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Building complexity into neuroscience and ocular research: modeling disease with co-culture of iPSC-derived cells

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Introduction

Neurodegenerative and retinal diseases are increasingly recognized as disorders driven by interactions between neurons, glial cells, and immune populations. Growing evidence suggests neuroinflammation is a key contributor to disease progression across diverse disorders including amyotrophic lateral sclerosis (ALS), Parkinson's, Huntington's and Alzheimer's disease, and age-related macular degeneration (dry-AMD).

Microglia, the resident immune cells of the central nervous system and retina, regulate tissue homeostasis, inflammatory signaling, and response to injury, and are thought to play a key role in disease progression. Human induced pluripotent stem cells (iPSCs) can be used to produce microglia with defined genetic or patient backgrounds facilitating the use of iPSC-derived co-culture systems to investigate interactions between microglia and neighboring cell types, including neurons, astrocytes, or retinal cells. These models provide valuable insights into cell-cell interactions in the maintenance of healthy tissues, and disease pathology-associated cellular crosstalk that are not apparent in monoculture systems.

This whitepaper explores the role of microglia in central nervous system (CNS) and retinal disease, examines the opportunities and practical challenges associated with developing complex co-culture models, and discusses how advances in human iPSC technology are supporting the adoption of New Approach Methodologies (NAMs) in preclinical research. ALS and AMD co-culture models highlight how building complexity into cell-based *in vitro* models can reveal disease-relevant phenotypes whilst maintaining reproducibility and support the development of more predictive tools for translational research.

To facilitate co-culture model adoption, Axol Bioscience provides human iPSC-derived microglia, neurons (cortical, striatal and motor), astrocytes, and retinal cells (RPE) along with optimized culture media and detailed co-culture protocols to derisk generation of translationally-relevant data for preclinical drug discovery research. Together, these characterized cell types provide the foundation for constructing robust co-culture systems that enable investigation of disease-relevant interactions between neurons, glia, and retinal cells. These platforms support mechanistic studies, target validation, toxicity assessment, and phenotypic drug screening while providing a physiologically relevant framework for translational research.

The role of microglia and astrocytes in neuroinflammation

The nervous system depends on coordinated communication between multiple cell types. Neurons rely on astrocytes for metabolic support, microglia for immune surveillance and synaptic regulation, oligodendrocytes for myelination, and vascular cells for nutrient delivery. Consequently, many physiological and pathological processes emerge from interactions between cellular populations rather than from the behavior of a single cell type^{5,6}.

Microglia are key regulators of CNS and retinal health. Microglia are resident immune cells, providing immune surveillance, debris clearance, and supporting tissue homeostasis. They are essential for maintaining neural function and dynamically respond to their environment. During disease progression, they can adopt reactive states characterized by inflammatory signaling, oxidative stress and complement activation, contributing to chronic neuroinflammation, neuronal dysfunction, and degeneration^{1,2,10,11}.

Astrocytes, another sub-type of glial cell type resident in the brain, have roles in synaptic regulation, neurotransmitter homeostasis, metabolic support, and maintenance of the blood-brain barrier^{9,23}. Astrocytes also undergo disease-associated changes and interact closely with microglia, amplifying or modulating inflammatory responses within the nervous system^{23,24}.

Modeling disease mechanisms by recreating the reactive states of microglia and astrocytes can be achieved through inflammatory stimulation, exposure to conditioned media, or co-culture with neurons and other glial cell types. Here we focus on co-culture models to facilitate the investigation of cellular crosstalk, inflammatory signaling pathways, and neuronal network activity under controlled, disease-relevant conditions^{6,7}.

Developing physiologically relevant human co-culture systems

Practical considerations in establishing complex co-culture systems

As co-culture systems become increasingly sophisticated, researchers must balance biological complexity with experimental robustness. Different cell types have distinct maturation timelines, metabolic requirements, and environmental preferences. Establishing culture conditions that support multiple populations simultaneously requires careful optimization and characterization^{5,6}.

Microglia present a unique challenge because their phenotype is highly dependent on environmental cues and interactions with neighboring cells^{5,6}. Additional considerations arise when using patient-derived iPSC models to recapitulate disease-associated phenotypes arising from both genetic and sporadic forms of disease^{25,26}.

For example, ALS patient-derived microglia carrying C9orf72 mutations display altered inflammatory signaling and phagocytic activity compared with unaffected donor controls. Other considerations include donor-to-donor variation, reproducibility across experimental batches, standardizing analytical approaches, and the integration of functional readouts from multiple cell types^{25,26}.

Key considerations for successful co-culture model generation

- Quality, viability and density of individual cell types
- Controlling activation of cells through handling
- Media composition, including cytokines and growth factor requirements that change in co-culture when compared to monoculture models
- Maturation process and timing of cell addition
- Analytical readouts and ensuring sufficient power in the experiment

Characterizing human iPSC-derived microglia for inclusion in co-culture models

For robust disease modeling, iPSC-derived microglia should recapitulate both homeostatic and disease-associated phenotypes. axoCells™ iPSC-derived microglia display the expected elongated and ramified morphology characteristic of resting human microglia (figure 1A). After thawing, cells mature over seven days and express canonical microglial markers, including IBA1, TMEM119, CX3CR1, and P2RY12. This marker profile is consistent with a homeostatic microglial identity (figure 1B).

