

3.6.5.2 Small monomeric GTPases in GtoPdb v.2026.1

Elena Faccenda¹

1. University of Edinburgh, UK

Abstract

Small G-proteins, are a family of hydrolase enzymes that can bind and hydrolyze guanosine triphosphate (GTP). They are a type of G-protein found in the cytosol that are homologous to the alpha subunit of heterotrimeric G-proteins, but unlike the alpha subunit of G proteins, a small GTPase can function independently as a hydrolase enzyme to bind to and hydrolyze a guanosine triphosphate (GTP) to form guanosine diphosphate (GDP). The best-known members are the Ras GTPases and hence they are sometimes called Ras subfamily GTPases.

Contents

This is a citation summary for 3.6.5.2 Small monomeric GTPases in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [11].

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

3.6.5.2 Small monomeric GTPases

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=896>

RAS subfamily

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=897>

Introduction to RAS subfamily

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=897>

Enzymes

HRAS

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2822>

NRAS

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2823>

KRAS

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=2824>

ARF GTPase 6

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3324>

TBC1 domain family member 15

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3328>

RAB subfamily

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=938>

Enzymes

[RAB27A, member RAS oncogene family](#)

References

1. Alessi DR and Pfeffer SR. (2024) Leucine-Rich Repeat Kinases. *Annu Rev Biochem* **93**: 261-287 [PMID:38621236]
2. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N and Perucho M. (1988) Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. *Cell* **53**: 549-54 [PMID:2453289]
3. Baines AT, Xu D and Der CJ. (2011) Inhibition of Ras for cancer treatment: the search continues. *Future Med Chem* **3**: 1787-808 [PMID:22004085]
4. Bauer A, Amegadzie A, Smaligo A, Wigman B, Lanman BA, Mohr C, Emmetiere F, Stellwagen JC, Medina JH and Pettus LH *et al.*. (2024) Macrocyclic KRAS inhibitors and methods of use Patent number: WO2024107686A1. Assignee: Amgen Inc.. Priority date: 14/11/2023. Publication date: 23/05/2024.
5. Bezniakow N, Gos M and Obersztyn E. (2014) The RASopathies as an example of RAS/MAPK pathway disturbances - clinical presentation and molecular pathogenesis of selected syndromes. *Dev Period Med* **18**: 285-96 [PMID:25182392]
6. Blum R, Jacob-Hirsch J, Amariglio N, Rechavi G and Kloog Y. (2005) Ras inhibition in glioblastoma down-regulates hypoxia-inducible factor-1alpha, causing glycolysis shutdown and cell death. *Cancer Res* **65**: 999-1006 [PMID:15705901]
7. Bos JL. (1989) ras oncogenes in human cancer: a review. *Cancer Res* **49**: 4682-9 [PMID:2547513]
8. Bröker J, Waterson AG, Smethurst C, Kessler D, Böttcher J, Mayer M, Gmaschitz G, Phan J, Little A and Abbott JR *et al.*. (2022) Fragment Optimization of Reversible Binding to the Switch II Pocket on KRAS Leads to a Potent, In Vivo Active KRAS^{G12C} Inhibitor. *J Med Chem* **65**: 14614-14629 [PMID:36300829]
9. Braun BS and Shannon K. (2008) Targeting Ras in myeloid leukemias. *Clin Cancer Res* **14**: 2249-52 [PMID:18413813]
10. Brzezinska AA, Johnson JL, Munafo DB, Crozat K, Beutler B, Kiosses WB, Ellis BA and Catz SD. (2008) The Rab27a effectors JFC1/Slp1 and Munc13-4 regulate exocytosis of neutrophil granules. *Traffic* **9**: 2151-64 [PMID:18939952]
11. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
12. Burner GC and Loeb LA. (1989) Mutations in the KRAS2 oncogene during progressive stages of human colon carcinoma. *Proc Natl Acad Sci USA* **86**: 2403-7 [PMID:2648401]
13. Catz SD. (2014) The role of Rab27a in the regulation of neutrophil function. *Cell Microbiol* **16**: 1301-10 [PMID:24964030]
14. Cheng H, Li P, Chen P, Irimia A, Bae JH, Brooun A, Fagan P, Lam R, Lin B and Zhang J *et al.*. (2023) Structure-Based Design and Synthesis of Potent and Selective KRAS G12D Inhibitors. *ACS Med Chem Lett* **14**: 1351-1357 [PMID:37849557]
15. Collins MA and Pasca di Magliano M. (2013) Kras as a key oncogene and therapeutic target in pancreatic cancer. *Front Physiol* **4**: 407 [PMID:24478710]
16. Condakes ML, Civiello RL, Venables BL, Danahy DB, Moore RR, Balachander SB, Chourb LS, Downes DP, Drexler DM and Dzhekueva L *et al.*. (2026) Optimization of α -Fluoro, β -Heteroaryl Acrylamide Warheads for KRAS^{G12C} Active-State Inhibition. *J Med Chem* [PMID:41770619]
17. Cooper WA, Lam DC, O'Toole SA and Minna JD. (2013) Molecular biology of lung cancer. *J Thorac Dis* **5 Suppl 5**: S479-90 [PMID:24163741]
18. Ebi H, Faber AC, Engelman JA and Yano S. (2014) Not just gRASping at flaws: finding vulnerabilities to develop novel therapies for treating KRAS mutant cancers. *Cancer Sci* **105**: 499-505 [PMID:24612015]
19. El Otmani H, Daghi M, Tahiri Jouti N and Lesage S. (2023) An overview of the worldwide distribution of LRRK2 mutations in Parkinson's disease. *Neurodegener Dis Manag* **13**: 335-350 [PMID:38305913]
20. Endres NF, Do S, Mroue R, Terrett JA, Saabye M, Oh A, Hunsaker T, Chan E, Tran JC and Nguyen LK *et al.*. (2026) Discovery and Characterization of Divarasib (GDC-6036), a Potent Covalent Inhibitor of KRAS G12C *J Med Chem*
21. Fell JB, Fischer JP, Baer BR, Blake JF, Bouhana K, Briere DM, Brown KD, Burgess LE, Burns AC and Burkard MR *et al.*. (2020) Identification of the Clinical Development Candidate MRTX849, a Covalent KRAS^{G12C} Inhibitor for the Treatment of Cancer. *J Med Chem* [PMID:32250617]
22. Goitre L, Trapani E, Trabalzini L and Retta SF. (2014) The Ras superfamily of small GTPases: the unlocked secrets. *Methods Mol Biol* **1120**: 1-18 [PMID:24470015]

