SUBJECT | SUMMARY OF FIRST WORKING GROUP MEETING OF COST ACTION CA18133 "EUROPEAN RESEARCH NETWORK ON SIGNAL TRANSDUCTION"

Belfast, Northern Ireland, United Kingdom
28-30 October, 2019

The 1st ERNEST Working Group Meeting: ***GPCR Pharmacology: Activation, Signalling and Drug Design*** was held at Queen's University Belfast (QUB) on 28-30 October 2019. The conference began on Monday afternoon with a welcoming talk from the local organiser, **Dr Irina Tikhonova** (QUB). She was followed by Pro-Vice-Chancellor for Education and Students at QUB, **Prof David Jones**, who spoke about development strategies, the importance of networking of scientists from different countries, and the worthwhile tourist attractions of the host city. Next, the Chair of ERNEST, **Dr Martha Sommer**, presented ERNEST's primary objectives and goals, the management and organizational structure of the Action, the Working Groups of ERNEST, and plans for the upcoming meetings, training schools, and international cooperations (see Annex 1). She was followed by Vice-Chair **Dr Jana Selent**, who presented the Action's 3-phase plan for generating a *holistic, multidimensional signalling map* (Annex 1). Action participants were informed that the Working Groups will be soliciting their data for curation and integration, and that ERNEST is seeking volunteers for the 'Mapping Group' to help coordinate these efforts.

The President of the British Pharmacological Society, **Prof Steve Hill** (University of Nottingham) gave the **Opening Talk**: *The molecular pharmacology of GPCRs – Future prospects, fantastic opportunities and a role for learned societies in supporting the future of our discipline.* He emphasised the new technologies available for the study of GPCRs and ligand binding kinetics, as well as current challenges in pharmacology, future strategies for the community, and the importance of supporting early career scientists. He promoted the upcoming annual meeting of the BPS in Edinburgh.

The **Early Career Committee** (ECC) organized that the following scientific sessions were chaired by Early Career Investigators (ECI's). Many thanks to these Chairs for their assistance in moderating the sessions! Stefan Mordalski, Ali Isbilir, Warispreet Singh, Kamil Kuder, Maria Majellaro, Willem Jespers, Vigneshwaran Namasivayam, Lalitha Vaishnavi Subramanyan, Anastasia Gusach, Tomasz Stepniewski, Paschalina Pallaki, Rebecca Diez-Alarcia, Almudena Pino-Angeles, and Edin Muratspahic .

Prof Edda Klipp (Humboldt University Berlin) opened **Session 1: *Signalling Map Strategy and Systems Biology***, with *Mathematical modelling of signal transduction dynamics*, in which she presented an overview of computational modelling and its applicability in cellular signalling processing, especially networks containing G protein-coupled receptors. Next, **Dr Maria Waldhoer** (InterAX Biotech AG) presented *Integrating experimental and computational pharmacology for intelligent drug design,* focused on systems biology approaches combined with signalling assays for faster and more efficient drug discovery and development. Maria emphasized that the time component is essential to reveal 'true bias' of GPCR agonists. **Dr Rune Linding** (Humboldt University Berlin) presented *Deep Hidden Physics Modeling of Cell Signaling Networks*. He talked about identifying and describing drug targets for cancer treatment, modelling of complex diseases, applications of deep learning in biological forecasting and uncovering of underlying mechanisms of tumor-specific networks.

Next, Ramon Guixa Gonzalez, Supriya Gaitonde, Tonis Laasfeld, Lalitha Vaishnavi Subramanyan and Arnau Cordomi presented 'flash talks' to promote their posters at the meeting.

After a short break, first session resumed with the presentation of **Prof Michel Bouvier** (University of Montreal), entitled *Exploring use of unsupervised clustering to associate signalling profiles of GPCR ligands to clinical response*. He discussed the multidimensional signalling profile of GPCRs and prediction of ligand features based on the ligand profiles and development of different clustering methods that could serve as a tool for estimation of potency, effectivity, and potential side effects. The essential questions brought up by Michel's talk, namely what exactly is bias signalling / pathway selectivity, and how should these phenomenon be precisely defined and measured within the GPCR research community, will be addressed within ERNEST by a focused committee at future meetings.

Next, **Dr Maria Marti-Solano** (MRC Laboratory of Molecular Biology, Cambridge) gave a lecture about *Receptor isoform diversity in context-dependent GPCR signalling.* She explained how GPCRs isoforms could be the source of physiological receptor signalling complexity, especially in different tissues and resulting in different drug responses among patients. **Prof Martine Smit** (VU University Amsterdam) presented her studies on viral GPCRs that activate oncogenic signalling networks. She proposed the use of nanobodies, in combination with photo-immunotherapy, that could selectively kill cells expressing the viral receptors. Martine is coordinator of ONCORNET2.0, a Marie Skłodowska-Curie Innovative Training Network (ITN), and ERNEST looks forward to working closely with this ITN in the future. **Prof Ozge Sensoy** (Istanbul Medipol University) presented an overview of *Different Approaches used for Modulation of GPCR signalling.* She discussed hetero-bivalent ligands, different aspects of arrestin regulation and signalling, as well as the role of post-translational modifications in GPCRs.

