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A panoramic view on GPCRs: The 1st Belin Symposium for Interdisciplinary GPCR research

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Abstract:

On April 12, 2018, 41 GPCR researchers gathered at the Freie Universität Berlin, Germany. The purpose of the 1st Belin Symposium for Interdisciplinary GPCR research was to bring together research groups from various scientific disciplines based in Berlin and Potsdam who work on GPCRs. The meeting addressed mainly young researchers (i.e. advanced PhD students, Post-Docs and young group leaders) who presented their research in talks and poster sessions. The symposium provided a forum to discuss common questions in GPCR biology with researchers who address the same question from different angles. The meeting was an excellent venue for networking on the young researcher level and encouraged future interdisciplinary research in Berlin.

Main text:

G protein-coupled receptors (GPCRs) form the largest class of cell-membrane receptors and continue to be one of the important drug target classes[1]. Since the advent of the “crystallization era” about 10 years ago the field has made a quantum leap forward towards understanding the complex biology of GPCR activation and signaling[2]. However, fairly soon after a plethora of different structures including inactive and active receptors as well as receptor-G protein-complexes were

published, it became clear that high-resolution structures are not sufficient to explain the complex nature of GPCR biology[2]. Therefore, besides crystallography, the field uses a broad toolbox of biophysical, computational and pharmacological methods which allow capturing the inherent dynamics of GPCRs[3] and are suitable to understand in more detail current hot topics in GPCR biology: i.e. allosteric modulation[4,5], biased signaling[6] and polypharmacology to name a few[7]. The latter aspects have attracted a lot of interest in drug discovery as they may open up novel strategies to modulate GPCR function more succinctly[8]. In addition to studying GPCRs on the atomic and molecular level, a lot of effort is put into translation of the novel *in vitro* findings into *in vivo* settings and disease models[9]. The growing understanding of the complexity of GPCR signaling requires to address major research questions from different angles spanning disciplines as diverse as biochemisty, biophysics, computational biology, pharmacology, cell biology and *in vivo* models. A highly interdisciplinary approach to pursue this avenue has proven valuable in many cases and may be the strategy of choice for the next generation of scientists[10].

Figure 1: The participants of the 1st Berlin Symposium for Interdisciplinary GPCR research. In the middle of the first row: the organizers Dr. Marcel Bermudez (FU Berlin) and Dr. Andreas Bock (MDC).

At the 1st Berlin Symposium for Interdisciplinary GPCR research which took place on April 12, 2018, a group of 41 junior scientists convened at the Institute for Pharmacy of the Freie Universität Berlin, Germany (Figure 1). The group was composed of researchers from the Freie Universität Berlin, the Charité-Universitätsmedizin Berlin, the Max-Delbrueck-Center for Molecular Medicine, the Leibniz Institute for Molecular Pharmacology, the German Center for Neurodegenerative Diseases (DZNE) Berlin and the Fraunhofer Institute for Cell Therapy and Immunology Potsdam-Golm. The participants represented a mélange of scientific disciplines with strong expertise in medical biophysics including X-ray crystallography and Cryo-EM complemented by pharmacology, computational biology and advanced microscopy. In addition to the groups with a stronger *in vitro* focus, a large party of *in vivo*-oriented and clinical

scientists came from disciplines such as anesthesiology, cardiology and vascular medicine, immunology, neuroscience and endocrinology. Scientific highlights of the meeting included novel strategies to express and produce large quantities of GPCRs in various hosts[11] or by using eukaryotic cell-free protein synthesis[12] (Michal Szczepek, Patrick Scheerer lab, Charité-Universitätsmedizin and Anna Zemella, Stefan Kubick lab, Fraunhofer IZI, Potsdam-Golm). Large-scale purification is necessary to conduct crystallization trials to capture atomic-resolution snapshots of different GPCR states and to perform biophysical experiments to study GPCR dynamics. In addition to heterotrimeric G proteins, β-arrestins are considered as important downstream signaling proteins of GPCRs. However, how GPCRs activate arrestins has not been understood. Very recent data have revealed that arrestins can be activated independently by both the receptors' transmembrane core and the C-terminus. This has important implications for biased arresing signaling[13] (Martha Sommer, Charité-Universitätsmedizin). The design of novel GPCR agonists with limited side effects has attracted much interest over the last years. Two talks given at the symposium focused on this aspect. Researchers from the Chaité have recently succeded in developing an analgesic which targets μ-opioid receptors specifically in pathologic tissue in the periphery. This novel pH-sensitive fentanyl derivative appears to be an effective analgesic but is endowed with less side effects such as respiratory depression and obstipation which are commonly associated with classical opioidergic painkillers[14] (Viola Spahn, Christoph Stein lab, Charité-Universitätsmedizin). Another strategy in GPCR drug discovery is to develop biased ligands which favor one pathway over others. In vascular disease it may be valuable to design G-protein-biased ligands (Till Althoff, Charité-Universitätsmedizin). In addition to the above-mentioned aspects, compartmentalized GPCR signaling[15] (Andreas Bock, Martin Lohse lab, MDC), implications of GPCR trafficking on cellular

