JOINT FRENCH SOCIETY FOR MEDICINAL CHEMISTRY – EVOTEC – INSTITUT PASTEUR

Excellence in Molecular Design Symposium

March 14th, 2023

SPONSORS

PROGRAM

8:35 - 9:10 **Arrival of attendees** – Institut Pasteur – Vaugirard Entrance
205 rue de Vaugirard 75015 Paris

9:10 am	**Conferences** at Amphitheater Duclaux – Duclaux Building

9:10 am **Welcome address**
Dr Jean-Yves Ortholand - President of the French Society for Medicinal Chemistry
Dr Gilbert Lassalle - SVP Head of Medicinal Chemistry France, Evotec
Dr Olivier Sperandio - Group Leader & Head of the iPPI-DB initiative, Institut Pasteur

9:30 am **Dr Christoph Grebner** - Sanofi, Frankfurt, Germany
"Artificial intelligence and explainability in molecular design"

10:00 am **Dr Gilles Labesse** - University of Montpellier, Montpellier, France
"Structure-Based and Integrative Design of B-Raf Inhibitors Devoid of Deleterious PXR Binding"

10:30 am	**Coffee break and meet the partners/ participants** at Centre François Jacob

11:15 am **Dr Fredrik Zetterberg** – Galecto, Inc., Göteborg, Sweden
"Discovery of GB1211, the first orally available galectin-3 inhibitor to advance into clinical development as a potential treatment for cancer and fibrosis indications"

11:45 am **Andreas Luttens** - **2022 winner of Evotec Prize** - University of Uppsala, Uppsala, Sweden
"Discovery of Enzyme Inhibitors through Virtual Screening of Vast Chemical Space"

12:15 pm	**Lunch and meet the partners/ participants** at Centre François Jacob

1:45 pm **Dr Quentin Perron, Co-founder & CSO** - Iktos, Paris, France
"DockAI: Efficient Exploration of ultra-large chemical spaces using Active Learning."

2:00 pm **Dr Raquel Rodriguez Perez** - Novartis, Basel, Switzerland
"Machine learning-based predictions of ADME properties in pharmaceutical industry"

2:30 pm **Dr Stefania Monteleone** - Evotec, Abingdon, United Kingdom
"FMO-guided Identification of PPI Hotspots and Modulators"

3:00 pm	**Coffee break and meet the partners/ participants** at Centre François Jacob

3:45 pm **Dr Christophe Zimmer / Dr Olivier Sperandio** - Institut Pasteur, Paris, France
Dr Christophe Zimmer – "Deep learning and imaging for antibiotic drug discovery"
Dr Olivier Sperandio – "Prediction of functional binding sites using 3D fully convolutional neural networks »

4:30 pm **Dr Merveille Eguida** - University of Strasbourg, Strasbourg, France
"Automated target-focused library design using subpocket similarity combined with generative chemistry"

5:00 pm **Closing remarks**

Dr. Christoph Grebner

Sanofi, Frankfurt, Germany

« Artificial intelligence and explainability in molecular design »

C. Grebner*, Frankfurt/Germany, A. Koetter*, Frankfurt/Germany, H. Matter*, Frankfurt/Germany, G. Hessler*, Frankfurt/Germany

Dr. Christoph Grebner, *Synthetic Molecular Design, Integrated Drug Discovery, Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, D-65926 Frankfurt am Main, Germany

In drug discovery, understanding of structure-activity relationships guides the search of novel chemical matter in hit identification as well as subsequent compound optimization.
A variety of different artificial intelligence-based methods for generating molecules are available nowadays. Together with different scoring schemes ranging from 2D and 3D similarity [1], docking [2] to machine learning models for property predictions [3], they largely influence the accessible chemical space. Therefore, it is important to carefully design and setup artificial intelligence-based molecule generations in a specific project setting. We present our integrated workflow for molecular design and discuss various aspects in artificial intelligence-based drug design as well as applications of explainable artificial intelligence and uncertainty estimations for interpreting structure-activity-relationships [4].

[1] Grebner, C. et al, *J. Med. Chem.* **2020**, 63, 16, 8809–8823.
[2] Sauer, S. et al, *Front. Chem*. **2022**, 10:1012507.
[3] Grebner, C. et al, *ChemMedChem* **2021**, *16*, 3772.
[4] Harren, T. et al, *J. Chem. Inf. Model.* **2022**, 62, 447-462.

