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COMMENTARY—EXPLORING THE BIOLOGY OF GPCRs: FROM IN VITRO TO IN VIVO

Exploring the Biology of G Protein–Coupled Receptors from In Vitro to In Vivo

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ABSTRACT

In August 2014, an international group of researchers gathered for 5 days at the Lorentz Center in Leiden, The Netherlands, to explore the technical and conceptual issues associated with the analysis of G protein–coupled receptor functions utilizing information from crystal structure models to the use of model organisms. This collection of review articles evolved from the 5-day meeting, with brief presentations and structured discussion periods that were designed to identify key questions remaining in understanding G protein–coupled receptor function and to propose novel strategies by integrating scientific disciplines to guide future research.

The family of G protein–coupled receptors (GPCRs) plays a key role in cellular communication and features prominently in all areas of biology and human health. Not surprisingly, GPCRs are one of the most favored targets in modern drug discovery. Traditionally, GPCRs have been studied in bioassays as well as other physiologic experiments, which have led to the discovery of many GPCR-based drugs. However, with the advent of biochemical and molecular biology approaches, GPCR research has developed in two increasingly different directions: functional expression and in vitro biochemical/biophysical analyses and an increasing diversity of in vivo models.

The workshop focused on bringing together individuals that visualize GPCR function from a structural and signaling aspect, as is prevalent in the GPCR drug development field (principally in vitro), with those who study GPCR function in biologic networks (principally in vivo). The apparent disconnect was addressed by bringing together individual researchers from different scientific backgrounds who may favor chemistry and/or pharmacology meetings with others who may favor genetics meetings into one setting. Each half-day session focused on a particular theme, and following the brief 15-minute presentations, questions were generated from the thought-provoking data presentation period. To focus the discussions, the program addressed five major issues in GPCR biology:

1. Structural and functional aspects of GPCRs;
2. Intracellular scaffolds and context-dependent signaling;
3. Temporal regulation of GPCR actions;
4. Noncanonical GPCR signaling; and
5. Measuring GPCR activities in real-time in vivo.

The group of 55 participants from diverse disciplines and backgrounds were then separated into two discussion groups. The afternoons were spent discussing questions and how we may creatively address them using ideas from colleagues who take a different approach to understanding functional response. Each morning, the results of the discussion period were presented to the group. As the two groups often approached questions differently, the discussion periods inspired more discussion that carried forward into poster sessions and into the evenings. In all, the meeting afforded an opportunity to talk among colleagues who often do not intersect. For example, this format provoked significant discussions into how genetically modified model organisms could be used to test the structural insights uncovered by biophysical analysis and provided insight into the power of pharmacological probes for testing genotypic and phenotypic correlations. The cross-fertilization of ideas and approaches helped define fundamental principles of GPCR function and construct future directions in the GPCR field. Moreover, they formed the basis of nine review articles in this dedicated minireview series covering topics such as

The meeting "Exploring the Biology of GPCRs from in vitro to in vivo" (http://www.lorentzcenter.nl/lc/web/2014/657/info.php3?wsid=657&venue=Oort) would not have been possible without the Lorentz Center's generous financial support and that of COST (GLISTEN CM1207), the Leopoldina, and other sponsors.
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ABBREVIATION: GPCR, G protein–coupled receptor.

interpretation of GPCR crystal structures, importance of ligand residence time, GPCR multimers, the promise of biased signaling in vivo, spatial and temporal aspects of GPCR signaling, studying GPCR signaling with resonance energy transfer biosensors in vivo, model organisms in GPCR research, and a novel class of adhesion GPCRs and GPCR signaling networks from a systems biology perspective (Hoffmann et al., 2015; Langenhan et al., 2015; Lohse and Hofmann, 2015; Luttrell et al., 2015; Monk et al., 2015; Piscitelli et al., 2015; Roth et al., 2015; van Unen et al., 2015; Vischer et al., 2015). Scientists with expertise in in vitro and in vivo GPCR studies participated in the different reviews, thus bridging these fields. In addition, junior scientists who had presented their posters via short slide presentations fueled discussions and played inspiring roles in several of these reviews.

Altogether, this Lorentz Center GPCR workshop, with its unique interactive format, will inspire future research questions and collaborations to explore the fundamental principles of GPCR signaling. Five years from now, we foresee a follow-up of this GPCR workshop, in which we will address today's research questions and answers gathered in coming years.

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