Microsymposium

"Various Aspects of Early Drug Discovery - from Artificial Intelligence to Preclinical Considerations"

16.III.2023

Aula Główna Uniwersyteckiego Centrum Stomatologii (UCS)

11:00 – 11:45	*Can we talk to a protein? Implementation of artificial intelligence in structural biology and drug discovery,* Dr Grzegorz Popowicz
11:45 – 12.15	*DYRK1A inhibitors Leucettines and TGF-β inhibitor additively stimulate insulin production in beta cells, organoids, and isolated mouse islets,* Dr Anna Czarna
12:15 – 12.45	*Molecular dynamics simulations to study protein-ligand complexes,* Dr Till Siebenmorgen
12:45 – 13:45	Break
13:45 – 14:15	*The Quantum Mechanics of PEX14 - Hints electrons give us to target this protein,* Dr Filipe Menezes
14:15 – 14:45	*Silmitasertib (CX-4945), a clinically used CK2-kinase inhibitor with additional effects on GSK3β and DYRK1A kinases – a structural perspective,* Dr Przemyslaw Grygier
14:45 – 15:15	*Virtual screening in search for new IKK-β inhibitors,* mgr Emilia Sługocka
15:15 – 15:45	*Polarizable force field and DFT calculations in analysis of the interactions between cyclodextrins and Endocrine Disrupting Chemicals*, mgr Anna Mazurek

Dr Grzegorz Popowicz, Institute of Structural Biology, Helmholtz Zentrum München

"Can we talk to a protein? Implementation of artificial intelligence in structural biology and drug discovery."

Artificial intelligence is making rapid changes in nearly all aspects of life. In structural biology Alfa Fold 2 allow access to accurate prediction of protein folds over entire proteomes. AI can help us understand protein structure and improve structure based drug discovery. Our team develops AI models that are able to comprehend protein structure and translate the structural information into visual data understandable to everyone. We introduced hidden state variable theory to build translational AI models that allow us to "communicate" with the protein using nearly human language. We show that structural AI models can help in drug discovery and understanding protein -ligand information. Screening and docking done by the AI models is far superior to traditional methods. Moreover, AI is able to comprehend protein dynamics and induced fit allosterics.

Dr Anna Czarna, Małopolskie Centre of Biotechnology, Jagiellonian University

"DYRK1A inhibitors Leucettines and TGF-β inhibitor additively stimulate insulin production in beta cells, organoids, and isolated mouse islets"

The decreased β-cell mass and impaired β-cell functionality are the primary causes of all types of diabetes mellitus (DM). Nevertheless, the underlying molecular mechanisms by which β-cell growth and function are controlled are still not fully understood. In this work, we have revealed that leucettines, known as DYRK1A inhibitors, serve as compounds that can improve glucose-stimulated insulin secretion (GSIS) in rodent β-cells and isolated islets, as well as hiPSC-derived β-cells islets. We confirmed that DYRK1A is expressed in murine insulinoma cells MIN6. In addition, we indicated that treatment with selected Leucetin stimulates proliferation of β-cells and promotes MIN6 cell cycle progression to the G2/M phase. This effect was also confirmed by increased levels of cyclin D1, which is highly responsive to the proliferative signals. Among other leucettines, Leucettine L43 had a negligible impact on β-cell proliferation, but markedly impair GSIS. However, Leucettine L41, in combination with LY364947, significantly promotes GSIS in various cellular diabetic models, including MIN6 and INS1E cells in 2D and 3D culture, iPSC-derived β-cell islets derived from iPSC, and isolated mouse islets by increased insulin secretion and decreased glucagon level. Our findings confirmed an important role for DYRK1A inhibitors as modulators of β-cells function and suggested a new potential target for diabetes. Moreover, we show in detail that Leucettine derivatives represent promising antidiabetic agents and are worth further evaluation, especially *in vivo.*

Dr Till Siebenmorgen, Institute of Structural Biology, Helmholtz Zentrum München

“Molecular dynamics simulations to study protein-ligand complexes”

Proteins constitute one of the central molecules of life that are involved in almost all cellular processes. These molecules perform most of their functions by interacting through assemblies, like protein-protein complexes or protein complexes with small molecules. To study such complexes with computational methods, molecular dynamics (MD) simulations are well suited. They account for an atomistic representation of the solute, proper treatment of the aqueous environment, and full flexibility of the partner molecules. We recently developed the MISATO database, a structural dataset that contains amongst others 17000 simulated protein-ligand complexes. An overview of strategies and potential pitfalls in MD to simulate protein-ligand complexes will be given. Additionally, an introduction to the recently developed RS-REMD method to study the binding affinity of protein-ligand complexes will be given.

