript analysis of the human and mouse EGF-TM7 molecule, FIRE. *DNA Seq*. 2006;17(1):8-14. doi:10.1080/10425170500355737
759. Kuznetsov D, Tegenfeldt F, Manni M, et al. OrthoDB v11: annotation of orthologs in the widest sampling of organismal diversity. Nucleic Acids Res. 2022;51(D1):D445-D451. doi:10.1093/nar/gkac998
760. Alok A, Lei Z, Jagannathan NS, et al. Wnt proteins synergize to activate β-catenin signaling. J Cell Sci. 2017;130(9):1532-1544. doi:10.1242/jcs.198093
761. Wang J, Miao Y, Wicklein R, et al. RTN4/NoGo-receptor binding to BAI adhesion-GPCRs regulates neuronal development. Cell. 2022;185(1):218. doi:10.1016/j.cell.2021.12.017
762. Lala T, Doan JK, Takatsu H, Hartzell HC, Shin HW, Hall RA. Phosphatidylserine exposure modulates adhesion GPCR BAI1 (ADGRB1) signaling activity. J Biol Chem. 2022;298(12):102685. doi:10.1016/j.jbc.2022.102685
763. Oda K, Shiratsuchi T, Nishimori H, et al. Identification of BAIAP2 (BAI-associated protein 2), a novel human homologue of hamster IRSp53, whose SH3 domain interacts with the cytoplasmic domain of BAI1. Cytogenet Genome Res. 1999;84(1-2):75-82. doi:10.1159/000015219
764. Shiratsuchi T, Oda K, Nishimori H, et al. Cloning and characterization of BAP3 (BAI-associated protein 3), a C2 domain-containing protein that interacts with BAI1. Biochemical and biophysical research communications. 1998;251(1):158-165. doi:10.1006/bbrc.1998.9408
765. Zencir S, Ovee M, Dobson MJ, Banerjee M, Topcu Z, Mohanty S. Identification of brain-specific angiogenesis inhibitor 2 as an interaction partner of glutaminase interacting protein. Biochem Biophys Res Commun. 2011;411(4):792-797. doi:10.1016/j.bbrc.2011.07.029
766. Hamoud N, Tran V, Aimi T, et al. Spatiotemporal regulation of the GPCR activity of BAI3 by C1qL4 and Stabilin-2 controls myoblast fusion. Nat Commun. 2018;9(1):4470. doi:10.1038/s41467-018-06897-5
767. Devenport D, Oristian D, Heller E, Fuchs E. Mitotic internalization of planar cell polarity proteins preserves tissue polarity. Nat Cell Biol. 2011;13(8):893-902. doi:10.1038/ncb2284

