Title of Challenge: InPulse

Background

Cardiovascular (CV) safety liabilities are one of the most common causes of drug attrition in both the nonclinical and clinical setting (Kola and Landis 2004; Laverty et al. 2011; Valentin and Hammond 2008). These liabilities manifest in a variety of ways that include structural injuries and derangements in CV function. Changes in contractility may lead to clinical heart failure and even death. Important classes of drugs, such as anti-neoplastic tyrosine kinase inhibitors, are currently facing particular safety challenges with this effect.

iPS cell-derived cardiomyocytes (iPSC-CMs) have shown early promise for replacing animal use in CV research and many pharmaceutical companies and academic researchers are developing assay platforms to identify potential electrophysiological and structural liabilities earlier in development (i.e. ‘pre-animal’) (Cohen et al. 2011; Guo et al. 2011a; Guo et al. 2011b; Harris et al. 2013; Peng et al. 2010; Qu et al. 2013). A similar capability for contractility assessments would be very useful from a scientific and 3Rs perspective.

Historically, there has been a heavy reliance on highly invasive, technically demanding, surgically instrumented telemetered animal models in preclinical studies that provide indirect measures of contractility in vivo. More recently, imaging (e.g. echocardiography) has been used as an investigative and mechanistic tool both preclinically and clinically but it is low throughput and labour intensive. The only in vitro/ex vivo models that are available are perfused whole heart models from animals and isolated cardiac cells from animals and humans. There is no currently validated/qualified human-derived in vitro system for assessing drug-induced changes in contractility under varying levels of physiologic load.

The ability to study changes in cardiac contractility in vitro would allow the investigation of potential causes of long QT syndrome that are both hERG and non-hERG dependent. This would allow a more accurate prediction of potential drug-induced cardiac toxicity in preclinical and clinical settings; thus help to reduce attrition. Mechanistic understanding of changes in cardiac contractility from in vitro models would also be relevant to efficacy studies earlier in the drug discovery process.

The rapid development of human iPS cell technologies and materials sciences provides an opportunity to develop a dynamic, human-relevant assay system to screen and characterize novel drug candidates for cardiac contractility liabilities. Recent publications have demonstrated that the extracellular matrix, morphology and orientation of cardiac cells are important for cardiac contractility and calcium signalling in cardiac myocytes and there have been significant advances in substrates for monitoring contractile tension (Guo et al. 2011b; Harris et al. 2013; Kola, I., and Landis, J. 2004). However, there is the need for a robust in vitro model that reflects the 3D architecture of cardiac tissue with mature cell phenotypes.

3Rs benefits

- Assessment of developmental drug pre-candidates on cardiac contractility relies exclusively on the use of animals prior to clinical trials. A typical study uses 12-24 dogs
- A physiologically relevant 3D in vitro model will replace the use of animals in these studies and reduce the number of animals needed to assess the mechanism of action of any drug-induced effect
- An in vitro system where load can be adjusted to model the pathophysiology of disease tissue could also be used to reduce animal use in efficacy studies. A typical efficacy study uses approximately 24 mice
Once validated, an *in vitro* platform could be used to screen compounds and provide earlier go/no-go decisions hence reducing the number of animals used to test compounds that would ultimately fail in development.

**Need for collaboration**

A wide range of expertise is essential to solve this Challenge including experts in physiology, pharmacology, iPS cell technology and bioengineers. The pharmaceutical industry will provide expertise into what is needed from the platform in the drug development setting and is also uniquely positioned to provide support for testing and validating the system.

**Overall aim**

To generate a physiologically-relevant contractility platform with cells that are phenotypically ‘mature’, possess a robust contractile apparatus, move calcium between intracellular and extracellular spaces and metabolically generate substantive amounts of energy.

**Key deliverables**

There are platforms available to identify potential electrophysiological and structural changes in iPS cell cardiomyocytes. However, there are different considerations for measuring contractility, including the phenotypic characteristics needed by the cellular substrate, the endpoints measured, and the optimum culture conditions.

A suitable platform would require small quantities of compound and cells and have a medium-throughput capability consistent with its potential use in identifying CV safety liabilities earlier in drug development. Ideally, the optimal platform should permit the integration of quantitative measures of contractile motion or force and intracellular calcium transients as one important mediator of that force. The system should employ a mechanism to variably alter the load to mimic physiologic and pathophysiological conditions.

Applications which go beyond the currently available technologies for cardiotoxicity (e.g. high throughput screens, tissue platforms) are required for this Challenge.

**Phase 1**

- Development of a cell culture platform that produces iPSC-CMs with a mature phenotype driven by load (e.g. improvements in action potentials, heterogeneity, calcium and contractility measurements)
- Maturity demonstrated by, for example:
  - Shape, structure, organisation
  - Proteome expression profile
  - Index of function (e.g. ryanodine:IP3 receptor ratio)
  - Biochemical and physiological methods
  - Imaging to demonstrate sarcomeric organization and myofilament deposition
- Demonstration of a relationship or a collaboration with the expertise needed for Phase 2

**Phase 2**

Development of a cell culture matrix which would:

- Support 3D growth and development of mature iPSC-CMs as seen in the intact tissue
- Allow the cells to ‘move’ under the influence of a dynamically variable electrical stimulus
- Permit collection of quantitative measures of motion or force that could also perform under ‘load’ conditions that might reflect a range of physiologic conditions that mimic varying conditions in patients. Comparisons to adult ventricular stiffness/elasticity would
create impactful and aid translational comparisons. Measurement of contraction can be in any direction and could use any technology (linear vs. circumferential measurements).

- Be capable of measuring action potentials, calcium and contractility simultaneously in a collection of cells.

Demonstration of robust commercialisation/uptake strategy

Sponsor in-kind contributions

Phase 1

The sponsor will provide data on expected mature phenotype profile of iPSC-CMs

Phase 2*

- Data that exists for contractile alterations of reference tool compounds and of terminated candidates
- Echocardiographic data
- Mitochondrial, transcriptomic, electrophysiological, physiological and pharmacological data and support.
- Relevant clinical data
- In house testing and validation of new platform including integrated cross-species PK-PD (concentration-effect) comparison and translation across a range of compounds spanning multiple therapeutic areas.

Duration

Phase 1: six months. Phase 2: up to three years

Budget

Phase 1: up to £100K. Phase 2: up to £1 million

Sponsor

GlaxoSmithKline

*All animal studies have been ethically reviewed and carried out in accordance with national regulatory and legal requirements and company policies on the care, welfare and treatment of animals.

References