Dr Filipe Menezes, Institute of Structural Biology, Helmholtz Zentrum München

"The Quantum Mechanics of PEX14 - Hints electrons give us to target this protein"

Abstract: Electronic properties are essential to understand the interactions between a protein and potential inhibitors. Yet, the use of quantal methods in drug discovery is still at its infancy. We introduce a series of novel algorithms that allow a quantum mechanical analysis of protein-ligand complexes, giving us the opportunity to look at what electrons request when binding takes place. The new techniques are applied to the challenging interface between PEX14 and PEX5, giving us a deeper understanding of protein-ligand interactions for a family of inhibitors.

Dr Przemyslaw Grygier, Małopolskie Centre of Biotechnology, Jagiellonian University

"Silmitasertib (CX-4945), a clinically used CK2-kinase inhibitor with additional effects on GSK3β and DYRK1A kinases – a structural perspective"

A clinical casein kinase 2 inhibitor, CX-4945 (silmitasertib), shows significant affinity towards the DYRK1A and GSK3β kinases, involved in down syndrome phenotypes, Alzheimer's disease, circadian clock regulation and diabetes. This off-target activity offers an opportunity for studying the effect of DYRK1A/GSK3β kinase system in disease biology and possible line extension. Motivated by dual inhibition of those kinases, we solved and analyzed crystal structures of DYRK1A and GSK3β with CX-4945. We built a quantum-chemistry-based model to rationalize the compound affinity for CK2, DYRK1A and GSK3β kinases. Our calculations identified a key element for CK2's sub-nanomolar affinity to CX-4945. The methodology is expandable to other kinase selectivity modelling. We show that the inhibitor limits DYRK1A and GSK3β mediated cyclin D1 phosphorylation and reduces kinase mediated NFAT signaling in the cell. Given CX-4945's clinical and pharmacological profile, this inhibitory activity makes it an interesting candidate with potential for application in additional disease areas.

Emilia A. Slugocka, PhD candidate, Department of Pharmaceutical Chemistry, Jagiellonian University Medical College

"Virtual screening in search for new IKK-β inhibitors"

Complex etiology underlying the neurodegenerative diseases, combining disruptions in diverse signaling pathways, reshaped the research of new therapeutical approaches. Neuroinflammatory background of neural death is one of the hypotheses being under extensive studies. IKK-β, as
an integrated part of the IκB kinases complex (IKK) plays a crucial role in the modulation of a pro-inflammatory signaling pathway, controlling the release of the NF-κB. The presentation regards virtual screening in search for new potential inhibitors of IKK-β. Employed structural models were prepared and validated via virtual screening benchmark. Interaction models were developed by structure-based drug design methods. Conformational characterization of the prepared models, followed by energy minimization based on molecular dynamics simulation, led to the selection of the final structures for prospective screening with CNS-oriented databases (ASINEX, ChemSpace, Otava). Finally, the fingerprint-guided clustering enabled the selection of molecules with potential inhibitor activity and drug-like properties. Among selected compounds, the derivatives of pyrrolo[3,4-c]pyrazol-6-one demonstrated promising in vitro activity and space for further structural optimization.

Mgr Anna Mazurek, Department of Organic and Physical Chemistry, Medical University of Warsaw

"Polarizable force field and DFT calculations in analysis of the interactions between cyclodextrins and Endocrine Disrupting Chemicals"

Abstract: Endocrine Disrupting Chemicals (EDCs) are chemical substances external to a human body present for instance in pesticides or resulting from the depolymerization of organic materials used in the industry. EDCs mimic the endogenous hormones and cause a hormonal imbalance evoking for ex. fertility alterations or sex organ cancers. Also hormones delivered as pharmaceutics are described as EDCs. Those substances are usually steroid hormones characterized by a low solubility in water hence by a poor bioavailability. Therefore, in terms of EDCs we stand in front of two problems. The first on is their removal from the environment so that they are not absorbed by a human organism. The second one is bioavailability enhancement in case of the medication. Cyclodextrins (CDs) seem to be one of the possible solutions for both of those issues.

Knowledge about the inner structure and interaction energies of the specific EDCs-CDs complexes is a crucial information about the complexation possibility. Performance of experimental analyses for the systems in question can be supported by the molecular modelling. Here, we concentrated on application of the Density Functional Theory (DFT) based calculations and on the usage of a AMOEBA polarizable force field (FF) later intended to be applied for the Free Energy Perturbation simulations. Both of those approaches are gaining their importance among the molecular modelling techniques. Nowadays, DFT approach can be applied for much bigger systems than even a decade ago. In turn, polarizable FFs are currently starting to be used for systems other than proteins. At the same time, the development of the two above mentioned molecular modelling techniques using the EDCs-CDs complexes as an example, can deliver conclusions useful also for the analysis of the macromolecular systems.