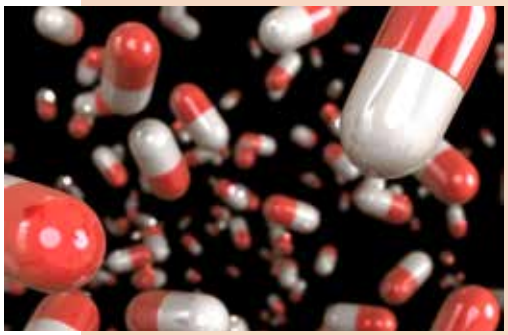
Early-Phase Drug Discovery

In partnership with the North Carolina Translational & Clinical Sciences (NC TraCs) Institute, RTI International is participating in the Early-Phase Drug Discovery Service (EPDD) to help researchers navigate challenges in the drug discovery process and move technologies toward development. This new RTI-based NC TraCS service can provide researchers with biological assay development and optimization, hit or lead identification, medicinal chemistry optimization, in vitro absorption, distribution, metabolism, excretion, and toxicology (ADMET), and in vivo pharmacokinetics.



Overview

Early stages of the drug discovery process contain hurdles that must be cleared before more robust drug development can commence. Once a molecular target is selected, drug discovery begins with identification of a hit and progresses toward a lead candidate through a series of structural optimizations. If no hit or lead molecules exist, a researcher must have a validated biological assay that can be optimized for high-throughput screening (HTS). Screening hits typically do not possess optimal drug-like properties. Therefore, their affinity, selectivity, and pharmacokinetic (PK) properties must be improved through structural modifications by a medicinal chemist. Once acceptable drug-like properties have been achieved, efficacy is validated through proof-of-principle studies in vivo. The most promising set of optimized compounds is then slated for further development. The EPDD can assist researchers by providing target development and assay miniaturization, identification of hits through HTS in a 25,000-compound library, lead optimization, in vitro ADMET assays, and preliminary in vivo PK studies.

Services will be provided on a tiered basis. Tier 1 consists of consulting services designed to inform the researcher of gaps in his or her early-phase drug discovery plan. The level of effort for this service is expected to range from 4 to 10 hours. Tier 2 services would include conducting the necessary research to fill gaps identified in the Tier 1 assessment. The level of effort for these services could range from 20 to 40 hours.

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Services

General Biological Technologies

The EPDD has well-established capabilities for developing cell lines and assays via transient or stable cell transfections and for adapting assays for use in HTS. Assay endpoints can include but are not limited to receptor binding in 96-well format, receptor activation via calcium mobilization, β-arrestin recruitment, GTP-γ-S binding, cAMP generation, membrane potential, high-content assays for receptor internalization or nuclear translocation, and medium throughput electrophysiology. RTI also has excellent behavioral pharmacology capabilities.

Hit/Lead Discovery

The identification of hit or lead compounds for a macromolecular target is the first step toward preclinical drug discovery. The chosen discovery path is highly dependent on the number of previously identified leads, the types of leads available (peptides or small molecules), or both. A library of compounds can be screened at the target of interest to identify hits. The EPDD has the ability to screen compound libraries in 96- and 384-well based assays. It currently has a 25,000-compound, hand-selected, high-diversity library that can be screened through all new targets.

Computational methods can also be used. These include computing conformational libraries and physiochemical properties for several known ligands in "bioactive" conformations. Virtual screening of commercial or proprietary libraries can be conducted on >16 million ligands. When the target receptor/protein structure is known, both ligand-based (3D-pharmacophore) and structure-based design approaches may be jointly applied.

In Vitro ADMET Battery

Once suitable leads are discovered, EDPP can conduct iterative studies to evaluate drug-like properties using a battery of in vitro tests. These typically include determination of solubility, stability in biological fluids, gut and blood–brain barrier (BBB) permeability, hepatic toxicity, hepatic metabolism, and hERG inhibition. This battery typically leads to the identification of compounds with favorable drug-like properties. Upon identification of suitable advanced leads, in vivo assessment of pharmacokinetics is undertaken. Finally, we have developed novel computational approaches to structure-based metabolism and toxicity prediction that complement confirmatory in vitro probes.

In Vivo Pharmacokinetics

Snapshot model. A compound's ability to cross the BBB and have an appropriate elimination half-life ($t_{1/2}$) is an important drug-candidate selection criterion. Our strategy employs a first-pass "snapshot" PK analysis in a limited number of animals to broadly determine BBB penetration and $t_{1/2}$ in plasma and brain.

Detailed PK study. The concentration over time of the test substance in blood (or serum, plasma, or brain) and select tissues is evaluated using noncompartmental methods. Depending on the stage of development, intravenous or oral administration is used.

Leadership Team

Hernan Navarro, PhD

Hernan Navarro is Vice President of Discovery Sciences at RTI and the Director of the EDPP Service. He has expertise in pharmacology, drug discovery, and assay development.

Scott Runyon, PhD

Scott Runyon is the Director of the Center for Drug Discovery at RTI and has expertise in chemical synthesis and drug design and development.

More Information

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