

ReNeuron

Corporate Presentation

April 2018

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Michael Hunt, Chief Financial Officer
Dr Rick Beckman, Chief Medical Officer



Changing
patients' lives

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ReNeuron Snapshot

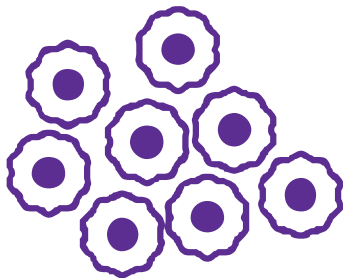
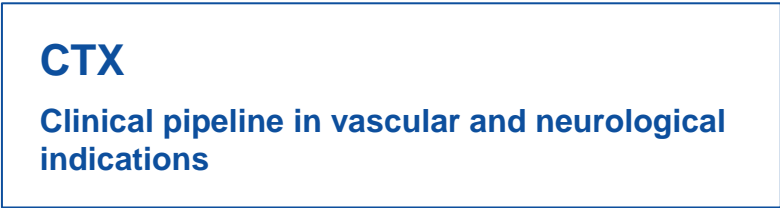
Multi-asset, allogeneic cell therapy company with lead programmes in clinical development in the US

- CTX stem cell therapy candidate for stroke disability:
 - Positive long term data from Phase IIa clinical trial
 - IND approval for Phase IIb, placebo-controlled clinical trial. To commence in 40 US centres in mid-2018
- hRPC stem cell therapy candidate for retinal diseases:
 - Retinitis Pigmentosa program - Phase IIa study underway at Mass Eye and Ear Infirmary, Boston
 - Phase IIb studies planned to commence in 2019 in Retinitis Pigmentosa and Cone Rod Dystrophy
- Exosome nanomedicine platform:
 - Positive pre-clinical data with ExoPr0 exosome therapy candidate demonstrates potential of ExoPr0 to target multiple diseases
- Solid foundations:
 - Cash position at last reporting date (30 Sep 2017) - £45.3m (\$63m)
 - Strong management team and solid institutional investor support
 - Clinical operations managed from newly established US office in Boston, MA

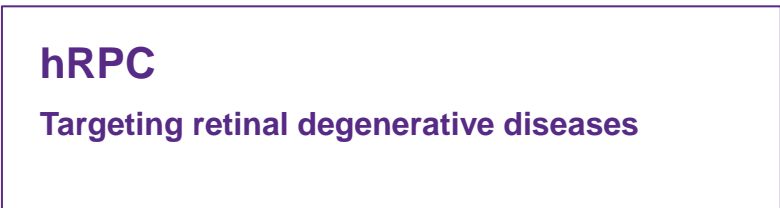
Unique platform technologies



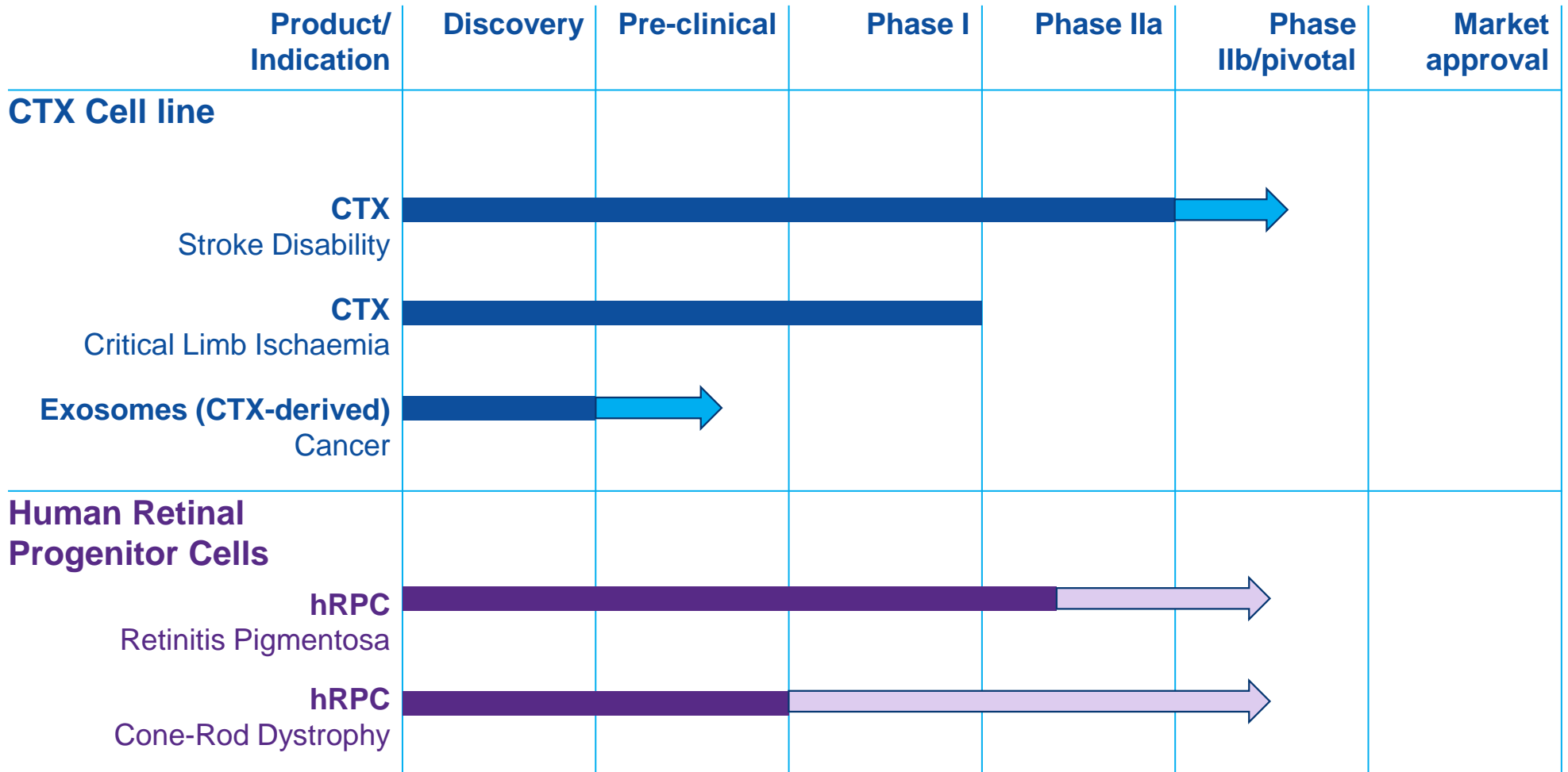
Originally derived from
single neural stem cell



Retinal stem cell
population



Pipeline



Well backed and well funded

- Quoted on AIM
- Backed by major generalist and specialist life science institutional investors:

35.5%

Woodford Investment
Management

9.5%

Wales Life
Science Fund

9.3%

Invesco

5.7%

Aviva

£45.3 million (US\$63 million)

Cash on balance sheet (as at 30 September 2017) – runway into H1 2019

Market potential according to analyst estimates*

Indication	Assumptions	Peak Annual Sales
CTX for stroke	1.76 million strokes/year (total US/EU/Japan) 85% survival, 85 % ischaemic Peak penetration 5% US/EU/Japan Treatment cost \$40,000 EU to \$60,000 US/Japan	\$1.1bn - \$3.9bn
hRPC for RP	Prevalence 1:4000, ~244,000 cases (total US/EU/Japan) Peak penetration 7.5% US/ EU Per-eye treatment cost \$50,000 EU to \$100,000 US/Japan	\$0.5bn - \$1.8bn

- Applicability of hRPC in other hard-to-treat ophthalmic diseases could provide upside potential
- Longer-term upside from exosome platform

*Stifel July 2016, N+1 Singer April 2017, Edison May 2017

Strong management team

Senior Management



Olav Hellebø
Chief Executive Officer
(Schering-Plough, Novartis, UCB, Clavis)
Board member



Michael Hunt
ACA
Chief Financial Officer
(Biocompatibles, Bunzl)
Board member



Dr. John Sinden
Chief Scientific Officer and co-Founder



Dr. Randolph Corteling
Head of Research



Sharon Grimster
VP Development and General Manager, Wales
(F-Star, Antisoma, Celltech)