Functionally, these iPSC-derived microglia cells model core aspects of human microglial immune activity.

- Readily internalize pHrodo-labelled substrates over a 24-hour period, a process that is abolished by cytochalasin D, confirming actin-dependent phagocytosis (figure 1C).

- Chemotactic responsiveness is demonstrated through C5a-directed migration assays, where microglia show dose-dependent movement toward chemotactic gradients (figure 1D).
- Inflammatory profiling following stimulation with LPS, IFN- γ , or both reveals cytokine release patterns (figure 1E) aligned with established microglial activation responses, providing a robust system to study neuroinflammation and immune-retinal interactions.

The use of these iPSC-derived microglia for development of reproducible co-culture models of neurodegenerative and retinal disease that reveal new insights into disease pathology are described below.

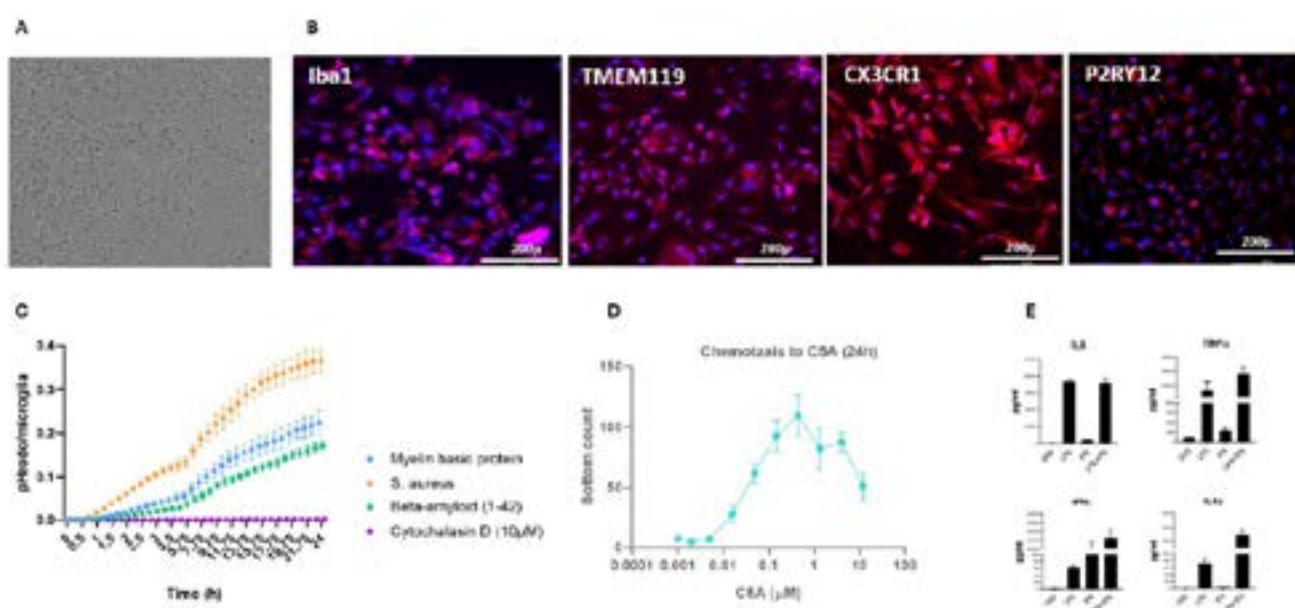


Figure 1. (A) iPSC-derived microglia show resting, ramified morphology. (B) Cells mature over seven days and express IBA1, TMEM119, CX3CR1, and P2RY12. (C) pHrodo substrate uptake is actin-dependent, as blocked by cytochalasin D. (D) C5a induces dose-dependent chemotaxis. (E) LPS and IFN- γ stimulation elicits expected cytokine release, demonstrating utility for modeling microglial immune activity.

1. Co-culture models of neurodegenerative disease

Neurodegenerative diseases remain among the most challenging therapeutic areas in biomedical research. Recent advances have highlighted that dysregulated microglial and astrocyte responses contribute to the pathogenesis of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, ALS, and Huntington's disease. Historically, preclinical research has focused largely on preventing neuronal loss or restoring neuronal function. However, it is becoming clear that neuronal degeneration cannot be fully understood without considering cell-cell interactions and the cellular environment^{1, 8}.

Activated microglia and altered immune signaling have been reported in the pathology of Parkinson's disease, Huntington's disease, frontotemporal dementia, and Alzheimer's disease, suggesting that neuroinflammation is a common feature of neurodegeneration, leading to new promising therapeutic avenues^{1, 2, 21, 22}.

ALS: a case study in complex disease biology involving multiple cell types

Although motor neuron degeneration remains the defining pathological feature of ALS, substantial evidence demonstrates that disease progression is influenced by neighboring glial and immune cell populations. Astrocytes and microglia contribute to inflammatory signaling, neuronal stress responses, and changes in the local microenvironment that affect motor neuron function and survival^{13, 14}.

