Sup'Biotech Accelerated Learning Series

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

Wednesday, June 14th, 2023
Sup'Biotech, 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)

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High-throughput screening (HTS) 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 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-Throughpu 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

"Biophysical methods for hit validation"

Oksana Reznichenko

Post-doctoral fellow
Chemogenomic and Biological Screening platform (PF-CCB)

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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 various techniques used to quantify the affinity, kinetics, and thermodynamics of drug-target interactions, including fluorescence-based methods, isothermal titration calorimetry (ITC), microscale thermophoresis (MST), surface plasmon resonance (SPR) and interferometry (BLI and GCI). By the end of the course, students will have a thorough understanding of how biophysical methods can be used in drug discovery and development.

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

11:00-12:00

"ADME studies in early drug discovery" 🇫🇷

Florence Leroux

Research engineer
INSERM U1177 Drugs & Molecules for living Systems. Responsable de la plateforme de criblage à haut contenu et haut débit, ARIADNE-Criblage

Institut Pasteur, LILLE

https://pasteur-lille.fr/centre-de-recherche/plateformes-technologiques/ariadne-criblage-plateforme-de-criblage-a-haut-contenu-et-haut-debit/

The course will show why compound activity and compound potency are not the only parameters to optimize in medicinal chemistry projects. Indeed, the compounds must reach their target in vivo to induce their effects, which is accompanied by physicochemical constraints such as being soluble, stable etc .... The students will learn what can be the fate of a molecule administered to an animal, and which *in vitro* or *in vivo* assays can be carried out to measure these ADME parameters which characterize the phenomena of Absorption, Distribution, Metabolism and Elimination. To illustrate, we will take examples of studies performed on the ARIADNE-ADME academic platform at the Lille Institut Pasteur.

Selected paper from the speaker:

Beyond the Rule of 5: Impact of PEGylation with Various Polymer Sizes on Pharmacokinetic Properties, Structure–Properties Relationships of mPEGylated Small Agonists of TGR5 Receptor. Hoguet V,(…) **Leroux F**,(…) and Charton J. J Med Chem. 2021 Jan 20 https://doi.org/10.1021/acs.jmedchem.0c01774

Recommended reading:

The Importance of PK–PD. Barrow JC and Lindsley CW. J Med Chem 2023 Mar 29 https://doi.org/10.1021/acs.jmedchem.3c00514

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

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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
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The preclinical test of new pharmaceutical molecules or vaccines requires 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, which is crucial to ensure successful drug discovery campaigns against a wide range of viruses, including SARS-CoV-2. Additionally, the course covers experimental design, methods for data analysis commonly used in preclinical studies, practical aspects of animal handling and care, animal welfare regulations, animal behavior, and limitations of animal models. 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)