Dr. Rick Beckman
Chief Medical Officer
(Ophthotech, Neurotech, Alcon, Becton Dickinson, Allergan)



Shaun Stapleton
Head of Regulatory Affairs
(Elly Lilly, Boehringer Ingelheim, Ipsen, RRG)

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Chairman
(Autolus, Algeta, Heptares, Abingworth)

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Dr. Claudia D'Augusta
(Tigenix, Deloitte & Touche, Apax)

Prof. Sir Chris Evans OBE
(Arix, Arthurian)

Dr. Michael Owen
Chair - ReNeuron Scientific Advisory Board
(Zealand Pharma, Avacta, Kymab, GSK, ICRF)

Future clinical milestones by programme

CTX for stroke disability

- Mid 2018 – Phase IIb commencement
- H2 2019 – Phase IIb data

hRPC for retinitis pigmentosa

- H1 2019 – Phase I/IIa data
- 2019 – Phase IIb commencement

hRPC for cone-rod dystrophy

- 2019 – Phase II commencement

Exosomes for cancer (solid tumours)

- 2019 – Phase I commencement

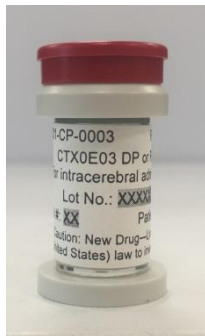


CTX cell line

CTX cell product

CTX - an allogeneic, cryopreserved human neural stem cell product

- Manufactured under cGMP with a 6 month shelf life
- Product to be readily ordered, shipped and stored at the hospital
- CTX platform allows for commercial scale manufacturing at attractive COG
- Excellent safety profile - no immunogenicity issues post-administration



CTX delivered in cryo-shipper



Straightforward, controlled thawing at hospital site



Administer to patient 'on demand'

Similar to a conventional 'off-the-shelf' pharmaceutical / biologic drug

Allogeneic vs Autologous cells

- **Allogeneic Cells**

- One tissue harvest for many patients with scaled production
- Characterisation of product provides consistency across lots
- CTX established six month shelf life
- Costs spread over larger production base
- Realistic reimbursement projections
- No evidence of CTX generating an immune response in any patients treated

- **Autologous Cells**

- Tissues harvested from a specific patient for his/her treatment
- Cell potency dependent upon age and health of each patient
- Usually limited shelf life with fresh cells
- Cost of cell preparation per preparation
- Unknown reimbursement scenario

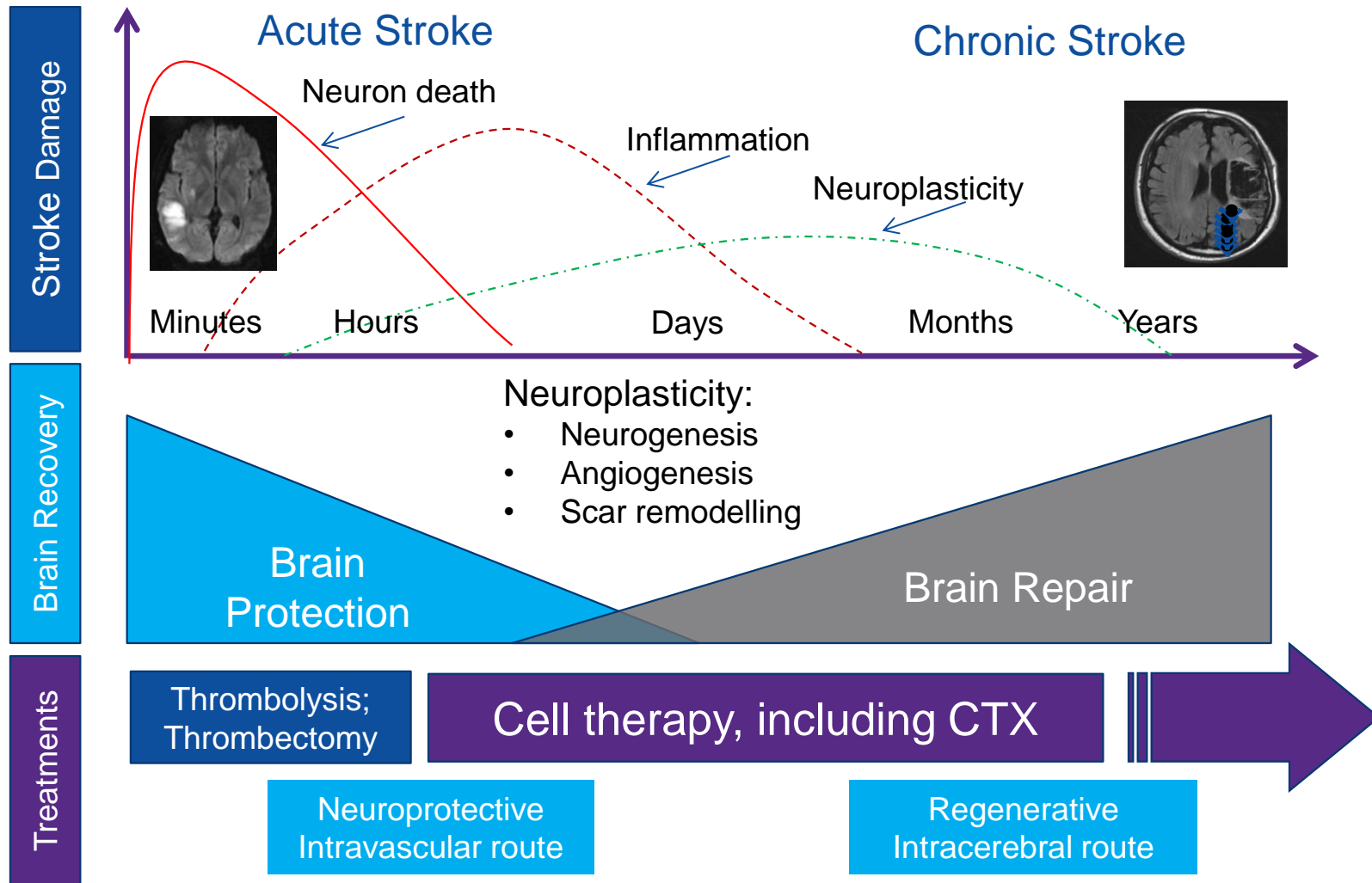
Allogeneic cells offer commercial advantages over autologous preparation

CTX for stroke disability: unmet medical need



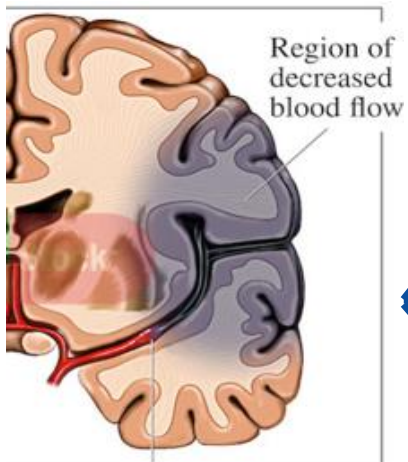
- Stroke is the single largest cause of adult disability
- Annual health/social costs: >\$70 billion in the US
- Only one pharmaceutical treatment option available within 4 hours of stroke onset
- No treatment options available for stroke patients months to years later
- CTX administration promotes repair in the damaged brain

Two distinct cell therapy strategies for stroke

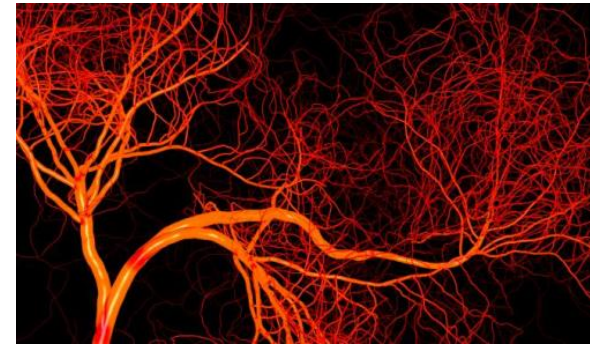


ReNeuron is a pioneer in treating chronic stroke patients

CTX promotes anatomical plasticity in the brain



Formation of new blood vessels (angiogenesis)



