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A new technology for direct cell reprogramming

Japanese scientist Shinya Yamanaka changed the course of cell therapy in 2007 when he showed that mature human cells could be induced into an embryonic-like state.[1] The discovery of induced pluripotent stem (iPS) cells won Dr Yamanaka the Nobel Prize in Physiology or Medicine in 2012, which he shared with the UK cell biologist Sir John Gurdon.

Since then, an increasing number of companies have been using iPS cells for disease modelling and drug screening and a few are developing medical therapeutics. A question now is whether the significant findings of Dr Yamanaka and colleagues can be taken to new levels by applying engineering principles to biology to make any cell type from any other cell type without going through the pluripotent stem cell, or even progenitor cell state. This is the challenge we have undertaken at Mogrify Ltd, a UK biotech that was founded in 2016 in order to commercialise direct cell reprogramming technology.

The basis of the technology is a network-based algorithm which is designed to find the transcription factors that can deliver changes to a cell's state. Of the roughly 20,000 human genes, about 2,000 are transcription factors. These transcription factor genes code for proteins whose function is to bind DNA and regulate the production of all proteins. Most transcription factors target multiple genes and together they make up a regulatory network which acts like an electronic circuit. Each person has many cell types but the DNA in these cells is the same. The main difference between cells is which parts of the regulatory network are activated and thus which proteins are being produced at any given time. Therefore, each cell type can be defined as a state of gene expression and, as Dr Yamanaka showed, the use of molecular biology methods, such as viral vectors, can induce a state change to convert one cell type to another.

In the decade since Dr Yamanaka's discovery, however, there have been surprisingly few new human cell conversions. This is despite efforts to carry forward his approach by numerous cell biology groups.

Dr Yamanaka used expert knowledge and information from academic literature to make a long list of potential transcription factors and then spent years of trial and error to find the right combination. Unfortunately, with a couple of thousand transcription factors to choose from, this gives more than one hundred trillion combinations of four factors to explore. And a cell conversion may require many more than four factors.

How can this be done? Scientists have been increasingly adding RNA sequencing data to assist in the selection of a long list of factors, expanding the repertoire beyond expert knowledge in an unbiased way. This has mostly been applied in an unsophisticated way by experimental cell biology labs who may have a resident informatician, but there have been one or two exceptions to this where understanding of the cell's transcriptional regulatory network has been taken into account.

Our approach is to systematically predict which factors are required for a given cell conversion. Using a network-based approach, big data and a few key algorithms, we make our predictions about cell conversions. This is not artificial intelligence or machine learning. It involves measuring the state of the starting cell and the endpoint and then predicting how to artificially manipulate the control network.

This is done at a minimum number of key points in order to flip the cell to a state close enough to the target so that natural control mechanisms then take over and an equilibrium, determined by evolution, can be achieved. Thus, the induced trans-differentiation does not follow developmental processes, nor require any understanding of them, but engineers the most direct path to the target.

In our first three laboratory experiments, cell conversions using our algorithm were successful with no trial and error. We are now scaling up the technology so see whether we can achieve conversions of therapeutic value.

In the past, some people believed that failures to achieve novel cell conversions could be blamed on an invisible epigenetic barrier. However, we have found that in many cases, with the right combination of transcription factors, this is not the case. Epigenetics definitely plays an important role in cell state and cell identity. But generally speaking, it appears to follow what is initiated by the transcription factor mediated network of protein expression. Arguably in trans-differentiation, where you are not driving the cell along developmental lineages from a pluripotent state, the fate may actually be less influenced by epigenetics misdirecting a cell down the wrong path, or controlling its maturity. Some cell conversions will probably require epigenetic intervention in the end. But for now, it looks like there are many cases where a uniquely transcriptional approach will be sufficient.

There is reason to be excited about human cells and the potential for new cell therapies and regenerative medicines. Many different cell types make up the tissues and organs in the human body, giving us numerous ways to treat injury, disease and ageing. For example, putting cardiomyocytes into an area of the heart damaged by a heart attack might restore some of the lost function and reverse some permanent damage. Elsewhere, modified T cells are being used to treat certain cancers and promise to treat many more types in the future.

Ultimately, the most seductive possibility is that we will be able to reprogram cells *in vivo* without the need for transplantation or laboratory cell culture.

Reference: K. Takahashi, K. Tanabe, M. Ohnuki, M. Narita, T. Ichisaka, K. Tomoda, S. Yamanaka Induction of pluripotent stem cells from adult human fibroblasts by defined factors *Cell*, 131 (2007), pp. 861-872

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