Medicinal Chemistry Core

The Medicinal Chemistry Program of the Experimental Therapeutics Institute aims to become a resource available to basic and clinical research investigators at Mount Sinai who are interested in employing small molecule chemistry to furnish research tools or to develop new experimental small molecule therapeutics. Chemists in the Program will be operating in a newly renovated medicinal chemistry laboratory space located in the Icahn Medical Institute Building and in an environment conducive to interdisciplinary research, for example with biophysical (x-ray, NMR) and computational researchers; this capitalizes on existing strengths within Mount Sinai School of Medicine.

To initiate the search for novel small molecule agents, research groups will run HTS assays in conjunction with the ETI’s Translational Chemical Biology Center. The Center’s compound collection currently comprises approximately 115,000 lead-like small molecule compounds (see the TCBC description for details) and when screening hits have been identified medicinal chemists will be available to work collaboratively with the research teams in three progressively more interdisciplinary phases:

i. **Hit confirmation and resupply** - Data from an HTS campaign will be triaged to eliminate false positives or artifacts: compound purity from the active wells will be assessed, and material re-synthesized, scaled-up and purified. Hit compounds may then be interrogated in detail in the screening assay or other follow-up assays as appropriate to confirm useful levels of activity.

ii. **Hit to Lead Chemistry** - Confirmed hits will then be assessed and ranked based on a number of factors in addition to potency, particularly chemical tractability. A chemically tractable lead will be of reasonably low molecular weight structure (<500 Da), which is amenable to rapid analog synthesis to facilitate exploration of structure activity relationships. Depending on the molecular type additional analogs may be available from commercial sources, or parallel libraries will be designed and synthesized to explore various sites for modification and improvement of the structure. A successful screening campaign will yield three or four tractable lead series suitable for this type for early exploration. Compound series where potency and selectivity can be usefully modulated will be characterized in more detail with respect to drug-like properties, and where appropriate with respect to predictive pharmacology models generated by the Systems Pharmacology Core (see the SPCC description for details). Medicinal chemists, together with biologists and pharmacologists will also work with Mount Sinai’s OTBD to develop a strategy to define and protect intellectual property on novel composition of
matter. In vitro leads of this type may serve as research tools for interrogation of novel disease targets or as jumping off points for further optimization.

iii. **Lead Optimization** - Based on an assessment of biochemical potency, cell based activity, overall physicochemical profile and input from models from the SPBCC, one series may be selected for further optimization. The objectives of the lead optimization are to increase potency in cell-based assays and to test molecules in more downstream *in vitro* and *in vivo* functional assays. *In vitro* ADME parameters such as microsomal stability and physical properties such as aqueous solubility will be monitored as leads progress. When an adequate balance of potency and physicochemical properties is achieved, initial rodent PK (iv, ip and oral) will be obtained in conjunction with scientists in the Pharmacokinetics and Pharmacodynamics Core of the ETI (*see the PCC description for details*). At this stage in lead optimization broader pharmacological profiling of leads is appropriate: for example selectivity profiling versus panels of receptors and enzymes. Early *in vitro* safety parameters may also be assessed, for example hERG channel or CYP450 activity. These assays may identify additional parameters that require optimization or influence go/no decisions on continued optimization; they will also provide input for model development by the SPBCC on novel experimental therapeutics discovered at the institute.

Optimized leads produced by the ETI will have *in vivo* efficacy in animal models (either disease or biomarker), at an acceptable dose and route of administration, with no obvious toxicity or metabolic liabilities. Medicinal chemistry is central to the design and synthesis of these leads, and chemists will interact with scientists in the TCBC, SPBCC and PPC of the ETI as projects progress.

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