



# HARVARD MEDICAL SCHOOL

## The Harvard Program in Therapeutic Science (HiTS)

### ARMENISE-HARVARD DEAN'S BASIC SCIENCE GRANT

#### Overview

Since its inception, the Giovanni Armenise-Harvard Foundation has provided the Dean of Harvard Medical School (HMS) with vital income transfers in support of the Armenise-Harvard Dean's Basic Science Grant. The unrestricted nature of these transfers allows the Dean to allocate funds annually toward strategic priorities in the greatest need of supplementary funding. Because of this generous provision incorporated in the Armenise Foundation's founding articles, Harvard Medical School has continued to lead academic medical centers globally, educating future leaders while advancing science for the benefit of people around the globe.

During the 2012-2013 fiscal year, \$1,678,000 was made available to Dean Flier through the Armenise-Harvard Dean's Basic Science Grants. At the Dean's direction, these funds were used to support the new **Laboratory of Systems Pharmacology (LSP)**, a state-of-the-art research facility currently under construction in the Armenise Building on the HMS Quadrangle (the LSP opened in temporary quarters this past summer, and will move to the new facility in the spring of 2014). The centerpiece of the new Harvard Program in Therapeutic Science (HiTS) launched earlier this year at HMS, the LSP is an interdisciplinary research facility that will apply innovative, computationally intensive and data-rich approaches to diseases such as cancer and inflammation, with a focus on developing the knowledge and assays needed to treat individual patients with the right drugs, overcoming drug resistance, and developing a rational approach to combination therapy.

Embodying one of the Dean's top priorities, the HiTS is a broad-based program that aims for nothing less than reinventing drug discovery. There is broad agreement in both academe and industry that the science of pharmacology and the process of drug discovery urgently need rethinking and redesign. Drug development is too uncertain and too expensive, too few therapies result in long-term improvement in patient health, and effective drugs are lacking for many serious diseases. The HiTS will tackle these challenges by harnessing recent developments in quantitative and systems pharmacology, and by building an interdisciplinary community of investigators spanning research and clinical practice in academe, industry and regulatory agencies.

At the center of this unusual collaborative, and located in the LSP, will be some of the world's most distinguished investigators from Harvard Medical School, Harvard University, HMS-affiliated hospitals – such as Massachusetts General Hospital, Brigham and Women's Hospital and the Dana Farber Cancer Institute – and from MIT and Tufts. The pioneering efforts of the LSP, and the broader HiTS, will lead to the creation of new models for the study and development of therapeutic drugs, the engagement and training of a new generation of scientists and clinicians in pharmacology, and will address fundamental challenges facing pharmaceutical companies and regulatory agencies, such as the FDA, in creating and approving new medicines. In sum, the program aims to provide a conceptual basis for precise and predictive pharmacology, which will improve the lives of patients with serious diseases and increase the quality and affordability of medical care.



The HiTS has four conceptually distinct but linked components: i) the **Laboratory of Systems Pharmacology** will provide custom-built space for approximately 60 bench and computational investigators who are “co-localized” to foster unique and productive new collaborations; ii) a technology-focused



**Peter Sorger, PhD**

Therapeutics Foundry and Technology Cluster (the TTC) will comprise six linked core facilities; the unique feature of the TTC will be the use of advanced informatics and modeling approaches to break down barriers between different technologies and create a unified picture of drug action; iii) a multifaceted Regulatory Sciences Program will promote innovative research and education focused on the basic and clinical sciences underlying evaluation and regulation of medicines, medical devices, and medical diagnostics; and (iv) a Therapeutics Training Program will provide PhD and MD students with rigorous multidisciplinary training in the sciences relevant to identifying and developing novel diagnostics and therapeutics, understanding and elucidating mechanisms of drug action, and understanding clinical failure.

The HiTS, and specifically the LSP, are under the direction of **Peter Sorger, PhD**, the Otto Kraymer Professor of Systems Pharmacology at HMS and a distinguished research scientist and educator. Known internationally as a leader in the field of systems biology, Professor Sorger has focused in his work on pathways that control life and death decisions in human cancers. His research involves both experimental and computational biology, and he has pioneered approaches to modeling signal transduction at the single-cell level.

## The Laboratory of Systems Pharmacology (LSP)

A model of innovation at the core of the HiTs, the LSP is a dynamic research environment uniquely organized to promote intense and sustained interaction among investigators whose backgrounds range widely from experimental to computational biology and from basic to translational to clinical research. Pursuing new approaches in quantitative and systems pharmacology, investigators here aim to transform the science of drug discovery and development from a target-centered to a network-centered endeavor that incorporates leading edge computational tools and analysis.

Among the projects to be initiated in the LSP during the Laboratory’s first year:

- ❖ *Program in Simulation and Modeling (PRISM)*

Investigators will develop theories and software tools for understanding drug action at the level of networks of biomolecules and groups of interacting cells. Such progress will lead to fundamental advances in mathematical and experimental approaches for analyzing complex regulatory networks and, in consequence, to a better theoretical understanding of polypharmacology (the treatment of diseases by modulating more than one target – an important area of integration between systems biology and drug discovery) and combination therapy.

- ❖ *Systems Pharmacology Applied to Cancer (SPARC)*

Cancer is particularly amenable to, and in need of, a systems-level understanding of new and existing drugs. This project aims to understand and ultimately predict drug sensitivity and the emergence of resistance by applying “multiplex” measurement and modeling methods to the preclinical and clinical phases of a drug trial. The initial goal will be improved understanding of cancer pathways, but the ultimate aim is

to establish biomarkers and methods that can be used to guide therapy in individual patients.

❖ *Systems Toxicology Advancing Regulation of Therapeutics (START)*

The toxic response of a cell following exposure to therapeutics has traditionally been classified along a single dimension. LSP researchers propose to classify this response using an index of subtle molecular changes in genes and protein signaling that not only tracks the status and health of the cell but also provides information about the cause of damage. It is hoped that such a multidimensional response signature will serve as a specific mechanism-based predictive test of toxicity, thereby reducing or eliminating toxic compounds before they reach patients.

The pioneering efforts of the **Laboratory of Systems Pharmacology**, and the broader Harvard Program in Therapeutic Science, will advance drug discovery in ways that promise more targeted and efficacious medicines for the future. Scientists in the LSP will develop network-level computational models of drug mechanism of action in genetically diverse cells which, in turn, will provide unique insights into the determinants of drug sensitivity, acquired resistance, and combination therapy. These discoveries will ensure better therapies and improved health for people across the globe.

Securing sufficient financial support for critical new initiatives in their early stages, such as the **Laboratory for Systems Pharmacology**, presents an enormous challenge to Harvard Medical School. Dean Flier and his inner cabinet remain deeply grateful for the Armenise-Harvard Dean's Basic Science Grants, as they continue to afford the funds needed to advance strategic priorities at HMS.

§ § §