Speeding up neuroscience research

Generating publishable data in 12 weeks

bit.bio case study
Deepak Srivastava, PhD,
Professor of Molecular Neuroscience,
King's College London

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It took Professor Deepak Srivastava's lab at King's College London just 12 weeks to generate publishable data on schizophrenia risk factors. This dramatically short research timeline was driven by the lab's push to maximise the value of their students' time at the bench and was achieved by adopting precision reprogrammed human iPSC-derived glutamatergic neurons in their experiments.

In this case study, you will learn about Professor Srivastava's research, find out how his lab use the latest stem cell-derived tools to unpick the complex biology of neurological disorders and how the use of opti-ox™ powered human iPSC-derived cells has enabled his lab to optimise their time at the bench.

In the lab of Deepak Srivastava, professor of molecular neuroscience at King's College London and leader of the MRC Centre for Neurological Disorders, you will find scientists conducting cutting-edge research to interrogate the underlying biology of the synapse, with a focus on how molecular mechanisms impact cognitive function. Ultimately, his research aims to uncover opportunities to better treat psychiatric conditions, many of which have a considerable unmet therapeutic need.

"In the brain, communication between neurons occurs at the synapse. When this chemical interface misbehaves, it can manifest as psychiatric conditions like schizophrenia" says Deepak Srivastava. "To understand synaptic biology, we take a reductionist approach to asking questions. We use the latest induced pluripotent stem cell technologies to create a simplified model of the human brain that contains the fundamental cell types that we're interested in" explains Professor Srivastava. "This allows us to ask very specific and detailed questions about the functions of genes or different compounds in a laboratory setting".

By using neurons derived from human induced pluripotent stem cells (hiPSCs), Professor Srivastava's research group gains a window into the nanoscopic biology governing neuronal function without having to rely on animal models.

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In a recent publication, Professor Srivastava's lab utilised hiPSC-derived excitatory neurons to model how exposure to elevated levels of a specific pro-inflammatory cytokine during pregnancy may impact an individual's propensity to develop schizophrenia during their lifetime[1,2].

Scientists have previously observed that people have an increased likelihood of developing psychiatric disorders such as schizophrenia if their mother experiences severe infections during pregnancy. Further evidence from animal models shows that increased levels of cytokines released by the mother's immune system can impact the foetus' neurodevelopment[3,4,5,6]. Utilising hiPSCs-derived neurons, Professor Srivastava sought an answer to whether similar molecular and mechanical changes to the synapse also occur in humans when exposed to cytokines during development.

Following cytokine exposure, immature hiPSC-derived glutamatergic neurons from bit.bio showed significant changes in the expression of several protein pathways associated with synaptic activity. These results aligned with changes previously observed in tissues from patients with schizophrenia and animal models of the disorder. Professor Srivastava published these results under peer review in 2022 in Frontiers in Psychiatry, laying the groundwork for further research into the link between cytokine exposure and schizophrenia[1].

"Our field needs a better understanding of how to use animal and cellular models together more effectively to drive translational research forward, ultimately to the benefit of patients," explained Professor Srivastava. But using hiPSC-derived cells has always been a challenge for the field. When using the best available directed differentiation protocols in the literature, it can still take over 100 days to generate neurons that show a mature synaptic activity. It's also hard to ensure consistency across batches of cells using these methods, so the pathway to reliable, publishable data using these models is long and challenging.

"What I think is really remarkable is that this study, including the stem cell work and follow-up experimentation, was completed by a student in my lab who joined us on a 12-week rotation." continues Professor Srivastava. "They could do this so quickly because our lab had access to a new technology to generate human excitatory neurons from bit.bio using transcription factor reprogramming. We found that bit.bio's hiPSC-derived neurons displayed mature synchronous electrophysiological activity in 28 days, four times faster than was possible before."

"Transcription factor-mediated reprogramming basically tricks the iPS cells to jump straight to a neuron. All we need to do is to add doxycycline for a few days in order to generate glutamatergic neurons that we can start working on" Professor Srivastava remarks.

