

## Project 6 - Kostenis lab



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### Molecular modes of action and application of cell-permeable inhibitors for heterotrimeric G proteins

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#### Publications


Benkel, T., Zimmermann, M., Zeiner, J. *et al.* How Carvedilol activates  $\beta_2$ -adrenoceptors. *Nat Commun* **13**, 7109 (2022).


<https://doi.org/10.1038/s41467-022-34765-w> 


Patt J, Alenfelder J, Pfeil EM, Voss JH, Merten N, Eryilmaz F, Heycke N, Rick U, Inoue A, Kehraus S, Deupi X, Müller CE, König GM, Crüsemann M, Kostenis E. (2021) *An experimental strategy to probe Gq contribution to signal transduction in living cells.* **J Biol Chem.** doi: <https://doi.org/10.1016/j.jbc.2021.100472> 


Hermes C, Richarz R, Wirtz DA, Patt J, Hanke W, Kehraus S, Voß JH, Küppers J, Ohbayashi T, Namasivayam V, Alenfelder J, Inoue A, Mergaert P, Gütschow M, Müller CE, Kostenis E, König GM, Crüsemann M. (2021) *Thioesterase-mediated side chain transesterification generates potent Gq signaling inhibitor FR900359.* **Nat Commun.** doi: [10.1038/s41467-020-20418-3](https://doi.org/10.1038/s41467-020-20418-3). 

Holze J, Bermudez M, Pfeil EM, Kauk M, Bödefeld T, Irmen M, Matera C, Dallanoce C, De Amici M, Holzgrabe U, König GM, Tränkle C, Wolber G, Schrage R, Mohr K, Hoffmann C, Kostenis E, Bock A. (2020) *Ligand-Specific Allosteric Coupling Controls G-Protein-Coupled Receptor Signaling.* **ACS Pharmacol Transl Sci.** 3(5):859-867. doi: [10.1021/acsptsci.0c00069](https://doi.org/10.1021/acsptsci.0c00069). PMID: 33073186; PMCID: PMC7551708. 

Annala S, Feng X, Shridhar N, Eryilmaz F, Patt J, Yang J, Pfeil EM, Cervantes-Villagrana RD, Inoue A, Häberlein F, Slodczyk T, Reher R, Kehraus S, Monteleone S, Schrage R, Heycke N, Rick U, Engel S, Pfeifer A, Kolb P, König G, Bünemann M, Tüting T, Vázquez-Prado J, Gutkind JS, Gaffal E, Kostenis E (2019) *Direct targeting of Gαq and Ga11 oncoproteins in cancer cells* **Sci. Signal.** doi: [10.1126/scisignal.aau5948](https://doi.org/10.1126/scisignal.aau5948) 

Malfacini D, Patt J, Annala S, Harpsøe K, Eryilmaz F, Reher R, Crüsemann M, Hanke W, Zhang H, Tietze D, Gloriam DE, Bräuner-Osborne H, Strømgaard K, König GM, Inoue A, Gomeza J, Kostenis E. (2019) *Rational design of a heterotrimeric G protein α subunit with artificial inhibitor sensitivity.* **J Biol Chem.** doi: [10.1074/jbc.RA118.007250](https://doi.org/10.1074/jbc.RA118.007250) 

Imhof D, Reher R, Kühl T, Annala S, Benkel T, Kaufmann D, Nubbemeyer B, Odhiambo JP, Heimer P, Bäuml CA, Kehraus S, Crüsemann M, Kostenis E, Tietze D, König GM. (2018) *Deciphering specificity determinants for FR900359-derived Gαq inhibitors based on computational and structure-activity studies.* **ChemMedChem** doi: [10.1002/cmdc.201800304](https://doi.org/10.1002/cmdc.201800304) 

Murat S, Bigot M, Chapron J, König GM, Kostenis E, Battaglia G, Nicoletti F, Bourinet E, Bockaert J, Marin P, Vandermoere F. (2018) *5-HT<sub>2A</sub> receptor-dependent phosphorylation of mGlu<sub>2</sub> receptor at Serine 843 promotes mGlu<sub>2</sub>receptor-operated G<sub>i/o</sub> signaling.* **Mol Psychiatry** doi: [10.1038/s41380-018-0069-6](https://doi.org/10.1038/s41380-018-0069-6) 

Grundmann M, Merten N, Malfacini D, Inoue A, Preis P, Simon K, Rüttiger N, Ziegler N, Benkel T, Schmitt NK, Ishida S, Müller I, Reher R, Kawakami K, Inoue A, Rick U, Kühl T, Imhof D, Aoki J, König GM, Hoffmann C, Gomeza J, Wess J, Kostenis E

(2018); *Lack of beta-arrestin signaling in the absence of active G proteins*, **Nat Commun**, doi:10.1038/s41467-017-02661-3<sup>doi</sup>

Crüseemann M, Reher R, Schamari I, Brachmann AO, Ohbayashi T, Kuschak M, Malfacini D, Seidinger A, Pinto-Carbó M, Richarz R, Reuter T, Kehraus S, Hallab A, Attwood M, Schiöth HB, Mergaert P, Kikuchi Y, Schäberle TF, Kostenis E, Wenzel D, Müller CE, Piel J, Carlier A, Eberl L, Koenig GM (2017); *Heterologous expression, biosynthetic studies and ecological function of the selective Gq-signaling inhibitor FR900359*, **Angew. Chem. Int. Ed.**, doi: 10.1002/anie.201707996<sup>doi</sup>

Matthey M, Roberts R, Seidinger A, Simon A, Schröder R, Kuschak M, Annala S, König GM, Müller CE, Hall IP, Kostenis E, Fleischmann BK, Wenzel D (2017); *Targeted inhibition of Gq signaling induces airway relaxation in mouse models of asthma*, **Sci Transl Med.**, 2, 407, doi:10.1126/scitranslmed.aag2288



Klepac K, Kilic A, Gnad T, Brown LM, Herrmann B, Wildermann A, Balkow A, Glöde A, Simon K, Lidell ME, Betz MJ, Enerbäck S, Wess J, Freichel M, Blüher M, König G, Kostenis E, Insel PA and Pfeifer A (2016); *The Gq signalling pathway inhibits brown and beige adipose tissue*, **Nat commun**, 7, 10895, doi: 10.1038/ncomms10895<sup>doi</sup>

Schrage R, Schmitz AL, Gaffal E, Annala S, Kehraus S, Wenzel D, Büllersbach KM, Bals T, Inoue A, Shinjo Y, Galandrin S, Shridhar N, Hesse M, Grundmann M, Merten N, Charpentier TH, Martz M, Butcher AJ, Slodczyk T, Armando S, Effer M, Namkung Y, Jenkins L, Horn V, Stößel A, Dargatz H, Tietze D, Imhof D, Galés C, Drewke C, Müller CE, Hölzel M, Milligan G, Tobin AB, Gomeza J, Dohlmann HG, Sondek J, Harden K, Bouvier M, Laporte SA, Aoki J, Fleischmann BK, Mohr K, König GM, Tüting T and Kostenis E (2015); *The experimental power of FR900359 to study Gq-regulated biological processes*, **Nat Commun**, 6, 10156, doi: 10.1038/ncomms10156<sup>doi</sup>

## Links

1. <http://www.pharmbio.uni-bonn.de>