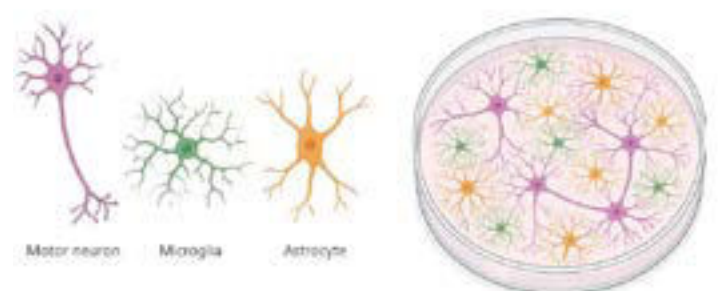
iPSC technologies have enabled researchers to study these interactions directly in patient-derived cells. Motor neurons carrying ALS-associated mutations, including C9orf72, SOD1, and TDP-43, exhibit disease-relevant phenotypes such as altered morphology,

hyperexcitability, impaired network dynamics, and pathological protein handling^{13, 15}. Importantly, these phenotypes can be modified by the presence of astrocytes and microglia. Studies using human co-culture systems have shown that glial cells influence neuronal firing behavior, synchronization of motor neuron networks, inflammatory signaling pathways, and responses to stress^{15, 16}.

Developing tri-culture systems for modeling ALS

Modeling ALS with iPSC-derived motor neurons, microglia and astrocytes

Axol Bioscience generated iPSC-derived motor neurons from donors carrying C9orf72 expansion, TDP-43 A382T, and SOD1 D109Y mutations, alongside unaffected controls, and characterized their morphology, neuronal activity, and disease-associated phenotypes (figures 2-5). Using live-cell calcium imaging, immunocytochemistry, and TDP-43 analysis, the study demonstrated that ALS motor neurons exhibit distinct morphology, firing frequency, and network synchronization compared with healthy controls. Incorporation of astrocytes and microglia in a human tri-culture model altered motor neuron burst activity and synchronization, highlighting the significant influence of neuroimmune interactions on neuronal function.



Representation of a motor neuron-microglia-astrocyte tri-culture model

Distinct patterns of activity in monoculture are observed in iPSC-derived motor neurons from patients with ALS or unaffected donors

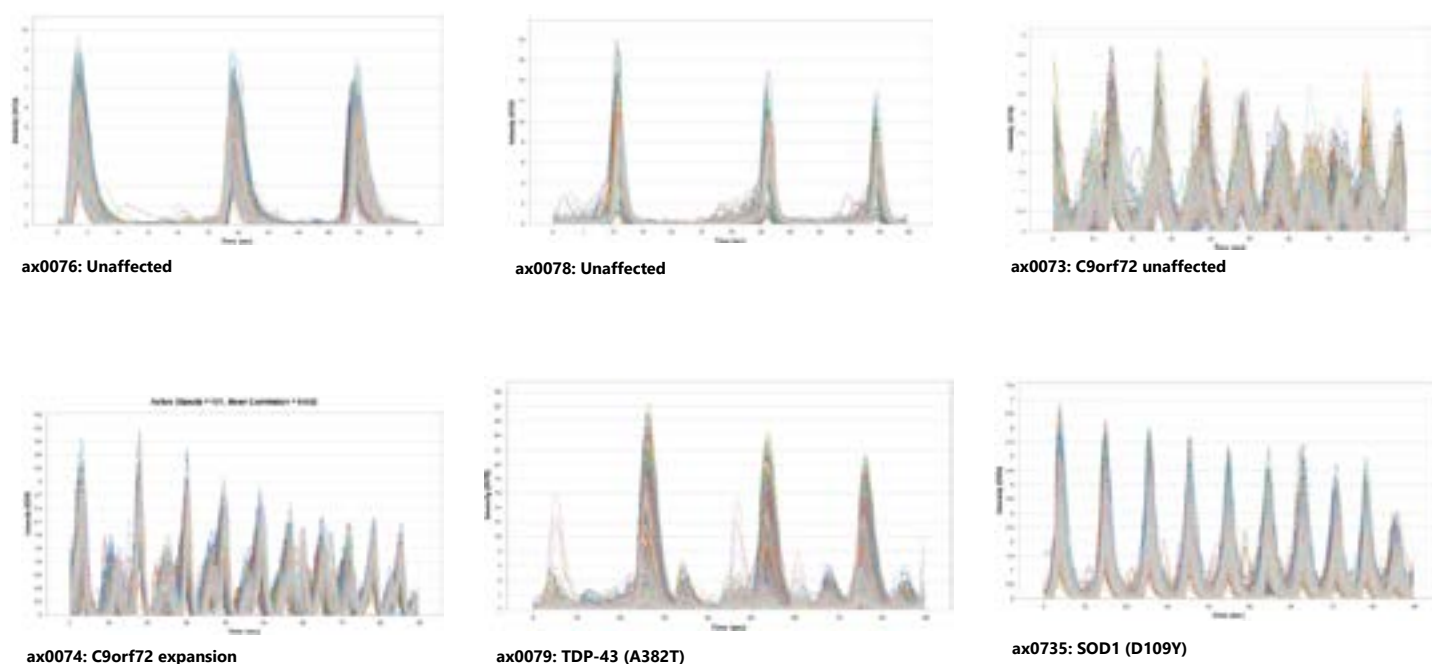


Figure 2. The unaffected donor cells exhibited highly synchronized firing, characterized by a higher mean burst duration and a lower burst rate. In contrast, the C9orf72 affected donor cells displayed a hyperexcitable phenotype, showing less synchronized firing. Notably, all affected donor cells (C9orf72, SOD1, TDP-43) demonstrated an increased burst rate, indicating an increase in neuronal excitability typical of hyperexcitability. The C9orf72 and TDP-43 donor cells also displayed less synchronized firing