What is Schizophrenia?

Schizophrenia includes symptoms such as hallucinations, delusional and disorganised thinking, and social withdrawal. Worldwide, 0.32% of the population – over 24 million people – have the condition. It often begins in early adulthood, and although symptoms can improve over a person's lifetime, many people never wholly recover.

Schizophrenia is hallmarked by increased dopamine release between neurons, leading to hallucinogenic symptoms. There is also increasing evidence that dysfunction of synapses, particularly on glutamatergic neurons, may also contribute to the disorder. The underlying cause of the dopamine imbalance or synaptic dysfunction varies between patients and involves both genetic and environmental factors, as well as their molecular and cellular-level knock-on effects.

Schizophrenia is a disorder with a clear unmet therapeutic need. No clear diagnostic test exists on the market, and treatment relies on antipsychotic drugs that only address specific symptoms[7].

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bit.bio case study Professor Deepak Srivastava, King's. December 2023

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“I think it’s always good to have a bit of healthy scepticism about new technologies and what they can achieve” continues Professor Srivastava. “We asked ourselves: ‘Do all of the cells in the culture consistently become neurons without contamination from glial cells?’ During several in-depth cell characterisation studies, we learned that – yes, they really do. bit.bio’s cells worked for us no matter whose hands they were in. You don’t even need previous experience with stem cells to make them work. They did what they said they would ‘on the tin’ every time.”

“My student, the lead author in the study, had no opportunities for face-to-face training during his 12-week project, which took place under pandemic conditions,” Professor Srivastava recalls. “Within this tight timeframe, he generated a series of data that formed a critical backbone for his publication. Based on our experience, I’d say that the three main advantages of bit.bio’s cells for our research are speed, reproducibility, and ease of use. Now, we want students to keep using these cells, as they can really maximise the value of their time at the bench.”

bit.bio would like to thank Professor Srivastava for the detailed discussions about his work and his collaboration in writing this case study.

Read Professor Srivastava’s recent publication on the effects of cytokines at the synapse during human development

Read about Professor Srivastava’s research and the initiatives he is involved in to improve our understanding of human neurological disorders

ioGlutamatergic Neurons™ by bit.bio

ioGlutamatergic Neurons are human excitatory neurons precision reprogrammed from human iPSCs with opti-ox (optimised inducible overexpression)[8].

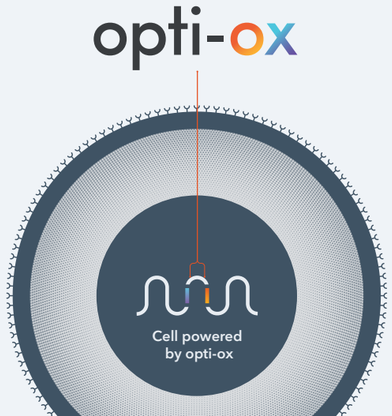
opti-ox precision cell reprogramming enables any human cell to be manufactured consistently at scale through the faithful expression of transcription factors in iPSCs.

Cell-fate-defining transcription factors controlled by an inducible genetic switch are integrated into two genomic safe harbour sites (GSHs) in the stem cell genome. GSHs protect the integrity of the cell and the expression of the inserted transcription factors by avoiding gene silencing.

As every iPSC in the population contains the same inducible program in their GSHs, entire iPSC populations can be precisely, consistently and rapidly converted into glutamatergic neurons at scale.

With access to a consistent, defined source of human iPSC-derived glutamatergic neurons, researchers like those in Professor Srivastava’s lab have to spend significantly fewer resources optimising their cell culture and iPSC differentiation. Instead, they are able to shift focus to the rapid generation of high-impact data, helping them get to publication faster.

Explore ioGlutamatergic Neurons



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Who we are

bit.bio combines the concepts of cell programming and biology to provide human cells for research, drug discovery and cell therapy, enabling a new generation of medicines.

This is possible with our precision human cellular reprogramming technology opti-ox – a gene engineering approach that enables unlimited batches of any human cell to be manufactured consistently at scale.

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