Session 1 concluded with two promotional talks. First, **Prof Andrew Tobin** (University of Glasgow) presented plans for collaboration between ***ACS Pharmacology and Translational Science*** and ERNEST in a *Special Issue: Advances in GPCR Signal Transduction*. All ERNEST members are encouraged to submit an article, letter, review, perspective, or viewpoint. Second, **Prof Ines Liebscher** and **Dr Simone Prömel** (University of Leipzig) introduced their new COST Action (Adhere 'n Rise, CA18240) focused on adhesion GPCRs and invited all ERNEST members to take part. In addition, ERNEST and Adhere 'n Rise plan to work together to advance the objectives of both Actions.

On the Monday evening, a **Welcome Reception** with Deputy Lord Mayor Councillor Peter McReynolds, took place at the opulent early-20th-century Belfast City Hall. The welcoming lectures were given by **Michael Livingstone**, a local historian, and **Dr Aidan Seeley** from the British Pharmacological Society.

The second day of the meeting began with **Session 2*: Macromolecular Interactions in Signalling Pathways***. **Dr Chris Tate** (MRC Cambridge) presented *Molecular basis for high affinity agonist binding at the beta 1 adrenoceptor.* He presented active-state structures of the turkey β1-adrenoceptor in complex with a conformation-specific nanobody and four different agonists, comparison of which indicated the connection between the tightness of ligand-receptor interactions and agonist efficacy. He also presented an exciting new cryo-EM structure of arrestin-2 in complex with a chimeric GPCR in a nanodisc. Next, **Prof Moran Shalev-Benami** (Weizmann Institute of Science) delivered *Deadly Spiders & Scary Zombies NOT a Halloween Story - A Near Atomic Resolution Glance into the CNS.* She explained the technical basis for recent advancements in single particle electron cryo-EM, which is currently revolutionizing the field. She presented high-resolution structures of two transmembrane receptors expressed in neurons (cannabinoid receptor 1 and teneurin) and discussed their architecture and proposed mechanisms of action. **Anastasia Gusach** (Moscow Institute of Physics and Technology) introduced her recently-founded institute and presented *Structural insights into ligand binding and disease-related mutations of Cysteinyl Leukotriene Receptor type 2*. **Dr Christoph Klenk** (*University of Zurich*) closed the session with a talk on *High-resolution crystal structure of parathyroid hormone 1 receptor in complex with a peptide*.

After a short break, **Prof Jamie Davies** (University of Edinburgh) opened **Session 3: *Public Web Resources***, with an overview of the *IUPHAR / BPS Guide to PHARMACOLOGY database*. He was followed by **Prof David Gloriam** (University of Copenhagen) who introduced *The G protein-coupled receptor database, GPCRdb* and its useful tutorials and tools for data visualisation, design of experiments and future development plans. Next, **Prof Jana Selent** (Pompeu Fabra University) gave a

lecture titled *GPCRmd brings G protein coupled receptors to Life.* She emphasised the importance of better understanding of receptor dynamics and ligand-receptor interactions for scientists of various backgrounds. She presented the progress of GPCRmd, an open-access resource for molecular dynamics simulations, as well as the idea of standard protocols for GPCR MD simulations that could improve transparency and reproducibility of such data created by different research groups.

Session 3 closed with flash talks presented by Milan Sencanski, Maria Majellaro, Angela Sefanachi, Marcel Bermudez and Przemyslaw Miszta, followed by lunch and a poster session.

Session 4: *Molecular Modulators of Signal Transduction* opened with **Dr Chris De Graaf** (Sosei Heptares) and his lecture *Computational Medicinal Chemistry Approaches for GPCR Structure-Based Drug Discovery.* He showed how GPCR structures in combination with computational and experimental studies can be used for a better description and prediction of the molecular and structural determinants of ligand-receptor binding affinity, kinetics, potency, and selectivity. Chris ended his talk with a self-written musical homage to ERNEST. **Dr Christofer Tautermann** (Boehringer Ingelheim) then gave a talk about *Peculiar GPCR ligand kinetics uncovered by MD-simulations*, specifically about M3 muscarinic receptor agonists and uncovering their modes of action, followed by **Dr Agnieszka Kaczor** (University of Lublin) on *Multi-target ligands of aminergic GPCRs as potential antipsychotics*. **Dr Almudena Pino-Angeles** (Queen's University Belfast) continued with *Structural features of extra-helical transmembrane allosteric sites in GPCRs in different lipidic environment.* She presented molecular dynamic studies and structural features of allosteric sites in the Proteinase-Activated Receptor 2, C5a Receptor, and Glucagon Receptor. **Prof Irina Moreira** (Coimbra University) closed the session with her lecture *How Artificial Intelligence and big data could be applied to GPCR functional understanding.* In her talk, she focused on her characterization of the Dopamine Receptor family and data-driven GPCR drug discovery.