Morphology of iPSC-derived motor neurons from affected donors differs from donors unaffected by ALS (monoculture)

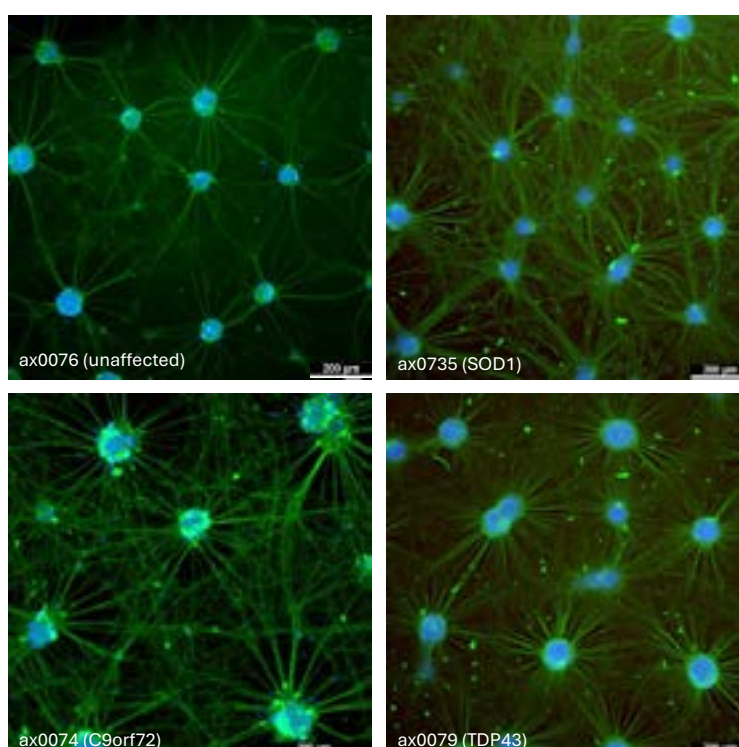


Figure 3. Following ICC imaging, day 21 motor neurons demonstrated expression of the neuronal marker SMI-32 (green), with nuclei stained with DAPI (blue), and exhibited characteristic neuronal morphology, with observable differences between cell lines that may contribute to neuronal dysfunction.

Microglia and astrocytes at 21 days under tri-culture conditions

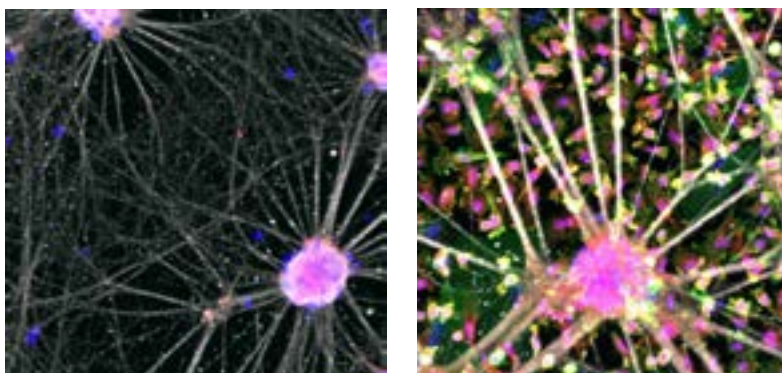


Figure 4. Confocal images of control motor neurons cultured in monoculture (left) or in tri-culture with isogenic microglia and astrocytes (right). Images were acquired at day 21 of motor neuron culture (microglia and astrocytes were introduced after cultures were established and were under co-culture conditions for ~11 days). Green = CD44, Red = IBA1, Blue = Hoechst 33342, White = β III-tubulin.

Timing of addition of microglia and astrocytes alters the burst activity of motor neurons in tri-culture

Co-culture of motor neurons from an unaffected donor with isogenic astrocytes and microglia increases burst strength of spontaneously firing motor neurons. Earlier addition induces earlier increases in burst amplitude (figure 5).

During the process of establishing an optimized co-culture, different timepoints of addition for the microglia and astrocytes and different cell densities were tested. Late addition of glial cells did not alter

neuronal firing substantially when compared to motor neurons in monoculture, regardless of the number of microglia and astrocytes added. Addition of glial cells at earlier timepoints during neuronal maturation led to an increase in neuronal burst strength with highly synchronized firing networks. This effect was observed across a range of cell densities (figure 5).

The ability of microglia and astrocytes to alter motor neuron activity demonstrates how co-culture systems can reveal phenotypes not observed in neuronal monocultures that can be used for more physiological disease modeling and evaluation of novel therapeutics.