23. Hansen R, Peters U, Babbar A, Chen Y, Feng J, Janes MR, Li LS, Ren P, Liu Y and Zarrinkar PP. (2018) The reactivity-driven biochemical mechanism of covalent KRAS^{G12C} inhibitors. *Nat Struct Mol Biol* **25**: 454-462 [PMID:29760531]
24. Hop PJ, Lai D, Keagle PJ, Baron DM, Kenna BJ, Kooyman M, Shankaracharya, Halter C, Straniero L and Asselta R *et al.*. (2024) Systematic rare variant analyses identify RAB32 as a susceptibility gene for familial Parkinson's disease. *Nat Genet* **56**: 1371-1376 [PMID:38858457]
25. Janes MR, Zhang J, Li LS, Hansen R, Peters U, Guo X, Chen Y, Babbar A, Firdaus SJ and Darjania L *et al.*. (2018) Targeting KRAS Mutant Cancers with a Covalent G12C-Specific Inhibitor. *Cell* **172**: 578-589.e17 [PMID:29373830]
26. Jiang J, Jiang L, Maldonato BJ, Wang Y, Holderfield M, Aronchik I, Winters IP, Salman Z, Blaj C and Menard M *et al.*. (2024) Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers. *Cancer Discov* **14**: 994-1017 [PMID:38593348]
27. Johnson JL, Monfregola J, Napolitano G, Kiosses WB and Catz SD. (2012) Vesicular trafficking through cortical actin during exocytosis is regulated by the Rab27a effector JFC1/Slp1 and the RhoA-GTPase-activating protein Gem-interacting protein. *Mol Biol Cell* **23**: 1902-16 [PMID:22438581]
28. Johnson JL, Ramadass M, He J, Brown SJ, Zhang J, Abgaryan L, Biris N, Gavathiotis E, Rosen H and Catz SD. (2016) Identification of Neutrophil Exocytosis Inhibitors (Nexinhibs), Small Molecule Inhibitors of Neutrophil Exocytosis and Inflammation: DRUGGABILITY OF THE SMALL GTPase Rab27a. *J Biol Chem* **291**: 25965-25982 [PMID:27702998]
29. Kettle JG, Bagal SK, Bickerton S, Bodnarchuk MS, Boyd S, Breed J, Carbajo RJ, Cassar DJ, Chakraborty A and Cosulich S *et al.*. (2022) Discovery of AZD4625, a Covalent Allosteric Inhibitor of the Mutant GTPase KRAS^{G12C}. *J Med Chem* **65**: 6940-6952 [PMID:35471939]
30. Kettle JG, Bagal SK, Bickerton S, Bodnarchuk MS, Breed J, Carbajo RJ, Cassar DJ, Chakraborty A, Cosulich S and Cumming I *et al.*. (2020) Structure-Based Design and Pharmacokinetic Optimization of Covalent Allosteric Inhibitors of the Mutant GTPase KRAS^{G12C}. *J Med Chem* **63**: 4468-4483 [PMID:32023060]
31. Kim D, Herdeis L, Rudolph D, Zhao Y, Böttcher J, Vides A, Ayala-Santos CI, Pourfarjam Y, Cuevas-Navarro A and Xue JY *et al.*. (2023) Pan-KRAS inhibitor disables oncogenic signalling and tumour growth. *Nature* **619**: 160-166 [PMID:37258666]
32. Komori T and Kuwahara T. (2023) An Update on the Interplay between LRRK2, Rab GTPases and Parkinson's Disease. *Biomolecules* **13** [PMID:38002327]