Dr. Gilles Labesse

University of Montpellier, France

« Structure-Based and Integrative Design of B-Raf Inhibitors Devoid of Deleterious PXR Binding »

Dabrafenib is an anticancer drug currently used in the clinics, alone or in combination. However, we showed that dabrafenib strongly activate the human nuclear receptor pregnane X receptor (PXR). PXR activation increases the clearance of various chemicals and drugs, including dabrafenib itself.
Therefore, there is a need for rational design of a potent protein kinase B-Raf inhibitor devoid of binding to the secondary target PXR and resisting rapid metabolism.
Analyzing the mode of binding of Dabrafenib to both PXR and its primary target, B-Raf-V600E, we were able to derive new compounds with nanomolar activity against B-Raf and no detectable affinity for PXR.

Dr. Fredrik Zetterberg

Galecto, Inc., Göteborg, Sweden

« Discovery of GB1211, the first orally available galectin-3 inhibitor to advance into clinical development as a potential treatment for cancer and fibrosis indications »

Inflammation, immune responses, cell migration, autophagy and cell signaling are all important physiologic functions where members of the protein family galectins play an important role. Members of this family of proteins, in particular galectin 3, have also been associated with disease pathology of for example fibrosis and cancer. Fibrosis targets different organs such as lung, liver, heart and skin and upon progression eventually results in organ failure. In industrialized nations, fibrosis has been estimated to account for 45% of all deaths, which emphasizes the need to develop treatments targeting different organs.

Galecto's first small molecule galectin-3 inhibitor to advance into clinical development, GB0139, is being developed as an inhaled treatment for idiopathic pulmonary fibrosis (IPF). This compound is currently in Phase 2b trials after a successful phase 1/2a trial where GB0139 showed clinical activity on biomarkers typical for IPF. GB0139 is not suitable for oral delivery, and therefore, Galecto developed a new series of high affinity and orally available galectin-3 inhibitor compounds. This lecture will discuss recent progress in pharmacology of galectin-3 and the discovery process leading up to selection of GB1211, the first orally available galectin-3 inhibitor to advance into clinic development, and the progress in the clinic so far.

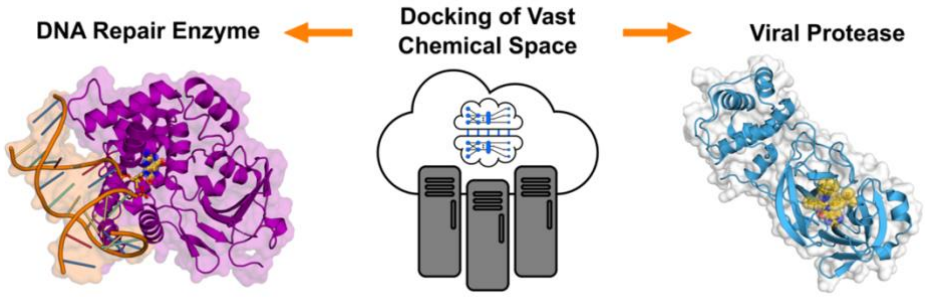
Andreas Luttens

🏆 2022 winner of Evotec Prize

University of Uppsala, Sweden

« Discovery of Enzyme Inhibitors through Virtual Screening of Vast Chemical Space »

Computational chemistry is turning the traditional model of drug discovery on its head. Molecular docking algorithms can predict a molecule's interaction with a target protein in seconds, making it possible to evaluate large libraries of chemical substances. Furthermore, this approach is not restricted to molecules that are physically available. The size of virtual libraries with commercially available compounds is growing rapidly and >30 billion novel make-on-demand molecules are currently available from chemical suppliers. These libraries provide interesting opportunities to identify potential therapeutic agents that can readily be synthesized and tested for their activity. However further development of effective strategies for navigation in this enormous chemical space is required. We explored complementary virtual screening strategies against two unrelated enzymes involved in infectious diseases and inflammation. We docked ultra-large libraries of several hundred million molecules to the enzymes' active sites and top-scoring compounds were experimentally evaluated. Inhibitor-bound crystal structures enabled docking of tailored virtual libraries and facilitated hit-to-lead optimizations. Our advanced inhibitors showed promising activities in relevant cell models and are excellent starting points for further drug development against challenging targets.



