

# iPSCs and the future of personalised medicine

“From bench to bedside” describes the process whereby the results of research done in the laboratory are directly used to develop new therapeutics to treat patients. In the last decade, the sequencing of the human genome and subsequent genome-wide association studies have spawned a reverse approach to drug development: “from bedside to bench” enables researchers to derive and test therapeutic options based on the known genotypic and phenotypic profiles of individual patients or patient subpopulations. The goal is to develop more personalised or predictive therapeutics that optimise efficacy and minimise adverse events.

Personalised medicine is usually associated with drug-diagnostic combination products. Yet the field is still wide open and new tools are under development. Induced pluripotent stem cells (iPSC) can be one of these tools.

Induced pluripotent stem cells are embryonic-like stem cells that are derived from adult tissue. They were first reported in 2007 in separate discoveries by James Thomson in the US and Shinya Yamanaka in Japan.<sup>1,2</sup> Dr Thomson’s laboratory was also the first to culture human embryonic stem cells in 1998.<sup>3</sup> iPSCs have several advantages over embryonic stem cells. They do not carry the ethical, political or legal baggage associated with embryonic stem cells; also the tissue needed to create iPSCs, such as cells from a standard blood draw, is easily obtained and unlimited in supply. In fact, recent work has shown that iPSCs and cardiomyocytes can be created from banked blood.<sup>4</sup> In addition, iPSCs have the same capacity of pluripotency as embryonic stem cells, and thus can make any cell type in the body. And, because the genotype and phenotype of the donor are known, they can be employed in *in vitro* clinical trials, ie, to study human biology and disease in a dish, and thus have the potential to drive advances in predictive medicine.

How can iPSCs be used in personalised medicine? One potential application is in genome-wide association studies. An example is a project that has recently been funded in the US by the National Heart, Lung and Blood Institute to identify genetic contributions to hypertension. The Institute has awarded \$6.3 million over five years to the Medical College of Wisconsin and Cellular Dynamics International, to generate induced pluripotent stem cell lines from blood samples from a group of Caucasian and African-American families. Prior genome-wide association studies of the same patient groups had identified genes linked to potential disease-causing mutations.

Under the grant, Cellular Dynamics International will develop iPSC lines from an unprecedented 250 individuals from an epidemiological database and differentiate them into cardiomyocytes. The Medical College of Wisconsin will then use these cells as a tool to determine associations with genotypic differences within the population and the biology of cardiomyocytes derived from them. This process can be applied to multiple diseases and disease subtypes because a significant rate-limiting step – access to representative human cells for *in vitro* analysis has been overcome.

This has become possible because the industrialisation of human iPSCs and terminal cell production enables the

underlying biology of patient populations to be studied. Cells can now be manufactured in the quantity, quality and purity required by researchers and drug discovery scientists to conduct large-scale, high throughput experiments.

The industrialisation of stem cell technology will accelerate the development of cell models for use in predictive or personalised medicine. For example, somatic cells derived from identified patients with specific diseases and/or genetic profiles could be used for high throughput screening of new chemical entities (NCEs) to identify potentially efficacious or toxic drug candidates. Under this scenario, it is possible that drug candidates will be identified with profiles that predict benefit or risk to specific patient populations.

The primary challenge in applying iPSC cell technology, especially as therapeutics, is its short history. Human iPSC technology is only four years old. As is the case with embryonic stem cells, the long-term safety of iPSCs has not yet been determined. Cellular reprogramming originally involved steps that incorporated foreign DNA into the genome, drawing into question the safety of the underlying genetic changes that occurred. However, current non-integrating methods, including episomal reprogramming, have made the process less genetically invasive, decreasing safety concerns. As an important first step, these human iPSC-derived cells can be employed in predictive testing to benefit healthcare now, while continuing to validate this option for future cellular therapy.

Traditionally, drug therapy has been optimised for large “general” populations rather than targeted subpopulations that have been prospectively identified through genotypic or phenotypic profiles as responders, or identified as at risk of adverse events. The transition to “bedside to bench,” driven by the development of human cell-based tools based on iPSC technology, means that drug developers may be able to better minimise side effects. Additionally, this new human cellular model also offers an opportunity for pharmaceutical companies to develop more targeted and effective drugs that are more likely to move through clinical development successfully.

## References:

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