Direct cell reprogramming

Mogrify and Astellas to address hearing loss

It took Nobel Laureate Shinya Yamanaka and colleagues years of hard work to identify the transcription factors that would make it possible to induce mature human cells into an embryonic-like state for use in disease modelling and drug screening. The induced pluripotent stem cells (iPSCs) that were created as a result of this work have had a huge impact on drug research and development. The global market for iPSCs has been estimated by some analysts to have reached $2.8 billion in 2021, with more growth still to come.

Yet this expansion has not been happening in isolation. While many companies are working on improvements to the iPSC technologies, others are examining the potential of direct cell reprogramming, a relatively new approach. This involves the conversion of cells from one lineage to another by identifying and then activating combinations of transcription factors that are unique to each cell type. Transcription factors are the proteins that control the rate of transcription of genetic information from DNA to messenger RNA by binding to a specific DNA sequence.

UK-based Mogrify Ltd is one of this growing number of companies which are using sequencing and other data to identify the precise combination of proteins that play a role in a desired cell type. The company was founded in 2016 and since then, has developed a technology platform enabling it to identify optimal combinations of transcription factors. On 5 July, it announced a collaboration with Astellas Pharma Inc to research a new way of treating sensorineural hearing loss by the use of *in vivo* regenerative medicine.

Sensorineural hearing loss is the most common form of permanent hearing loss which is the result of damage to the hair cells in the inner ear, or to the nerve pathways between the inner ear and the brain. The collaboration will aim to identify transcription factors that could lead to the recovery of function in this hearing loss. Mogrify will use its technology to predict the most suitable factors. Astellas in turn will conduct experiments to see which combinations of factors work in preclinical testing. The goal is to drive the generation of new hair cells from healthy cells in the local environment.

In an interview Louise Modis, Mogrify's chief scientific officer, said the collaboration plays into the two companies' strengths. Mogrify has a proprietary algorithm that its founding scientists developed which can sift through vast amounts of data to identify promising transcription factor combinations. Astellas has years of pharmaceutical drug development experience and a growing presence in the cell and gene therapy field.

"They [Astellas] would like to replace hair cells. They and others have tried to do this before with small molecules and it hasn't worked out," she said. The two companies believe the factor approach will work and this is the basis of the collaboration.

Mogrify and Astellas have had time to get to know each other. Astellas' corporate venture arm, Astellas Venture Management, has been a strategic investor in Mogrify for more than a year, most recently participating in a Series A financing in May 2021 alongside Parkwalk Advisors. This relationship has been a key driver behind the partnership.

Writing in *Nature* in June 2021, Haofei Wang and colleagues say that direct cell reprogramming is having a significant impact on traditional views of cell identity and cell fate determination. Challenges remain, but these are offset by the number of cell types that can be generated by the new methods[1].

Direct cell reprogramming can be done using *ex vivo* or *in vivo* methods. The approach being taken by Mogrify and Astellas is *in vivo* because they want to replace cells that have been structurally integrated into an organ during early development. Cochlear hair cells are post-mitotic which means that they do not regenerate naturally, leading to permanent hearing loss when there is damage. "You simply can't deliver those cells that need to be structurally integrated…as an injection," Dr Modis said with reference to the *ex vivo* method. "For all sorts of technical reasons they won't survive the journey and when they get there they won't know what to do."

The *in vivo* approach

On the other hand, the *in vivo* approach, which stimulates the generation of hair cells locally is expected to provide a functional cure. "We are providing the factors to tell the neighbouring cells to please recreate their missing friends, please recreate the hair cells that would normally have been sitting right there," the executive said.

There are parallels between this approach and certain types of gene replacement therapy. There are no parallels with gene editing which is a completely different science. "We're creating a cell but we're not editing the genome," Dr Modis commented. Direct cell reprogramming is related to gene replacement therapy in the sense that gene replacement involves identifying a missing protein, returning that protein to the patient, and recovering the function of the cells where that protein was missing. The Mogrify technology is giving the cell back.

Hypothetically, a single person with a hearing loss identified at birth could be treated with a gene therapy with a view to correcting a congenital hearing loss. If that same person, tragically, also had sensorineural hearing loss he or she could also receive the Mogrify factors to stimulate the generation of hair cells locally from neighbouring cells.

"In that case you might want to give two therapies. But we're possibly decades down the line in terms of how this would play out medically," Dr Modis said.

Reference: 1. Haofei Wang et al, Direct cell reprogramming: approaches, mechanisms and progress, *Nature*, June 2021, Volume 22.

This article was prepared by the *MedNous* editor on the basis of an interview with Dr Louise Modis, CSO of Mogrify Ltd, and a literature search.