After a break, **Session 5: *Advanced Methodologies and Technologies***, began with **Prof Martin Caffrey** (Trinity College Dublin) and his talk *Lipid Mesophases for Membrane Protein Structure, Function and Drug Design Studies*. He explained the *in meso* method, which has been a powerful tool used to obtain high-resolution structures of many GPCRs. Next, **Dr Frank Bernhard** (Goethe University Frankfurt) spoke about *Co-Translational Insertion of GPCRs into Nanomembranes.* He showed how this method can be used in large scale ligand binding assays or identification of protein domains necessary for the ligand recognition. **Dr Claire Hatty** (Nanotemper Technologies) presented *Characterising GPCR stability and interactions with nanoDSF and MST,* in which she summarised technologies based on monitoring thermal unfolding and aggregation of proteins using intrinsic tryptophan and tyrosine fluorescence. Next, **Dr Nuska Tschammer** (CRELUX) gave a talk about *Fragment-Based Approach to Leverage Challenging Targets: human STING.* **Dr Josef Lazar** (Czech Academy of Sciences) closed the session with *Sensitive and versatile imaging of G-protein signalling events by polarization-resolved fluorescence microscopy*. He showed how polarization microscopy can be used to observe protein-protein interactions and conformational changes in membrane proteins inside living cells, which has obvious applications for the study of GPCRs and G protein signalling.

A poster session followed, after which a **Ping Pong Session with Industry** took place. This round-table discussion was a great opportunity for early career researchers to find out more about possible scientific career paths and to ask questions about research positions in pharmaceutical companies. The meeting participants then enjoyed food, drink and traditional Irish dancing and music at the **Conference Dinner** in the Great Hall of the QUB.

The last day of the meeting began with **Session 6: *Molecular Modulators of Signal Transduction*** and a lecture by **Prof Eamonn Kelly** (University of Bristol), *Clarity or confusion in the field of biased agonism at opioid receptors?* He addressed current challenges in the development of more precise drugs that cause less side effects. Next, **Dr Sophie Bradley** (University of Glasgow) gave a talk about *Targeting G protein-coupled receptors in neurodegenerative disease.* She presented M1-muscarinic acetylcholine receptors as an attractive target for the treatment of neurodegenerative disorders such as Alzheimer's disease. Her studies based on mice models have shown that targeting these receptors with ligands directing the signalling towards phosphorylation-dependent pathways could have beneficial effects in the clinic. **Masa Rutar** (University of Ljubljana) then presented *Characterization of BILF1*

receptors encoded in epstein-barr virus and porcine lymphotropic herpesviruses. She summarized her studies on selected viral G protein-coupled receptors (vGPCRs), which play an important role in infection, especially in post-transplant patients. She presented studies using transcription factor assays focused on characterization, activation, internalization and location of these receptors that present a potential target for a therapy. **Alexander Hauser** (University of Copenhagen) concluded Session 6 with his talk *Discovery of peptide-receptor pairs expands the human signalling system.* He described a novel method for pairing ligands to orphan GPCRs that combines the generation of an endogenous peptide library with computational methods and experimental assays using multifaceted screening platform.

After a short break, **Session 7: *Macromolecular Interactions in Signalling Pathways*** began with a lecture by **Prof Patrick Casey** (Duke-NUS Medical School), *Involvement of G12 proteins in tumorigenesis and metastasis,* in which he described the role of upregulated G protein signalling in cancer progression, as well as work identifying microRNAs and secreted molecules that act as important regulating factors. Next, **Erica Cecon** (Institut Cochin) gave a talk entitled *Gi/o and Gq/11 proteins cooperate in asymmetric GPCR dimers to activate ERK*. She presented her studies of the signal transduction of melatonin MT1 and MT2 receptors. **Dr Julien Hanson** (University of Liege) presented *GPR101 promotes growth hormone secretion in the pituitary through Gs and Gq/11-dependent pathways.* He described the molecular basis of acrogigantism and the characterization of an orphan receptor GPR101 involved in growth hormone secretion and thus potential drug target for the treatment of growth-related disorders. The final scientific session of the meeting concluded with a talk by **Prof Graeme Miligan** (University of Glasgow) on *GPCR dimerization, moving from in vitro to in vivo analysis*.

The meeting was concluded by the ERNEST Chair Martha Sommer, who thanked the local organisers and participants and announced the upcoming meetings. These will be:

Istanbul, Turkey, March 28-30, 2020 (with associated Training School March 26-27)

Bari, Italy, October 12-14, 2020

In conclusion, the first ERNEST meeting was very successful and inspirational. Besides showcasing exciting research in GPCR pharmacology and signal transduction from Europe and beyond, the future course and plan of action for the Network were presented and heavily discussed. ERNEST aims to bring together scientists from different disciplines and expertise to collectively address controversies and shortcomings in the field, and to curate and integrate data and knowledge in the Network for the development a multi-dimensional map of GPCR signal transduction. All ERNEST members are encouraged to contribute to these exciting and potentially game-changing endeavours!

Twitter account for this meeting: **#ERNEST19**

Annex 1 – Slides from the Opening of the Meeting (presented by Martha Sommer and Jana Selent)

Many thanks to **Agnieszka Sztyler** (Charité Medical University Berlin) for preparing the notes on which this report is based.