PROGRAM

"Advanced Techniques for Drug Discovery: From Screening Strategies to Preclinical Animal Testing"

http://vu.fr/MCTOX24

Wednesday, June 12th, 2024

SupBiotech, 66 rue Guy Moquet, 94800 Villejuif

9:00-10:00

"Screening strategies and technologies"

Jeanne Chiaravalli

Research engineer
Chemogenomic and Biological Screening platform (PF-CCB)

Institut Pasteur, PARIS

https://research.pasteur.fr/en/member/jeanne-chiaravalli/

High Throughput screening (HTS) and High Content Screening (HCS) methods are critical in drug discovery as they enable rapid testing of large compound libraries to identify potential drug candidates. The course will provide an overview of HTS/HCS methods, including assay development, compound screening, data analysis, and hit validation. Students will learn about the different types of assays used in HTS, such as biochemical, cell-based, and phenotypic assays, as well as the various technologies involved in compound screening. The course will also cover data management and analysis methods, including statistical analysis and visualization.

Selected paper from the speaker:

Chen KY, Krischuns T, Varga LO, Harigua-Souiai E, Paisant S, Zettor A, **Chiaravalli J**, Delpal A, Courtney D, O'Brien A, Baker SC, Decroly E, Isel C, Agou F, Jacob Y, Blondel A, Naffakh N, , A highly sensitive cell-based luciferase assay for high-throughput automated screening of SARS-CoV-2 nsp5/3CLpro inhibitors., Antiviral Res 2022 May; 201(): 105272. (Link)

Recommended reading:

Blay V, Tolani B, Ho SP, Arkin MR, High-Throughput Screening: today's biochemical and cell-based approaches, Drug Discov Today 2020 Oct 25(10)
https://pubmed.ncbi.nlm.nih.gov/32801051/

10:00-11:00

"AI-assisted drug discovery"

Olivier Sperandio

CRCN Inserm
CNRS UMR3528 Structural Bioinformatics Unit Head of Chemoinformatics & Proteochemometrics Institut Pasteur

https://research.pasteur.fr/fr/team/group-olivier-sperandio/

This lecture explores into the transformative influence of advanced technologies and computational methods on drug discovery over recent decades. It contrasts phenotypic drug discovery and High Content Screening (HCS) with target-based drug discovery (TBDD), highlighting how each strategy has adapted to leverage high-throughput screening (HTS) and artificial intelligence (AI). HCS, benefiting from automated HTS and AI-driven image analysis, focuses on observing disease-relevant phenotypes in cells, despite the challenge of needing further investigations to pinpoint drug targets. Conversely, TBDD utilizes detailed knowledge of biological targets to design drugs, supported by technologies like cryogenic electron microscopy and AI-enhanced computational chemistry. The lecture will also explore AI's growing role in refining drug discovery processes, from enhancing molecular docking to generating novel drug candidates. Lastly, it will discuss the potential of AI to bridge the gap between phenotypic and target-based approaches, accelerating target identification and exploring new chemical spaces for drug development.

Selected papers from the speaker:

A comprehensive dataset of protein-protein interactions and ligand binding pockets for advancing drug discovery.
Moine-Franel A, Mareuil F, Nilges M, Ciambur CB, **Sperandio O.** Sci Data. 2024 Apr 20;11(1):402. doi: 10.1038/s41597-024-03233-z.

InDeep: 3D fully convolutional neural networks to assist in silico drug design on protein-protein interactions.
Mallet V, Checa Ruano L, Moine Franel A, Nilges M, Druart K, Bouvier G, **Sperandio O.** Bioinformatics. 2022 Feb 7;38(5):1261-1268. doi: 10.1093/bioinformatics/btab849.

Recommended reading:

Unlocking the potential of generative **AI** in **drug discovery**.
Gangwal A, Lavecchia A.Drug Discov Today. 2024 Apr 23:103992. doi: 10.1016/j.drudis.2024.103992. Online ahead of print.

11:00-12:00

"Biophysical methods for hit validation"

Oksana Reznichenko

Bioscience field application scientist
Malvern Panalytical, LYON

https://www.linkedin.com/in/oksana-reznichenko-097b5612a/

The use of biomolecular interaction methods in HTS validation is a critical step in drug discovery and chemical biology research. This course will introduce the biophysical methods used for studying drug-target interactions. Students will learn about the techniques used to quantify the affinity, kinetics, and thermodynamics of drug-target interactions, such as isothermal titration calorimetry (ITC) and grating coupled interferometry (GCI). Additionally, this course will introduce dynamic light scattering (DLS) and assessing sample quality for drug discovery applications.

