# Challenge 13: InPulse

**Q. Does it matter if you are seeing contractility directly or can you look at the associated effects/parameters?**

A. The Challenge is about contractility but it could also be about identifying an early/subtle change that will indicate an effect on contractility, before you see a structural effect.

**Q. Why would you want to know why a drug is having an effect on contractility?**

A. The effect on contractility and how acceptable this may be will depend on the class of the drug, as different therapeutic margins may be acceptable e.g. long-term treatment for hearing loss vs. pancreatic cancer treatment (risk vs. benefit). You need to know the maximum dose you can give with significant safety effects, i.e. you need to know the therapeutic index to be able to make decisions. Also, if we can understand the mechanism of action the medicinal chemists can adapt accordingly.

**Q. Cross-species assays do not link up well for electrophysiology e.g. rats do not have the hERG channel, how comparable are assays of contractility across species?**

A. The concentrations/dose effects may be different but overall the contractility effect is very consistent.

**Q. How predictive are the animal models for contractility?**

A. The direct ones are quite predictive. There is a remarkable degree of concordance for each assay across species compared to electrophysiology.

**Q. Did the Hamer at al. study in the presentation pick up calcium transients?**

A. No, just contractility.

Our focus is on the technology to develop an assay for contractility.

It needs to be cheaper than the published method (and if using iPS cells rather than isolated myocytes, then it will be cheaper). The fresh isolated myocytes tend to de-differentiate. We need something that will be translatable to a universal platform.

The Challenge assay needs to be as good as or better than this assay, but cheaper and higher throughput.

**Q. iPS cells - what source should be used? Different cells behave in different ways. Do we need to use a variety to show they behave in the same way or use a single commercially available source?**

A. The technology is the focus rather than the cell line. We will consider all options, but it would be good to be able to compare the results to what has already been done, and commercially available cell lines are widely used. Initially, the Challenge is to find the quickest way to the end result. Once the technology has been developed, it can be transferred to other cell lines later. It doesn't really matter what the cells are, as long as they are stem cells. The cells should be of high quality.

**Q. I would imagine that it should be as close to the physiological situation as possible, so you can then translate to human?**

A. This will be an *in vitro* model so there will be limitations. It should be physiologically relevant in terms of effects of beta blockers, different agonists etc. We want the cells to be able to bulk up, as would occur in humans.

**Q. In terms of the platform, what are the requirements?**

A. Something that does not constrain contraction. Therefore, the material needs to be flexible enough to adapt (i.e. not as rigid as PDMS). It is about finding the right technology to show that your substrate works, that your cells will look like mature myocytes, and that you can demonstrate contractility.

**Q. Accumulation of dosing and chronic effects - how do you evaluate that in a cell-based model?**

A. Some of these, due to chronic exposure we will to be able to capture in an *in vitro* cell based model. As it is a culture based system, we will only be able to capture up to a few weeks at most.

**Q. How do you define medium-throughput?**

A. 10s of compounds per day rather than 100s (although potential for higher throughput would be great). Medium-throughput is the end goal, but it doesn't have to start out like that. We need the right physiology and pharmacology first and then it can be scaled up. It needs to be initially amenable to only do a few compounds or up to 20 or 30 per day.

**Q. If we were successful, would you be happy to publish our findings?**

Yes, we would want to publish the findings.

**Q. Would you provide data, compounds etc for this Challenge?**

A. Not in Phase I, but if you are successful in proceeding to Phase 2, then yes we could provide compounds, data and validation work. Phase I is about demonstrating the relevant physiology and pharmacology.

For further information and to be put in contact with the sponsors, please email

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