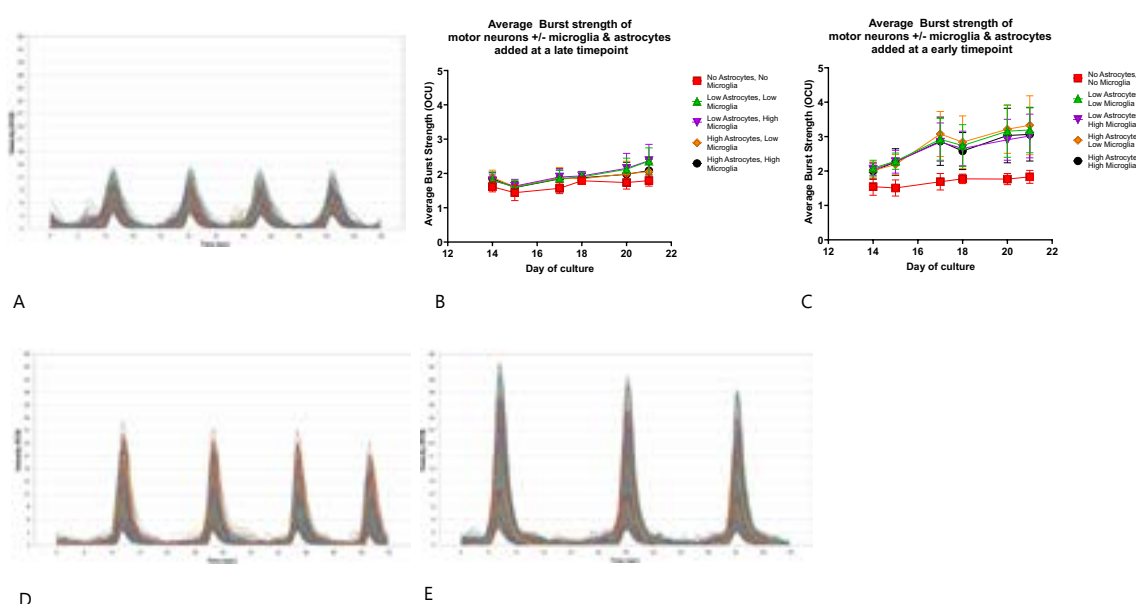


Figure 5. Spontaneous neuronal activity measured on an IncuCyte S3 to assess motor neuron firing and synchronicity in monoculture and with the addition of microglia and astrocytes at different densities and timepoints. (A) Motor neuron monoculture on day 21 without accelerator supplement, (B) motor neurons with astrocytes and microglia added late, day 21, $n=3$, (C) motor neurons with astrocytes and microglia added early, day 21, $n=3$, (D) Glia added late, (E) Glia added early.

2. Co-culture in retinal disease translational research

Although neurological and retinal disorders have traditionally been studied separately, the retina is a developmental extension of the CNS and contains specialized neuronal and glial populations organized into highly interconnected cellular networks^{3,4}. These neuronal and glial cell populations, including microglia, share many of the biological processes observed in the brain, including immune surveillance, inflammatory signaling, oxidative stress, and complement activation^{3,4,17}.

Many of these mechanisms are implicated in both neurodegenerative and retinal diseases, highlighting important biological links between the two fields^{17,18}. Retinal changes are also increasingly being investigated as potential biomarkers of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia, and multiple sclerosis²⁷. Interestingly, human retinal models are being used to investigate mechanisms of both retinal and neurodegenerative disease, with human iPSC-derived retinal organoids shown to recapitulate key Alzheimer's disease-associated pathologies, including amyloid- β accumulation and phosphorylated tau, providing a platform for disease modeling and therapeutic discovery²⁸.

Research into treatments for retinal diseases has historically focused on preventing the loss, dysfunction, and atrophy of photoreceptors, retinal pigment epithelial cells (RPE), and retinal ganglion cells. However, increasing evidence has highlighted the crucial role of microglia and inflammation in disease progression, such as in AMD, as well as the role of astrocytes and retinal ganglion cells in the progression of glaucoma^{3,4,17,18}.

Age-related macular degeneration is a leading cause of irreversible vision loss worldwide. Although therapies are available for neovascular AMD, treatment options remain limited for the more common dry form of the disease¹⁷. The generation of co-culture models for preclinical drug discovery to better recapitulate disease phenotypes is an important step forward to support translational studies and identification of new drug targets.

The role of microglia in dry-AMD progression

A growing body of evidence supports a role for chronic inflammation in AMD pathogenesis. Under non-pathological conditions, microglia normally reside in the inner retina. During AMD progression, as in many other retinal degenerative diseases, retinal microglia migrate and accumulate in the subretinal space, between the RPE and photoreceptor cells. However, the role of microglia in AMD progression is not yet fully understood. While they may initially have a beneficial role by clearing cellular debris that accumulates in the subretinal space, their continuous presence may contribute to establishment of chronic inflammation and drive disease progression^{17,18}.

Importantly, microglia also interact with the complement system, a pathway that has been studied extensively in the context of AMD. Complement activation can modulate microglial recruitment and activation, while activated microglia can contribute to complement-mediated inflammatory responses, potentially creating a positive feedback loop that exacerbates retinal damage¹⁷⁻¹⁹.

