Improving physiological relevance in neurological disease drug development

How Concept Life Sciences is building more reliable, consistent *in vitro* assays using ioMicroglia

bit.bio case study
Elise Malavasi, Ph.D,
Principal Scientist,
Concept Life Sciences

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Overview

Elise Malavasi, Ph.D., is a Principal Scientist at Concept Life Sciences, a leading contract research organisation, where she specialises in the development and use of *in vitro* assays for neurobiological research. Of particular interest to Elise is the development of functional assays for microglia, a cell type that is increasingly viewed as a therapeutic target in neurodegenerative disease. To support drug development, these assays would need to be amenable to long-term use, meaning it is crucial that the cells used show lot-to-lot consistency.

Such consistency has been challenging to develop with primary cell lines, and from human induced pluripotent stem cell (hiPSC) derived cells generated using directed differentiation. Therefore, Elise and her colleagues have partnered with bit.bio to test the utility of ioMicroglia* in their functional assays. They've found bit.bio's cells to be highly functional and, critically, to have lot-to-lot consistency. Elise's team is now exploring the use of ioMicroglia in more complex model systems. This work opens the door for Concept Life Sciences to offer more human-relevant models to their clients and better support CNS-targeted drug development.

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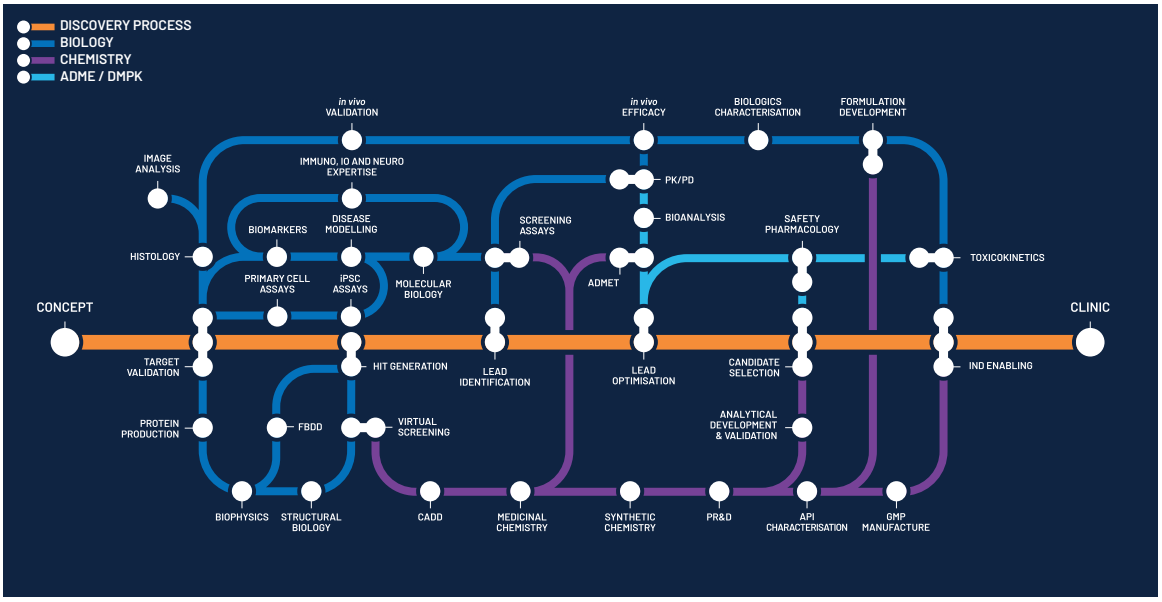
The need for a predictable, physiologically relevant human microglia in neuroscience drug development

"Given the attrition rates in neuroscience drug development, advances in the quality and reliability of human induced pluripotent stem cells could be transformative for the pharmaceutical industry," explains Elise Malavasi, Ph.D., an expert in the development of *in vitro* assays for applications in neurobiological research. Elise serves as Principal Scientist in the neuroscience division at Concept Life Sciences—a leading contract research organisation serving the pharmaceutical, biotech and agrochemical industries—where she is acutely aware of the industry's need for better preclinical models and the promise of human induced pluripotent stem cell (hiPSC)-derived cells.

Approximately 97% of CNS-targeted drug candidates entering phase 1 clinical trials will never make it to market[1], with some disease-specific therapeutics nearing 100% failure[2]. Such a low success rate is due, in part, to the low predictive validity of preclinical models, many of which rely on non-human or immortalised cell lines—models which often fail to recreate key genetic and physiological features of human disease[3]. "Having a human model system that behaves predictably is crucial," emphasises Elise.

"ioMicroglia from bit.bio offered a solution by providing consistent and reproducible human iPSC-derived microglial cells"



Stages of the drug discovery pipleine supported by Concept Life Sciences.