33. Landry ML, Malhotra S, Beresini M, Chan C, Chan E, de la Cruz CC, Endres NF, Evangelista M, Gustafson A and Hu D *et al.*. (2026) Discovery and Optimization of a Potent, Efficacious, and Brain-Penetrant Inhibitor of KRAS G12C. *J Med Chem* [PMID:41769711]
34. Lanman BA, Allen JR, Allen JG, Amegadzie AK, Ashton KS, Booker SK, Chen JJ, Chen N, Frohn MJ and Goodman G *et al.*. (2020) Discovery of a Covalent Inhibitor of KRAS^{G12C} (AMG 510) for the Treatment of Solid Tumors. *J Med Chem* **63**: 52-65 [PMID:31820981]
35. Lanman BA, Wurz RP, Verma R, Osgood T, Gaida K, Mohn D, Chen YC, Diaz G and Saiki AY *et al.*. ND01 - AMG 410: An H/NRAS-sparing pan-KRAS inhibitor with dual GTP(on)/GDP(off)-state activity for the treatment of diverse KRAS-mutant tumors <https://www.abstractsonline.com/pp8/#!/20273/presentation/7352>. Accessed on 20/08/2025.
36. Leini R, Kapp J, Kopra K and Pantsar T. (2025) Binding modes of the KRAS(G12C) inhibitors GDC-6036 and LY3537982 revealed by all atom molecular dynamics simulations. *Sci Rep* **15**: 24843 [PMID:40640254]
37. Li Q, Xie K, Lin B and Gong Y. (2025) TBC1D24 promotes the progression of the breast cancer cells via ARF6/PLD axis under hypoxia. *Sci Prog* **108**: 368504251367649 [PMID:40790967]
38. Li Y, Jiang M, Liang S, Chen Z, Qiang P, Zhang L, Zhang X and Yang S. (2025) TBC1D15 Expression Indicates the Toxicity of Gold Nanoparticles on Mitochondria in PC-12 Cells. *ACS Omega* **10**: 30127-30136 [PMID:40727815]
39. Liu B, Cotesta S, Gerspacher M, Leblanc C, Lorthois ELJ, Machuaer R, Mah R, Mura C, Rigollier P and Schneider N *et al.*. (2021) Pyrazolyl derivatives useful as anti-cancer agents Patent number: WO2021120890A1. Assignee: Novartis. Priority date: 20/12/2019. Publication date: 24/06/2021.
40. Liu M, Bryant MS, Chen J, Lee S, Yaremko B, Lipari P, Malkowski M, Ferrari E, Nielsen L and Prioli N *et al.*. (1998) Antitumor activity of SCH 66336, an orally bioavailable tricyclic inhibitor of farnesyl protein transferase, in human tumor xenograft models and wap-ras transgenic mice. *Cancer Res* **58**: 4947-56 [PMID:9810004]
41. Malhotra S, Xin J, Do S and Terrett J. (2022) Fused ring compounds Patent number: US11236068B2. Assignee: Pharmaron, Hoffmann La Roche (originally Genentech). Priority date: 09/11/2018. Publication date: 01/02/2022.
42. Mugarza E, van Maldegem F, Boumelha J, Moore C, Rana S, Llorian Sopena M, East P, Ambler R, Anastasiou P and Romero-Clavijo P *et al.*. (2022) Therapeutic KRAS^{G12C} inhibition drives effective interferon-mediated antitumor immunity in immunogenic lung cancers. *Sci Adv* **8**: eabm8780 [PMID:35857848]