aging (Arthur Gibert, Ralf Schülein lab, FMP), strategies to use GPCR internalization to overcome defects of hormone transport (Sarah Paisdzior, Heike Biebermann lab, Charité-Universitätsmedizin), and the impact of cannabinoid receptor signaling in cortical neuron signaling were discussed (Alexander Stumpf, Dietmar Schmitz lab, DZNE Berlin). The topic of allosteric modulation of GPCRs was presented highlighting the development of negative allosteric modulators for TSH receptors (Patrick Marcinkowski, Gerd Krause lab, FMP). Focusing on cutting-edge technology, high-end (super-resolution) microscopy methods and their application to study various aspects of GPCR oligomerization, trafficking and signaling were discussed[16] (Paolo Annibale, Martin Lohse lab, MDC).

The meeting was the first of its kind to concentrate the entire GPCR expertise available in Berlin and outskirts with a strong focus on junior scientists. The participants presented their research in talks and poster sessions. The heterogeneity of the group provided the possibility to discuss one's own research with scientists from completely different fields. This not only inspired the researchers to pursue new ideas but also fostered interdisciplinarity.

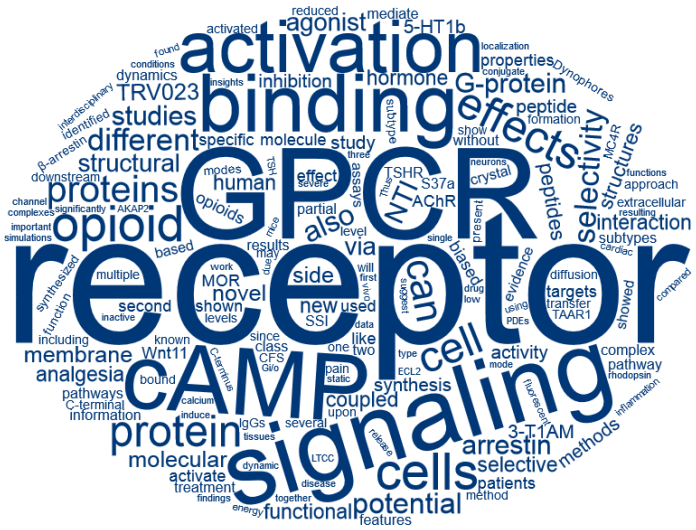

Figure 2: Word cloud generated by all abstracts submitted by the participants highlighting the interdisciplinarity of the meeting.

In addition to the scientific focus of the meeting, the participants discussed about the pros and cons of interdisciplinary research at an early stage of a scientific career (Marcel Bermudez, Gerhard Wolber lab, FU Berlin). How interdisciplinary can a young researcher be? Despite the rather obvious fact that interdisciplinary research is a highly valuable approach to tackle large and complex research questions related to GPCR biology, it can also be a burden in terms of positioning oneself in the field. Pursuing a career in academia is often successful when people can be assigned to a specific topic which may be in contrast to being interdisciplinary. With regard to funding, interdisciplinary projects are usually more complex and require more time to be published. This is often difficult for young researchers as contract times are limited.

In summary, the 1st Belin Symposium for Interdisciplinary GPCR research provided a forum to discuss interdisciplinary GPCR research within Berlin and a networking platform for junior scientist. Given the large variety of disciplines present and techniques available, Berlin stands out as a highly attractive and competitive environment for interdisciplinary GPCR research.

Author contribution:

AB and MB wrote the manuscript. AB and MB read and approved the manuscript.

Conflict of interest:

None.

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Link to the website:

http://www.bcp.fu-berlin.de/pharmazie/faecher/pharmazeutische_chemie/wolber/gpcr_symposium/index.html

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