Formation of new neurons (neurogenesis)



Formation of new connections between neurons (synaptogenesis)

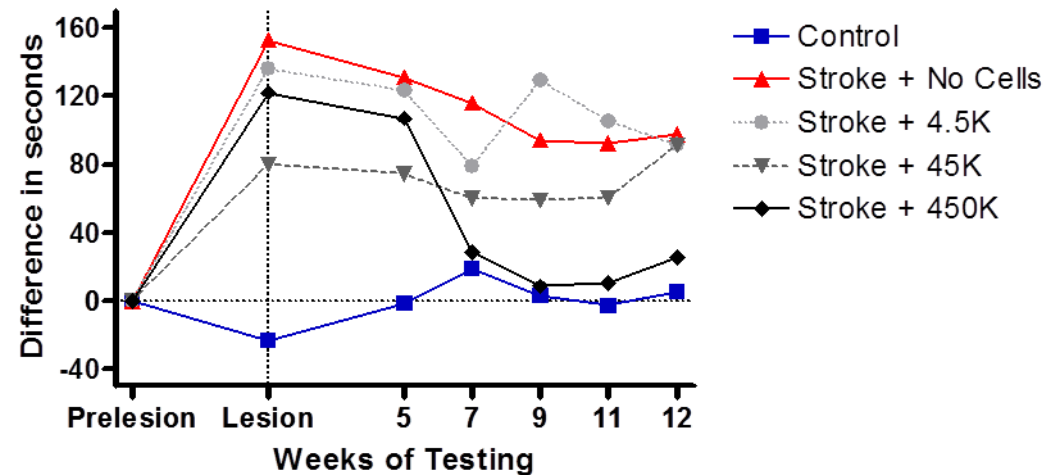


Implanted CTX cells modulate the immune system to promote repair by

Strong pre-clinical proof of concept

- MCAO* in the rat used to model stroke damage in similar regions of the brain to those seen in stroke patients
- Panel of behavioural tests to characterise dysfunction and recovery
- Injection of CTX into same region of brain as in the patients
- Reductions in “permanent” disabilities
- Restoration of function weeks after CTX administration
- Dose response demonstrated – unique in field of cell therapy
- Motor-related efficacy demonstrated with CTX in other models of neurological disease

Reduction in permanent dysfunction



CTX administration led to recovery of tape removal from the affected forelimb in a dose dependent manner

Stroemer et al. Neurorehab Neural Repair 2009

Well validated pre-clinical models predict efficacy in chronic stroke

* Middle cerebral artery occlusion

CTX for stroke disability: Phase I data published

Articles

THE LANCET

Human neural stem cells in patients with chronic ischaemic stroke (PISCES): a phase 1, first-in-man study



Dheeraj Kallada, John Sinden, Kenneth Pollock, Caroline Haig, John McLean, Wilma Smith, Alex McConnachie, Celestine Santosh, Philip M Bath, Laurence Dunn, Keith W Muir

Summary

Background CTX003 is an immortalised human neural stem-cell line from which a drug product (CTX-DP) was developed for allogeneic therapy. Dose-dependent improvement in sensorimotor function in rats implanted with CTX-DP 4 weeks after middle cerebral artery occlusion stroke prompted investigation of the safety and tolerability of this treatment in stroke patients.

Published Online
August 3, 2016
[http://dx.doi.org/10.1016/S0140-6736\(16\)30513-X](http://dx.doi.org/10.1016/S0140-6736(16)30513-X)
See the full text on the journal website

- Phase I dose escalation safety study published with 24 months follow up
 - 11 disabled, stable stroke patients, 6 months to 5 years post stroke
 - Single, straightforward neurosurgical procedure, Doses at 2, 5, 10, 20 million cells
- No cell-related or immunological adverse events
- Significant improvement in NIH Stroke Scale, 3 patients improved in Modified Rankin Score

PISCES II – Completed Phase II study

- Aim of the PISCES II study:
 - To demonstrate effect of CTX cells on improving outcome of patients during rehabilitation phase following an ischemic stroke
 - To provide further safety data in a larger group of patients
- Inclusion Criteria
 - Male and female patients; aged 40-89; 2-12 months after a stroke
 - Upper limb dysfunction (Inability to pick up a 1” cube and place on a shelf)
- Study Procedures
 - CTX 20 million cells injected into brain (putamen) on affected side, Follow up for 12 months
- Outcome measures
 - **Modified Rankin Score**, Barthel Index, ARAT, Fugl-Meyer
- Treated 23 patients in 8 centres across the UK
- Median Age: 62 yrs (41-79), Median time from stroke to treatment: 7 months (2-13)

PISCES II efficacy – summary of all key endpoints

Test	Responder definition	3 months n/N (%)	12 months n/N (%)
ARAT Test 2	≥2 points	1/23 (4%)	3/20 (15%)
Total ARAT	≥6 points	3/23 (13%)	5/20 (25%)
Modified Rankin	≥ 1 point	7/23 (30%)	7/20 (35%)
Barthel Index*	≥9 points	8/17 (47%)	8/16 (50%)

- Six and 12 month results were similar so six months will be proposed as primary measure in future studies

Reduction in disability after CTX administration – maintained to 12 months

* Six patients had a baseline score >90 and could therefore not meet the criteria of a responder (maximum score = 100). Therefore n=17 at 3 months.

PISCES 2 –mRS response in patients with remaining arm movement

Total Subjects			Subjects with NIHSS upper limb score < 4 at baseline (BL)	
Day	N	n* (%)	N	n* (%)
Baseline	23	-	14	-
30	23	3 (13.0%)	14	3 (21.4%)
90	23	7 (30.4%)	14	6 (42.9%)
180	23	6 (26.1%)	14	5 (35.7%)
365	23	7 (30.4%)	14	6 (42.9%)

- In all patients the response rate in mRS was 30%
- In patients who had some upper limb movement at baseline, the RR was 43%
 - There is a good scientific reason why patients with some arm movement may respond better
 - This indicates some ability of the CorticoSpinal Tract to transmit signals from the motor cortex to the spinal column

PISCES II study - conclusions

- Rate of patient improvement in patients with established disability due to stroke has greatly exceeded what we expected
- CTX intracerebral injection was well tolerated
 - Adverse Events were attributed to surgical procedure or stroke complications
- Future studies will be focussed on the patient subgroups with the strongest response in PISCES II



Potential of CTX in stroke warrants moving into a randomised controlled study

PISCES III



- IND approved – study to commence in US in mid-2018
- Randomised, placebo-controlled Phase IIb study
- Entry criteria:
 - Ischemic stroke 6-12 months previously
 - modified Rankin Score (mRS) of 3 or 4
 - Some residual Upper Limb movement
- Primary endpoint:
 - Response as measured by mRS six months post treatment
- Key Secondary endpoints
 - Response measured by Barthel Index
 - Improvement in Lower Limb and Trunk function: Timed Up and Go test
 - Improvement in Upper Limb function: Chedoke Arm and Hand Activity Inventory (CAHAI)
 - Durability of Response measured out to 12 months

PISCES III



- CRO contracted
 - Academic supporting PI
 - Years of experience with cardiovascular studies
- US sites use “Hub and Spoke”
 - Larger number of recruiting and testing sites (approx 30) and smaller number of surgical sites (approx 10)
 - Improves masking of Endpoint Assessment
 - Flexibility and efficiency in getting patients treated
- n=110 patients, 1 to 1 randomisation, CTX 20 million cell dose as used in PISCES II
 - Assumption of 35% RR in CTX group and 12.5% Placebo group
 - Adequately powered; approximately 1 year recruitment
- Comprehensive training, certification of Investigators, and masked centralised review of the Primary Endpoint
- Expected response rate in mRS is clinically meaningful and commercially viable
 - Enrolment restricted to patients with some arm movement – enhanced response rate

Expect this study to be considered Pivotal for regulatory review

PISCES III assumed placebo response

Limited data sets in chronic stroke patients for comparisons:

