2015-2016 Novel Clinical and Translational Methods (NCTM) Pilot Program Application

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Project Title: Novel Drug Screening Method for Pulmonary Hypertension

Applying for:
• Phase I (Identify Novel Methodological Development Need)

This application qualifies as:
• N/A
Goals, Objectives, or Aims:

The estimated cost of bringing one new drug to the clinic has increased to ~$1.2 billion, up from ~$800 million in 2003. The current drug discovery process includes two stages: 1) Discovery, beginning with molecular identification and validation, to in vitro cell testing and then evaluation in preclinical animal models. This process takes about 6 years on average, with ~98% molecules failing and 2% going to the next stage; and 2) Clinical Trials, which may take 7 years and current estimates suggest an approximate 80% failure rate. The largest losses faced during drug development occur when drugs fail late (i.e. in Phase III Clinical Trials and at the post-marketing stage). The majority of drug recalls in the past 40 years have been due to lack of efficacy, drug toxicity (e.g. Micturin, Rezulin), or unpredicted adverse effects of drug interactions (e.g. Posicor, Hismanal) in human patients. Existing preclinical models can provide a window into human physiology for determining drug safety and effectiveness. However, as many as 60% of late-stage drug development failures are due to unforeseen drug action, absorption, metabolism, and toxicity profiles that might have been predicted if mimetic physiological models of human tissues were available earlier in drug development. Therefore, novel methods of constructing mimetic human physiological tissue models, as more accurate approaches to molecular identification and target validation as well as drug screening, are desperately needed to provide more efficient and predictive drug discovery for a variety of diseased conditions including cardiovascular diseases such as pulmonary arterial hypertension (PAH).

PAH is an idiopathic syndrome characterized by obstruction of lung arteries as a result of the emergence of hyperproliferative and apoptosis-resistant vascular cells, inflammation, and vasoconstriction. The vascular obstruction increases the afterload faced by the right ventricle (RV), leading to fatal RV failure. At present, PAH mortality remains high (15% at 1-year) even in the face of current treatments. Further, the 10 currently approved PAH therapies are expensive ($20K-$100K per drug/per year) and primarily promote pulmonary artery vasodilation. These currently utilized drugs do not address key pathologic abnormalities in the vasculature and largely ignore the RV, the status of which is the main determinant of the prognosis. Academic centers and pharmaceutical companies both have undertaken intensive searches for new drugs to treat this devastating disease. Unfortunately, there is an extremely high attrition rate of new drugs in clinical trials, including even late stage trials, which is largely due to the lack of drug efficacy or ineffectiveness of drug-targeted molecules in human patients. Some have attributed the poor response/outcome to the very poor correlation between studies in small animals, currently used as “gold standards” for molecular identification and drug responses in human patients with PAH.

The requesting investigator, Kurt R. Stenmark, MD, an expert in PAH, has published numerous research papers and reviews on the cellular and molecular mechanism underlying pathogenesis and progression of PAH, and has worked with academic centers and pharmaceutical companies to evaluate PAH drugs. Our goal is to ultimately partner with bioengineers to develop complex bio mimetic human tissue systems that will allow the use of human cells in sophisticated microenvironmental conditions that mimic the normal and PAH-diseased human pulmonary artery. To that end, two specific questions are asked, eliciting novel methods to address them.

Q1. Do biophysical, biochemical, and physiological features of pulmonary artery tissues in human pulmonary vascular diseases, including various stages and types of PAH, provide prediction sets for disease phenotype as well as drug action, efficacy, and toxicity?

Q2. Can we utilize iPSCs as patient-specific cell models to derive healthy and diseased pulmonary artery tissues, showing similar drug response profiles as primary pulmonary artery cells?

It is expected that novel bioengineering methods will be developed collaboratively in this preliminary study for future large-scale projects related to target molecule identification and validation in PAH drug discovery.

Rationale or Background.

PAH is a fatal cardiovascular disease. Currently utilized drugs show at most, only modest results in delaying the disease progression and do not reduce mortality in patients with severe PAH. Thus, there are ongoing intensive efforts aimed at developing improved PAH pharmacotherapy. However, as with many other diseases, as mentioned above, major obstacles in getting drugs successfully into clinical trials have been identified. Overcoming these drug development obstacles becomes extremely critical for translating new findings in the basic laboratory into the clinic. Accurate and cost-effective preclinical models that provide high correlation with human patients, more predictive strength for molecular target validation, and more efficient path for drug screening and evaluation, when compared to current cell/tissue models and animal models are thus needed.

