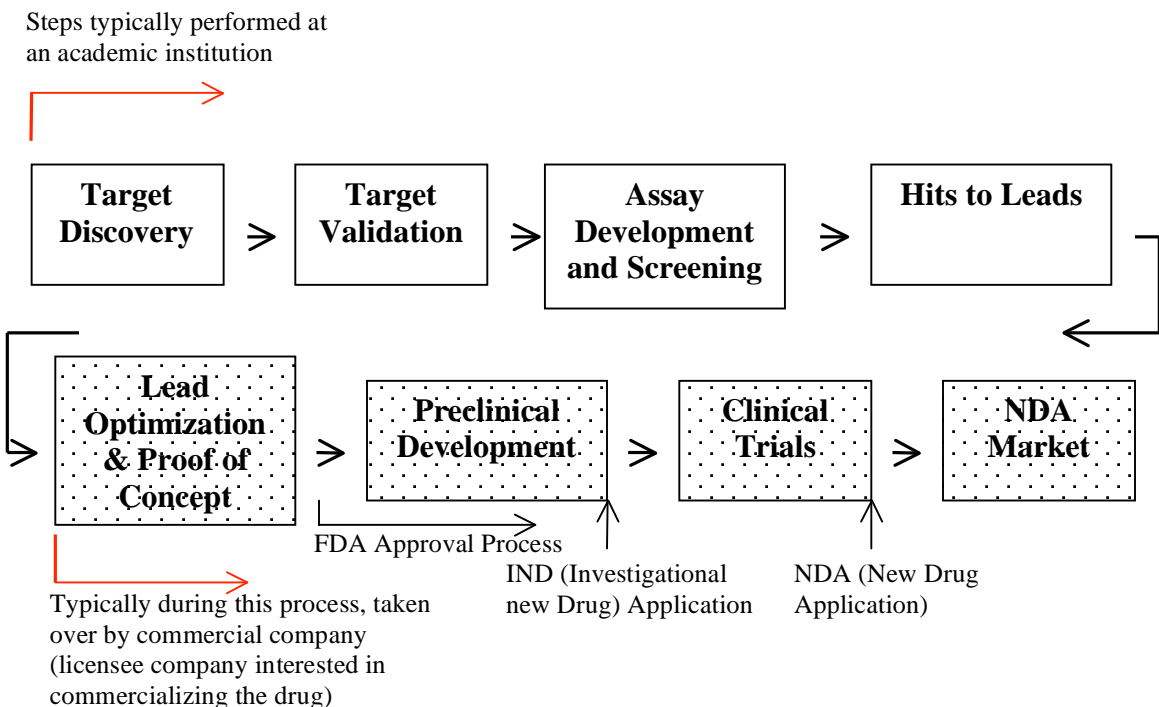


Drugs (Small Molecules) and Biologics Development

Much of the intercampus research is focused on biomedical translational research, considered to be moving from basic discoveries along the developmental pathway toward patient care. To help support this research, we have outlined the steps needed to move from discovery to FDA approval and listed the Cornell resources available on both campuses that can be useful at each step.

Drugs (Small Molecules)

While there is no one way to get to a drug candidate, the current model for the development of small molecules as therapeutic drugs generally involves finding a compound that interacts appropriately with a specific natural component of the disease process, known as the drug target. A generalized scheme for targeted drug discovery involves the following steps. Please click on those steps of interest to find Cornell Ithaca and WMC resources that can be useful.



Target Discovery

The identification of therapeutic targets requires knowledge of a disease etiology and the biological systems associated with it. Molecular biology has revolutionized the process of drug discovery. Today, the collective contribution of genomics, proteomics and bioinformatics allows for the much more rapid and precise discovery of those genes and/or proteins involved in the etiology of diseases.

Weill Cornell Medical College Resources:

Cell Screening

(http://www.med.cornell.edu/research/rea_sup/cel_scr.html)

Computational Biology (http://www.med.cornell.edu/research/rea_sup/comp_genom.html)

DNA Sequencing

(http://www.med.cornell.edu/research/rea_sup/dna_seq.html)

Electron Microscopy (http://www.med.cornell.edu/research/rea_sup/elec_microscopy.html)

Flow Cytometry

(http://www.med.cornell.edu/research/rea_sup/flow_cyto.html)

Genetically Engineered Mouse Phenotyping

(http://www.med.cornell.edu/research/rea_sup/mouse_phenotyp.html)

Mass Spectrometry

(http://www.med.cornell.edu/research/rea_sup/mass_spec.html)

