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EDITORIAL

Human stem cell models for predictive cardiac safety pharmacology

'Safety pharmacology' is a relatively young and rapidly developing discipline that aims to predict potential negative effects before a new drug is first administered to patients. It is unique in the sense that it is not only supposed to identify the risk of rare undesirable pharmacodynamic effects on specific cells and tissues but also the systemic effect on the whole individual. The core focus is on the most sensitive target organs: the liver, the central nervous system, the respiratory system and the cardiovascular system. The cardiovascular system is of particular interest since effects on the heart may not only be chronic as for other organs but may also be immediately life threatening: 'sudden cardiac death' can be the tragic outcome. It is becoming increasingly clear that drugs can pass all of the present regulatory requirements and be authorized for prescription to patients or even sold 'over the counter' for many years before rare and lethal adverse effects become apparent. One of the best-known examples is the drug terfenadine, used to treat allergic rhinitis (hay fever). After being on the market for almost 15 years, the drug was withdrawn as it became evident that it could prolong the cardiac 'QT interval', the time between two electrical peaks on an electrocardiogram (ECG), and as a result induce serious ventricular tachyarrhythmias (rapid heart beat), including the potentially lethal Torsades de Pointes (TdP).

Identification of QT interval prolongation on an ECG has become a biomarker for TdP. It has led to the withdrawal of several other drugs from the market in the United States, including cisapride, thioridazine, and grepafloxacin. Many others have been required by the Food and Drug Administration (FDA) to carry additional safety labeling warning of the potential risk. QT prolongation is often caused by drug interference with the human Ether-a-go-go Related Gene (hERG). The hERG gene encodes the Kv11.1 potassium channel and is essential for cardiac action potential repolarization; if blocked it will prolong the QT interval and there will be an increased risk of ventricular arrhythmias. Assessing drug-induced prolongation of the QT interval has been the major preoccupation of cardiac safety pharmacology, under the assumption that a prolonged QT indicates an increased probability of TdP.

One of the most difficult tasks in safety pharmacology however, is how best to conduct reliable high throughput screening to predict the risk of ventricular arrhythmias at an early stage in drug development. It is presently common practice to screen for hERG/I_{Kr} effects using either planar patch clamp technology or ligand binding assays. However, these methods, although high throughput, are known to generate false positives, false negatives and relatively variable values for IC_{50} (the dose of a drug causing 50% of the final effect) when compared to conventional (low throughput) patch clamp electrophysiology. Pharmaceutical companies continue to use them nevertheless but err on the side of caution because of the wisdom of hindsight and are now likely to avoid further development of any compounds that show I_{Kr} blocking in these assays in early stage tests. This may result in unnecessary rejection of potentially valuable clinical compounds. Several drugs used in the clinic, like verapamil for example, inhibit I_{Kr} without actually prolonging the QT interval or inducing TdP, while others prolong the action potential without inducing TdP (Shah and Hondeghem, 2005). hERG block at a concentration close to the therapeutic range for a drug should be considered a serious warning signal and warrants further study.

Several tests are based on isolated cardiac tissues. These include Purkinje fibers, papillary muscles and ventricular trabeculae from animals. None is yet versatile and predictive enough to convince regulators that a drug that does not adversely affect these tissues be regarded as safe. The regulatory authorities usually require more complex *in vivo* telemetry studies in larger animals like dogs and pigs (ICH topic S7B). Nevertheless, it is still not possible to quantify risk/benefit assessment for TdP liability accurately on the basis of the current preclinical assays (Pugsley et al., 2008). This is where cardiomyocytes derived from human pluripotent stem cells may be useful. These cells have a significant potential to be developed into a model with a relatively high predictive value for cardiac safety pharmacology. These are human cells and, as far as we can tell, they can share many features of human adult ventricular cardiomyocytes and can in principle be scaled up to reproducibly produce large cell numbers.

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In this issue of Stem Cell Research two independent groups produced cardiomyocytes from human embryonic stem cells and use electrophysiology to asses their response to a selection of well characterized drugs (Jonsson et al., 2010; Otsuji et al., 2010). This complements a third paper published in the previous edition of Stem Cell Research which showed systematic analyses of cardiac field potentials in response to a variety of cardiac and non-cardiac drugs (Braam et al., 2010). All three papers are presented as potential model systems for evaluating safety pharmacology of the heart.

The key question that arises from these papers is whether the models have actually been validated. Do the models accurately predict the safety liability of a drug candidate once applied to humans? All three papers provide evidence that the stem cell derived cardiomyocytes do respond to the drugs as predicted. For example E-4031, a classical hERG-blocker was tested in all three papers and demonstrated to induce a dose dependent prolongation of the field or action potential. In addition to examining action potential prolongation, the paper of Jonsson et al describes measurement of parameters like reverse use dependence, triangulation of the action potential and beat-to-beat variability. It has been suggested that these parameters often change before action potential duration (Shah and Hondeghem, 2005). Therefore it will be of interest in the future to see how these parameters behave on stem cell derived cardiomyocytes when drugs are tested that have a well-documented clinical history. The paper by Braam et al is the first attempt to compare drug responses of the cells at concentrations measured in the plasma of patients quantitatively (Braam et al., 2010).

Whilst the collection of papers represents a good start to developing this type of drug safety platform, there is clearly a need for refinement of the differentiation and culture protocols. For example, whilst Otsuji and colleagues show that prolonged culture improves the maturation of the cells, which directly affects the drug response, direct comparison with concentrations of drugs in patients is not shown and culture of the cells for up to 8 months in a labor-intensive protocol is required. This limits the applicability of the procedure. Jonsson and colleagues show clear heterogeneity between individual beating clusters with ventricular-like, atrial-like and nodal-like action potentials. For this reason, they selected clusters with a ventricular-like action potential (it is expected that drug effects on cardiomyocytes of the ventricle are likely to represent the highest drug risk), but manual selection is not well suited for high throughput automated analyses. Further development of reproducible differentiation protocol to a specific cell type (for example ventricular cardiomyocytes) followed by a maturation step in a system that can be scaled up will be necessary for the successful implementation of the stem cell model.

Taken together, whilst the data presented in the three papers are promising, the technology is still under development and the models remain to be fully validated. In an ideal world, drugs would be ranked against a range of other drugs to generate a 'clinical ranking order', which could assist in validation. For TdP, ranking in this way does not exist, in part because its incidence is rare and calculations of its incidence cannot be made with sufficient accuracy. What needs to be done is validation of the model by testing a larger panel of compounds in a blinded screening assay. A range of positive and negative controls would need to be included with a known effect (or lack of it) in humans. Once validated in this way, these models may eventually be used to flag potentially unsafe drugs early in the preclinical development phase. The sooner a potentially adverse effect is detected the sooner a company can develop an adequate risk management strategy. That can involve further optimization of the lead compound with the aim of enhancing the risk benefit profile, development of a whole new drug or, in the worst case, abandoning the compound. In the long run this could however not only increase safety but also reduce costs of production since many later and more expensive assays in whole animals, like dogs, would not need to be carried out for drugs with significant safety issues. The studies published here show that human embryonic stem cell derived cardiomyocytes have the potential to be developed into a reasonably inexpensive, predictive human cardiac safety pharmacology model. This may allow researchers to perform drug discovery research and cardiac safety pharmacology in parallel. The outcomes of each process can inform the decision making in the other, ultimately leading to more effective drug development.

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