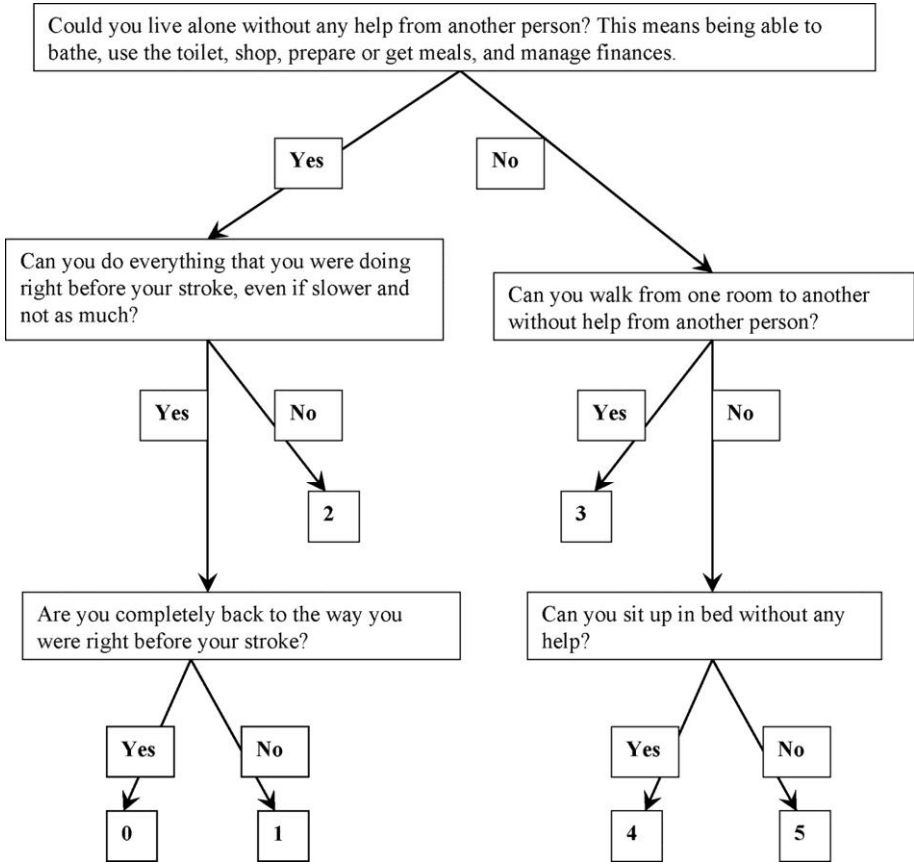
- MILESTONE cross over treatment with dalfampridine had placebo response rate of 13.5 percent in improved walking speed
- EVEREST trial of cortical stimulation demonstrated long term placebo response rate of 15 percent in Fugl-Meyer and arm motor ability at 24 weeks post-treatment
- Functional recovery completed within 12.5 weeks in 95% of patients (Barthel Index) n= 1,197 patients (Jorgensen 1995)
- SanBio Phase I/II study in 18 chronic stroke patients recorded no improvements in mRS
- No change in mRS in patients with placebo over one year (Mikami 2011) n=25 patients

Assumed placebo response rate of 12.5% for mRS in PISCES III

Piscas III study sufficiently powered to detect efficacy

Modified Rankin Score

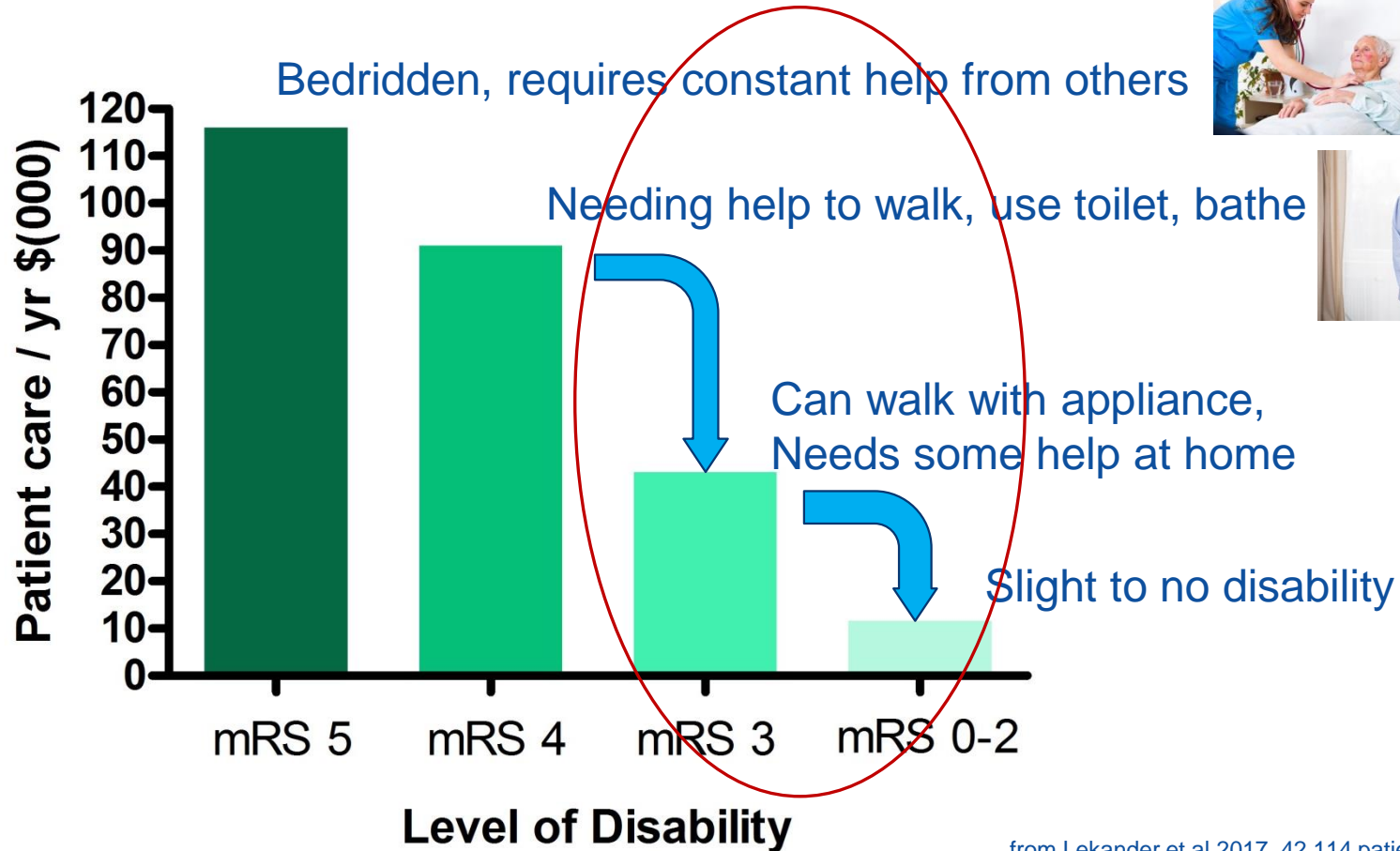
Category
5 Bedridden, completely dependent on others
4 Needing help to walk, use toilet, bathe
3 Can walk, but need still need help at home
2 Mostly recovered, but still has limitations
1 Slower than before, but no limitations
0 Back to pre-stroke life