Accumulating evidence, including our own, have shown a number of pathological disparities and drug responses between animal models and human patients, making animal models poor predictors of clinical efficacy of potential new therapies in PAH. Physiological in vitro systems reflecting biophysical, compositional and functional characteristics of the human pulmonary artery could be instrumental in improving drug screening and clinical efficacy prediction. To comprehensively assess candidate pharmacotherapy, ‘ideal’ in vitro systems must recapitulate the complexity of diseased tissue property and pathophysiology as well as the genetic diversity of patients, thus interrogating complex human
pathology for drug evaluation. *We thus request novel methods to facilitate the development of such in vitro human vascular disease models, which also reflect mechanistic end points and predict drug efficacy on disease progression.*

The complexity and diversity of PAH resulting from the interactions of environmental and genetic factors, pose significant hurdles to the development of novel therapies and contribute to poor prediction of drug efficacy when using small animal model systems. In human PAH, recent studies have demonstrated that changes in the local vascular microenvironment including tissue stiffness, extracellular matrix composition, and flow dynamics identify various disease conditions and might be linked to differential responses of the vasculature in PAH patients to therapeutic agents. There are also significant genetic variations in patients in which PAH is observed, which can further complicate our interpretation of drug effects. Therefore, many would agree that before attempting large trials of new high potential, but high-risk drugs that involve testing in a large human population and ever-increasing costs, novel drug screening methods are needed to provide both economic, rapid, and accurate prediction of drug efficacy in humans. Also needed in these model systems would be the ability to delineate drug action mechanisms in the complex and diverse environments that are manifested in the human PAH patient. Therefore, *recapitulating (1) sophisticated tissue microphysiological environments and (2) human pulmonary artery tissues with patient-specific cells representing a variety of patient populations, we might allow investigators to overcome the current obstacles to translating new molecular mechanistic findings and new drugs to the clinic.*

To build mimetic tissue models, current 3D in vitro technologies lack discernable tunable properties such as mimetic tissue stiffness, geometry, and biomolecular signal presentation. Commercial matrix products such as Matrigel, Perfecta3D®, GravityPLUSTM, and exVive3DTM are often used to construct 3D tissues in vitro. However, the limitations of these matrices are obvious: their composition are either not well defined or fixed with limited tunability and their biophysical properties are connected tightly with the biochemical features, and thus cannot allow one to tune those separately. Recent development in tissue engineering provides several other 3D biomaterial tools that could be used for in vitro tissue models for drug screening. However, these biomaterials will still need significant improvements to achieve innovative regulation of tissue matrix parameters, i.e. stiffness and geometry. We will need novel methods to precisely control 3D in vitro microenvironment parameters to enable our investigations of complex disease pathology efficiently, accelerating preclinical drug discovery and reducing late clinical stage failure.

In addition to the use of 3D matrices, another innovation trend occurring in the development of cell models for drug discovery is the use of high-throughput drug screening assays. High-throughput methods become enormously promising to rapidly identify chemical targets in early-stage drug development, efficacy, and risk assessment. However, most current drug screening assays are based on two-dimensional (2D) cell-based systems, which do not adequately reflect the three-dimensional (3D) environments with complex diseased signatures found in human physiological systems. Inadequate representation of human tissues in vitro during pre-clinical testing can result in inaccurate predictions of drug compound effects on target tissues and organs.

In summary, compared to existing cell/tissue models, “ideal” mimetic tissue constructs that we aim to have for translational PAH studies should exhibit the following novel features:

- Integration of 3D geometry and human artery tissue properties (biophysical stiffness and biochemical composition)
- Ability to capture diseased tissue pathology
- Long-term viable, functional tissue culture capabilities including repair or regenerative capability
- Amenable to various high-throughput automation technologies
- Ease of use, simple handling and low reagent requirement

**Potential broader utility, impact & significance**

The envisioned novel methods, by focusing the technology towards human pulmonary artery tissue models with structures and properties reflecting advanced diseased stages found in human PAH patients, would be broadly applicable to construct other diseased tissue models for drug screening in other cardiovascular and non-cardiovascular diseases. The significance of the project also represents a large class of addressable functions of these potential tissue models: (a) capturing complex disease signatures for the discovery and evaluation of drugs or other therapeutic interventions with better prediction of drug functions in vivo, (b) developing complex tissue models to elucidate cellular mechanisms for future advancements in biology and medicine labs, and (c) screening of multivariate environments to optimize cell therapy or regenerative outcomes such as cell differentiation efficiency and/or mature functionality.