

## **NCATS/Lilly Scholarship Program Project Proposals**

### **Project 1: Biomarker-Driven Approach for Dose Selection in Early Drug Development**

#### **Functional Area: Clinical Pharmacology/Translational Medicine**

**Problem Statement:** Dose selection is one of the most important aspects of any drug development program. A clinical development program generally starts with exploring safety and tolerability of a drug candidate over a wide dose range in phase 1 trials, followed by evaluation of the efficacy and safety across a narrower dose range in the target patient population in phase 2 trials. The phase 3 trials are confirmatory trials that test whether the doses identified in phase 2 trials are efficacious in a broader population. Testing an appropriate dose range in the phase 2 trials increases the likelihood to identify the most optimal dose(s) for phase 3 trials. It is therefore important to design a phase 1 program that uses all available tools to define an optimal dose range for phase 2 trials.

**Program Description:** The qualified candidate will have the opportunity to work with one of the clinical teams in either neuroscience or diabetes therapeutic area under the guidance of the mentor. The actual therapeutic area will be determined by the timing of the fellowship start relative to the progress of the identified molecules within those areas. He or she will interact with team members from different functional groups to design and implement a clinical trial that will evaluate the safety, pharmacokinetic (PK) and pharmacodynamic (PD) properties of an early phase drug candidate, participate in the analysis of safety and biomarker data, and identify a potential dose range to be explored in subsequent clinical trials. In this process, he or she will participate in the selection of various safety and target engagement biomarkers for the clinical trial, collect relevant data, and collaborate with PK/PD scientists and statisticians to interpret the results. In addition, he or she may be involved in the preparation of various documents to support a clinical trial in the pharmaceutical industry, interaction with regulatory agencies and ethics committees, and collaboration with investigator sites. Data generated from these trials may be published according to Lilly internal policy.

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**Project 2: Regulatory Sciences in Translational Medicine**  
**Functional Area: Global Regulatory Affairs**

Eli Lilly and Company Global Regulatory Affairs (GRA) desires to sponsor a NCATS Scholar for a 6-12 month externship. The successful candidate will be assigned to work within a neuroscience drug development team to advance a new chemical or biological entity through the earliest phase of drug development. The GRA project will provide the scholar an opportunity to develop a regulatory strategy and regulatory filings while working within a medical team developing the study protocol(s) and executing the clinical study(s). Depending on the start date and duration of externship, the successful candidate will lead the team in regulatory negotiations to support the trial design and may join the team in Washington for face-to-face meetings with the FDA. The scholar will learn all the regulatory requirements for conducting an early phase clinical study under an IND. Further, the scholar will gain a broad understanding of the regulatory requirements and deliverables for conducting clinical trials across all phases of development and regulatory filing for a New Drug Application (NDA). Within the NCATS Scholar program all scholars will be given a portion of their time to meet together to establish networks across the program and across Lilly Research Laboratories to further enrich the experience and ensure a robust and integrated understanding of pharmaceutical drug development. Candidates with MD or PhD with training in neurology/psychiatry/psychology are preferred. Candidates with experience in conducting Phase 1 and Phase 2 clinical trials are desirable.

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### **Project 3: Impact of Polypharmacy in Oncology**

#### **Functional Area: Drug Metabolism and Disposition**

Oncolytics have moved from single agent to multi agent therapy to increase efficacy and decrease reoccurrence. While developing new drug candidates for oncology it is imperative to quickly test multiple drug combinations to increase efficacy and more rapidly understand the tumor types that will respond to a new drug candidate. Many oncolytics have a narrow therapeutic window, therefore the increased risk of drug-drug interactions due to polytherapy could put the patients at an increased risk of safety or efficacy concerns. In addition to polytherapy for treatment of the disease, patients also taking standard of care medications such as anti-inflammatory drugs. Drug-drug interactions can occur due to changes in accumulation at the site of toxicity and/or changes in plasma concentrations. Polypharmacy increases the risk of one drug blocking an important clearance pathway of a coadministered drug possibly leading to safety concerns (drug-drug interactions). The increased knowledge of clearance pathways of drugs and the advancement in both static and dynamic modeling human disposition and of possible interactions gives scientists an opportunity to predict when these interactions might occur and to design better clinical trials.

The Fellow will work closely with scientist in the Drug Disposition, Clinical Pharmacology and physicians in Oncology to study the drug-drug interaction potential for oncolytics. The Fellow will compile a list of coadministered oncolytics and standard of care medications and work with the Lilly oncology physicians to determine which drugs or drugs under development might be combined and the possible dosing schedules of the compounds. The fellow will complete a literature survey to detail what is known about the clearance pathways (metabolizing enzyme and transporters) of the drugs and also which clearance pathways the drugs may inhibit in a clinical setting. After compiling the known data the Fellow will work with the principal mentors to determine what key data needs to be generated for the compounds in the laboratory or in clinical studies. The fellow will work with modelers in drug disposition to build both static and dynamic models of the individual drugs and predict possible interactions during coadministered. The Fellow will participate in the translation the results of the models to devise strategies for drug combinations in the clinic. If appropriate the Fellow will publish their strategy for coadministration of oncolytics. The Fellow who completes this opportunity will learn the key information that is needed understand drug-drug interactions, from the bench work, to the literature, to modeling, culminating in application to the clinic.