Algorithm from Bruno et al, 2010

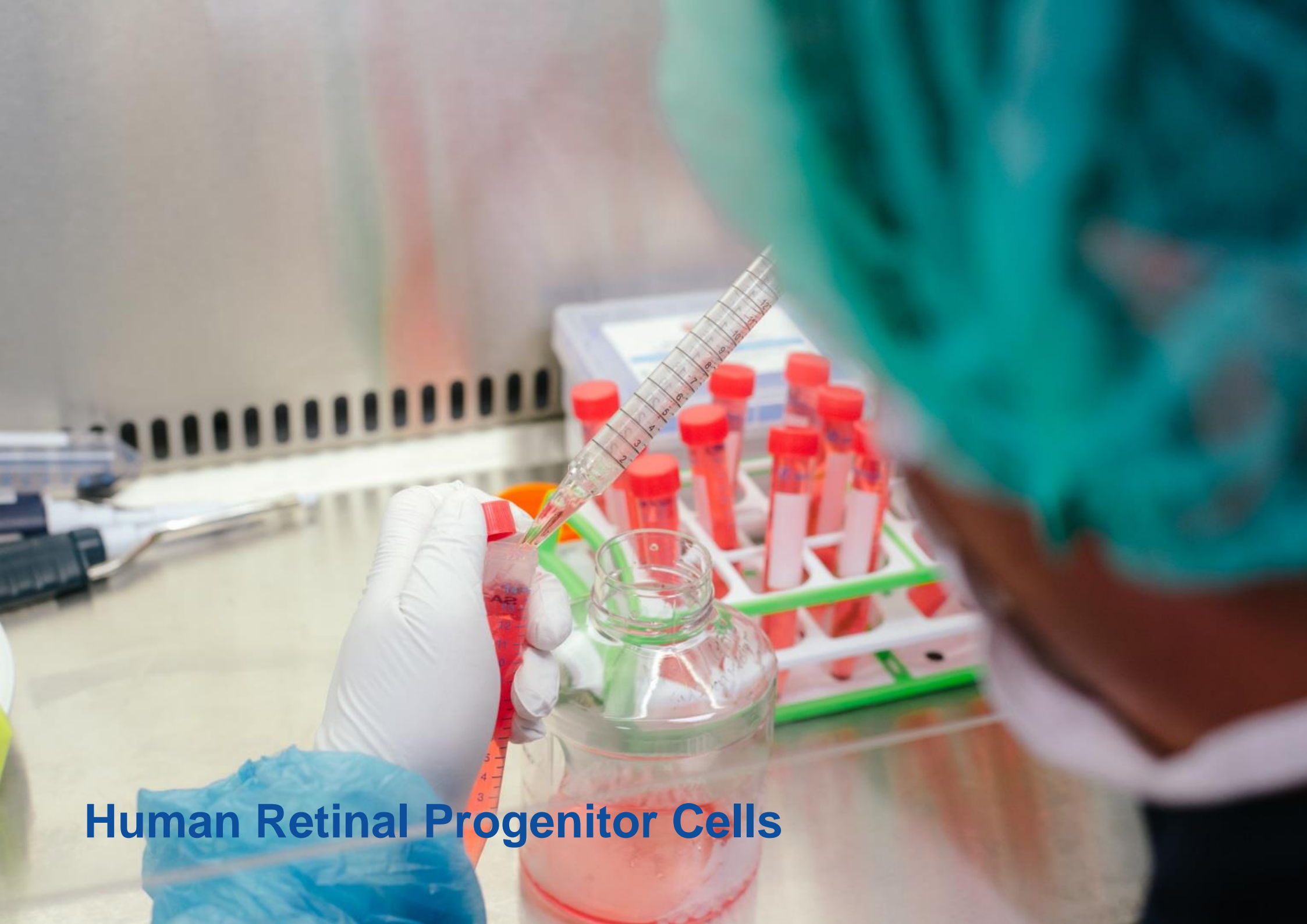
Improvement by one category is a significant change in a patient's life

Costs of disability – mRS scale



from Lekander et al 2017, 42,114 patients from 2007-2012
Costs from Sweden, translated into \$

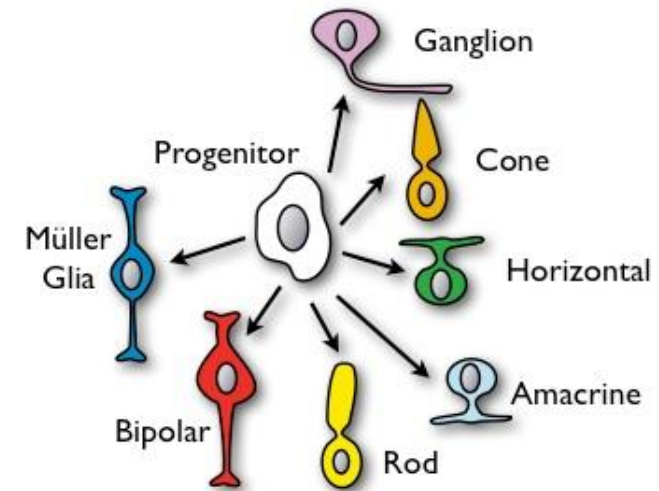
Reductions in disability result in substantial reductions in patient care costs



Human Retinal Progenitor Cells

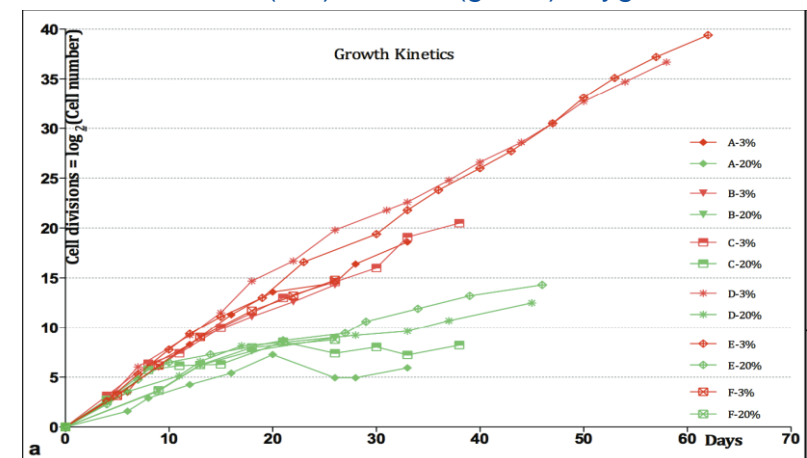
hRPC is a cell-based retinal therapy

- Retinal progenitor cells (RPCs) are a promising therapeutic approach to diseases of the retina because these cells possess the capacity to¹⁻³:
 - Differentiate into retinal neurons/glia
 - Become integrated post-implantation
 - Support and rescue host cells to improve retinal processing of visual information
- Human RPCs (hRPCs) isolated from fetal retina at 16-18 weeks, can be reproducibly maintained and allowed to proliferate in numbers needed for clinical application.⁴
 - Low oxygen conditions maintains both multipotency and self-renewal properties *in vitro*
- Mechanism(s) of action of RPCs include:
 - Integration of implanted cells into host retinal tissue
 - Trophic support of host cells



From S. Georgi, York College of PA

Expansion potential of cells from six different donations in 3% (red) vs 20% (green) oxygen⁴



¹Klassen et al (2004) Prog Retin Eye Res 23(2), 149-181;
²MacLaren et al (2006) Nature 444, 203-207; ³Luo et al (2014) J Biol Chem 289, 6362-6371; ⁴Baranov et al (2014) Tissue Eng Part A 20(9-10), 1465-75;

Retinal platform

- The intrinsic regenerative capacity of cells in retina is limited^{1,2}.
- Any preservation of retinal structure/function balance can greatly impact vision loss associated with retinal disease
- Our program is based on subretinal injection of hRPCs
 - Pre-clinical testing program demonstrates:
 - Rescue of photoreceptors to preserve vision
 - Maturation of injected hRPCs
 - Frozen formulation in clinical trial
 - Ship and thaw on demand
- Collaborations:
 - Schepens Eye Research Institute (Harvard Medical School)
 - Massachusetts Eye and Ear Infirmary (MEEI)
 - University College London – Institute of Ophthalmology, UK
- Initially targeting inherited retinal degenerative diseases
 - Characterized by progressive loss of photoreceptors



Broad application across a range of retinal diseases

¹Ader et al (2014) Regenerative Biology of the Eye, A Pebay (Ed), doi: 10.1007/978-1-4939-0787-8_8; ²So and Yip (1998) Vis Res 38, 1525-1535.

hRPCs may slow visual loss associated with inherited retinal disease (IRD)

Retinitis Pigmentosa:
primary loss of rod
photoreceptors.



45 causative genes/loci (non-syndromic)¹

Cone Rod Dystrophy:
primary loss of cone
photoreceptors.