Retinal co-culture systems

Development of a human iPSC-derived retinal co-culture system for dry-AMD

To study the role of inflammation in RPE atrophy during AMD progression *in vitro*, Axol Bioscience has developed an RPE-microglia co-culture model. After identifying culture conditions that enabled the prolonged co-culture of these two cell types, AMD-relevant stressors were introduced into the system. A key finding from this human iPSC-derived model was that A2E, a lipofuscin component associated with AMD, induced little microglial activation in monoculture but triggered microglial proliferation and elevated secretion of inflammatory cytokines, including IL-1 β , TNF- α , IL-6, and IL-10, when microglia were co-cultured with RPE cells.

In the presence of microglia, RPE cells also showed greater sensitivity to A2E- and blue light-induced stress, highlighting the importance of cell-cell interactions in shaping inflammatory responses.

To extend this work and provide a more physiologically relevant *in vitro* model of the outer retina, Axol Bioscience is developing a tri-culture system comprising iPSC-derived RPE cells, photoreceptors, and microglia. This will enable investigation of how chronic stress affects communication between these three cell types, and how these interactions contribute to inflammation and ultimately retinal degeneration, providing a more representative system for evaluating potential therapeutic strategies targeting the complex cellular mechanisms underlying AMD.



Representation of an RPE-microglia co-culture model

Characterization of iPSC-derived RPE cells

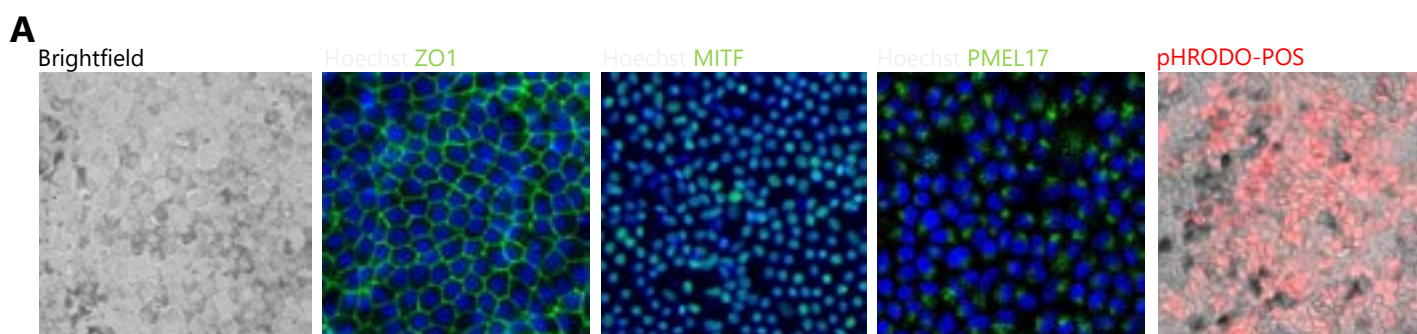


Figure 6. iPSC-derived RPE cells exhibit typical pigmentation and cobblestone morphology. They express key RPE markers, including ZO1, MITF, and PMEL17. They are also capable of phagocytosing pHrodo-conjugated bovine photoreceptor outer segments (POS).