Microarray

(http://www.med.cornell.edu/research/rea_sup/microarray.html)

Optical Microscopy (http://www.med.cornell.edu/research/rea_sup/opt_microscopy.html)

Phosphorimaging

(http://www.med.cornell.edu/research/rea_sup/phosphorimag.html)

Synthetic Chemistry Core Facility

(http://www.med.cornell.edu/research/rea_sup/syn_core.html)

Transgenic mouse

(http://www.med.cornell.edu/research/rea_sup/transgen_mouse.html)

X-Ray Developing

(http://www.med.cornell.edu/research/rea_sup/xray_dev.html)

Cornell-Ithaca Resources:

DNA Sequencing and Genotyping

(<http://cores.lifesciences.cornell.edu>)

DNA Microarrays

(<http://cores.lifesciences.cornell.edu>)

Proteomics and Mass Spectrometry

(<http://cores.lifesciences.cornell.edu>)

Protein Production and Characterization

(<http://cores.lifesciences.cornell.edu>)

Fermentation Facility (http://www.biotech.cornell.edu/index.cfm/page/scf_index/fermentation.htm)

Microscopy and Imaging

(<http://cores.lifesciences.cornell.edu>)

Electron Microscopy

(<http://www.cimc.cornell.edu/Pages/research2.htm>)

Flow Cytometry

(<http://www.people.cornell.edu/pages/jls269>)

Computational Biology

(<http://cores.lifesciences.cornell.edu>)

Target Validation

A potential target must undergo a validation process— its role in disease must be clearly defined before drugs are sought that act on it, or before it is used to screen large numbers of compounds for drug activity. Typically this involves inhibiting the potential target *in vivo* and determining the outcome. This could involve making a knock-out mouse or employing RNAi in cell culture.

WCMC Resources:

Transgenic mouse core

(http://www.med.cornell.edu/research/rea_sup/transgen_mouse.html)

Cornell-Ithaca Resources:

Transgenic Facility

(<http://cores.lifesciences.cornell.edu>)

Assay Development and Screening

Once a target has been validated, it is used to find compounds that interact with it in the way that would improve the disease outcome. This is typically done by developing an assay that tests compounds for the desired activity on the target. These assays fall into different categories and all of these are needed for successful drug development.

- *In vitro* and cell-based assays usually depend on a surrogate marker of the effect of the drug, e.g. from cell growth or cytotoxicity to reporter gene assays.
- *In vivo*/animal model can determine pharmacological properties as well as efficacy
- High-throughput screening aims at rapidly testing the efficacy of a large number of compounds.

The screening of target assays with large libraries of existing compounds usually identifies a few “hits”, *i.e.* compounds that have the desired effect on the target.

WCMC Resources:

Cell Screening

(http://www.med.cornell.edu/research/rea_sup/cel_scr.html)

High Throughput Screening (HTS) facility, housed at Rockefeller University:

(<http://www.rockefeller.edu/highthroughput/highthroughput.php>)

Synthetic Chemistry Core Facility

(http://www.med.cornell.edu/research/rea_sup/syn_core.html)

Nearby resources for WMC investigators:

Memorial Sloan Kettering HTS facility:

(<http://www.mskcc.org/mskcc/html/52147.cfm>)

Hits to Leads

The screening of target assays with large libraries of existing compounds usually identifies a few “hits”, *i.e.* compounds that have the desired effect on the target. These hits serve as the basis for the development of lead compounds that have the necessary degree of activity towards the target. This development occurs through many different paths, *e.g.* further screening of other similar compounds and other methods that help determine structure-activity relationships (SAR). Potency and dose-dependence studies of hits are essential steps in hit verification. One of the goals throughout the discovery of novel drugs is to establish and confirm the mechanism of action. In an ideal scenario, the mechanism of action remains consistent from the level of molecular interaction of a drug molecule at the target site through the physiological response in a disease model, and ultimately in the patient.

Recent patent law decisions indicate that patents for treating a disease state by using compounds that interact appropriately with a given target are only obtainable if such compounds are identified. Hence, it is becoming important for academic scientists interested in filing such patents to find hits and/or test them or known compounds with this activity in animal models of that disease.

