A reproducible and scalable Huntington's disease human cell model

Senior scientist Dr Tony Oosterveen discusses bit.bio's new ioDisease Model portfolio, including new models for Huntington's disease to help advance *in vitro* research and drug discovery.

What challenge is the industry facing with cell models, in your opinion?

During my scientific career, I have extensively studied how signalling molecules and transcription factors impose an identity on neurons during development of the central nervous system and applied this knowledge to generate different subtypes of dopaminergic neurons from induced pluripotent stem cells (iPSCs). As a senior scientist at bit.bio, I am now using this expertise to develop scalable and defined human neuronal cell models for drug discovery as well as to address fundamental questions in neuroscience.

The biopharma industry is limited by a lack of reliable, reproducible cell models that generate translatable and reflective data about actual human disease. Scientists currently use *in vitro* methods and animal models that often cannot sufficiently reproduce the actual disease. Human iPSC-derived neurons, however, offer scientists a relevant model system, though this can be hindered by low scalability, heterogeneous populations and long, complex conventional differentiation protocols. Furthermore, expressing transcription factors to reprogramme iPSCs has been problematic as the systems used are prone to silencing. Such challenges are hindering the discovery and development of better treatments targeting neurodegenerative disorders.

What is bit.bio's proposed solution to this challenge with its ioDisease Model cells, including the new ioGlutamatergic Neurons HTT$^{50CAG/WT}$?

Our solution is to provide iPSC-derived, precision reprogrammed glutamatergic neurons that have a disease mutation that reflects the actual disease genotype, which can be used as an i*n vitro* cellular disease model. This precision reprogramming provides the batch-to-batch consistency that scientists require. To achieve this, we used CRISPR-Cas9 gene editing to introduce an abnormal expansion of 50 CAG repeats into the first exon of the Huntingtin gene within bit.bio's wild type ioGlutamatergic Neurons to generate ioGlutamatergic Neurons HTT$^{50CAG/WT}$. These highly characterised human iPSC-derived glutamatergic neurons accurately represent the disease genotype *in vitro*. When precision reprogrammed using our proprietary opti-ox^{TM} platform, the engineered cells rapidly mature into functional excitatory neurons that consistently form complex neuronal structures and express typical biomarkers in as little as 11 days.


Dr Tony Oosterveen
Senior Scientist and CNS Lead, bit.bio

With this system, we can consistently produce cells at high purity, in a truly scalable manner. Now a high-throughput assay can be confidently repeated months apart and yield a very similar result.

How do you precision reprogramme cells to a particular cell type?

At bit.bio, we have developed a technology to express transcription factors in a robust manner, enabling accurate control of iPSC differentiation. The opti-ox system provides a next-generation precision reprogramming approach.

The benefits of opti-ox reprogramming are:

1. opti-ox is an inducible system that precisely controls transcription factors to efficiently reprogramme cells to a specific cell type – at a scale of billions of cells
2. opti-ox uses two distinct 'genomic safe harbours', which helps to prevent gene silencing, common with other iPSC reprogramming methods. The inserted transcription factors are protected from the spreading of heterochromatin, ie, gene silencing. The result is safe, robust expression of the transcription factors, enabling the precise reprogramming of entire cultures of iPSCs into any specific cell type on an industrial scale.

As opti-ox is an inducible gene expression system, we can amplify iPSCs to billions of cells, then switch on opti-ox and express a unique combination of transcription factors for a set time and within days, the cells convert into the cell type of interest.

What impact do you think ioDisease Model cells will have on drug discovery and development?

Our ioGlutamatergic Neurons HTT$^{50CAG/WT}$ ioDisease Model can be coupled with the isogenic wild type ioGlutamatergic Neurons as a negative control allowing scientists to compare how the cells behave in a healthy versus diseased state. Together this information improves understanding of the disease state facilitating greater insight into the efficacy of new potential therapeutics.

Ultimately, we hope our ioDisease Model cells will help provide more effective therapies for neurodegenerative diseases such as Huntington's disease. I believe that it is crucial to use the right human model to successfully translate research into the clinic and help patients – which is exciting!

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For further information, visit:
www.bit.bio

ioGlutamatergic Neurons

HTT·50CAG/WT

Next-generation disease model to study Huntington's disease

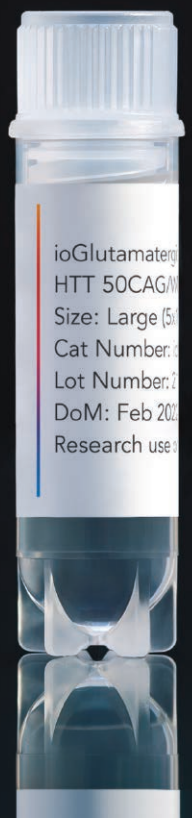
Get data fast
Human iPSC-derived excitatory neurons mature in as little as 11 days.

Do more with every vial
Industry-leading seeding densities save you money in every experiment.

Stop battling variance
opti-ox™ driven cellular reprogramming ensures consistency between every batch of cells.

Make true comparisons
Be confident in your data by pairing the disease model with our genetically matched control.

Learn more at www.bit.bio



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