Dr. Quentin Perron

Iktos, Paris, France

« DockAI: Efficient Exploration of ultra-large chemical spaces using Active Learning »

Hit discovery, is often the first and most critical step in the process of a drug discovery campaign upon target identification and characterization. This is often achieved by virtually screening (via protein-ligand docking) large chemical libraries (~10^6) in order to narrow down a vast pool of compounds to a more manageable set of potential hits that can be further evaluated, and this has led to some success over the last two decades [1]. With the advent of make-on-demand ultra large chemical libraries [2] the possible chemical search space has increased by orders of magnitude (~10^9), and the deployment of traditional virtual screening methods has become prohibitively long and costly [3]. To address this we have developed a proprietary solution called DockAI which is a fast, low cost, and highly effective AI-based method for virtual screening of ultra large scale databases of virtual compounds. It is based on an active learning approach, which allows us to identify most promising compounds for further evaluation, by docking only a small fraction (typically <1%) of the whole database. Drug discovery campaigns are venturing into novel modalities, drugging more challenging targets, and rapid, cost-effective and technically efficient active-learning based docking tools like DockAI are expected to become a part of the solution.

[1] Lionta, Evanthia, et al. "Structure-based virtual screening for drug discovery: principles, applications and recent advances." Current topics in medicinal chemistry 14.16 (2014): 1923-1938.

[2] Hoffmann, Torsten, and Marcus Gastreich. "The next level in chemical space navigation: going far beyond enumerable compound libraries." Drug discovery today 24.5 (2019): 1148-1156.

[3] Acharya, Atanu, et al. "Supercomputer-based ensemble docking drug discovery pipeline with application to COVID-19." Journal of chemical information and modeling 60.12 (2020): 5832-5852.

Dr. Raquel Rodriguez Perez

Novartis, Basel, Switzerland

« Machine learning-based predictions of ADME properties in pharmaceutical industry »

Absorption, distribution, metabolism, and excretion (ADME) properties play an important role in the success of drug candidates. Unfavorable pharmacokinetics (PK) can prevent that compounds progress in drug development and early ADME/PK properties' screening aims at reducing the number of molecules failing in the development process. This talk will focus on how to use machine learning to leverage historical ADME/PK data and make predictions for new compounds. Machine learning models developed for PK property predictions will be presented, as well as some of their applications at NIBR. Such models are applicable to large libraries, virtual compounds, and generative chemistry workflows. Hence, predictions enable early informed decisions and compound prioritization, aiming at reducing late-stage attrition. However, using machine learning-based predictions to support decision-making in a drug discovery project involves important considerations. Current challenges and future directions for improving the use of ADMET models in industry will be discussed.

Dr. Stefania Monteleone

Evotec, Abingdon, United Kingdom

« FMO-guided Identification of PPI Hotspots and Modulators »

Stefania Monteleone

Evotec (UK) Ltd., 114 Milton Park, Abingdon, Oxfordshire OX14 4SA, United Kingdom

Protein-protein interactions (PPIs) play a crucial role in protein functions and signalling. The development of PPI-focused drugs highly depends on the availability of structural data and on the accuracy of the tools that are used to identify the key interacting residues at the interface (hotspots). Fragment Molecular Orbital (FMO) is a fast and accurate QM method that provides the list of interactions between residues, including their strength (in kcal/mol) and chemical nature (electrostatic or hydrophobic).

Here, FMO and PPI exploration were combined in a novel workflow (FMO-PPI[1]) to identify not only the PPI hotspots, but also the intramolecular interactions and significant water bridges that stabilize the interface. To illustrate this, FMO-PPI was applied to a dataset of protein-protein complexes that represent different protein subfamilies and its results were compared to published mutagenesis data.

Furthermore, FMO-PPI analyses can also be used to support structure-based drug design of PPI inhibitors and molecular glues. Here, examples of its application to the hit-to-lead and lead optimisation phases of PPI modulators will be shown.

