Bioengineering human cardiac tissue

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Over the past few years, advances in pluripotent stem cell culture and directed differentiation protocols (Hudson *et al.*, 2012) have made it possible to create human tissue organoids. Very recently cerebral, intestinal, stomach, lung and neural networks have all been reported and have the ability to self-organise and to recapitulate their tissues of origin in both geometry and function, provided the correct environment is provided (Shamir & Ewald, 2014). This represents a revolution in the use of tissue culture for the modelling of development and/or disease. This is because even minor alterations in protein functions or environment can have profound effects on tissue function.

We are now able to use human pluripotent stem cells to produce large numbers of human cardiomyocytes as a research tool or potentially for regenerative applications. In traditional 2D cultures these human cardiomyocytes recapitulate some of the properties of native heart tissue, however, many properties more closely resemble embryonic-like cardiomyocytes (Yang, Pabon & Murry, 2014). In order to enhance the maturation of the human pluripotent stem cell cardiomyocytes we have used tissue engineering to produce human cardiac organoids. These organoids have enhanced maturation and we can also record functional properties in these tissues (*e.g.* electrophysiology, calcium transients, force measurements). However, despite this significant progress, we still had only progressed to a fetal-like state as assessed using functional assays, genetic markers, morphology and proliferation capacity. This indicates that we have still not found the major drivers of cardiac maturation.

Tissue engineered in general is a labour intensive and resource intensive pursuit where > 1million cells are required to produce each tissue and it is very time-consuming to record functional properties from each tissue. Therefore, screening for maturation conditions in such a platform is very difficult. We have therefore miniaturised our cardiac tissue engineering system into a 96-well, semi-automated screening platform. This has facilitated our screening for drivers of maturation, drivers of cardiac regeneration and can also be used for industrial applications.

Hudson J, Titmarsh D, Hidalgo A, Wolvetang E & Cooper-White J. (2012). Primitive cardiac cells from human embryonic stem cells. *Stem Cells Dev* **21,** 1513-1523.

Shamir ER & Ewald AJ. (2014). Three-dimensional organotypic culture: experimental models of mammalian biology and disease. *Nature Rev Molec Cell Biol* **15**, 647-664, doi:10.1038/nrm3873.

Yang X, Pabon L & Murry CE. (2014). Engineering adolescence: maturation of human pluripotent stem cell-derived cardiomyocytes. *Circ Res* **114,** 511-523, doi:10.1161/circresaha.114.300558.