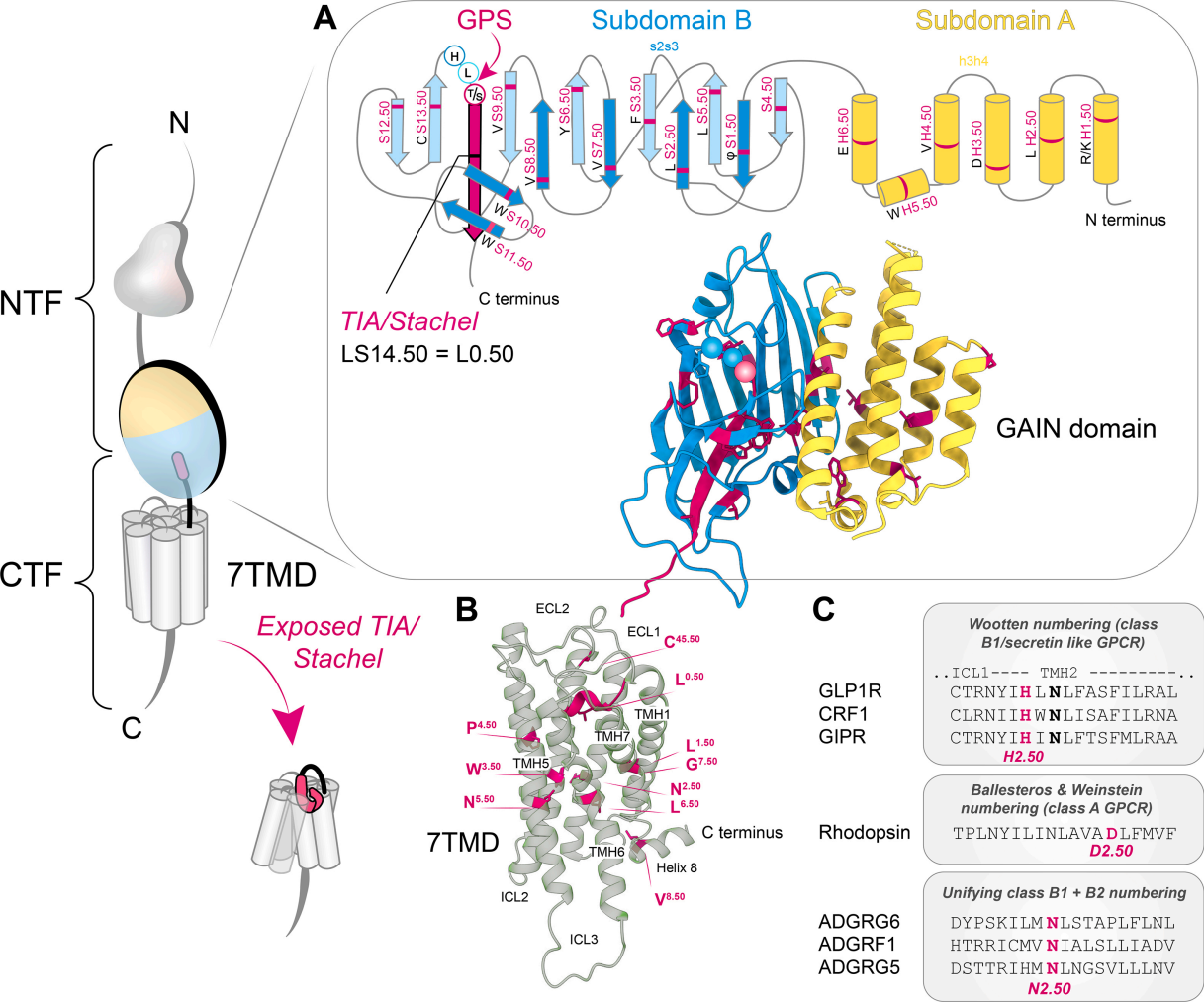
768. Lei Y, Zhu H, Yang W, Ross ME, Shaw GM, Finnell RH. Identification of Novel CELSR1 Mutations in Spina Bifida. PLoS ONE. 2014;9(3):e92207. doi:10.1371/journal.pone.0092207
769. Salašová A, Yokota C, Potěšil D, Zdráhal Z, Bryja V, Arenas E. A proteomic analysis of LRRK2 binding partners reveals interactions with multiple signaling components of the WNT/PCP pathway. *Mol Neurodegener*. 2017;12(1):54. doi:10.1186/s13024-017-0193-9
770. Lindenmaier LB, Parmentier N, Guo C, Tissir F, Wright KM. Dystroglycan is a scaffold for extracellular axon guidance decisions. eLife. 2019;8:e42143. doi:10.7554/elife.42143
771. Stacey M, Chang GW, Davies JQ, et al. The epidermal growth factor–like domains of the human EMR2 receptor mediate cell attachment through chondroitin sulfate glycosaminoglycans. Blood. 2003;102(8):2916-2924. doi:10.1182/blood-2002-11-3540
772. Stacey M, Lin HH, Hilyard KL, Gordon S, McKnight AJ. Human Epidermal Growth Factor (EGF) Module-containing Mucin-like Hormone Receptor 3 Is a New Member of the EGF-TM7 Family That Recognizes a Ligand on Human Macrophages and Activated Neutrophils*. J Biol Chem. 2001;276(22):18863-18870. doi:10.1074/jbc.m101147200
773. Stacey M, Chang GW, Sanos SL, et al. EMR4, a novel epidermal growth factor (EGF)-TM7 molecule up-regulated in activated mouse macrophages, binds to a putative cellular ligand on B lymphoma cell line A20. The Journal of biological chemistry. 2002;277(32):29283-29293. doi:10.1074/jbc.m204306200
774. Wandel E, Saalbach A, Sittig D, Gebhardt C, Aust G. Thy-1 (CD90) Is an Interacting Partner for CD97 on Activated Endothelial Cells. J Immunol. 2012;188(3):1442-1450. doi:10.4049/jimmunol.1003944
775. Chang H, Hou P, Wang X, et al. CD97 negatively regulates the innate immune response against RNA viruses by promoting RNF125-mediated RIG-I degradation. *Cell Mol Immunol*. 2023;20(12):1457-1471. doi:10.1038/s41423-023-01103-z
776. Chen H, Rosen CE, González-Hernández JA, et al. Highly multiplexed bioactivity screening reveals human and microbiota metabolome-GPCRome interactions. Cell. 2023;186(14):3095-3110.e19. doi:10.1016/j.cell.2023.05.024
777. Cerny O, Godlee C, Tocci R, et al. CD97 stabilises the immunological synapse between dendritic cells and T cells and is targeted for degradation by the Salmonella effector SteD. *PLoS Pathog*. 2021;17(7):e1009771. doi:10.1371/journal.ppat.1009771
778. Huang BX, Chen H, Joo Y, et al. Interaction between GPR110 (ADGRF1) and tight junction protein occludin implicated in blood-brain barrier permeability. iScience. 2023;26(4):106550. doi:10.1016/j.isci.2023.106550
779. Bauer L, Edwards J, Heil A, et al. Mesenchymal Transglutaminase 2 Activates Epithelial ADAM17: Link to G-Protein-Coupled Receptor 56 (ADGRG1) Signalling. Int J Mol Sci. 2024;25(4):2329. doi:10.3390/ijms25042329
780. Chatterjee T, Zhang S, Posey TA, et al. Anti-GPR56 monoclonal antibody potentiates GPR56-mediated Src-Fak signaling to modulate cell adhesion. J Biol Chem. 2021;296:100261. doi:10.1016/j.jbc.2021.100261
781. Southern C, Cook JM, Neetoo-Isseljee Z, et al. Screening β-Arrestin Recruitment for the Identification of Natural Ligands for Orphan G-Protein–Coupled Receptors. *SLAS Discov*. 2013;18(5):599-609. doi:10.1177/1087057113475480
782. Popova NV, Plotnikov A, Deev IE, Petrenko AG. Interaction of calcium-independent

