WHY A REVOLUTION?

Chronic Liver Diseases can lead to Hepatocellular Cancer with limited therapeutic options.

The University of Pittsburgh (Pitt) and UPMC have a long history as leaders in developing the knowledge and clinical procedures required to treat liver diseases. Thomas Starzl, MD, the pioneering liver transplant surgeon-scientist, led the development of multiple technical advances for organ procurement and preservation, liver transplantation, and immunosuppressive therapies beginning in the 1980s in Pittsburgh. Today, Pitt and UPMC are considered international leaders in investigating and treating liver diseases as represented by the interdisciplinary Center for Liver Diseases led by Satdarshan (Paul) Singh Monga, MD, who is an international leader in liver regeneration and hepatocellular cancer (HCC), and the University of Pittsburgh Drug Discovery Institute (UPDDI) led by D. Lansing Taylor, PhD, a leader in the development of the liver-on-a-chip for toxicology and disease models, and fluorescence-based imaging technologies for discovery and diagnostics.

HCC is the fifth most common malignancy worldwide and ranks as the second most common cause of cancer-related deaths. Today, patient prognosis is very poor due to the lack of an understanding of the molecular basis of the disease leading to limited therapeutic options. The only approved therapeutic for HCC is sorafenib, a drug that improves survival but does not impact tumor progression. Hence, HCC remains a major unmet clinical need. A majority of HCC occurs in the background of liver injury due to chronic liver diseases such as Hepatitis B, Hepatitis C, metabolic toxicity due to alcohol or aflatoxins (produced by specific molds), and nonalcoholic steatohepatitis (NASH). Chronic liver injuries lead to continuous inflammation, the proliferation of liver cells, and liver damage. As liver cells proliferate in this adverse environment to sustain function, they acquire DNA damage and mutations that eventually lead to HCC. In particular, NASH is becoming more common in the United States due to the rise in obesity. In the last ten years the rate of obesity has doubled in adults and tripled in children. This trend suggests that HCC will increase in parallel to the increase in NASH. Indeed, the HCC incidence increased by 3.1 percent every year from 2008 to 2012 along with death rates.

The complexity of the cellular injuries that can cause HCC suggests that a quantitative systems pharmacology (QSP) approach would be critical in understanding the abnormalities in the cellular networks that lead to disease initiation and progression to HCC. This would involve a comprehensive program harnessing the new field of QSP with the goal of translating this knowledge into optimized prognostic indicators and therapeutic strategies leading to drug discovery and development efforts for individual genetically defined cohorts of HCC patients. QSP, a paradigm shift in investigating the causes and treatments of disease, is defined as determining the mechanism(s) of disease progression and mechanism(s) of the action of drugs on multi-scale biological systems through iterative and integrated experimental and computational methods to optimize the development of diagnostic and therapeutic strategies. Pitt has established a strategy and practical platform to implement QSP within the University of Pittsburgh Drug Discovery Institute (UPDDI). QSP is rooted in understanding the patient and patient data including the identification of DNA aberrations, the inference of the networks involved in disease progression through a range of genomic and computational pathology analyses, the generation of multi-scale experimental models of disease including animal models engineered to exhibit disease genomics and phenotypes, as well as human liver-on-chip models that incorporate patient-derived, induced pluripotent stem cells that can literally create part of the patient’s liver on an experimental chip. Additional experimental and computational tools in our QSP platform include software to predict the interaction
of specific target proteins with approved drugs, phenotypic screening of experimental models, the rapid identification of molecular targets for compounds identified by phenotypic screening, and mathematical modeling of the networks identified as part of the progression of disease.

Determining the mechanisms directly linked to disease progression requires the development and integration of multidimensional, experimental, and computational QSP approaches. To meet this challenge, we have taken full advantage of the extraordinary resources and expertise in the Pittsburgh region to build a highly integrated, transdisciplinary team from the Center for Liver Diseases, the UPDDI, the University of Pittsburgh Cancer Institute, as well as multiple departments at the University of Pittsburgh and Carnegie Mellon University. Our HCC program spans the fields of clinical and translational medicine, cancer biology, drug development, computational and systems biology, and engineering. Additionally, this team includes members from industry including the GE Global Research Center, to assist in the implementation of a recently developed platform, MultiOmyx (MxIF), as well as five pharmaceutical companies who have agreed to serve as advisors to our program.

Translational investigative efforts are underway with the filing of patents on a liver-on-a-chip technology used to build patient-specific experimental disease models through the use of iPSC-derived liver cells to create “you-on-a-chip” to investigate the dynamics of HCC disease progression and individual drug testing. A patent has also been submitted on the genetic engineering of human iPSCs. Additional patents have been filed on additional technologies that are important to solving this challenge. These and future technologies will be translated through company formation and/or licensing and will be instrumental in reaching our five-year goal of identifying the mechanism(s) of disease progression and partnering our therapeutic development program with a pharmaceutical company.

Questions?

For more information on these and other QSP programs currently in development at the University of Pittsburgh, please contact:

D. Lansing Taylor, PhD
412-648-9200
dltaylor@pitt.edu

To find out how to support The Revolution Fund and its efforts to enhance patient-driven therapies through QSP programs, please contact:

Jennifer Griffin
412-623-2617
griffinj4@upmc.edu