10 cloned genes/3 loci (non-syndromic)²

Therapeutic benefit of hRPC approach not dependent on genetic causes of IRD

Retinitis pigmentosa (RP)

- RP is an inherited, degenerative eye disease^{1,2}
 - Onset varies from early childhood to 20s to even later
 - Early stage main symptom is night blindness
 - Progressive loss of peripheral vision (ie tunnel)
 - Incidence of RP is 1:4000 in US and worldwide
 - Estimated treatment population of 275,000 in the US and EU
- Orphan Drug Designation in EU and US & Fast Track Designation in US
- Phase I/IIa study ongoing in the US
 - Phase I dosing complete
 - Phase IIa commenced
 - Phase IIa readout H1 2019



NORMAL VIEW



VIEW WITH
RETINITIS PIGMENTOSA

www.eyehhealthweb.com/retinitis-pigmentosa

There is no approved drug treatment for Retinitis Pigmentosa

¹Hamel (2006) Orphanet J Rare Disease 1, 40;

²https://nei.nih.gov/health/pigmentosa/pigmentosa_facts

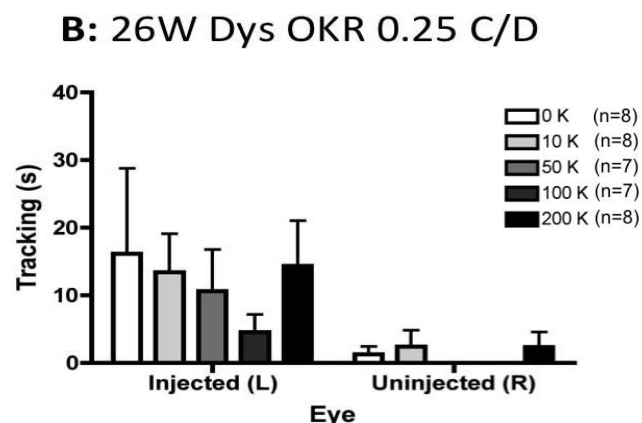
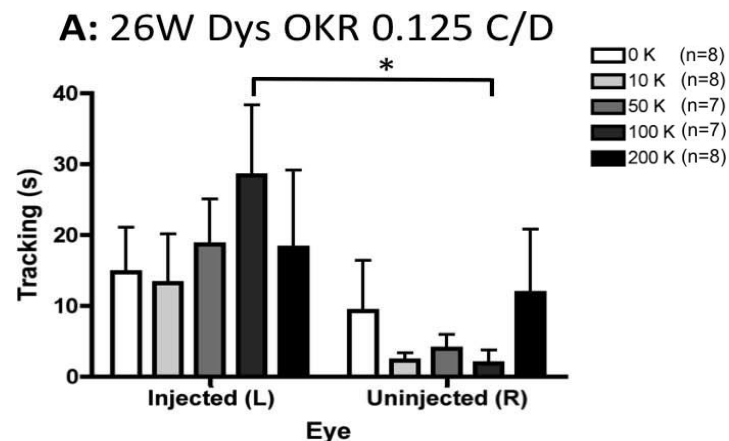
Subretinal implantation of RPCs

Summary of POC pre-clinical studies

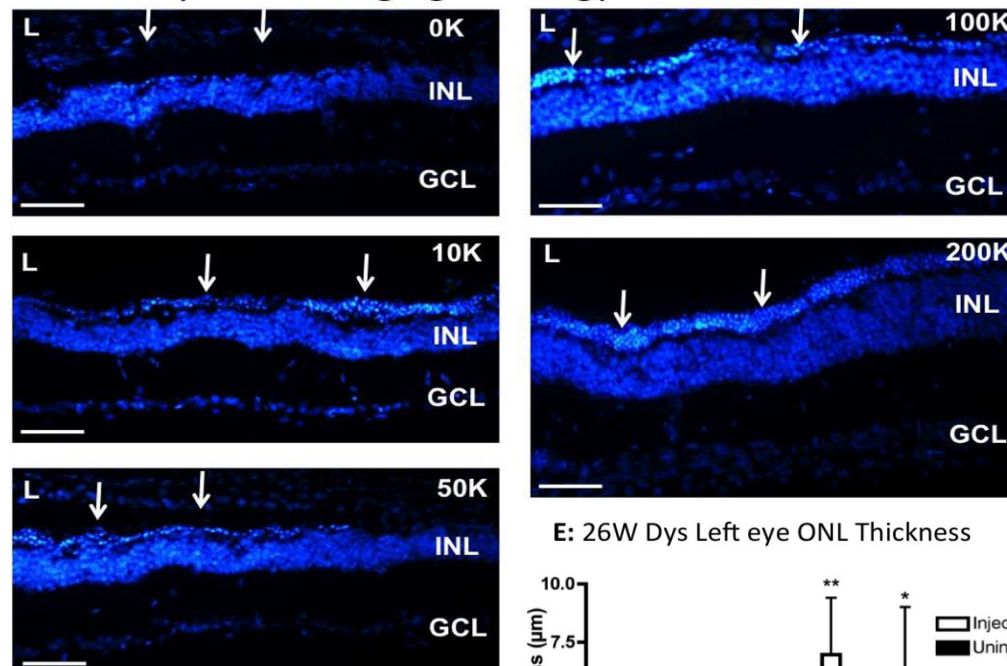
- Allogeneic implantation in pigs (using pRPCs):
 - RPCs derived from fetal pigs (pRPCs) survived and integrated following injection into pig eyes
 - Integration primarily within photoreceptor/outer nuclear layer
 - No signs of graft proliferation
 - Local immunosuppression did not have any effect on implantation efficiency
- RCS dystrophic rat study (using hRPCs):
 - Unilateral subretinal injection of hRPCs in dystrophic and wild-type (WT) rats survived/integrated up to 6 months post-implantation
 - At 3 and 6 months post-implantation, hRPC slowed the progressive decline of visual function and ONL thickness in injected eye of RCS dystrophic rats
 - No differences in visual function or ONL thickness in WT rats in injected eye vs non-injected eye

hRPCs reduce retinal degeneration and visual deterioration in RCS dystrophic rats

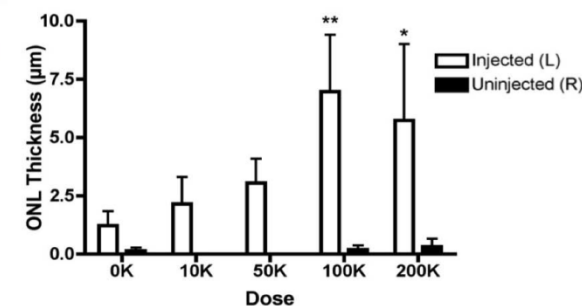
26 weeks post-implantation



D: 26W Dys dose-ranging histology



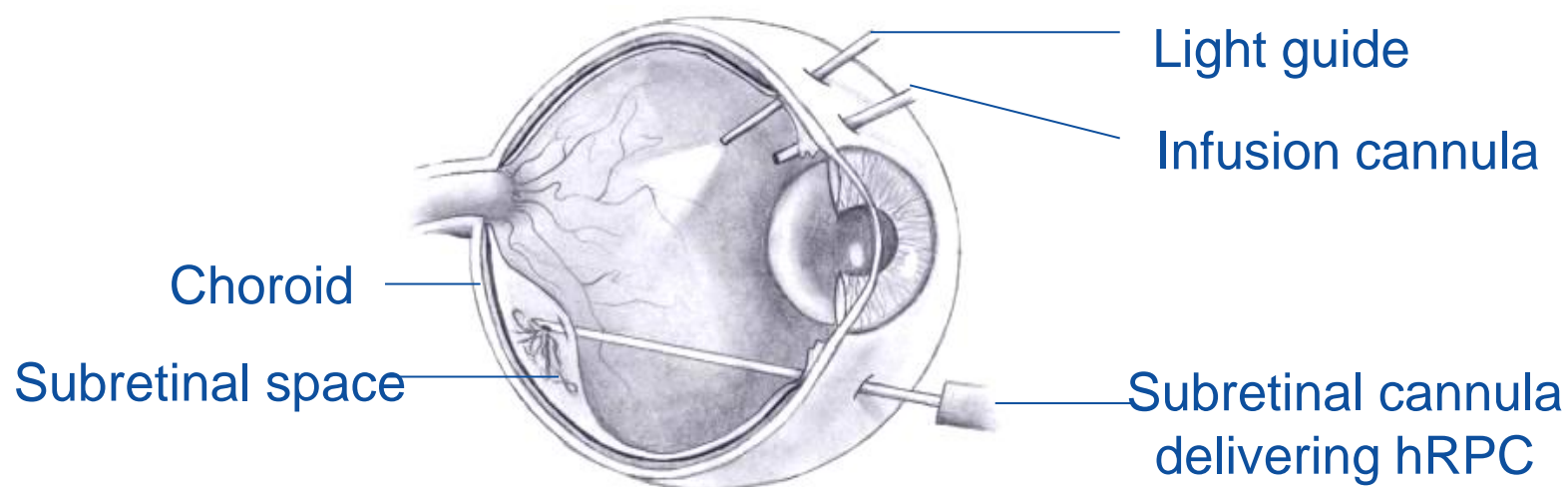
E: 26W Dys Left eye ONL Thickness



Both structural and functional efficacy of hRPCs observed 6 months post-implantation