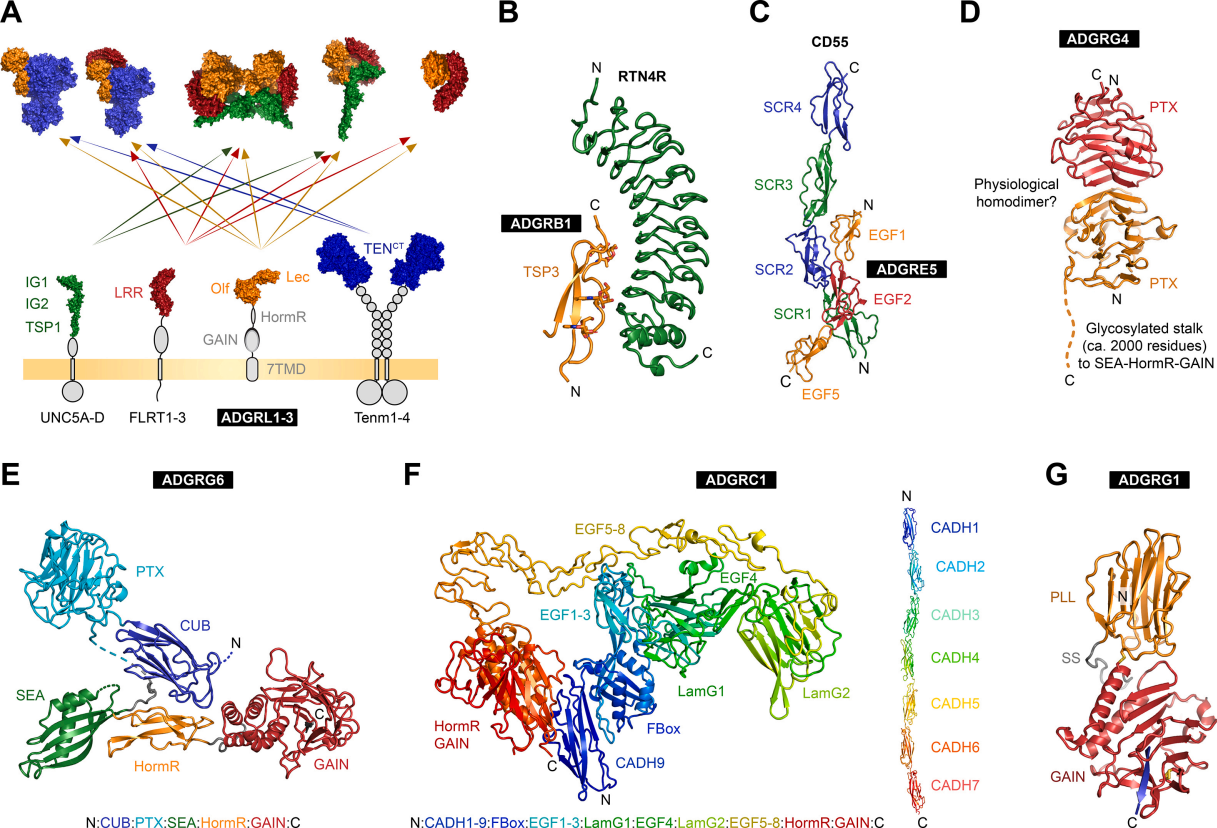
latrotoxin receptor with intracellular adapter protein TRIP8b. *Doklady Biochemistry and biophysics*. 2007;414:149-151. http://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed&cmd=retrieve&dopt=AbstractPlus&list_uids=17695324
783. Popova NV, Plotnikov AN, Ziganshin RK, Deyev IE, Petrenko AG. Analysis of proteins interacting with TRIP8b adapter. *Biochemistry Biokhimiia*. 2008;73(6):644-651. doi:10.1134/s0006297908060035
784. Chhabra KH, Bathina S, Faniyan TS, et al. ADGRL1 is a glucose receptor involved in mediating energy and glucose homeostasis. *Diabetologia*. 2024;67(1):170-189. doi:10.1007/s00125-023-06010-6
785. Kordon SP, Dutka P, Adamska JM, et al. Isoform- and ligand-specific modulation of the adhesion GPCR ADGRL3/Latrophilin3 by a synthetic binder. Nat Commun. 2023;14(1):635. doi:10.1038/s41467-023-36312-7
786. Bittner MA, Krasnoperov VG, Stuenkel EL, Petrenko AG, Holz RW. A Ca2+-Independent Receptor for α-Latrotoxin, CIRL, Mediates Effects on Secretion via Multiple Mechanisms. J Neurosci. 1998;18(8):2914-2922. doi:10.1523/jneurosci.18-08-02914.1998
787. Jackson VA, Meijer DH, Carrasquero M, et al. Structures of Teneurin adhesion receptors reveal an ancient fold for cell-cell interaction. Nat Commun. 2018;9(1):1079. doi:10.1038/s41467-018-03460-0
788. Yang J, Yin GN, Kim DK, et al. Crystal structure of LRG1 and the functional significance of LRG1 glycan for LPHN2 activation. Exp Mol Med. 2023;55(5):1013-1022. doi:10.1038/s12276-023-00992-4
789. Amisten S, Rezeli M, Grossi M, et al. The DNA repair factor ku80 binds and activates the adhesion receptor ELTD1/ADGRL4. Biochem Biophys Res Commun. 2025;764:151785. doi:10.1016/j.bbrc.2025.151785
790. Mühlfeld S, Schmitt-Wrede HP, Harder A, Wunderlich F. FMRFamide-like neuropeptides as putative ligands of the latrophilin-like HC110-R from Haemonchus contortus. *Molecular and biochemical parasitology*. 2009;164(2):162-164. doi:10.1016/j.molbiopara.2008.12.003
791. Adams DJ, Barlas B, McIntyre RE, et al. Genetic determinants of micronucleus formation in vivo. Nature. 2024;627(8002):130-136. doi:10.1038/s41586-023-07009-0
792. Tang T, Li L, Tang J, et al. A mouse knockout library for secreted and transmembrane proteins. Nat Biotechnol. 2010;28(7):749-755. doi:10.1038/nbt.1644
793. Skarnes WC, Rosen B, West AP, et al. A conditional knockout resource for the genome-wide study of mouse gene function. Nature. 2011;474(7351):337-342. doi:10.1038/nature10163
794. Speca DJ, Trimmer JS, Peterson AS, Díaz E. Whole exome sequencing reveals a functional mutation in the GAIN domain of the Bai2 receptor underlying a forward mutagenesis hyperactivity QTL. *Mamm Genome*. 2017;28(11-12):465-475. doi:10.1007/s00335-017-9716-5
795. Horie K, Yusa K, Yae K, et al. Characterization of Sleeping Beauty Transposition and Its Application to Genetic Screening in Mice. Mol Cell Biol. 2003;23(24):9189-9207. doi:10.1128/mcb.23.24.9189-9207.2003
796. Fairfield H, Srivastava A, Ananda G, et al. Exome sequencing reveals pathogenic

