Our progress towards changing patients’ lives

hRPCs for retinitis pigmentosa therapy

Pre-clinical data

- A rodent model of retinal degeneration was used to study the effects of our hRPC therapy. These hRPCs were injected subretinally (just beneath the photoreceptor layer of the retina).
- The results from this study demonstrated that these cells can treat retinal degeneration.

They are able to . . .

1. Preserve retinal structure and function.
2. Differentiate into components of the retina.

Phase 1 element of combined Phase 1/2a trial

- This study was a single centre, open-label, dose escalation trial to assess the safety of hRPCs in patients with established retinitis pigmentosa.
- Three different doses of hRPCs were tested.
- Patients received a single, subretinal injection of one dose and were followed up for one year.
- It was determined that subretinal injections of hRPCs at the three doses tested were safe and well tolerated.

- We successfully developed a cryopreserved formulation of our hRPC stem cell therapy.
- This will enable cells to be frozen for shipping/storage and be easily thawed at the point of clinical use.
- The success of this stage means that we were able to progress into the Phase 2a element of the combined Phase 1/2a study.
If the Phase 1/2a data continue to be positive, this will enable us to progress into a Phase 2b clinical trial in RP and potentially other retinal diseases.

Phase 2a element of combined Phase 1/2a study

• We progressed into the Phase 2a element of the combined Phase 1/2a study.
• We were able to expand our assessment of efficacy into RP patients that have a greater baseline level of visual acuity (clarity of vision).
• First cohort: As seen on Figure 2, all three of the first cohort of subjects in the Phase 2a part of the study reported a rapid and significant improvement in vision, on average equivalent to reading an additional three lines of five letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, the standardised eye chart used in clinical trials to measure visual acuity, as seen in Figure 1.

Second cohort: In March 2019, the dosing of the second cohort of three Phase 2a patients commenced. This dosing is now complete and dosing of the remaining two cohorts is in progress.
• These later cohorts comprise patients with a greater baseline level of visual acuity than those treated earlier in the study as we seek to assess preliminary efficacy in patient groups with differing levels of remaining vision. The clinical protocol allows for up to 12 patients to be treated in the Phase 2a element.

What does this mean for future development?

• If the Phase 1/2a data continue to be positive, this will enable us to progress into a Phase 2b clinical trial in RP and potentially other retinal diseases.

Figure 1

Figure 2

Cohort 5 efficacy results* – changes in letters read (ETDRS chart)

Subject 1 treated at Mass Eye & Ear  Subjects 2 and 3 treated at Retinal Consultants of Arizona

* Sixth annual Retinal Cell and Gene Therapy Innovation Summit, Vancouver, Canada – April 2019
Our progress towards changing patients’ lives

**CTX cells for stroke disability**

### Pre-clinical data
- A well-established rodent model of stroke was used to study the effects of our CTX cell therapy.
- The CTX cells were directly injected into the brain.
- Our results were particularly positive given that restricted blood supply to the brain, following a stroke, results in nerve cell death.
- The effects of our CTX cell therapy included the formation of new blood vessels, new nerve cells and new connections between nerve cells.

### Clinical trials: Phase 1 study
- In this study, we included 11 stable, disabled stroke patients who were between 6 months and 5 years post-stroke.
- This study was a single centre, open-label, ascending dose trial to assess safety.
- The CTX cells were directly injected into the putamen (an area of the brain), and patients were followed up for over two years post-implantation.
- It was determined that these CTX cell injections at the doses tested were safe and well tolerated.

### Clinical trials: Phase 2a study
- In this study, we included 23 disabled, stable stroke patients, who were between 2 and 13 months post-stroke.
- This study was a single arm, open-label trial using the highest dose tested in Phase 1. This trial was ‘single arm’ because all the patients were administered the same dose.
- CTX cells (20 million cells) were directly injected into the putamen, and patients were followed up for 12 months post-implantation.
- No cell-related safety issues were identified.
- The Modified Rankin Scale (or mRS, a globally used measure of functional disability and dependence in stroke sufferers) was used as a secondary end-point for this study.
- As shown by the figure to the left, 7 out of 20 (35%) patients demonstrated a clinically meaningful improvement at 12 months post-implantation. An even higher response rate (50%; 6/12) was observed in pre-specified patients who had some residual upper limb movement at time of treatment.

### Modified Rankin Scale (mRS)

<table>
<thead>
<tr>
<th>mRS</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk and attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
</tbody>
</table>

0  No symptoms at all
1  No significant disability despite symptoms
2  Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3  Moderate disability; requiring some help, but able to walk without assistance
4  Moderately severe disability; unable to walk and attend to own bodily needs without assistance
5  Severe disability; bedridden, incontinent and requiring constant nursing care and attention
Clinical trials: Phase 2b study

• Patient dosing commenced in the study PISCES III, a randomised, placebo-controlled clinical trial in 110 patients.

• We are seeking a one point or more improvement in the mRS scoring, at six months post surgery, in CTX-treated patients that have a mRS score of 3 or 4 at baseline.

• The study will be conducted in up to 40 sites of which 15 surgical sites and 22 assessment sites have been approved by the end of June 2018.

• Subject to relevant regulatory approvals, the ongoing PISCES III study may be expanded to include clinical sites in China.

• Top-line data from PISCES III is expected in late 2020.

What does this mean for future development?

• If the Phase 2b results are positive, our intention is to seek a partner to progress the programme through late clinical development and to commercialisation.
Our progress towards changing patients’ lives

CTX-derived exosomes as a novel drug delivery vehicle

Potential as a novel drug delivery vehicle

- Our studies have identified the potential of our exosome technology platform as both a novel therapeutic candidate and as a drug delivery vehicle. Our focus has been on the potential of our exosomes as a drug delivery vehicle.

- We have signed a collaboration agreement with a US-based pharmaceutical company to explore use of exosome technology as a novel delivery vehicle in gene therapy. The initial feasibility stage will optimise the process of loading molecules called oligonucleotides into exosomes. If successful, exosomes could be able to deliver these molecules to targeted parts of the body.

Scaleability

- We have tested the production of exosomes through our grant-funded collaboration between University College London and the Cell and Gene Therapy Catapult.

- The new data demonstrate the feasibility of scaling up the production of our CTX-derived exosomes utilising state-of-the-art bioreactor systems.

- This represents a significant advance towards an industrial scale production process without affecting the quality and consistency of the final product.

What does this mean for future development?

- We will continue to develop our CTX-derived exosomes as a novel vector for delivering third party biological drugs.

- We intend to pursue opportunities to capitalise on the significant scientific and life sciences industry interest in exosomes. We will do this by forming further value-generating business partnerships covering this exosome technology.
CTX-derived exosomes explained

What are exosomes?
The exosomes released by our CTX cells are nano-sized packages of signalling molecules.

Therapeutic agents can be attached to exosomes as cargo. Exosomes have the ability to deliver this cargo to specifically targeted cells in the body.

Advantages of exosomes as a delivery vehicle
- Natural carrier of nucleic acids and proteins, amenable for loading complex, hard-to-deliver therapeutic agents.
- Ease of bioengineering.
- Low immunogenicity.
- Intrinsically durable.

Advantages of ReNeuron’s exosome technology
- Stable, consistent, high-yield.
- Proven ability to load miRNA and proteins.
- There is a potential for exosomes to work as a therapeutic in gene therapy.
- Able to cross the blood brain barrier.
- Could be engineered to target particular tissues.