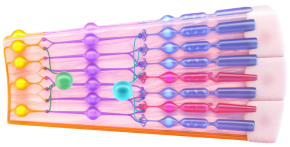
Retinal Organoids Products and Services



NEWCELLS
BEST BIOLOGY DRIVING *IN VITRO* INNOVATION

- ✓ Based in Newcastle upon Tyne, UK
- ✓ Strong links with global Pharmaceutical and Biotech companies and academic centres of excellence
- ✓ State of the art facilities located in The Helix science campus

How you can use Newcells' retinal products

Applications:
Disease modelling.
Drug safety and efficacy screening.
Gene therapy applications.

Services:
Services involving our retinal organoids and RPE.
Projects designed by leading global expertise.
Organoids produced in 96-well plates for HT.

Products:
Retinal Organoids available for shipment.
RPE in cryovials; expected availability 2022.
Contact us for details: enquiries@newcellsbiotech.co.uk

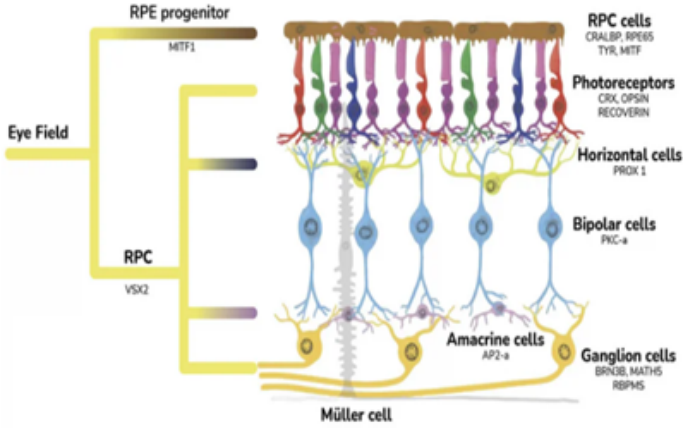
Best in Class *in vitro* models to accurately predict *in vivo* outcomes

- ✓ A passionate and dedicated team of industry leading experts who build our technical knowledge into all our products and services.
- ✓ Learning from human physiology, *in vivo* architecture, we build functional *in vitro models* through innovation and science. Our models incorporate the "best biology" which is predictive of the efficacy and safety of new drugs.
- ✓ Using our expertise in induced pluripotent stem cells (iPSCs), cellular physiology and organoid technology, we engineer models of kidney, retina, liver and lung from patient samples as well as from a range of preclinical species.

This drives CONFIDENCE in the drug discovery decision making process

The Retina: a complex organ

The retina is a sensory tissue at the back of the eye and is vital for visual perception, converting light energy into electrical signals sent to the brain for processing. It has a complex architecture comprising several key cell types. Retinal pigment epithelial cells support the photoreceptors and form one of the blood-retinal barriers.



Limitations of current retinal pre-clinical models

- Animal models do not recapitulate the correct phenotype of the human retina
- Human explants have a restricted window of use and tissue access is challenging
- Primary cells and cell lines of single retinal cell types do not mimic the interaction of the multiple cell types

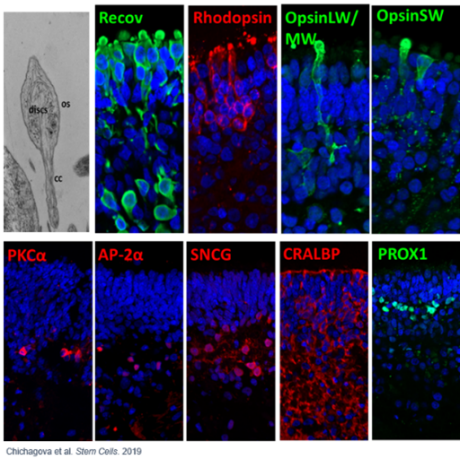
The Retina model in a dish

After 22 weeks in culture retinal organoids contain major retinal cell types

- Retinal organoids self-organize with different cell types assuming position allowing for formation of neural networks similar to that seen in vivo, recapitulating the architecture of the human retina.
- Retinal organoids are ~ 1.3 mm in diameter and contain ~ 40,000 cells.
- Primitive photoreceptor outer segments are formed leading to responsiveness to light.
- All cell layers allow drug permeation.
- The organoids respond to known toxins similar to that seen *in vivo*.

Tested for different applications

- Retinal disease modelling
- Toxicology
- Gene therapy



Chichagova et al. *Stem Cells*. 2019

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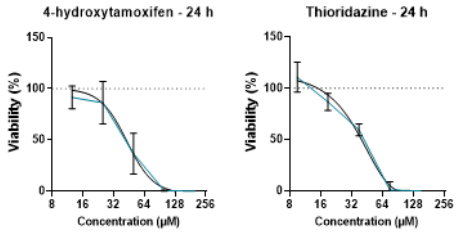
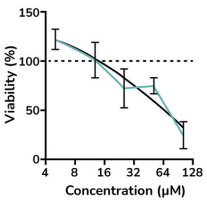
Toxicology

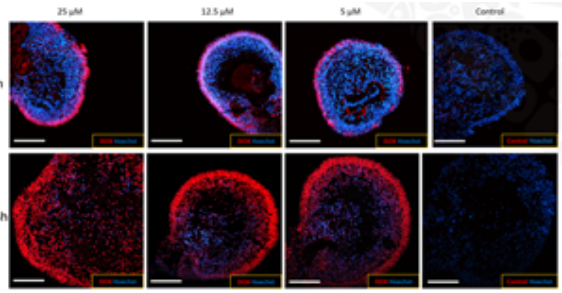
- ✓ Retinal organoids respond to compounds known to induce retinal toxicity in a dose response manner.
- ✓ Known non-toxic compounds have no effect on viability
- ✓ Doxorubicin has an intrinsic fluorescence allowing to test for organoid penetration
- ✓ Data demonstrates the ability for small molecules to penetrate the organoids.