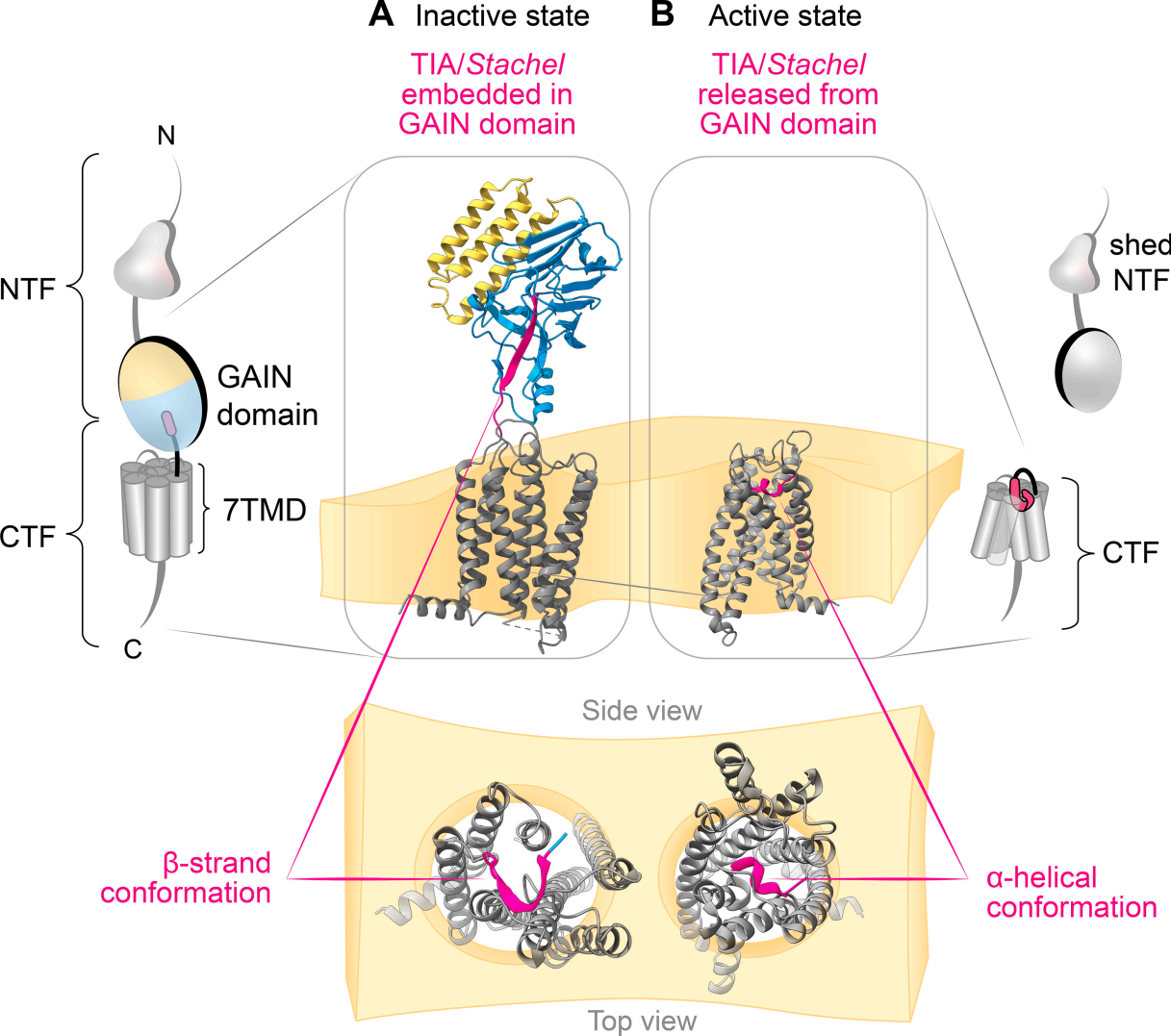
mutations in 91 strains of mice with Mendelian disorders. Genome Res. 2015;25(7):948-957. doi:10.1101/gr.186882.114
797. Curtin JA, Quint E, Tsipouri V, et al. Mutation of Celsr1 Disrupts Planar Polarity of Inner Ear Hair Cells and Causes Severe Neural Tube Defects in the Mouse. Curr Biol. 2003;13(13):1129-1133. doi:10.1016/s0960-9822(03)00374-9
798. Nolan PM, Peters J, Strivens M, et al. A systematic, genome-wide, phenotype-driven mutagenesis programme for gene function studies in the mouse. Nat Genet. 2000;25(4):440-443. doi:10.1038/78140
799. Ravni A, Qu Y, Goffinet AM, Tissir F. Planar Cell Polarity Cadherin Celsr1 Regulates Skin Hair Patterning in the Mouse. *J Investig Dermatol*. 2009;129(10):2507-2509. doi:10.1038/jid.2009.84
800. Qu Y, Glasco DM, Zhou L, et al. Atypical Cadherins Celsr1-3 Differentially Regulate Migration of Facial Branchiomotor Neurons in Mice. J Neurosci. 2010;30(28):9392-9401. doi:10.1523/jneurosci.0124-10.2010
801. Boutin C, Labedan P, Dimidschstein J, et al. A dual role for planar cell polarity genes in ciliated cells. Proc Natl Acad Sci. 2014;111(30):E3129-E3138. doi:10.1073/pnas.1404988111
802. Tissir F, Bar I, Jossin Y, Backer OD, Goffinet AM. Protocadherin Celsr3 is crucial in axonal tract development. Nat Neurosci. 2005;8(4):451-457. doi:10.1038/nn1428
803. Dickinson ME, Flenniken AM, Ji X, et al. High-throughput discovery of novel developmental phenotypes. Nature. 2016;537(7621):508-514. doi:10.1038/nature19356
804. Lin HH, Faunce DE, Stacey M, et al. The macrophage F4/80 receptor is required for the induction of antigen-specific efferent regulatory T cells in peripheral tolerance. J Exp Med. 2005;201(10):1615-1625. doi:10.1084/jem.20042307
805. Schaller E, Macfarlane AJ, Rupec RA, Gordon S, McKnight AJ, Pfeffer K. Inactivation of the F4/80 Glycoprotein in the Mouse Germ Line. Mol Cell Biol. 2002;22(22):8035-8043. doi:10.1128/mcb.22.22.8035-8043.2002
806. Veninga H, Becker S, Hoek RM, et al. Analysis of CD97 Expression and Manipulation: Antibody Treatment but Not Gene Targeting Curtails Granulocyte Migration. J Immunol. 2008;181(9):6574-6583. doi:10.4049/jimmunol.181.9.6574
807. Chiba Y, Yoshizaki K, Sato H, et al. Deficiency of G protein-coupled receptor Gpr111/Adgrf2 causes enamel hypomineralization in mice by alteration of the expression of kallikrein-related peptidase 4 (Klk4) during pH cycling process. FASEB J. 2023;37(4):e22861. doi:10.1096/fj.202202053r
808. Suzuki A, Yabuta N, Shimada K, et al. Individual disruption of 12 testis-enriched genes via the CRISPR/Cas9 system does not affect the fertility of male mice. *J Reprod Immunol*. 2024;163:104252. doi:10.1016/j.jri.2024.104252
809. Li S, Jin Z, Koirala S, et al. GPR56 Regulates Pial Basement Membrane Integrity and Cortical Lamination. J Neurosci. 2008;28(22):5817-5826. doi:10.1523/jneurosci.0853-08.2008
810. Sleckman BP, Khan WN, Xu W, et al. Cloning and Functional Characterization of the Early-Lymphocyte-Specific Pb99 Gene. Mol Cell Biol. 2000;20(12):4405-4410. doi:10.1128/mcb.20.12.4405-4410.2000
811. Sun P, He L, Jia K, et al. Regulation of body length and bone mass by Gpr126/Adgrg6.