WCMC Resources:

Cell Screening

(http://www.med.cornell.edu/research/rea_sup/cel_scr.html)

High Throughput Screening (HTS) facility, housed at Rockefeller University:

(<http://www.rockefeller.edu/highthroughput/highthroughput.php>)

Lead Optimization

The purpose of lead optimization is to develop compounds with the desired activity of the lead compounds that also have better drug-like characteristics in terms of the way they interact with the body. This process involves medicinal chemistry which blends synthetic chemistry, molecular modeling, computational biology assisted drug design if the NMR or crystal structure of the target is known, structural genomics, and pharmacology to discover and design new drugs, and investigate their interaction at the molecular, cellular, and whole-animal level.

It often involves the use of SAR (Structure Activity Relationships) to identify chemical structures that could have good inhibitory effects on specific targets and have low toxicity (non-specific activity).

Another important step in lead optimization involves animal pharmacokinetics (PK), pharmacodynamics (PD), and absorption, distribution, metabolism, and excretion (ADME) analyses to assess the general pharmacology and mechanisms of action of drugs.

WCMC resources:

Synthetic Chemistry Core Facility

(http://www.med.cornell.edu/research/rea_sup/syn_core.html)

Molecular Modeling

(http://www.med.cornell.edu/research/rea_sup/mol_modeling.html)

Nuclear Magnetic Resonance

(http://www.med.cornell.edu/research/rea_sup/nuc_mag_reson.html)

X-Ray Crystallography

(http://www.med.cornell.edu/research/rea_sup/xray_crystall.html)

Computational Biology

(http://www.med.cornell.edu/research/rea_sup/comp_genom.html)

Cornell-Ithaca Resources:

Computational Biology

(<http://cores.lifesciences.cornell.edu>)

Proof of Concept

The optimized drug lead has to be tested and provide proof of concept; a step usually performed in animal models of the disease. Proof of concept demonstrates the feasibility of the hypothesis. The drug candidate should fit into the hypothesis, have the expected effect on the disease outcome and be non-toxic.

Preclinical Development

The decision to take a new drug candidate into the preclinical development phase entails a significant commitment in terms of money, resources, and time. Nine in 10 compounds fail the preclinical testing and never get to the market, while development costs per approved drug amount to \$800 million. The average time to develop a new drug was 12 years and 10 months in 2002.

Once a compound is selected for drug development, the primary objective is to move through preclinical development as quickly as possible to be able to start testing the drug in human subjects. To move to the clinical evaluation, an Investigational New Drug (IND) application must be filed with the FDA. For more information on the IND, go to the IND Review Process at the FDA web site, <http://www.fda.gov/cder/handbook/ind.htm>).

During this period research is conducted to develop methods that demonstrate that the drug can be manufactured and purified in a consistent way under Good Manufacturing Methods. Preclinical research into the safety of the drug involves evaluating its toxicity in different animal species and by *in vitro* testing. The type of dosing anticipated for the compound will determine the extent of testing required, but typically toxicity studies are performed in two or more animal species for 14- or 28-days. However, extended duration studies would be required if chronic dosing regimens are expected. Animal studies determining the *in vivo* pharmacology of the drug are also required. Finally, detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks are also required.

Clinical Trials

Clinical development is divided into four phases: Phases 1 to 3 occur prior to drug approval and Phase 4 is post-marketing. For more information and other references on clinical trials, see <http://www.lillytrials.com/docs/education.html>.

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and may be conducted in subjects with the disease being studied, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.

Phase 2 includes the early controlled clinical studies conducted to obtain data on the effectiveness of the drug for a particular indication or indications in subjects with the disease or condition. This phase of testing also helps to determine the appropriate dose that should be used in larger controlled clinical trials and to identify the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase 3 studies are designed to be large, well-controlled trials that meet the requirements of FDA to demonstrate that the drug is safe and effective and has an overall positive benefit-risk relationship. Phase 3 studies usually include several hundred to several thousand people.

Phase 4 studies evaluate marketed drugs to learn more about side effects, especially long-term effects, and to learn more about the effectiveness of the drug, possibly in other conditions or diseases, or using different drug formulations.

WCMC Resources:

Biostatistics and Research Methodology

(http://www.med.cornell.edu/research/rea_sup/clin_method.html)

Institutional Review Board

(http://www.med.cornell.edu/research/rea_com/ins_rev_boa.html)

General Clinical Research Center

(http://www.med.cornell.edu/gcrc/pdf/GCRC_Flyer.pdf.)

Institute for Clinical Research (<http://www.med.cornell.edu/icr/>)

Cornell-Ithaca Resources:

Dept. of Biological Statistics & Computational Biology

(www.bscb.cornell.edu/consult.php)

Human Metabolic Research

(http://nutrition.cornell.edu/dns_hmruhome.html)