From molecule to patient

This course aims to understand the different processes that start with the discovery of new molecules and end with medical devices.

Prerequisites: Basic knowledge of how a cell works.

The material will be in English.

We recommend that you take the whole module.

1. Biomolecules and innovation.

Bérangère Avalle Bihan (3 hours)

Molecular diversity can be natural, as in the case of the diversity produced by the immune system, with the expression of antibodies or specific receptors, or it can be synthetic, with the generation of combinatorial libraries of biomolecules such as peptides, proteins, or even oligonucleotides. It is also possible to generate diversity in silico, using bioinformatics tools to develop algorithms that allow us to imagine the molecular structures that are likely to meet our needs.

Libraries are used for a variety of purposes. They can be a source of fundamental studies or a reservoir of new biomolecules that can be used in different fields.

The course will be structured as follows:

- Presentation of the different possibilities for designing and developing molecular diversity.
- Presentation of display technologies for molecular innovation.
- Example of the discovery of a molecule with therapeutic potential.
- Applications.

2. Exploitation of natural bioactive molecules: from extraction to food applications

Mirian Kubo (2 hours)

Many plants are known to be natural sources of bioactive compounds, such as herbs, spices, seeds, fruits, and vegetables. The interest in these natural compounds is not only for their biological value but also their economic impact, as most of them can be extracted from food by-products and underutilised plant species.

This course provides an overview of natural bioactive molecules: their sources, extraction methods, and biological activity. Examples of applications in the food industry will also be discussed.

- Extraction of molecules: sources; conventional and non-conventional extraction techniques.
- Biological activity: antimicrobial and antioxidant activities; in vitro and in vivo evaluation methods; toxicological and cytotoxicity studies; mode of action; relationship to human health.
- Applications: food preservatives; food additives; functional foods.

3. Modelling the interaction between small molecules and their protein targets

Irene Maffucci (3 hours)

Proteins are responsible for most cellular functions, so modulating (often inhibiting) their activity is of great therapeutic interest. Inhibition of a protein of interest can be achieved by the interaction of the protein with a small molecule capable of specifically binding to a key region for protein activity. The process of identifying or designing this small molecule can be very lengthy, requiring the screening of several thousand molecules. To make the task faster and more efficient, it is possible to use in silico methods such as docking. This approach makes possible to screen a large number of molecules in a limited time, but it can also provide molecular details of the interaction between the target protein and the selected molecules.

This course is structured as follows:

- Presentation of docking algorithms for pose prediction and scoring;
- Presentation of the different steps of a docking protocol: preparation of structures, docking, and analysis of results;
- Presentation of the different docking methods according to the model to be reproduced (key-lock, induced fit, conformational ensemble);
- Presentation of possible applications;
- Introduction to the Autodock software (practical example).

4. Using biomolecules for diagnostics. Case study: Diagnosis of Lyme disease

Séverine Padiolleau (3 hours)

Lyme borreliosis is a vector-borne disease transmitted by the bite of a tick infected with bacteria of the genus Borrelia. It is a multisystemic disease with a wide range of symptoms. It is the subject of much debate and controversy due to the limitations of current diagnosis. Although the presence of erythema migrans is a specific feature, it is not systematic and its absence is therefore a source of uncertainty in the diagnosis of the disease. The diagnostic methods currently available have limitations in terms of sensitivity, reliability, and cross-reactivity. As a result, current serological tests may give false-positive or false-negative results.

The course will be structured as follows

- Presentation of current issues in the diagnosis of Lyme borreliosis: incriminating pathogens, epidemiology, the concept of crypto infection, and the concept of immune escape.
- Presentation of currently approved tests, their principles, and limitations.
- Presentation of alternative techniques, the solutions offered, the advantages and limitations identified, and the prospects for development.
- Conclusion on the biotechnological approaches developed in the laboratory as part of the exploitation of molecular diversity and their potential applications for the implementation of a reliable diagnostic test.
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5. Microfluidics for Biochemistry and Cell Culture Applications

Anne Le Goff (3 hours)

Experimental evaluation of the performance of molecules of interest requires a large number of experiments to be performed in parallel, potentially using costly reagents. To speed up the process and limit costs, it can be advantageous to miniaturise these tests, mostly performed in liquid media, and use microfluidics.

- The scientific challenges of miniaturising liquid assays.
- Presentation of digital microfluidics: technological aspects of emulsion preparation and analysis; applications to screening experiments; single-cell experiments.
- Presentation of various applications of microfluidics for cell culture.
- Organ-on-a-Chip: definitions, issues, and technological challenges.

6. Biomaterials and Tissue Engineering

Timothée Baudequin (3 hours)

Advances in *in vitro* cell culture have gradually led to the emergence of a new discipline at the interface of biology, mechanics, and materials science: tissue engineering. Tissue engineering aims to develop organised, living but artificially reconstructed biological tissues to meet a variety of objectives (implantable replacements, alternative models to animal testing, etc.).

- A short history of cell culture
- From 2D culture to tissue engineering
- Goals and pillars of tissue engineering (cells, biomaterials, and microenvironment)
- Application examples: a first case study applied to the bone; definition of the cell/biomaterial/environment pillars in this example; examples for other tissues
- Towards the reconstruction of interfaces
- And in practice? Overview of techniques and visit to a platform.

7. From the laboratory to the patient

Julie Follet (3h)

The aim of this course is to provide an overview of the steps that separate the identification of interesting properties of a molecule or biomaterial in an academic laboratory from its marketing as a drug and/or medical device (MD).

Two main routes will be presented, from preclinical to post-marketing surveillance (TRL 4/5 -> 9 + drug/device adverse effect monitoring):

- Drug pathway
    - "Classic" pathway: example of monoclonal antibodies and/or tyrosine kinase inhibitors
    - Biosimilars

    - Advanced therapy medicinal products
- Medical devices pathway:
    - Biomaterials
    - Active implantable medical devices: insulin pump example
    - In vitro diagnostic devices:
        - Focus on digital medical devices
        - Advanced Omics

This section will include

- The relevant legal, regulatory, and standards references (which ones and why)
- The players involved (ANSM/HAS/EMA/ANS/ANSSI, etc.)

Strategies to accelerate the development and marketing of innovations will also be discussed:

- Virtualisation and digitalisation of clinical trials, step by step (identification of patient profiles, management of active files, recruitment, dematerialised execution and monitoring, data analysis, cross-referencing with other databases, etc.);

- Early access / compassionate mechanisms.