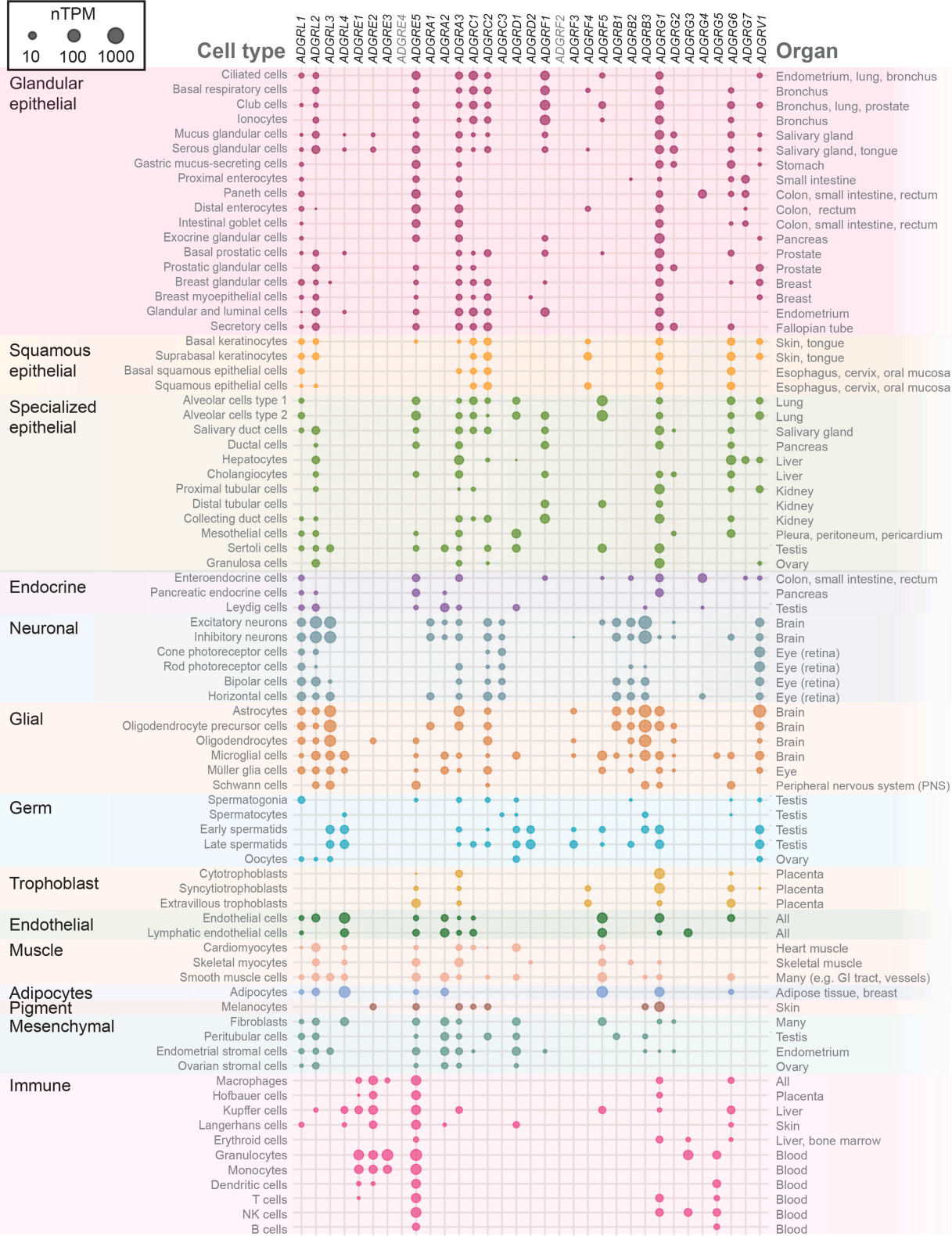
Sci Adv. 2020;6(12):eaaz0368. doi:10.1126/sciadv.aaz0368
812. Tobaben S, Südhof TC, Stahl B. Genetic Analysis of α-Latrotoxin Receptors Reveals Functional Interdependence of CIRL/Latrophilin 1 and Neurexin 1α*. J Biol Chem. 2002;277(8):6359-6365. doi:10.1074/jbc.m111231200
813. Wallis D, Hill DS, Mendez IA, et al. Initial characterization of mice null for Lphn3, a gene implicated in ADHD and addiction. *Brain Res*. 2012;1463:85-92. doi:10.1016/j.brainres.2012.04.053
814. Yagi H, Takamura Y, Yoneda T, et al. Vlgr1 knockout mice show audiogenic seizure susceptibility. *J Neurochem*. 2005;92(1):191-202. doi:10.1111/j.1471-4159.2004.02875.x
815. Yagi H, Tokano H, Maeda M, et al. Vlgr1 is required for proper stereocilia maturation of cochlear hair cells. *Genes Cells*. 2007;12(2):235-250. doi:10.1111/j.1365-2443.2007.01046.x
816. Yao L, Zhang L, Qi LS, et al. The Time Course of Deafness and Retinal Degeneration in a Kunming Mouse Model for Usher Syndrome. PLoS ONE. 2016;11(5):e0155619. doi:10.1371/journal.pone.0155619
817. Klein BD, Fu YH, Ptacek LJ, White HS. Auditory Deficits Associated with the Frings Mgr1 (Mass1) Mutation in Mice. *Dev Neurosci*. 2005;27(5):321-332. doi:10.1159/000086712
818. Johnson KR, Zheng QY, Weston MD, Ptacek LJ, Noben-Trauth K. The Mass1frings mutation underlies early onset hearing impairment in BUB/BnJ mice, a model for the auditory pathology of Usher syndrome IIC. Genomics. 2005;85(5):582-590. doi:10.1016/j.ygeno.2005.02.006

