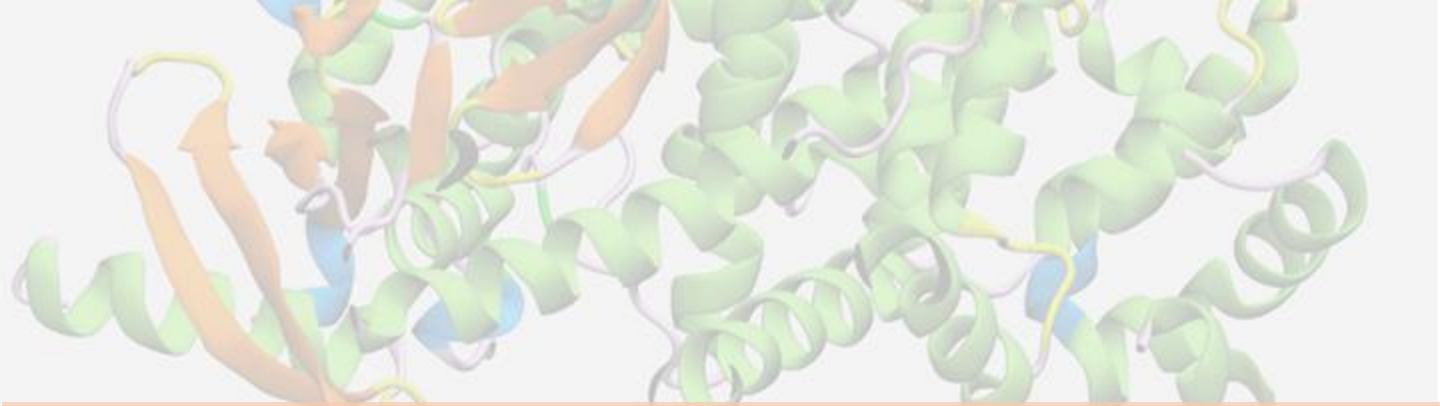


Allostery in Drug Discovery

ALLODD

Lecture Series on Allostery in Drug Discovery

05.06.2025

13:30 – 17:00

Charité Cross Over (CCO), Lecture Hall Ground Floor

Charité Campus Mitte

Virchowweg 6, 10117 Berlin

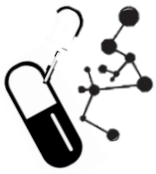
FMP

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956314.

About ALLODD

The **ALLODD** project is a collaboration between
23 academic and **industrial organizations** with **14 ESRs**.



Why Allostery in Drug Discovery?

Most current drugs are designed to bind directly to the primary active sites (also known as orthosteric sites) of their biological targets. Allosteric modulators offer a powerful yet underexploited therapeutic approach. They can elicit a richer variety of biological responses and, since they target less conserved binding sites, higher selectivity and less adverse effects may be obtained.

ALLODD aims to train a new generation of scientists in exploiting the concept of allostery in drug design, putting together a whole array of technologies to identify and characterize allosteric modulators of protein function that will be applied to therapeutically relevant systems.

Eyes on the Future

ALLODD approach is based on a combination of experimental and simulation techniques, including fragment Screening with structural characterization (cryo-EM, X-ray, NMR, H/D exchange), proteomics (MS/MS), ITC, DNA encoding libraries, Virtual Screening, Molecular Dynamics simulations-based methods, Synthetic Chemistry, and in vitro and cellular assays for the verification of results.

Allosteric targeting need not be achieved solely through the design of synthetic small molecules, but also can be reached via conformationally specific allosteric antibodies, which represents an important field of future research. There are already clear examples of monoclonal antibodies that allosterically target ion channels, GPCRs and RTKs, as well as cytokine and integrin receptors.

https://www.allodd-itn.eu/ @ALLODD_ITN **Allostery in Drug Discovery**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956314.

