Retina Australia Research Report 2025

Project Title:
Therapies for currently untreatable autosomal recessive IRDs

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What this project is about:
Inherited retinal diseases (IRDs) are conditions passed down in families that cause progressive vision loss. About half of all people with IRDs have a type called autosomal recessive IRD, which may affect a number of children in the same family. These conditions can have a major impact on daily life, independence, emotional health, and long-term wellbeing.
Most of these diseases happen because a gene is not working properly and cannot make the protein needed for healthy vision. For many of these small genes, a promising treatment approach is gene replacement therapy, where a correct copy of the gene is delivered to the eye using a harmless virus (AAV). One such therapy already exists for a particular small gene called *RPE65*, showing this strategy can work. However, most families with autosomal recessive IRDs still have no treatment available, and there has been very little pre-clinical testing for many of the relevant genes.
Our project aims to change that.

What we set out to do:
We focused on three main goals:

1. Grow "mini-retinas" from stem cells made from patients with mutations in a small IRD gene. These mini-retinas (retinal organoids) allow us to study the disease and test treatments in the lab.
2. Design and build new gene therapy tools using AAV viruses carrying a working copy of the gene.
3. Test whether the gene therapy works to correct the problems seen in the mini-retinas.

What we have achieved:
1. Growing patient-derived mini-retinas and identifying disease markers
We successfully grew retinal organoids from patients with changes in the small inherited retinal disease (IRD) gene.
In these mini-retinas, we observed features typical of retinal disease, such as:

- abnormal photoreceptor "outer segments" (the part of the cell needed for light detection),

- important proteins not being located where they should be,
- abnormalities in the photoreceptor cilia (the cell's connecting structure).

We also analysed gene activity to identify molecular changes linked to the disease. These markers are now being used to measure how well the potential therapy works.

2. Creating new gene therapy constructs

We designed and built gene therapy vectors using a clinical-grade AAV system. Importantly, we used a short photoreceptor-specific promoter, which helps target the treatment to the correct cells (rods and cones) while reducing the chance of side effects.

The small disease gene was successfully inserted into these vectors.

3. Testing whether the therapy works

We packaged these gene therapy constructs into an AAV type (AAV7m8) that works well for treating retinal organoids.

Early tests in patient-derived mini-retinas have shown encouraging signs of improvement. These early results suggest that the therapy may be able to treat some aspects of the disease.

Why this work matters:

There are no clinical trials or treatments for more than half of all autosomal recessive IRDs, even though many of the genes involved are excellent candidates for AAV-based gene therapy.

This project has:

- strengthened our ability to model retinal diseases using patient-derived stem cells,
- developed and optimised gene therapy tools for small IRD genes,
- generated early evidence that these treatments can work.

This paves the way for:

- advancing to GMP-grade (clinical trial-ready) viral vectors,
- expanding treatment development to additional genes,
- ultimately preparing for future clinical trials to bring gene therapy to families affected by these currently untreatable conditions.