[1]S. Monteleone *et al.*, *JCIM* 2022 62 (16), 3784-3799.

Dr. Christophe Zimmer

Institut Pasteur, Paris, France

« Deep learning for antibiotic drug discovery »

The antibiotic resistance crisis urgently calls for antibacterial compounds with novel modes of action. Phenotypic drug screening by high-throughput imaging is a target-agnostic approach to identify compounds with antimicrobial activity, but time-consuming follow-up studies are needed to identify drug targets for lead optimization. In a Pasteurian collaboration (with the teams of I. Boneca, S. Jang and S. Shorte), we are exploring the potential of artificial neural networks (deep learning) to directly determine modes of action from images alone. We will present preliminary results suggesting that deep learning can extract subtle phenotypes of drug-treated bacteria (*H. pylori* and *E. coli*) and predict the mode of action of compounds by comparison with known reference antibiotics using brightfield imaging alone. Pending further validation and extension to libraries of mutants, we foresee establishing a computational pipeline to predict the modes of action or molecular targets of chemical compounds, with the potential to speed up phenotypic drug discovery.

Dr. Olivier Sperandio

Institut Pasteur, Paris, France

« Prediction of functional binding sites using 3D fully convolutional neural networks »

Due their essential character, protein-protein interactions (PPIs) represent a wealth of putative therapeutic targets. Yet, given their number and diversity of roles, it is of primary importance to prioritize tractable PPI targets for drug development. To this end, with Dr Guillaume Bouvier, we have developed InDeep as a tool for predicting functional binding sites within proteins that could either host protein epitopes or future drugs. Leveraging deep learning on a curated dataset of PPIs, InDeep can proceed to enhanced functional binding site predictions either on experimental structures or along molecular dynamics trajectories. The benchmark of InDeep demonstrates that our tool outperforms state-of-the-art ligandable binding sites predictors. We are also presenting InDeep^{Net}, a Mol* web application that relies on InDeep models and that allows to make functional binding site predictions on any protein systems including on Alphafold2 models and on uploaded molecular dynamics trajectories.

Dr. Merveille Eguida

University of Strasbourg, France

« Automated target-focused library design using subpocket similarity combined with generative chemistry »

Identifying the first hits for a target in the early stages of drug discovery can be a challenge which, *inter alia*, relies on an efficient exploration of the chemical space. Besides screening ultra-large on-demand libraries made of billions of compounds which require huge computing resources [1], drug design would still benefit from screening focused libraries for a specific protein target with the idea that such libraries are customized to be enriched in hits for that target, enabling higher hit rates at lower costs.

By capitalizing on the protein pocket information available in constantly growing public databases, we here introduce POEM (Pocket-Oriented Elaboration of Molecules), a novel approach for designing focused compound libraries for virtual screening. Protein pockets are described as clouds of points with key shape and pharmacophoric properties [2]. In a first step, 3D fragmented ligands derived from other protein structures are aligned at specific positions in the target binding site on the basis of the estimated similarity between the fragment's protein microenvironment and the target pocket [3]. In a second step, pairs of compatible fragments are prioritized and linked by a generative method [4] to yield fully connected molecules. Accordingly, POEM is applicable to any druggable protein target, irrespective of prior ligand information.

As a first proof-of-concept, application of the above-described approach on a cyclin-dependent kinase 8 case study enabled to quickly design new sub-micromolar to single-digit nanomolar *in vitro* inhibitors [5]. Then, POEM was applied to design the first ligands of challenging protein targets, which are evaluated in ongoing experimental essays.

[1] Lyu, J. et al. *Nature* 2019, 566, 224–229
[2] Desaphy, J.; Azdimousa, K.; Kellenberger, E.; Rognan, D. *J. Chem. Inf. Model.* 2012, *52*, 2287–2299
[3] Eguida, M.; Rognan, D. *J. Med. Chem.* 2020, *63*, 7127–7142
[4] Imrie, F.; Bradley, A. R.; van der Schaar, M.; Deane, C. M. *J. Chem. Inf. Model*. 2020, 60, 1983–1995
[5] Eguida, M.; Valencia, C.; Hibert, M.; Villa, P. and Rognan, D. *J. Med. Chem*. 2022, 65, 13771-13783