Lecture Series on Allostery in Drug Discovery

05.06.2025, 13:30 – 17:00

Session 1 13:30 – 15:30	**Dr. Patrizio Mattei** Roche Innovation Center Basel, Pharma Research & Early Development (pRED), Basel *The Discovery and Early Development of Zosurabalpin*
	Prof. Gunnar Schulte Karolinska Institutet, Dept. Physiology & Pharmacology, Sec. Receptor Biology & Signaling, Stockholm *Dynamic Class F receptors – basis for transmembrane allostery*
15:30 – 16:00	**Coffee Break** (Atrium)
Session 2 16:00 – 17:00	**Prof. Torsten Schöneberg** Rudolf Schönheimer Institute of Biochemistry, Molecular Biochemistry, Medical Faculty, University of Leipzig *The Impact of Allostery in Biochemical Research and Drug Discovery*

Hosts:

Prof. Dr. Marc Nazaré (Leibniz Forschungsinstitut für Molekulare Pharmakologie)

Dr. Patrick Scheerer (Charité Universitätsmedizin Berlin)

Charité Cross Over (CCO), Lecture Hall Ground Floor
Charité Campus Mitte, Virchowweg 6, 10117 Berlin

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956314.

Abstracts
Session 1

Dr. Patrizio Mattei

Small Molecule Research, pRED Therapeutic Modalities Roche Innovation Center Basel, CH-4070 Basel.

The Discovery and Early Development of Zosurabalpin

Drug resistance to all existing classes of antibiotics has been on the rise in various gram-negative bacteria for several decades, but we have seen very few new antibiotics in development with the potential to overcome this threat. Any new antibiotic class that has the ability to treat infections caused by difficult to treat bacteria such as carbapenem-resistant Acinetobacter baumannii (CRAB) would be a significant breakthrough. Zosurabalpin is the first representative of a structurally distinct compound class of antibiotics, which has many features that position it to be a medical breakthrough. Phenotypic high-throughput screening of a library of tethered macrocyclic peptides (MCPs) identified RO7036668, which was selectively targeting Acinetobacter baumannii. Medicinal chemistry efforts rapidly resulted in RO7075573, which was able to cure bacterial infections in mice, where established antibiotics failed. However, these compounds suffered from poor intravenous tolerability and multi-organ toxicity in rats. The lead optimisation was guided by consideration of the antibiotic drug-like space and supported by a customised plasma compatibility assay, producing highly efficacious compounds with improved intravenous tolerability and no organ toxicity. The development compound zosurabalpin has completed phase 1 clinical trials, and if approved it would become the first antibiotic of a new class in more than 50 years to be used against infections caused by gram-negative bacteria. In the final chapter of the talk, the mechanism of action will be presented, which has been elucidated in a collaboration with Harvard University. By interacting with a protein target that is unique to gram-negative bacteria, zosurabalpin blocks the trafficking of lipopolysaccharide (LPS). Surprisingly, this new class of antibiotics binds both to the transport complex in the inner membrane, as well as the LPS itself, preventing its transport to the outer membrane.

Prof. Gunnar Schulte

Karolinska Institutet, Dept. Physiology & Pharmacology, Sec. Receptor Biology & Signaling., Stockholm.

Dynamic Class F receptors – basis for transmembrane allostery

Frizzleds (FZDs) in the class F of G protein-coupled receptors mediate cellular communication transmitting instructive information during embryogenesis ranging from stem cell proliferation to cell migration, organogenesis and cell polarity. Misinterpretation of FZD-mediated signals leads on one hand to developmental disorders and on the other hand to severe diseases such as cancer or fibrosis. The family of FZDs comprises ten paralogs (FZD1-10), which mediate cellular effects of the Wingless/Int-1 (WNT) family of secreted lipoglycoproteins. WNTs are FZD ligands and FZDs are thereby WNT receptors. WNTs bind FZDs on the extracellular cysteine-rich domain (CRD) and subsequent dynamic rearrangements lead to transmission of conformational changes to the intracellular side of the receptor, that is responsible for transducer coupling. FZDs can couple to heterotrimeric G proteins or the phosphoprotein Dishevelled (DVL), and diverse cellular effects emerge from distinct transducer coupling. Signal transduction through WNTs, FZDs, several associated coreceptors and intracellular transducers is a splendid example of transmembrane allostery, where extracellular events, similar to a gear box, are transmitted across the plasma membrane. The identification of state-stabilizing residues and molecular switches in FZDs together with the first FZD-targeting small molecules underline the importance of dynamic conformational changes and allosteric information transmission as the foundation of receptor activation and pharmacological targeting of FZDs by small drug-like molecules.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956314.