43. Nagasaka M, Li Y, Sukari A, Ou SI, Al-Hallak MN and Azmi AS. (2020) KRAS G12C Game of Thrones, which direct KRAS inhibitor will claim the iron throne? *Cancer Treat Rev* **84**: 101974 [PMID:32014824]
44. Nakayama A, Nagashima T, Nishizono Y, Kuramoto K, Mori K, Homboh K, Yuri M and Shimazaki M. (2022) Characterisation of a novel KRAS G12C inhibitor ASP2453 that shows potent anti-tumour activity in KRAS G12C-mutated preclinical models. *Br J Cancer* **126**: 744-753 [PMID:34795410]
45. Navarro E, Efthymiou AG, Parks M, Riboldi GM, Vialle RA, Udine E, Muller BZ, Humphrey J, Allan A and Argyrou CC *et al.*. (2024) *LRRK2* G2019S variant is associated with transcriptional changes in Parkinson's disease human myeloid cells under proinflammatory environment. *bioRxiv* [PMID:38854101]
46. O'Bryan JP. (2019) Pharmacological targeting of RAS: Recent success with direct inhibitors. *Pharmacol Res* **139**: 503-511 [PMID:30366101]
47. Ostrem JM, Peters U, Sos ML, Wells JA and Shokat KM. (2013) K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature* **503**: 548-51 [PMID:24256730]
48. Rasool S, Rasool V, Naqvi T, Ganai BA and Shah BA. (2014) Genetic unraveling of colorectal cancer. *Tumour Biol* **35**: 5067-82 [PMID:24573608]
49. Rotblat B, Ehrlich M, Haklai R and Kloog Y. (2008) The Ras inhibitor farnesylthiosalicylic acid (Salirasib) disrupts the spatiotemporal localization of active Ras: a potential treatment for cancer. *Meth Enzymol* **439**: 467-89 [PMID:18374183]
50. Shi Z, Weng J, Niu H, Yang H, Liu R, Weng Y, Zhu Q, Zhang Y, Tao L and Wang Z *et al.*. (2023) D-1553: A novel KRAS^{G12C} inhibitor with potent and selective cellular and in vivo antitumor activity. *Cancer Sci* **114**: 2951-2960 [PMID:37158138]
51. Smith EM, Chanaday NL and Maday S. (2025) Astrocytes mobilize a broader repertoire of lysosomal repair mechanisms than neurons. *bioRxiv* [PMID:40964267]
52. Spiegel J, Cromm PM, Zimmermann G, Grossmann TN and Waldmann H. (2014) Small-molecule modulation of Ras signaling. *Nat Chem Biol* **10**: 613-22 [PMID:24929527]
53. Stanley LA. (1995) Molecular aspects of chemical carcinogenesis: the roles of oncogenes and tumour suppressor genes. *Toxicology* **96**: 173-94 [PMID:7900159]
54. Tam IY, Chung LP, Suen WS, Wang E, Wong MC, Ho KK, Lam WK, Chiu SW, Girard L and Minna JD *et al.*. (2006) Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. *Clin Cancer Res* **12**: 1647-53 [PMID:16533793]
55. Tanada M, Tamiya M, Matsuo A, Chiyoda A, Takano K, Ito T, Irie M, Kotake T, Takeyama R and Kawada H *et al.*. (2023) Development of Orally Bioavailable Peptides Targeting an Intracellular Protein: From a Hit to a Clinical KRAS Inhibitor. *J Am Chem Soc* **145**: 16610-16620 [PMID:37463267]
56. Tröster A, Heinzlmeier S, Berger BT, Gande SL, Saxena K, Sreeramulu S, Linhard V, Nasiri AH, Bolte M and Müller S *et al.*. (2018) NVP-BHG712: Effects of Regioisomers on the Affinity and Selectivity toward the EPHrin Family. *ChemMedChem* **13**: 1629-1633 [PMID:29928781]