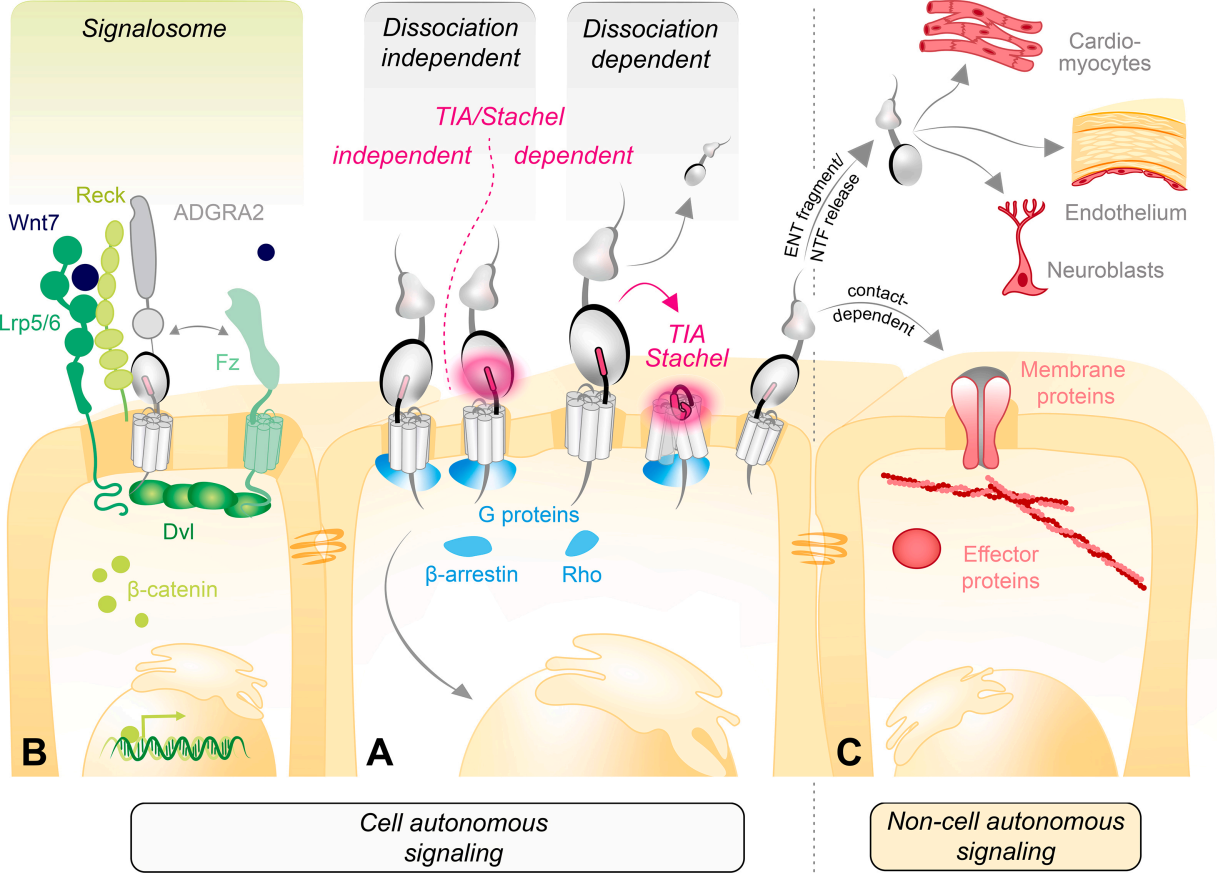

A
B
(LPHN1)
(LPHN2)
(LPHN3)
(ELTD1)
(CD97)
(EMR1)
(EMR2)
(EMR3)
(EMR4)
(GPR133)
(GPR144)
(GPR113)
(GPR116)
(GPR110)
(GPR111)
(GPR115)
(CELSR3)
(CELSR1)
(CELSR2)
(GPR124)
(GPR123)
(GPR125)
(GPR128)
(GPR56)
(GPR114)
(GPR97)
(GPR126)
(GPR64)
(GPR112)
(BAI2)
(BAI1)
(BAI3)
(VLGR1)
ADGRL1
ADGRL2
ADGRL3
ADGRL4
ADGRE5
ADGRE1
ADGRE2
ADGRE3
ADGRE4
ADGRD1
ADGRD2
ADGRF3
ADGRF5
ADGRF1
ADGRF2
ADGRF4
ADGRC3
ADGRC1
ADGRC2
ADGRA2
ADGRA1
ADGRA3
ADGRG7
ADGRG1
ADGRG5
ADGRG3
ADGRG6
ADGRG2
ADGRG4
ADGRB2
ADGRB1
ADGRB3
ADGRV1
Extracellular
PM
Intracellular
Topology based elements
Cleavage based elements
Shed NTF
NTF
ENT
TIA/Stachel
GPS
7TMD
CTF
ICT
RBL/Lec
OLF
PLL
eCUB
TSR_1
Cadherin
LRR
FBox
IgC1
Calx-β
EPTP
SEA
IgI-set
CUB
EGF_CA
EGF
GAIN
7TMD
HormR
laminin-G/PTX