24h

Cytotoxic

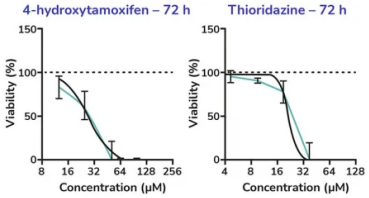




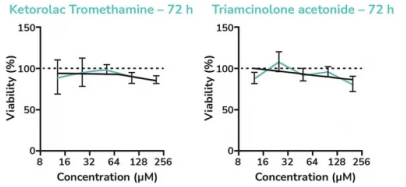


72h

Cytotoxic



Non-Cytotoxic



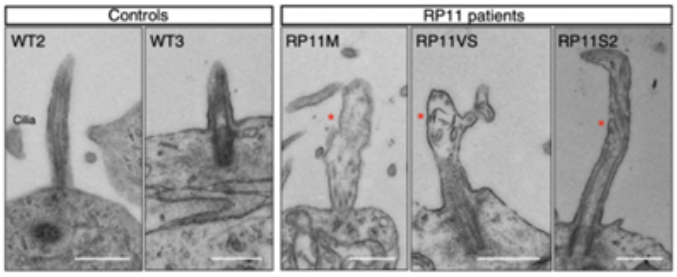
- ✓ Dose-response plots of known cytotoxic and non-cytotoxic retinal agents determined in retinal organoids using CellTiter-Glo® 3D ATP assay.
- ✓ Data is presented as the mean ± SD of at least 4 separate determinations.

Platform for disease modelling

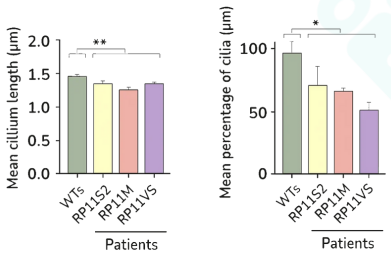
The generation of retinal organoids from retinitis pigmentosa Type 11 patients allows for the elucidation of the mechanism of retinal dysfunction. Large-scale transcriptomic analyses identified mis-splicing of target genes affected by PRPF31 mutations, providing molecular characterisation of splicing-factor RP clinical phenotypes. Cellular defects unravelled include dysfunctional RPE, disrupted cilia morphology in photoreceptors, progressive cellular degeneration and cellular stress. The cellular phenotype was rescued by CRISPR-CAS9 GENE editing.

First demonstration of the cellular phenotypes associated with retinitis pigmentosa using patient derived organoids and companion RPEs

This work and expertise was established in Newcells Biotech co-founder's lab Prof. Lako, Professor of Stem Cell Sciences, Biosciences Institute, Faculty of Medical Sciences, Newcastle University



Transmission electron microscopy showing shorter cilia in patient-derived photoreceptors, with abnormal bulbous morphology (red star). Scale bar 500 nm



Quantification of cilia length and frequency in photoreceptors showing significant reduction in RP11 patients compared to controls.

Reference: Buskin A, et al, Disrupted alternative splicing for genes implicated in splicing and ciliogenesis causes PRPF31 retinitis pigmentosa. Nat Commun. 2018 Oct 12;9(1):4234. Doi: 10.1038/s41467-018-06448-y.

Gene therapy: Advantages and limitations of current models

Human retinal explants

Advantages

- Physiological relevance

Limitations:

- Restricted window of use
- Questionable health of the tissue; the quality of data of a post-mortem retina depends on rapid isolation and a regular oxygen supply
- Gene expression can change rapidly post-mortem in a tissue-specific manner
- Other constraints include organ availability and ethical requirements of the state and institution where the procedure is conducted

Animal models

Advantages:

- End point assessments are well established. Translatable to humans
- Non-invasive *in vivo* imaging (and functional tests

Limitations:

- Findings often do not translate between models; further dose optimization is required to account for thicker barriers in larger animals preventing AAV diffusion or vector dilution in the vitreous
- Animal models are not suitable for evaluating CRISPR/Cas9-induced off-target mutations in the genome requiring an appropriate human model
- It is unclear whether time frame of intervention can be ascertained using animal models
- Animal models often exhibit differences in retinal cell surface receptors compared to the human retina making it challenging to study cell type specificity

Human iPSC-derived retinal organoids

Advantages:

- Human genetic background
- Contain main retinal cell types
- Unlimited supply and can be generated at scale
- Ability to generate disease -specific tissue
- Extended window of use
- Newcells retinal organoids at ~ day 150 of the differentiation have been successfully transduced by AAV vectors.
- Vector expression increased over time and was the highest after 4 weeks post-transduction

Visit our Retinal Organoid page

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