Clinical development – Ongoing Phase I/IIa

- FIH, dose escalation study in subjects with established RP in the US (NCT02464436)
- Phase I - 3 dose groups of 3 subjects each
- Phase IIa - 6 additional subjects at highest, safe dose
- Primary endpoint is safety, with visual acuity, visual field, retinal sensitivity and retinal structure as secondary efficacy measures
- Measurements in both treated and untreated eyes for comparison
- Phase I/IIa clinical site – Massachusetts Eye & Ear Infirmary, Boston (PI: Dr Eric Pierce)
- Scheduled to readout in H1 2019



Proposed hRPC Trials: RP (IIb) and CRD (II)

Objective:
Efficacy, Safety and
Tolerability of
subretinally
transplanted hRPCs

Primary endpoint:
Change in best-
corrected visual acuity,
from baseline to 6
months post-
implantation

Subject Population:
Subjects (>18 yo) w
best Corrected ETDRS
visual acuity in both
eyes within LogMAR
+1.3 to +0.5 inclusive
(20/400 to 20/63)*

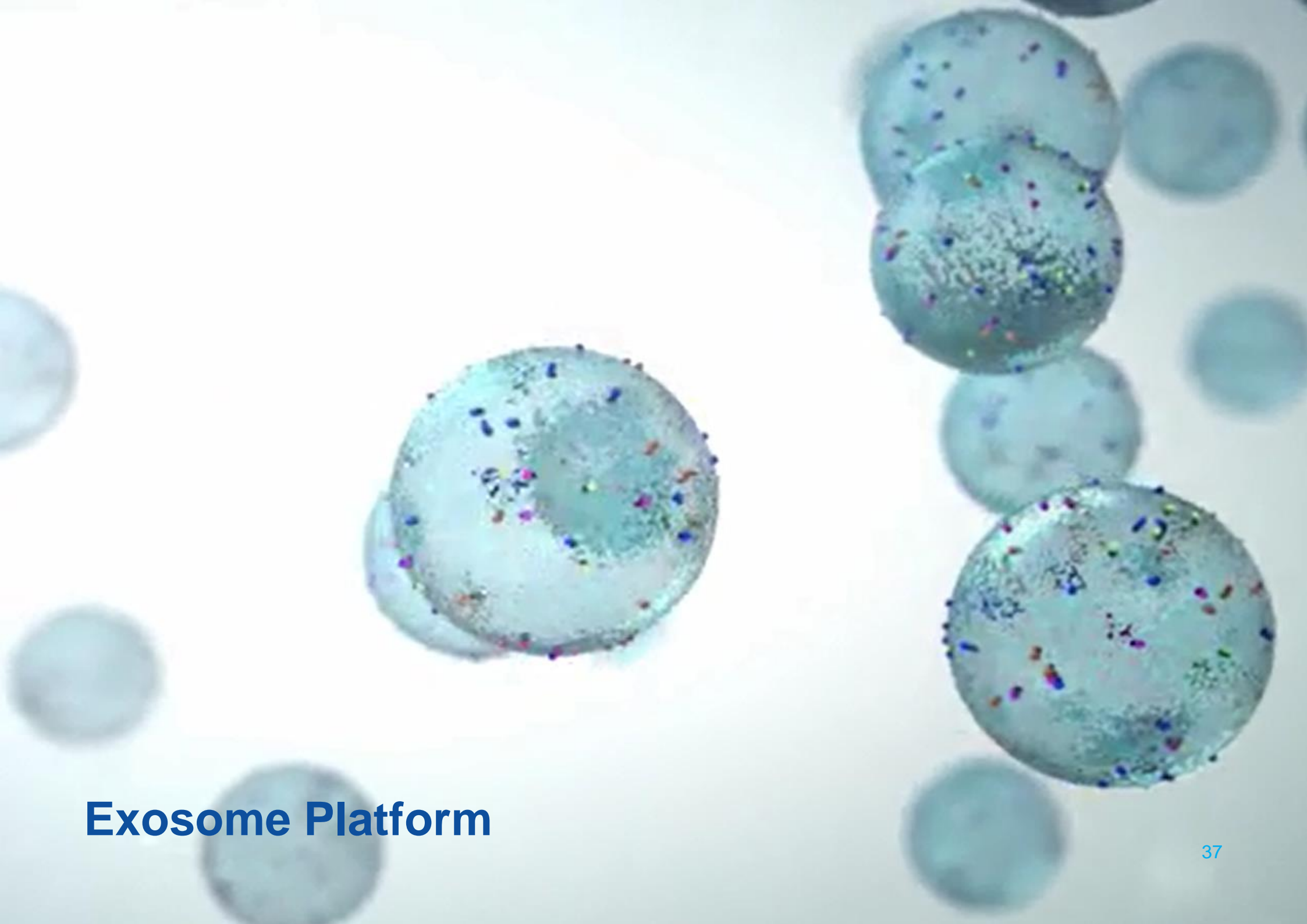
Approximate
US sites:
5

- Secondary objectives include evaluating changes in visual acuity, light sensitivity, full field sensitivity out to 12 months as well as assess changes in retinal thickness and central retinal fluorescence at 12 months. Also, assess subject-reported outcomes regarding vision and impact on independent mobility and quality of life. Assess treatment emergent adverse events out to 24 months
- *First three subjects (best corrected ETDRS VA 20/400 to 20/200) to receive hRPC treatment will have Day 14 safety data reviewed by the DSMB. If no safety considerations, recruitment will continue with VA inclusion criteria of 20/400 to 20/63.