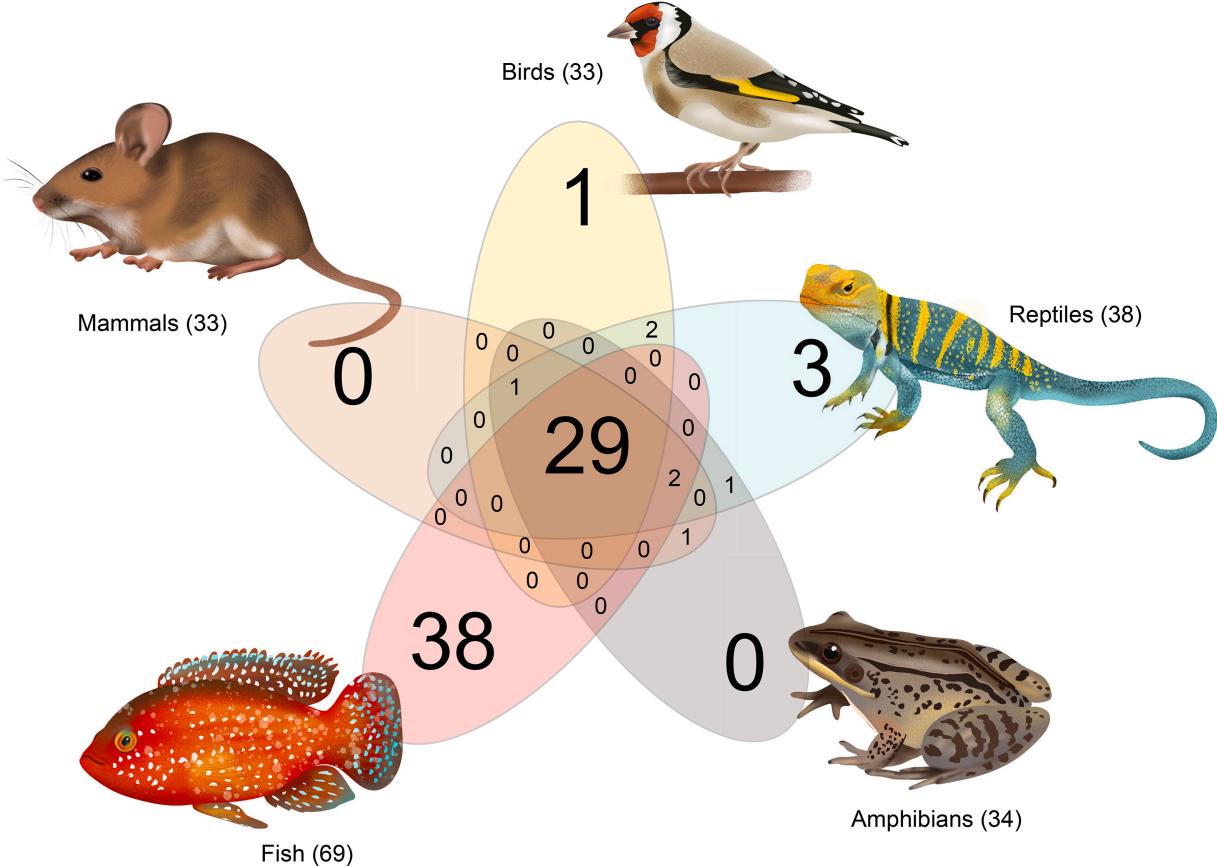

A
GPS
Subdomain B
Subdomain A
s2s3
h3h4
H
L
T/s
S12.50
C S13.50
V S9.50
V S8.50
Y S6.50
V S7.50
F S3.50
L S2.50
L S5.50
φ S1.50
S4.50
E H6.50
W H5.50
V H4.50
D H3.50
L H2.50
R/K H1.50
N terminus
W S10.50
W S11.50
C terminus
TIA/Stachel
LS14.50 = L0.50
GAIN domain
N
NTF
CTF
7TMD
C
Exposed TIA/
Stachel
B
ECL2
ECL1
C45.50
L0.50
TMH1
TMH7
P4.50
L1.50
G7.50
W3.50
TMH5
N2.50
N5.50
L6.50
7TMD
C terminus
TMH6
Helix 8
ICL2
V8.50
ICL3
C
Wootten numbering (class B1/secretin like GPCR)
..ICL1---- TMH2 ---------..
GLP1R CTRNYIHLNLFASFILRAL
CRF1 CLRNIIHWNLISAFILRNA
GIPR CTRNYIHINLFTSFMLRAA
H2.50
Ballesteros & Weinstein numbering (class A GPCR)
Rhodopsin TPLNYILINLAVADLFMVF
D2.50
Unifying class B1 + B2 numbering
ADGRG6 DYPSKILMNLSTAPLFLNL
ADGRF1 HTRRICMVNIALSLLIADV
ADGRG5 DSTTRIHMNLNGSVLLLNV
N2.50