Image courtesy of Concept Life Sciences.

However, building human models of the CNS is a difficult task, not least of all because primary human neurons and glial cells are in short supply. As a result, the scale and clinical relevance of compound screening is greatly limited. Researchers like Elise are looking to change this through the use of hiPSC-derived cells.

"For neuroscientists in particular," she explains, "hiPSC-derived cells are interesting because they give you access to human cell types and disease-relevant phenotypes that have previously been hard to come by."

Elise's team recently set out to develop assays that can be used to assess a drug candidate's effect on human microglia. These brain resident immune cells are increasingly recognised as having a role in neurodegeneration and have become common targets in drug development pipelines. Therefore, many of Concept Life Sciences' clients are likely to need reliable and scalable models that use human microglial cell lines.

"We use microglia in our assays to understand the effects of compounds on microglial functions, ranging from inflammatory cytokine response following activation, to other functional responses like phagocytosis and migration," explains Elise. While efficient derivation of microglia-like cells from human pluripotent stem cells is possible, current protocols lack the scale and robustness that's needed for drug development applications. "ioMicroglia from bit.bio offered a solution by providing consistent human iPSC-derived microglial cells," says Elise.

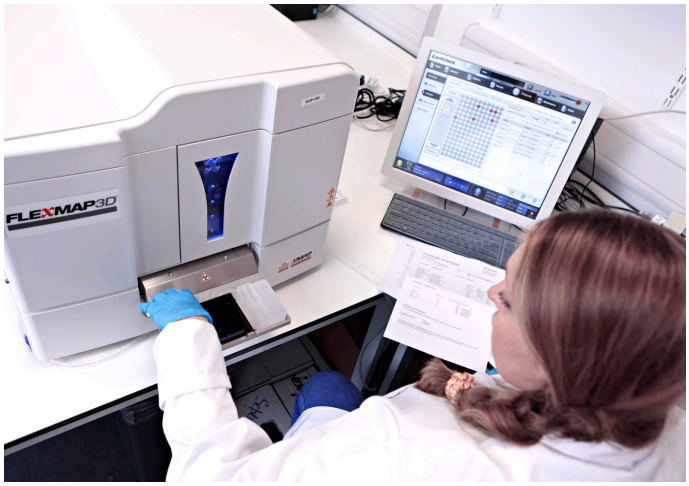
"A key advantage of ioMicroglia for us is the low inter-lot variability, which ensures consistent assay performance and facilitates long-term, and large-scale screening studies."

Accessing consistent human iPSC-derived microglia at scale

ioMicroglia are defined human microglial cells generated from iPSCs using bit.bio's opti-ox* precision cell reprogramming technology. Opti-ox is a gene engineering approach that uses dual genome-safe harbour targeting to achieve precise control over cell-fate-defining transcription factor expression while protecting the integrity of the cell and avoiding gene silencing. As every iPSC in the population is powered by opti-ox, entire iPSC populations can be consistently converted into functional microglia at scale.

"One of our recent aims has been the optimisation of microglial phagocytosis assays, and we have successfully used ioMicroglia to test the effect of different pro- and anti-inflammatory stimuli on the cells' phagocytic activity," says Elise. "A key advantage of ioMicroglia for us is the low inter-lot variability, which ensures consistent assay performance and facilitates long-term, and large-scale screening studies. Consequently, we can now screen multiple compounds over extended periods and be confident in the reliability and reproducibility of our findings."

With a consistent and scalable source of functional human microglia, Concept Life Sciences now has the potential to build more complex, human-relevant models for its clients. "We're excited about the possibility of collaborating with bit.bio on this further to explore other assays, including microglia cytokine release and microglia activation assays," explains Elise.