Establishment of an RPE-microglia co-culture system

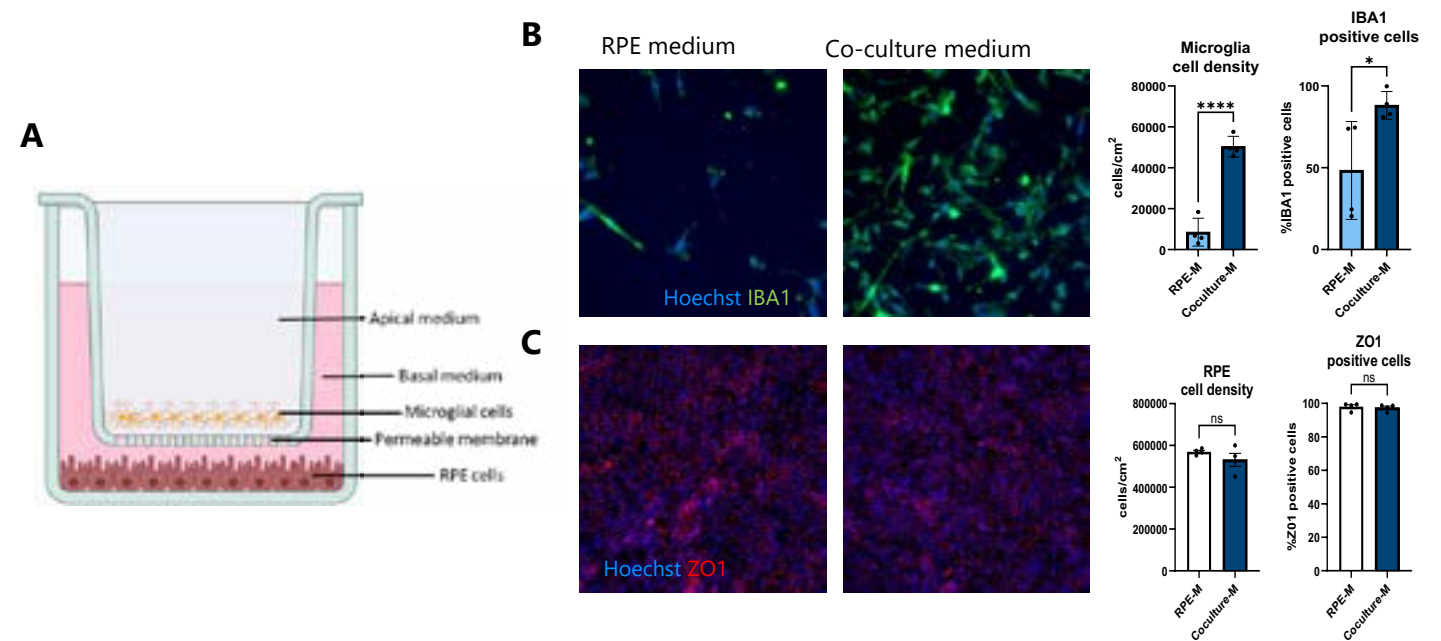


Figure 7. A. Schematic representation of the RPE-microglia co-culture system. B. The optimized co-culture medium improved microglia maintenance, as shown by increased microglial cell density in the insert and a higher percentage of IBA1 positive cells after 7 days of co-culture compared to PhenoCULT-RPE medium. C. RPE cell density was maintained in both PhenoCULT-RPE medium and co-culture medium after 7 days of co-culture with microglia. Tight junctions were also preserved under both conditions, as indicated by ZO-1 expression.

