EUROPEAN COOPERATION IN SCIENCE AND TECHNOLOGY

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COST Action CM1207

GLISTEN

GPCR-Ligand Interactions, Structures, and Transmembrane Signalling: a European Research Network

2013 | 2017

Objectives

G protein-coupled receptors (GPCRs) are the largest family of proteins involved in signal transduction across membranes and one of the most important pharmaceutical drug target classes. GLISTEN will

- Utilize the unprecedented number of X-ray structures of GPCRs solved recently to unravel details of the activation mechanism, ligand binding, and the effect of the membrane and other interaction partners on GPCRs.
- Make a concerted push in the investigation of GPCRs, in particular their activation mechanism and different ways to modulate their activity.
- Foster collaborations and multidisciplinary approaches which are instrumental in GPCR research.
- Transfer skills and knowledge among institutions through STSMs.
- Develop novel effector molecules to be used as lead structures for drug development, offering valuable new opportunities for European pharmaceutical research and industry.
- Educate ESRs, as they will be the ones carrying out most of the research and will constitute a generation off highly trained future investigators.

Main Achievements

- This Action was kicked off on May 3, 2013.
- We have planned a “Computational Chemistry for GPCRs” Workshop in Warsaw, Poland for October 8 & 9, 2013.

Chemistry and Molecular Sciences and Technologies (CMST)

Participating countries

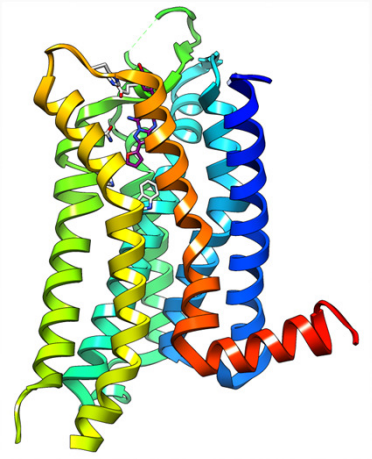
BE, CZ , DK, EE, FI, FR, DE, HU, IS, IL, IT, LV, MT, NL, PL, RS, SL, ES, SE, CH, UK

Contact details

Chair of the Action
Dr Peter Kolb
Emmy Noether Junior Group Leader
Philipps-University Marburg, Germany
peter.kolb@uni-marburg.de

Science Officer
Dr Lucia Forzi
Science Officer Chemistry and Molecular Sciences and Technology
COST Office
lucia.forzi@cost.eu

Website
www.glisten-gpcr.eu



The adenosine A_{2A} receptor, a prototypical GPCR.

COST is supported by the EU RTD Framework Programme

ESF provides the COST Office through a European Commission contract

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Working Group activities

Working Group 1 - Dynamics

- Most of the available GPCR structures represent energetically stable inactive-state conformations. How and at which rates receptors shift between inactive and active states is still unclear.
- WG1 will fill in the gaps between the static X-ray snapshots using techniques that explicitly take into account *dynamics* (NMR, FTIR, MD simulations, FRET, etc.).

Working Group 2 – Biased Signalling

- Different ligands that bind to the same GPCR protein are able to induce different downstream signalling protein pathways, resulting in *pathway bias*.
- Members of WG2 will develop and apply bias screening methodologies and assays to identify and further develop novel *biased* GPCR modulators. Biophysical approaches and molecular modelling studies using functional probes will provide insight into structural determinants of GPCR biased signaling.

Working Group 3 – GPCR Lipid/Protein Interactions

- Researchers in WG3 will investigate the interactions between GPCRs and partners that are *not* small molecules, such as membrane components, other GPCR monomers, G proteins, and PDZ domains.
- WG3 members will use and further develop a wide range of techniques specific for protein-protein and protein-lipid interactions.

Working Group 4 – Discovery & Design of GPCR Ligands

- WG4 will focus on the discovery, design and *optimisation* of *small molecules* that interact with GPCRs. This will provide new tracks in biomedical research and aid the other researchers in the Action.
- Members will seek and identify novel GPCR ligands for applications in medicinal chemistry, chemical biology, and structural biology (e.g. design of ligands to stabilise a particular GPCR conformation; cf. WG1).
- These research topics will be carried out through a combination of complementary experimental and computational methods.

Industry participation

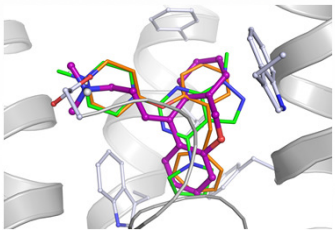
Heptares
Dr Andrea Bortolato,
Senior Computational Chemist,
United Kingdom
andrea.bortolato@heptares.com
www.heptares.com

Gedeon Richter
Akos Tarcsay,
Research Scientist,
Hungary
a.tarcsay@richter.hu
www.richter.hu

Griffin Discoveries
Dr. Rogier Smits
Managing Director
The Netherlands
rogier.smits@griffindiscoveries.com
www.griffindiscoveries.com

Beactica
Prof Helena Danielson,
Chief Scientific Officer,
Sweden
helena.danielson@beactica.com
www.beactica.com

Vivia Biotech
Dr Joan Ballesteros,
Chief Scientific Officer,
Spain
jballesteros@viviabiotech.com
www.viviabiotech.com



GPCR ligands discovered by structure-based virtual screening

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