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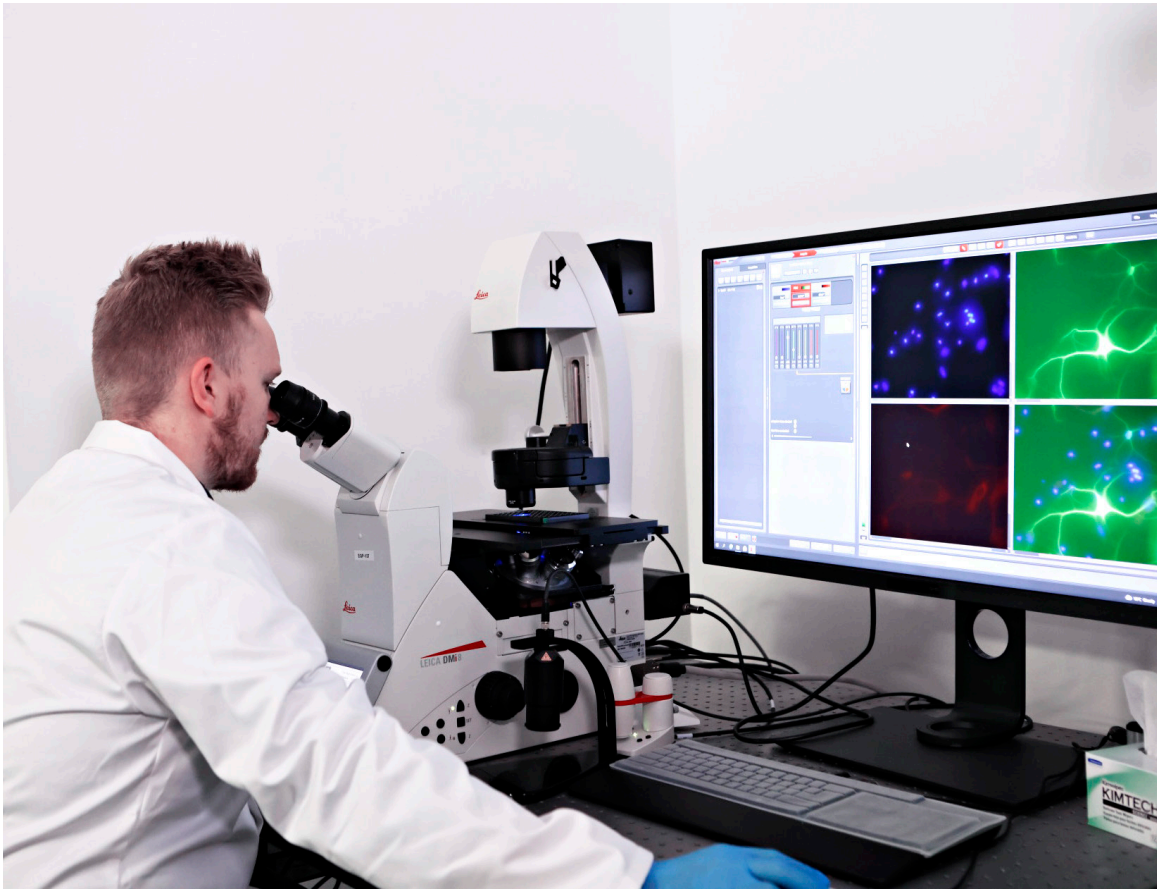
Ensuring the human element in assay development

Integrating human iPSC-derived microglia into Concept Life Sciences' workflows initially presented some challenges, explains Elise, "Using hiPSC-derived microglia was a relatively new area for us. Handling and treatment of the cells differed from our experience with other cell types we've used." However, the collaboration with bit.bio included support from a team of technical experts who provided hands-on guidance to the CRO's scientists.

"A big positive in our experience with ioMicroglia and bit.bio was the level of aftercare that we've been provided," says Elise. "We welcomed bit.bio's field application specialist and research scientist on-site to help our team gain confidence with handling the cells."

By leveraging bit.bio's expertise, Elise and the Concept Life Sciences team have gained the ability to integrate human microglia into their models and better support their clients' efforts in evaluating the therapeutic potential of microglia-targeted compounds.

Looking ahead, Elise's team is focused on expanding the application of human iPSC-derived microglia. "We want to begin to leverage the potential of these cells, not only in simple assays, but in more complex models as well," states Elise. "Bringing in defined cells such as ioMicroglia to help ensure our assays are reliable, perform consistently, and as expected, is crucial in enabling us to provide a comprehensive suite of drug development services."



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About bit.bio

bit.bio is a synthetic biology company focused on human cells, advancing medicine and enabling curative treatments. The company does this by industrialising the manufacture of human cells and making them more accessible.

bit.bio's opti-ox precision cell programming technology enables conversion of induced pluripotent stem cells into any desired human cell type in a single step, at industrial scale, while maintaining exceptional purity and consistency.

The company has a cell therapy pipeline, based on txCells, focused on serious diseases that lack effective treatments. The ioCells research cell product portfolio is opening up new possibilities in research and drug discovery.

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About Concept Life Sciences

Concept Life Sciences are a multi-disciplinary Contract Research Organisation based in the UK, providing market-leading scientific services globally. Over the past 25 years, Concept Life Sciences and its heritage companies have played a pivotal role in guiding numerous clients along their path to clinical success and many of these clients have evolved into enduring scientific collaborators. Our services are built on scientist-to-scientist communication, deep knowledge, flexibility and extensive in-house resources. Whether it is delivering whole programmes of research, or bespoke studies we deliver a collaborative client-centred approach. We are based across 4 research sites in the UK delivering discovery research as well as GMP, GLP and GCP-regulated work. Our services include discovery chemistry, specialist translational biology, biophysics, ADMET & DMPK, bioanalysis, toxicology, histology, process research and development and GMP manufacturing.

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