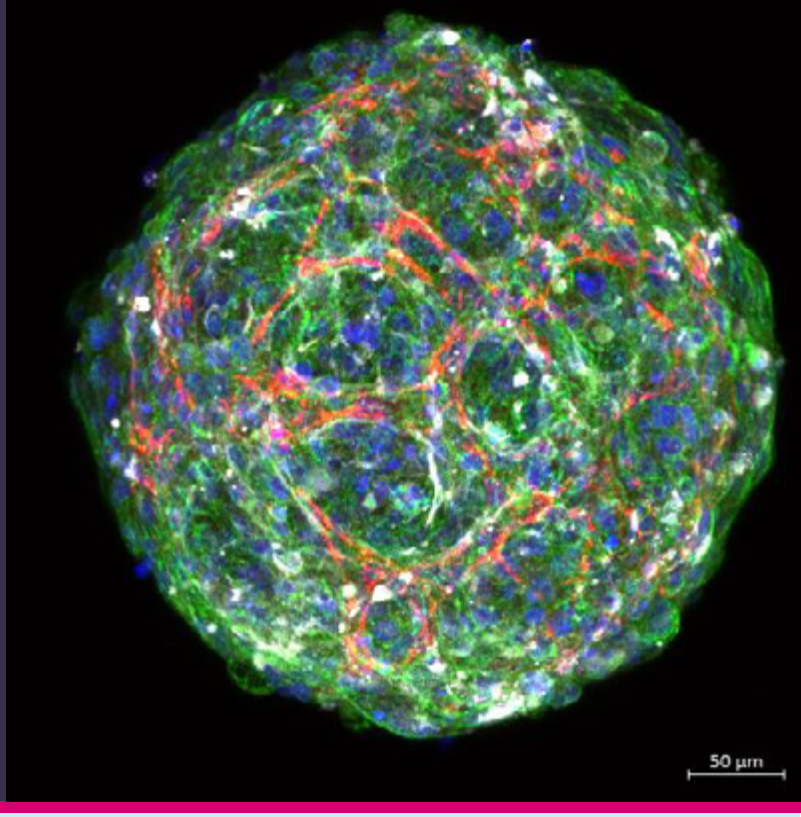
January 2023

CATAPULT
Medicines Discovery

Incorporating Diversity in Cardiac Testing – Making Mini Hearts



A confocal image of a multicellular mini heart, showing all three cell types (green = cardiomyocytes, red = endothelial cells, white = fibroblasts (blue is cell nuclei))

CYTOCHROMA

Background

Heart and circulatory diseases are the leading causes of death worldwide, and the race is on to develop treatments that can help people with these diseases.

While this is a focus of many drug discovery companies, they must first overcome a significant challenge: cardiotoxicity (toxicity of heart tissue). Many medicines show efficacy throughout development and appear safe in tissue models. However, they can go on to reveal undetected cardiotoxicity once they progress into clinical trials or launch onto the market.

It is important to note that the risk of death from heart disease differs by race and ethnicity, which means that patient gender, ethnicity, genetics and individual drug responses play their part in understanding how to develop medicines that work for individuals.

However, there is a significant gap in effective models and tests to predict cardiotoxicity that reflects the disparities observed in the clinic due to race and gender.

Edinburgh-based SME Cytochroma Ltd was established to address this lack of equality and diversity in drug development. It manufactures genetically diverse multicellular hepatic (liver) and cardiac (heart) models that better predict adverse reactions to medicines.

Cytochroma's accurate preclinical models are being designed to predict toxicity earlier, reducing expensive late-stage failures while cutting time and costs, and accelerating more, safer medicines to market.

Challenge

Unexpected cardiac and hepatic adverse effects are two leading causes of discontinuation of clinical trials and withdrawal of drugs from the market.

There is an immediate need for cardiotoxicity identification assays (tests) representing a variety of genetic backgrounds to better enable drug developers to select and promote the safest medicines, ensuring the best chance of clinical success.

Cytochroma provides predictive cell models from genetic backgrounds that the FDA has highlighted as lacking in clinical trials, enabling unique insight into how drugs will react in a diverse population early in the drug development process and preventing unexpected adverse reactions.

Output

Cytochroma secured an Innovate UK Biomedical Catalyst (BMC) grant to work with Medicines Discovery Catapult (MDC) on a proof-of-concept study to demonstrate the effects of gender and diverse ethnicities on cardiotoxicity, thus enabling more predictive cardiac drug discovery and development.

Cytochroma supplied MDC with the differentiated cells (derived from diverse patient sources) required to build a representative, three-dimensional cardiac model comprised of three essential cell types: cardiomyocytes (heart muscle for contraction), cardiac fibroblasts (for structure) and cardiac endothelial cells (blood vessel formation).

Currently, most tests look at only the cardiomyocyte element, but incorporating the other cell types allows an increased range of potential targets relevant to cardiotoxicity.

MDC's specialist scientists and Cytochroma's scientific team have created a better model that allows the exploration of the mechanism of action and toxicity across the different cell types. These 'mini hearts' spontaneously 'beat', like real hearts, and it is also possible to measure drug effects on electrical activity – similar to an electrocardiogram (ECG) test.

Working together, Cytochroma and MDC have been able to go one step further by incorporating patient genetic diversity into cardiac testing, enabling the comparison between patient-representative cardiac models and unlocking the genetic differences and subtleties unique to those identities to measure the toxicity effects on each individual.

The nature of this model enables cell types from different backgrounds to be combined in multiple groupings, for the first time identifying drug toxicity to a particular cell type or specific genetic background.

Outcome

Through this collaboration, MDC is validating Cytochroma's cardiac model that acts like a 'real' heart – spontaneously beating and exhibiting an electrical current.

Cytochroma is seeking to reproduce the gender and ethnic differences in cardiotoxicity seen in the clinic with this global first cardiac model. If this is successful, it will be possible to frontload testing for new drugs before they get into clinical trials, enabling researchers to identify issues earlier in the discovery pipeline.

MDC will also be applying some of its genomic technologies, like NanoString, which delivers direct profiling of an individual's gene expression, to characterise patterns or differences during toxicity profiling associated with genetic backgrounds.

Early identification of cardiotoxicity issues provides the opportunity to change or redesign molecules at a fraction of the cost compared to a medicine that progresses to clinical trials and subsequently has to be abandoned.

Impact

This proof-of-concept study between Cytochroma and MDC aims to show that it is possible to generate new cardiac assays that better represent the patient population than those that are currently available. The assays can also be used to understand which cells are potentially the targets for toxicity and how much influence the genetic background has.

Working in collaboration with MDC, Cytochroma benefits from its state-of-the-art microscopy, imaging facilities and the technologies used to generate the models and measure the beating and electrical activity of the 'mini hearts'.

Together, Cytochroma and MDC are developing a more detailed understanding of the role of genetic differences on cardiotoxicity. Improving the quality of existing cardiac models to make them more reflective of the human population, and doing so earlier in the discovery process, will ultimately save time and reduce the cost associated with the risk of carrying molecules forward, which may later fail. This will ensure that high-quality medicines are made available to patients more quickly and with a lower risk of cardiotoxicity.

Dr Kate Cameron, CEO and Founder, Cytochroma, said:

"This project has been a huge success: the capacity to model multicellular cardiac response from individual stem cell donors is a global first. This unique capacity to understand how genetic variance and gender play a role in cardiotoxicity has attracted significant interest from our existing and growing client base. It has been critical to work with MDC to develop these powerful new models with clinical relevance."