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### **Project 4: Development of a Nonclinical-to-Clinical Translational Hepatic Safety Model**

#### **Functional Area: Drug Metabolism and Disposition**

Several pharmaceutical companies (e.g., AstraZeneca, Glaxo Smith Kline, Merck, and Lundbeck) have published their hepatic safety screening strategies, by which they ostensibly select candidate compounds with lower risk of causing clinical drug-induced liver injury (DILI). Each of these approaches has been supposedly “validated” using a seemingly arbitrary list of marketed drugs that were classified as “hepatotoxic (H)” or “non-hepatotoxic (NH)”; however, Lilly subject matter experts have determined that many of the so-called hepatotoxic drugs are false positives because the criteria by which they were designated are likely inaccurate. Consequently, there has been a pressing need for a consensus list of structurally and/or pharmacologically related marketed drugs that can be classified as H versus NH on the basis of reliable information. Recently, such a database (i.e., WIKI) of 18 pairs of H and NH drugs has been created at Lilly based on detailed assessments of labeling information, dose range, published reports of nonclinical and/or clinical DILI, and clinical safety reports captured in the NIH LiverTox database (<http://livertox.nih.gov/>), which contains insights into proposed mechanism(s) of liver toxicity (e.g., reactive human metabolite pathways, hepatic transporter inhibition, etc.). Subsequently, a majority of these 36 “WIKI-DILI” drugs have been acquired by Lilly and internal experiments on these compounds have been initiated.

NCATS/NIH Fellow Responsibilities: The Fellow will have the unique opportunity to delve deeply into the science associated with drug-induced liver injury from both nonclinical and clinical perspectives. The Fellow will be provided with the WIKI-DILI compounds and will collaborate with Lilly scientists to design and execute hypothesis-driven experiments in accepted in vitro ADME models, as well as testing these compounds in novel liver models provided by external providers (e.g., Hepregen®) and in rodent animal models to explore biomarker and gene expression changes. These lines of investigation should improve our understanding of putative mechanisms of liver toxicity and may help discern the influence of reactive metabolite body burden on clinical DILI. In addition, the Fellow will have access to the commercially available PharmaPendium® database, which enables searching of nonclinical safety data in worldwide drug approval documents. Importantly, he/she would be able to learn from mentors and experts in our nonclinical and clinical safety organizations. Ultimately, the Fellow would be expected to develop a nonclinical-to-clinical translational hepatic safety model based on the data derived from the WIKI-DILI drug pairs and extensive literature searches. Beyond assisting Lilly’s internal efforts to mitigate issues related to DILI risk for our new clinical candidates, this translational hepatic safety model would be shared with scientists in government, academia, and pharma companies in order to advance our collective understanding of the likelihood of serious clinical hepatotoxicity for new investigational drugs.

## **NCATS/Lilly Scholarship Program Project Proposals**

### **Project 5: Tailoring Injection Therapeutics to Diabetes Spectrum of Disease**

#### **Functional Area: Global PK/PD & Pharmacometrics**

For patients with type 2 diabetes mellitus who are failing oral agents, their therapeutic options will escalate to subcutaneous injections of basal insulins, GLP-1 analogs, or various combinations thereof, before finally requiring complicated combinations of basal and prandial insulin or mixtures. However, there is no well-established prescriptive guidance that maps an optimal regimen to individual patients at different stage of their disease spectrum.

The qualified candidate will have an unique first-hand opportunity to learn about drug discovery and development from a senior level scientist in the Global PK/PD & Pharmacometrics group. Furthermore, he or she will work with scientists in global PK/PD, drug disposition, discovery, medical, marketing and regulatory to develop a whitepaper on optimal therapeutic treatment options based on patients' disease state and patient characteristics, such as, age, body mass index, insulin resistance, baseline glucose and HbA1c, mechanisms by which patients are failing prior medications (SGLT2, DPPIV or GLP-1). The candidate will interview subject matter experts in different functional areas, review available literature, summarize findings and conduct literature data analysis as needed. The candidate will have an opportunity work with a pharmacometrics expert to learn the key input and outputs of several quantitative mechanistic computational models of diabetes and provide summary level analysis results from literature to enable simulation-based evaluation of the therapeutic mapping. The whitepaper may include therapeutic alternatives, dosing recommendations, as well as a pros and cons assessment of the various available therapeutics depending on the etiology of metabolism dysregulation.

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### **Project 6: Implementation of a Virtual R&D Project for a Project-Focused Company**

**Functional Area: Chorus (A unique and independent business model designed to advance new molecules from preclinical to clinical proof of concept)**

Most large pharmaceutical companies have traditionally done everything from discovery, early development, and commercialization themselves. However, this model no longer works for many organizations in a fast changing environment such as that we live in today. If they are to thrive, they will need to improve their R&D productivity, reduce their costs, and tap the potential of the fast-paced, emerging research and technologies by collaborating with external organizations, such as academia, venture capital groups, and biotechnology companies. Lilly-Chorus and TVM Venture Capital Fund teamed up and spearheaded a virtual R&D model to rapidly evaluate technologies and form project-focused companies (PFC) to develop viable technologies to a point where the science and clinical risks of the asset are mitigated, so that Eli Lilly and Company is willing to purchase the PFC or asset for further development into a potential medicine.

At Chorus, we believe the best way to learn and to contribute is by playing a hands-on role within the organization. This unique opportunity at Lilly Chorus will enable the NCATS Scholar to understand and perform the role of an Assistant Asset Manager (AAM) and function as a rotating intern through the different functions at Chorus (regulatory, CMC, operations, and quality). At the end of this fellowship, the individual will have a deep insight on how different functions integrate in drug development and have direct operational experience in running a project.

This AAM role will start with shadowing the Asset Manager on the PFC project for at least two months and attend all meetings and discussions for the PFC (ramp-up period). After the ramp-up period, the AAM will work more independently (still under the guidance of the Asset Manager) in deciding and implementing the project. In conjunction, the individual will rotate through the different functions every two months at Lilly Chorus to understand the details on how each function contributes to the overall development of the program.