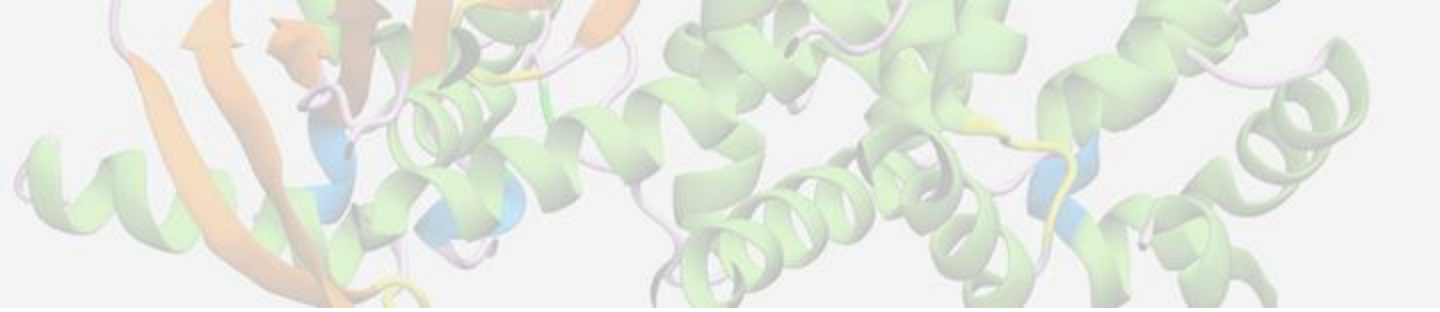
Abstract
Session 2

Prof. Torsten Schöneberg
Rudolf Schönheimer Institute of Biochemistry, Molecular Biochemistry, Medical Faculty, University of Leipzig.

The Impact of Allostery in Biochemical Research and Drug Discovery

Allostery, the regulation of protein function through ligand binding at sites distinct from the active site, is a central mechanism in cellular signaling and metabolic control. This lecture begins by establishing the conceptual foundations of allostery, tracing its etymology, historical models (including the Monod–Wyman–Changeux and Koshland–Némethy–Filmer frameworks), and its molecular manifestations across enzymes, binding proteins, and ion channels. Core principles such as cooperativity, structural transitions, and non-classical dynamic models are illustrated using well-characterized systems like hemoglobin, phenylalanine hydroxylase, and porphobilinogen synthase. The concept of allostery is then critically examined in the context of G protein–coupled receptors (GPCRs)—a major pharmacological target class—where classical models often fall short of explaining the complexity of receptor modulation. By applying a generalized allosteric framework to GPCR signaling, the lecture explores basal activity, allosteric agonism, and inverse agonism, and highlights the challenges and opportunities in aligning theoretical models with experimental observations. In doing so, it underscores the need for refined nomenclature and mechanistic clarity in studying and exploiting allosteric regulation, especially in drug discovery. The talk thus offers both a conceptual map and a critical application of allostery to a key protein family in biomedical research.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956314.



ALLODD Beneficiaries

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

Université de Strasbourg

FMP LEIBNIZ FORSCHUNGSINSTITUT FÜR MOLEKULARE PHARMAKOLOGIE

MERCK

NXERA

KAROLINSKA INSTITUTET ANNO 1810 Karolinska Institutet

1506 UNIVERSITÀ DEGLI STUDI DI URBINO CARLO BO

ttk

UNIVERSITAT DE BARCELONA

JÜLICH Forschungszentrum

Johnson&Johnson Innovative Medicine

ACADEMY OF ATHENS

universität wien

BRFAA BIOMEDICAL RESEARCH FOUNDATION ACADEMY OF ATHENS

ALLODD Partner Organizations

BAYER

21 Sci science 27 Co communication

ucb

astex pharmaceuticals

novo nordisk®

GAIN THERAPEUTICS

MŰEGYETEM 1782

INSTITUT PASTEUR

confo therapeutics

UNIVERSITÉ DE GENÈVE

VERITAS IUSTITIA LIBERTAS FREIE UNIVERSITÄT BERLIN

https://www.allodd-itn.eu/ @ALLODD_ITN **Allostery in Drug Discovery**

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 956314.