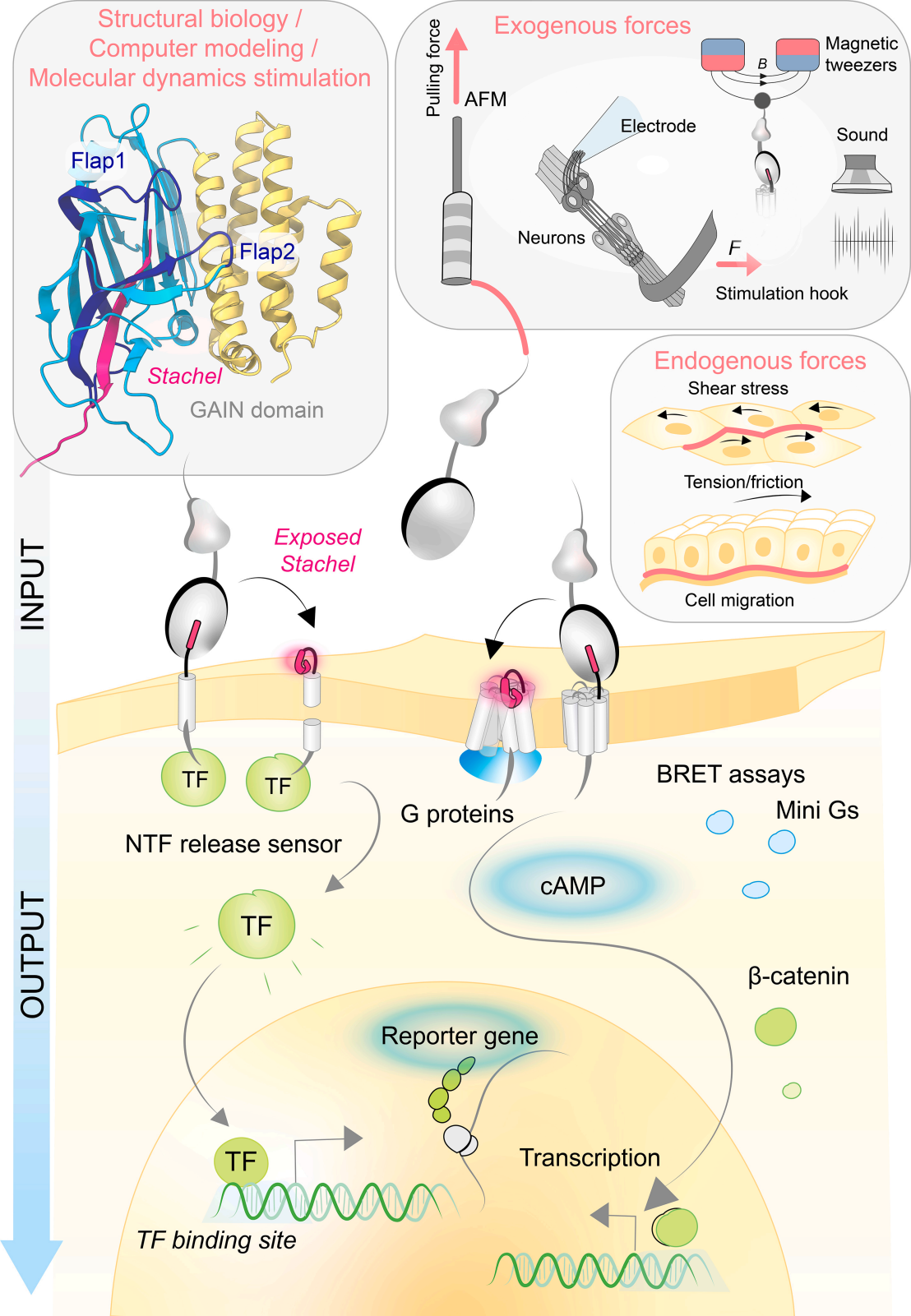

A
IG1
IG2
TSP1
LRR
Olf
Lec
HormR
GAIN
7TMD
TEN^CT
UNC5A-D
FLRT1-3
ADGRL1-3
Tenm1-4
B
RTN4R
ADGRB1
TSP3
N
C
C
CD55
SCR4
SCR3
SCR2
SCR1
EGF1
EGF2
EGF5
ADGRE5
D
ADGRG4
PTX
PTX
Physiological homodimer?
Glycosylated stalk (ca. 2000 residues) to SEA-HormR-GAIN
E
ADGRG6
PTX
CUB
SEA
HormR
GAIN
N:CUB:PTX:SEA:HormR:GAIN:C
F
ADGRC1
EGF5-8
EGF4
EGF1-3
LamG1
LamG2
HormR
GAIN
FBox
CADH9
N:CADH1-9:FBox:EGF1-3:LamG1:EGF4:LamG2:EGF5-8:HormR:GAIN:C
CADH1
CADH2
CADH3
CADH4
CADH5
CADH6
CADH7
G
ADGRG1
PLL
SS
GAIN


A Inactive state
B Active state
TIA/Stachel embedded in GAIN domain
TIA/Stachel released from GAIN domain
N
NTF
GAIN domain
7TMD
CTF
C
shed NTF
CTF
Side view
β-strand conformation
α-helical conformation
Top view


nTPM
10
100
1000
Cell type
ADGRL1
ADGRL2
ADGRL3
ADGRL4
ADGRE1
ADGRE2
ADGRE3
ADGRE4
ADGRE5
ADGRA1
ADGRA2
ADGRA3
ADGRC1
ADGRC2
ADGRC3
ADGRD1
ADGRD2
ADGRF1
ADGRF2
ADGRF3
ADGRF4
ADGRF5
ADGRB1
ADGRB2
ADGRB3
ADGRG1
ADGRG2
ADGRG3
ADGRG4
ADGRG5
ADGRG6
ADGRG7
ADGRV1
Organ
Glandular epithelial
Ciliated cells
Endometrium, lung, bronchus
Basal respiratory cells
Bronchus
Club cells
Bronchus, lung, prostate
Ionocytes
Bronchus
Mucus glandular cells
Salivary gland
Serous glandular cells
Salivary gland, tongue
Gastric mucus-secreting cells
Stomach
Proximal enterocytes
Small intestine
Paneth cells
Colon, small intestine, rectum
Distal enterocytes
Colon, rectum
Intestinal goblet cells
Colon, small intestine, rectum
Exocrine glandular cells
Pancreas
Basal prostatic cells
Prostate
Prostatic glandular cells
Prostate
Breast glandular cells
Breast
Breast myoepithelial cells
Breast
Glandular and luminal cells
Endometrium
Secretory cells
Fallopian tube
Squamous epithelial
Basal keratinocytes
Skin, tongue
Suprabasal keratinocytes
Skin, tongue
Basal squamous epithelial cells
Esophagus, cervix, oral mucosa
Squamous epithelial cells
Esophagus, cervix, oral mucosa
Specialized epithelial
Alveolar cells type 1
Lung
Alveolar cells type 2
Lung
Salivary duct cells
Salivary gland
Ductal cells
Pancreas
Hepatocytes
Liver
Cholangiocytes
Liver
Proximal tubular cells
Kidney
Distal tubular cells
Kidney
Collecting duct cells
Kidney
Mesothelial cells
Pleura, peritoneum, pericardium
Sertoli cells
Testis
Granulosa cells
Ovary
Endocrine
Enteroendocrine cells
Colon, small intestine, rectum
Pancreatic endocrine cells
Pancreas
Leydig cells
Testis
Neuronal
Excitatory neurons
Brain
Inhibitory neurons
Brain
Cone photoreceptor cells
Eye (retina)
Rod photoreceptor cells
Eye (retina)
Bipolar cells
Eye (retina)
Horizontal cells
Eye (retina)
Glial
Astrocytes
Brain
Oligodendrocyte precursor cells
Brain
Oligodendrocytes
Brain
Microglial cells
Brain
Müller glia cells
Eye
Schwann cells
Peripheral nervous system (PNS)
Germ
Spermatogonia
Testis
Spermatocytes
Testis
Early spermatids
Testis
Late spermatids
Testis
Oocytes
Ovary
Trophoblast
Cytotrophoblasts
Placenta
Syncytiotrophoblasts
Placenta
Extravillous trophoblasts
Placenta
Endothelial
Endothelial cells
All
Lymphatic endothelial cells
All
Muscle
Cardiomyocytes
Heart muscle
Skeletal myocytes
Skeletal muscle
Smooth muscle cells
Many (e.g. GI tract, vessels)
Adipocytes
Adipocytes
Adipose tissue, breast
Pigment
Melanocytes
Skin
Mesenchymal
Fibroblasts
Many
Peritubular cells
Testis
Endometrial stromal cells
Endometrium
Ovarian stromal cells
Ovary
Immune
Macrophages
All
Hofbauer cells
Placenta
Kupffer cells
Liver
Langerhans cells
Skin
Erythroid cells
Liver, bone marrow
Granulocytes
Blood
Monocytes
Blood
Dendritic cells
Blood
T cells
Blood
NK cells
Blood
B cells
Blood


Signalosome
Dissociation independent
Dissociation dependent
TIA/Stachel
independent
dependent
Reck
ADGRA2
Wnt7
Lrp5/6
Fz
Dvl
β-catenin
TIA
Stachel
G proteins
β-arrestin
Rho
ENT fragment/
NTF release
contact-dependent
Cardio-myocytes
Endothelium
Neuroblasts
Membrane proteins
Effector proteins
B
A
C
Cell autonomous signaling
Non-cell autonomous signaling


Birds (33)
Mammals (33)
Reptiles (38)
Fish (69)
Amphibians (34)
1
0
3
29
38
0
0 0 0 2 0 0 1 0 0 0 0 0 0 2 0 1 0 0 0 1 0 0 0 0 0 0


Structural biology /
Computer modeling /
Molecular dynamics stimulation
Flap1
Flap2
Stachel
GAIN domain
Exogenous forces
Pulling force
AFM
Magnetic tweezers
B
Electrode
Sound
Neurons
F
Stimulation hook
Endogenous forces
Shear stress
Tension/friction
Cell migration
INPUT
OUTPUT
Exposed Stachel
TF
TF
NTF release sensor
G proteins
BRET assays
Mini Gs
cAMP
TF
β-catenin
Reporter gene
TF
Transcription
TF binding site