Selected paper from the speaker:

Reznichenko, O., Leclercq, D., Franco Pinto, J., Mouawad, L., Gabelica, V., Granzhan, A. Optimization of G-Quadruplex Ligands through a SAR Study by Combining Parallel Synthesis and Screening of Cationic Bis(acylhydrazones). *Chem. Eur. J.* **2023**, *29*, e202202427. https://doi.org/10.1002/chem.202202427

Recommended reading:

Pollard, T. D. A Guide to Simple and Informative Binding Assays. *Molecular Biology of the Cell*, **2010**, *21* (23), 4061-4067 https://doi.org/10.1091/mbc.e10-08-0683

Renaud, JP., Chung, Cw., Danielson, U. *et al.* Biophysics in drug discovery: impact, challenges and opportunities. *Nat. Rev. Drug Discov.* **2016**, *15*, 679–698 https://doi.org/10.1038/nrd.2016.123

14:00-15:00

"Accelerating the development of new drugs - infrastructures and services to implement *in vivo* studies from maximal tolerated dose to efficacy testing"

Marion Bérard

Vétérinaire
Pôle Aide-Technique, Animalerie centrale,
Comité d'Ethique en Expérimentation Animale

Institut Pasteur, PARIS

https://research.pasteur.fr/fr/member/marion-berard/

Cellular and animal models are complementary approaches necessary to obtain a precise understanding of diseases and develop relevant preventive and therapeutic strategies. The use of animal models for biomedical research continues to be unavoidable to answer certain questions. The course will describe the infrastructures (animal facilities and equipments) and processes (ethics evaluation of projects, training, post-approval monitoring of procedures) allowing the implementation of *in vivo* studies at the Institut Pasteur. The technical assistance is a service proposed by the animal facility staff to implement experimental procedures on animals for the scientists (administration, sampling, surgeries, behavioral testing, or imaging of animals), following existing protocols or involving the development of new techniques/animal models. We will describe one of our latest projects designed together with the innovation department to accelerate the development of new compounds. Its goal is to define the maximal tolerated dose of the compounds prior to in vivo efficacy studies, in a standardized refined manner, reducing the number of animals used for this purpose.

Selected paper from the speaker:

Le Chevalier F., …, **Berard M.,** *et al.* Mice Humanized for Major Histocompatibility Complex and Angiotensin-Converting Enzyme 2 with High Permissiveness to SARS-CoV-2 Omicron Replication. Microbes and Infection, 2023 - in Press (link)

Recommended reading:

Chemical Safety and Animal Welfare, Progress made at the OECD (link)

15:00-16:00

"Development of preclinical animal models"

Emilie Giraud

Research engineer
Chemogenomic and Biological Screening platform (PF-CCB)

Institut Pasteur, PARIS

https://research.pasteur.fr/fr/member/emilie-giraud/

The preclinical studies of new pharmaceutical molecules or vaccines require animal testing to determine their safety and effectiveness before being tested in clinical trials on human patients. The course begins by highlighting the importance of animal models in medical research, ethical considerations related to their use, and the selection and characterization of reliable animal models for screening new drug candidates. The course is centered around developing an antiviral assay that measures a physiologically relevant and robust biological process, crucial to ensure successful drug discovery campaigns against a wide range of viruses, including SARS-CoV-2. Additionally, the course covers experimental design, common methods for data analysis used in preclinical studies, practical aspects of animal handling and care, animal welfare regulations, animal behavior, and limitations of animal models. Furthermore, the course will explore specific methodologies employed in preclinical studies, such as measuring antibodies post-vaccination in animals to understand the immune response induced by vaccination and to evaluate protection against viral pathogens like SARS-CoV-2. The course aims to equip students with a comprehensive understanding of using animal models in preclinical testing.

Selected paper from the speaker:

Planchais C, …, **Giraud E**, *et al.*, Potent human broadly SARS-CoV-2-neutralizing IgA and IgG antibodies effective against Omicron BA.1 and BA.2. J. Exp. Med. 2022 (link)

Recommended reading:

Caolann Brady, Tom Tipton, Stephanie Longet and Miles W. Carroll. Pre-clinical models to define correlates of protection for SARS-CoV-2. Frontiers in Immunology. 2023 (link)