Microglia increase RPE sensitivity to A2E and blue light-induced stress

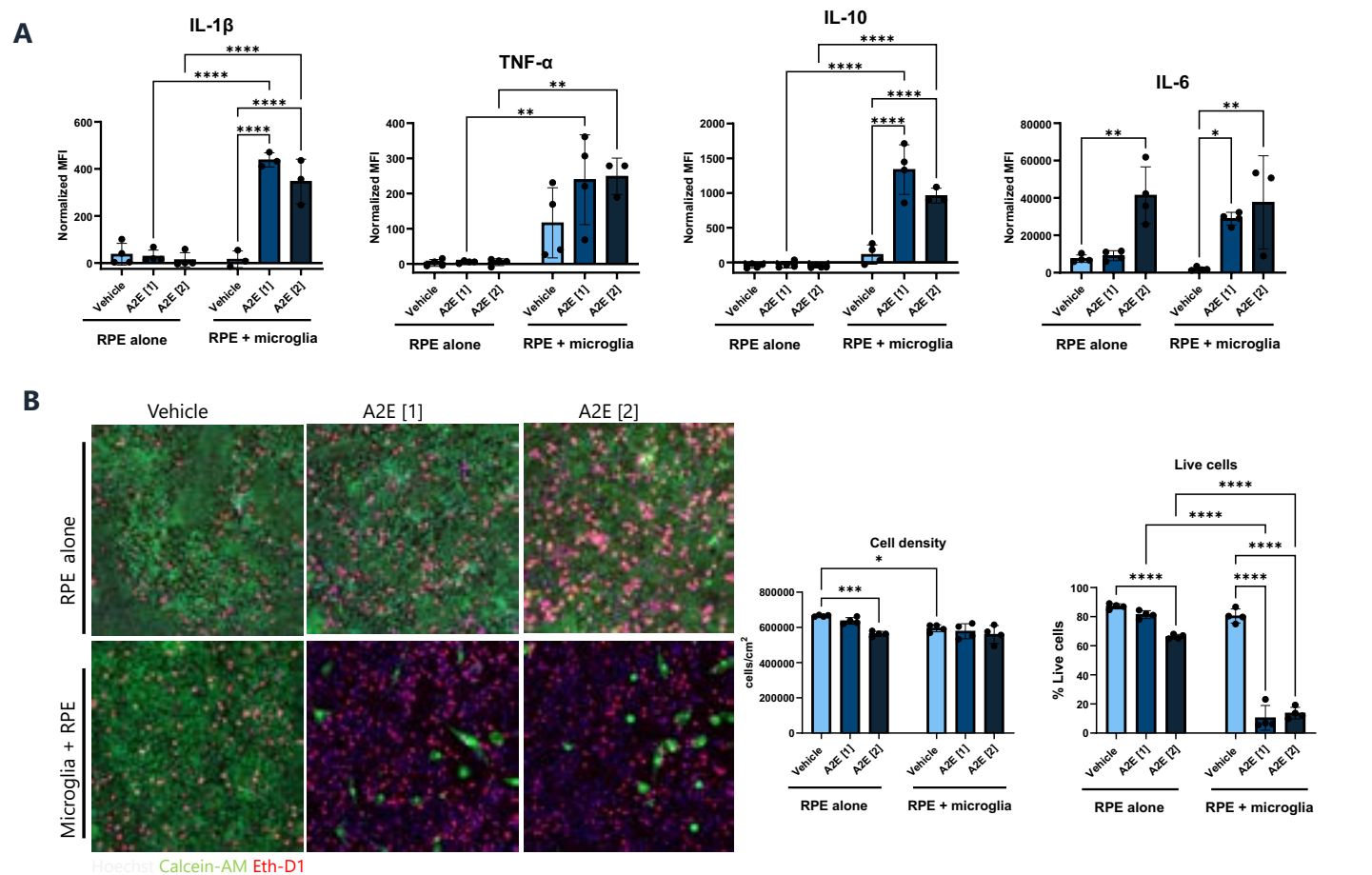


Figure 8. A. A2E treatment in RPE-microglia co-culture systems is associated with increased secretion of inflammatory cytokines (IL-1 β , TNF- α , IL-10, and IL-6), as measured by LegendPlex analysis. B. A decrease in RPE cell viability is observed following A2E and blue light exposure, with a greater reduction in co-culture compared to monoculture at equivalent A2E concentrations.

Emerging trends and future directions

Translational research continues to move toward increasingly sophisticated human-relevant systems that incorporate greater cellular diversity and more closely reflect tissue architecture. However, this drive towards complexity needs to be balanced with reproducibility, scale and accurate reflection of diversity in patient populations.

One area of development is the integration of microglia into three-dimensional brain organoids or assembloid platforms such as neurospheres and other microtissue platforms. These systems provide new opportunities to study neuroimmune interactions within tissue-like environments and have generated insights into neuronal maturation, network activity, and inflammatory signaling²⁰. Recent studies have also demonstrated the successful incorporation of microglia into human iPSC-derived retinal organoids, generating immunocompetent retinal models that more closely reflect the cellular complexity of the human retina and provide new opportunities to study retinal development and disease²⁹.

In parallel, advances in microphysiological systems and organ-on-chip technologies enable multiple human cell types to be combined within precisely controlled environments. In addition, similar approaches are emerging in ophthalmology, where researchers are developing multicellular retinal platforms containing RPE cells, photoreceptors, retinal neurons, and microglia¹⁹.

Complex human iPSC-derived cell models, combined with advances in single-cell transcriptomics, metabolomics, spatial biology, high-content imaging, and computational analysis are expected to further improve the ability to study cellular interactions at high resolution and accelerate the development of more predictive disease models.

As broader industry-wide adoption of NAMs, which include human-relevant cell-based models, continues, we expect to see the interplay between glial cell populations and other cell-types leading to new insights into human disease biology. Human iPSC-derived co-culture systems provide scalable and reproducible insights into disease, improving translational relevance, and supporting therapeutic discovery across neuroscience and ophthalmology.

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Glossary

Abbreviation / Term	Definition
A2E	Lipofuscin component commonly used to model retinal stress in AMD research.
ALS	Amyotrophic lateral sclerosis, a progressive neurodegenerative disease affecting motor neurons.
AMD	Age-related macular degeneration, a leading cause of age-related vision loss.
Astrocyte	Astrocytes are glial cells that support neuronal function and regulate immunity, neurogenesis, metabolism, and blood-brain barrier integrity.
Co-culture	An <i>in vitro</i> system containing two or more cell types to study cellular interactions.
CNS	Central nervous system, comprising the brain, spinal cord, and retina.
Cytokine	Cell-signaling protein involved in immune and inflammatory responses.
iPSC	Induced pluripotent stem cell capable of differentiating into multiple human cell types.
Microglia	Resident immune cells of the CNS and retina that regulate homeostasis and inflammation.
NAMs	New Approach Methodologies; human-relevant alternatives or complements to animal models.
Neuroinflammation	Inflammatory processes occurring within the CNS or retina.
Organoid	Three-dimensional stem cell-derived model that mimics aspects of tissue structure and function.
Phagocytosis	Cellular process of engulfing and clearing debris, pathogens, or dead cells.
Photoreceptor	Light-sensing retinal neuron responsible for vision.
RPE	Retinal pigment epithelium, a cell layer essential for photoreceptor support and retinal health.
TDP-43	RNA-binding protein commonly associated with ALS and frontotemporal dementia pathology.
Tri-culture	Co-culture model containing three cell types, such as neurons, astrocytes, and microglia.

Axol Bioscience

Axol Bioscience is a leading provider of human induced pluripotent stem cell (iPSC) technologies, specializing in the manufacture of high-performance iPSC-derived cells and the delivery of industry-leading laboratory services. With over a decade of expertise, Axol partners with global pharmaceutical companies, contract research organizations (CROs), biotechnology firms, start-ups, and academic institutions to advance the use of iPSC-based models in drug discovery and disease research.

The company operates across four key areas, neuroscience - including ALS, Alzheimer's, Huntington's, Parkinson's - neuroinflammation, ophthalmology dermatology and cardiovascular.

Axol offers scalable solutions including iPSC banking, reprogramming, gene editing, cell manufacturing, and quality control. The company is committed to closing the translational gap and developing physiologically relevant *in vitro* systems that improve consistency and relevance in human disease modeling and compound testing.

Axol is recognized for its scientific excellence, transparent collaboration and rigorous quality standards. Manufacturing operations are ISO 9001:2015 certified.



Poster

ALS with iPSC-derived motor neurons, microglia and astrocytes



Poster

Development of a human iPSC-derived retinal microphysiological co-culture system for dry age-related macular degeneration

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