57. Wang X, Allen S, Blake JF, Bowcut V, Briere DM, Calinisan A, Dahlke JR, Fell JB, Fischer JP and Gunn RJ *et al.*. (2022) Identification of MRTX1133, a Noncovalent, Potent, and Selective KRAS^{G12D} Inhibitor. *J Med Chem* **65**: 3123-3133 [PMID:34889605]
58. Wennerberg K, Rossman KL and Der CJ. (2005) The Ras superfamily at a glance. *J Cell Sci* **118**: 843-6 [PMID:15731001]
59. Wu Y, Zhou YM, Wu W, Jiang WR, Zhang XY, Song SY and Yao ZH. (2024) TBC1D15 Inhibits Autophagy of Microglia through Maintaining the Damaged Swelling Lysosome in Alzheimer's Disease. *Aging Dis* **16**: 3601-3624 [PMID:39812537]
60. Xie Y, Zhang W, Peng T, Wang X, Lian X, He J, Wang C and Xie N. (2024) TBC1D15-regulated mitochondria-lysosome membrane contact exerts neuroprotective effects by alleviating mitochondrial calcium overload in seizure. *Sci Rep* **14**: 23782 [PMID:39390030]
61. Xu H, Chen D, Lu J, Zhong L, Wang L and Ge J. (2025) ARF6 Promotes AML Progression via Activation of PI3K/AKT/mTOR Signaling. *Cancer Med* **14**: e70872 [PMID:40275490]
62. Yang Y, Qing L, You C, Li Q, Xu W and Dong Z. (2025) Methuosis key gene ARF6 as a diagnostic, prognostic and immunotherapeutic marker for prostate cancer: based on a comprehensive pan-cancer multi-omics analysis. *Discov Oncol* **16**: 882 [PMID:40410613]
63. Yoo JH, Shi DS, Grossmann AH, Sorensen LK, Tong Z, Mleynek TM, Rogers A, Zhu W, Richards JR and Winter JM *et al.*. (2016) ARF6 Is an Actionable Node that Orchestrates Oncogenic GNAQ Signaling in Uveal Melanoma. *Cancer Cell* **29**: 889-904 [PMID:27265506]
64. Yoshida N, Doisaki S and Kojima S. (2012) Current management of juvenile myelomonocytic leukemia and the impact of RAS mutations. *Paediatr Drugs* **14**: 157-63 [PMID:22480363]
65. Yu S and Li B. (2022) Compound for inhibiting krasg12c mutant protein, preparation method therefor, and use thereof Patent number: WO2022002018A1. Assignee: Suzhou Wentian Pharmaceutical Technology Co. Priority date: 03/07/2020. Publication date: 06/01/2022.

66. Zhang C, Liu Y, Yuan X, Yang X, Yang B, Huang Y, Wang F, He Z and Li Y. (2025) Identification and validation of ARF6 for a potential prognostic biomarker of acute myeloid leukemia. *Cancer Cell Int* **25**: 218 [[PMID:40542378](#)]
67. Zhang J and Lodish HF. (2007) Endogenous K-ras signaling in erythroid differentiation. *Cell Cycle* **6**: 1970-3 [[PMID:17721087](#)]
68. Zhao HG, Cruz-Rodriguez N, Johnson KC, Pomicter AD, Bates B, Bateman B, Haferlach T, Gu T, Ahmann J and Yan D *et al.*. (2026) The small GTPase ARF6 regulates sphingolipid homeostasis and supports proliferation in acute myeloid leukemia. *Haematologica* **111**: 135-148 [[PMID:40637748](#)]
69. Zhou F, Jiang T, Lin C, Cai L, He W and Lan J. (2021) Substituted heterocyclic fused cyclic compound, preparation method therefor and pharmaceutical use thereof Patent number: [WO2021083167A1](#). Assignee: GENFLEET THERAPEUTICS (SHANGHAI) INC. Priority date: 30/10/2019. Publication date: 06/05/2021.