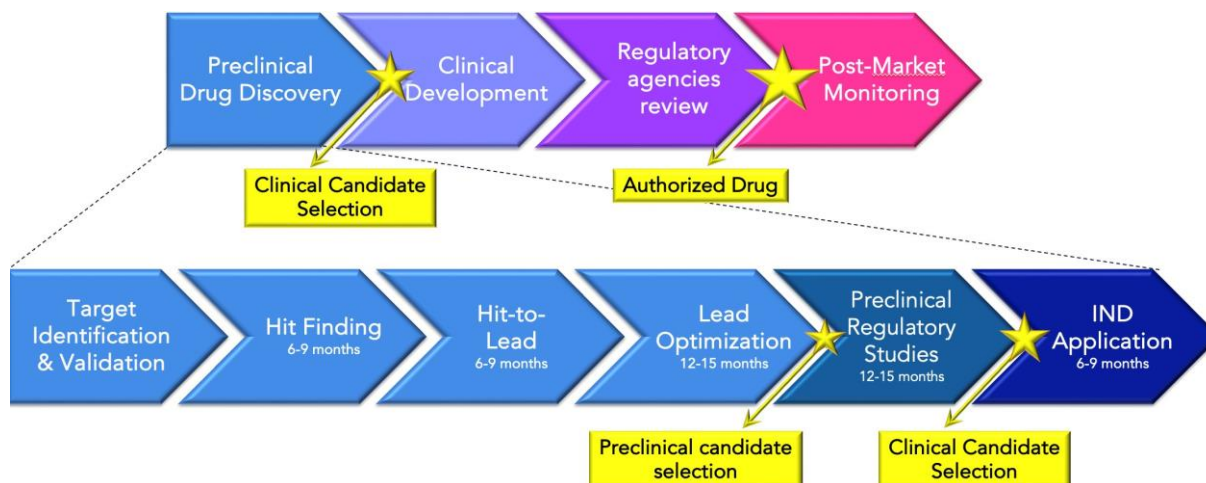25th September 2023
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Preclinical drug discovery: from Concept to First time in Human, a complex multidisciplinary and multiparametric process.

Drug Discovery Phases

Several milestones define the preclinical drug discovery process. Amongst the most important milestones are the selection of a preclinical candidate and the first administration to human.

Drug Discovery activities aim at reaching this first milestone, while the first phases of development called preclinical development aim at providing all necessary data on the drug candidate to write an IND[1] application and hopefully obtain the first Clinical Trial Authorisation (CTA). With the first administration to human will start the clinical development which aims at providing the necessary activity and safety data to support the filing for market authorization and price setting.

Drug Discovery is a complex, continuously evolutive process comprising successive phases punctuated by go/no-go decision between the initial concept and the delivery of a drug candidate matching a predefined profile. Drug discovery will be the cycle where the chemical and the activity spaces will be explored to provide the best candidate and several back up compounds according to a multi-parametric optimization process. It is important to remember that when the candidate is progressed into the next phase (i.e. preclinical development), the structure of the molecule cannot be modified.

Preclinical Drug Discovery is a continuing process: target identification and validation, hit finding and validation, hit to lead, early lead optimization, late lead optimization and drug candidate selection/profiling.

In order to progress to the next phase (go/no-go decision points), a series of physico-chemical parameters and pharmacological/pharmacokinetic and metabolism properties need to be measured to assess the activity/selectivity and the safety of the compounds.

The Drug Discovery phase starts with the biological **target identification (target ID) and validation.** This process is using multiple approaches e.g. patients' sources, genomic analyses, molecular biology.

The **hit finding**[2] methods can be diverse and several campaigns can be performed in parallel: fragment-based (FBDD), structure-based (SBDD), virtual screening, *de novo*-AI based screening, biophysics or high throughput screening (HTS), phenotypic screening, DNA-encoded libraries screening, etc.

When the hits are identified and validated with original solid samples, the first analoging step can start in order to explore the early SAR, to evaluate the potential of optimization of each chemical series.

This phase is called **hit-to-lead**[3] (H2L) is taking account of the prior art in terms of potential patentability, physicochemical properties, activity/selectivity and early ADMET[4] alerts.

Once the lead series with the highest potential is identified, additional efforts are provided for the optimisation of *in vitro* properties: activity/selectivity, drug metabolism & pharmacokinetic (DMPK) and safety (drug-drug interaction and toxicity). This is called the **early lead optimization (early LO)**.

The best compounds are then further optimized during a more complex phase that includes *in vivo* properties. At this stage about 15 parameters are considered: the *in vivo* pharmacodynamic properties in mechanistic and disease related animal assays, the dose ranging, the PK/PD relations on top of the previously early LO parameters.

This is the most complex and critical part of **the late optimization process (late LO)**.

One or several potential **preclinical drug candidates** are selected among the best optimized leads for *in vivo* profiling on pharmacodynamic and safety parameters. Patent applications are fully exemplified and filed.

At the end of this process, one preclinical drug candidate is selected for moving to the next critical phase that includes the **preclinical development regulatory studies**.

CMC (chemistry-manufacture-control) studies are performed to produce scale-ups GLP[5] than GMP[6] batches in order to investigate the chronic safety studies in rodent and nonrodent species with the appropriate galenic form. The full package includes the solid form, GMP batches, the stability studies, the galenic form selection, the pharmacodynamic profile, the development metabolism and kinetic and safety studies. This is called the **IND-enabling studies** (preclinical regulatory studies).

This is only at the end of this process that if the drug candidate offers an acceptable activity and safety margin that the drug candidate is proposed to the authorities for moving forward into the clinical phase 1 in healthy volunteers.

Medicinal chemists, organic chemists, molecular modelers, biochemists, biologists, pharmacologists, galenists and toxicologists are contributing to the full Drug Discovery and Development process.

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[1] **IND** = Investigational New Drug application. File requesting authorisation to administer an new drug to human in the context of a clinical trial, submitted to regulatory bodies (FDA, EMA, national bodies such as ANSM in France)
[2] **Hit** = compound which has the confirmed desired activity. To be optimized during the Hit-to-Lead phase
[3] **Lead** = representative of a series with sufficient potential (measured by potency, selectivity, pharmacokinetics, physiochemical properties, etc.) to be further optimized in order Lead-Optimization phases to become a preclinical candidate.
[4] **ADME** = Absorption, Distribution, Metabolism and Excretion. ADME studies investigate how a chemical is processed by a living organism.
[5] **GLP** = Good Laboratory Practices. GLP is the framework that enables regulatory agencies to be assured of the quality and integrity of safety data.
[6] **GMP** = Good Manufacturing Practices. GMP is the framework that enables regulatory agencies to be assured that products are consistently produced and controlled according to quality standards and that risks to patients receiving the drug are minimized.