MBG FOCUS TALK

hosted by Ditlev E. Brodersen & Poul Nissen

MINI-SYMPOSIUM

25 November 2021 from 11:00 - 12:00

Dept. Mathematics, aud. D1 (1531-113)

From 11:00-11:30 Prof. Dr. Lutz Schmitt

Dept. of Biochemistry, Heinrich-Heine-Universität Düsseldorf, Germany

Structure and efflux mechanism of the yeast pleiotropic drug resistance transporter Pdr5

From 11:30-12:00 Prof. Christian A. Olsen

Center for Biopharmaceuticals and Dept. Drug Design and Pharmacology
Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

Chemical Tools for Investigating Histone Deacetylase (HDAC) Enzymes

See seminar abstracts on page 2-3 of this announcement

Everyone interested is welcome to attend.

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DEPT. OF MOLECULAR BIOLOGY AND GENETICS
AARHUS UNIVERSITY

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25. november 2021, 11.00-11.30

Dept. of Mathematics, aud. D1 (1531-113)

Prof. Dr. Lutz Schmitt

Dept. of Biochemistry, Heinrich-Heine-Universität Düsseldorf, Germany

Structure and efflux mechanism of the yeast pleiotropic drug resistance transporter Pdr5

The ABC transporter Pdr5 of S. cerevisiae is a key player of the pleiotropic drug resistance (PDR) network that works as a first line of defense against a wide range of xenobiotic compounds. As the first discovered member of the family of asymmetric PDR ABC transporters, extensive studies have been carried out to elucidate the molecular mechanism of drug efflux and the details of the catalytic cycle. PDR5 turned out to be an excellent model system to study functional and structural characteristics of asymmetric, uncoupled ABC transporters. In this context, asymmetry refers to the fact that one of the two nucleotide binding sites (NBS) deviates from the canonical architecture, which as a consequence impairs ATP hydrolysis at this NBS. Pdr5 is one of the most extreme asymmetric or degenerated ABC transporters as all catalytic relevant amino acids of NBS1 are exchanged to non-active residues. Only, recently a protocol to purify Pdr5 in a functional state was established and allowed the first in vitro studies that also resulted in a structural analysis of Pdr5 by single particle cryo-EM. These structures revealed details of an ATP-driven conformational cycle, which mechanically drives drug translocation through an amphipathic channel, and a clamping switch within a conserved linker loop that acts as a nucleotide sensor. The conformation of one half of the transporter remains nearly invariant throughout the cycle, while its partner domain undergoes changes that are transmitted across inter-domain interfaces to support a peristaltic motion that displaces transport substrate.

All welcome

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MBG Focus Talks in Molecular Biology

Thursday 25 November 2021 from 11.30-12.00

Dept. Mathematics, aud. D1 (1531-113)

By Prof. Christian A. Olsen

Center for Biopharmaceuticals and Dept. Drug Design and Pharmacology
Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

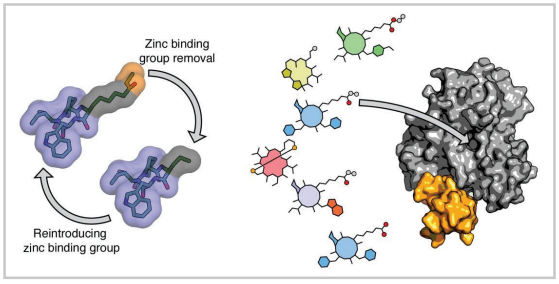
Chemical Tools for Investigating Histone Deacetylase (HDAC) Enzymes

Histone deacetylases (HDACs) are validated targets for treatment of certain cancer types and play numerous regulatory roles in biology, ranging from epigenetics to metabolism. Small molecules are highly important as tool compounds to probe these mechanisms as well as for the development of new medicines. Therefore, detailed mechanistic information and precise characterization of the enzyme substrate preference as well as the chemical probes used to investigate the effects of HDAC enzymes are vital.

Through profiling of both sirtuins and zinc-dependent HDACs, we have developed efficient assay formats for probe characterization and discovered enzymatic activities against novel acyllysine posttranslational modifications (PTMs).

Furthermore, we have interrogated Nature's arsenal of macrocyclic non-ribosomal peptide HDAC inhibitors by chemical synthesis and evaluation of more than 30 natural products and analogs. This furnished surprising trends in binding affinities for the various macrocycles, which were then exploited for design of highly potent class I and IIb HDAC inhibitors. Furthermore, thorough kinetic investigation revealed unexpected inhibition kinetics of important tool compounds as well as the approved drug Istodax (romidepsin). This work provides novel inhibitors with varying potencies, selectivity profiles, and mechanisms of inhibition and, importantly, affords insight regarding known tools compounds that will improve interpretation of their effects in biology and medicine.

Figure: Macrocyclic inhbitors of HDACs.



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