Summary

hRPC is a Phase II ready asset with regenerative potential

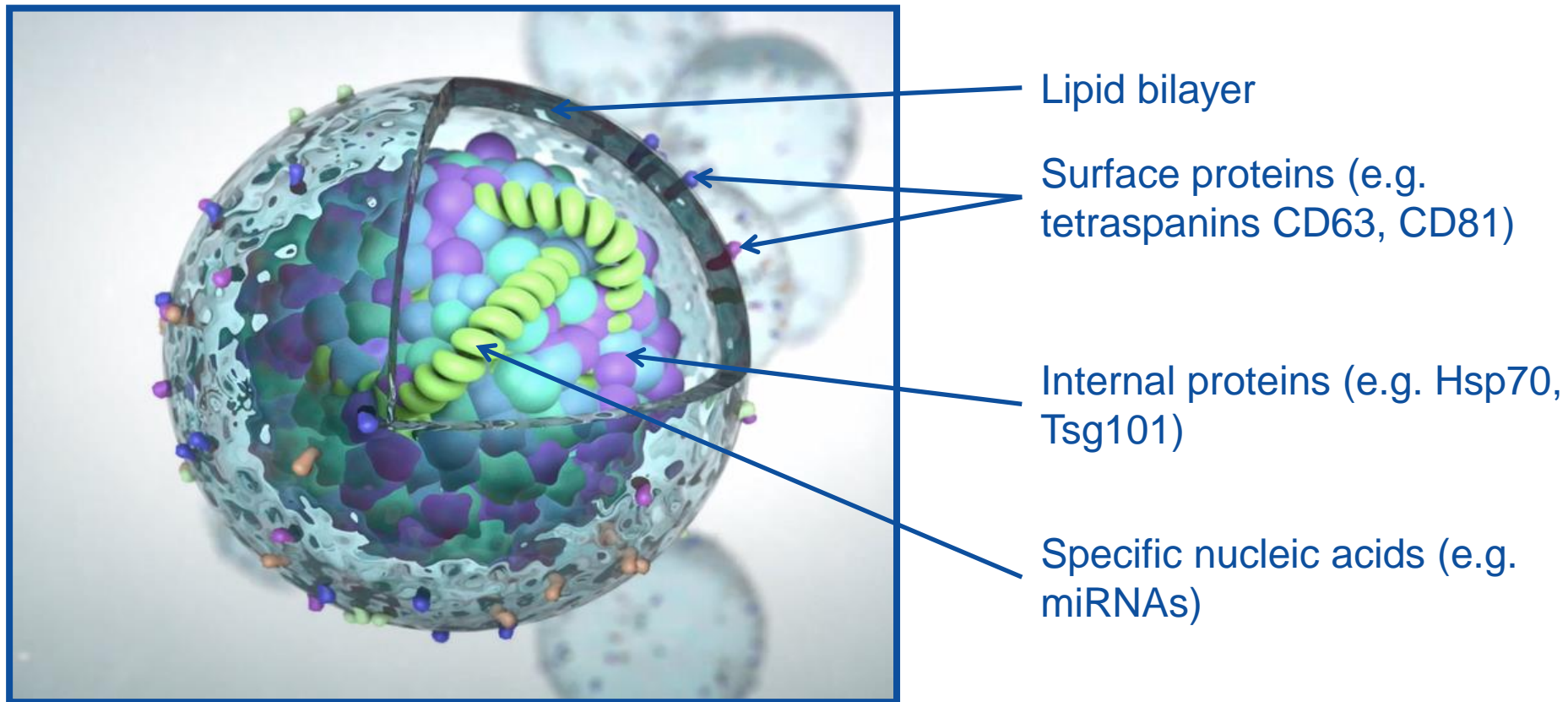
- There is a significant unmet medical need for a therapy that can treat vision loss associated with inherited retinal degenerative diseases.
- hRPC provides a cell-based therapeutic approach that may improve visual acuity and/or slow progression of disease.
- Preclinical evidence demonstrates subretinal injection of RPCs:
 - Survive and integrate primarily within the photoreceptor/outer nuclear layer.
 - Reduce retinal degeneration and visual deterioration in well-established dystrophic RCS animal model
- Currently, Phase I/IIa clinical trial ongoing in RP patients in US.
 - Readout in H1 2019
 - Dose-escalating long-term safety; feasibility of administration
- In parallel, designing next clinical trials in RP (Phase IIb) and CRD (Phase II) to commence 2019:
 - Working closely with established IRD centers in the US



Exosome Platform

Exosome therapeutics

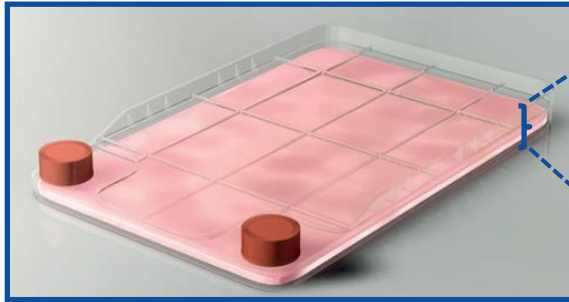
- Nano-scale vesicles (30-100nm) released by most cell types as a means of intercellular communication
- Considered to be a naturally-occurring liposomal delivery system
- Contain and transport bio-active lipids, proteins and nucleic acids



Three distinct applications for CTX-derived exosomes

- Base platform can be rapidly modified using different approaches to produce alternative products for specific applications:

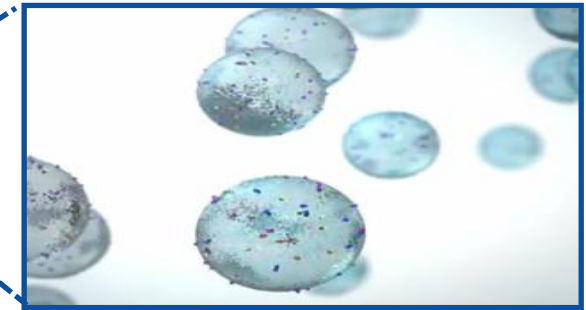
Endogenous CTX Exosomes



Bespoke CTX Exosomes



CTX Exosomes Delivery System



Culture Conditions

- Modification of e.g. growth / environmental conditions tailored to specific effects and/or targets

Modification of Producer Cells

- Directed expression through genetic modification for specific trafficking of desirable exosome cargoes

Extracted exosomes

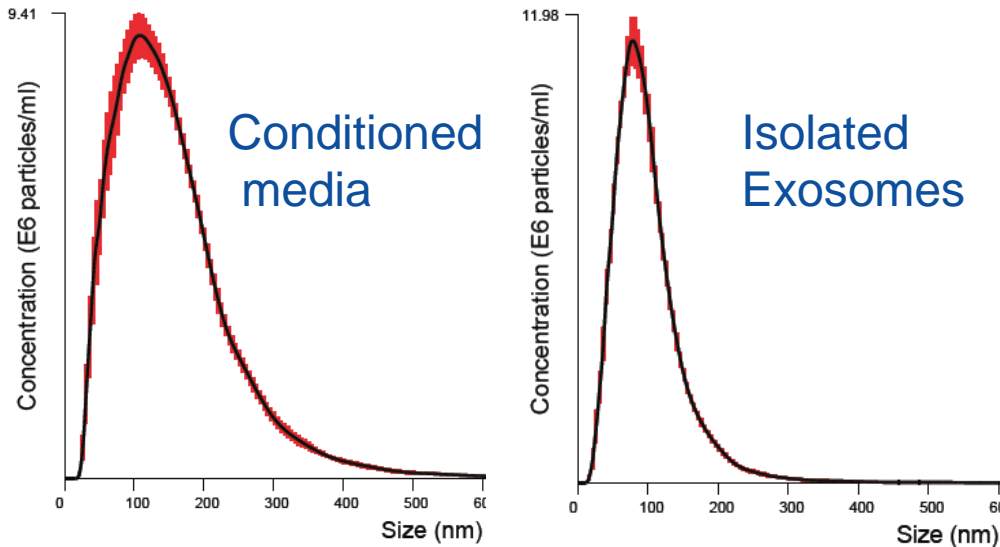
- Post-production loading of exogenous cargoes, e.g. siRNAs, proteins, small-molecule inhibitors

A global leader in stem cell-derived exosome manufacture

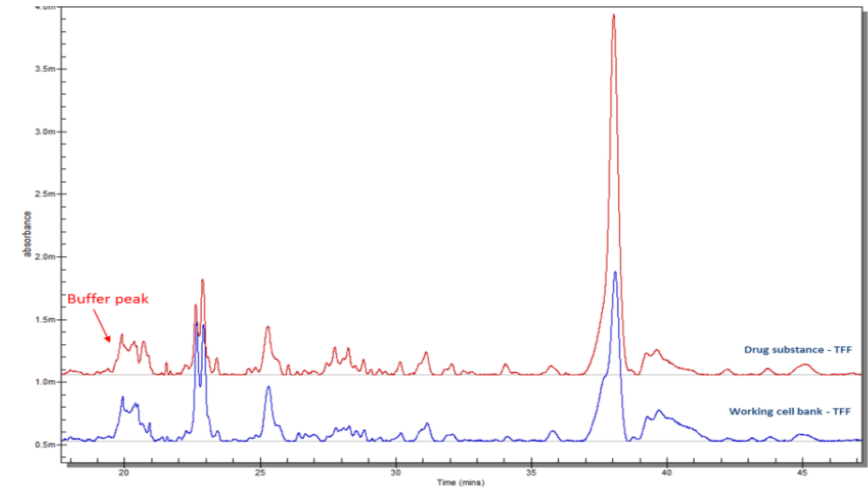
- Exosome platform established at ReNeuron in 2011
- Significant IP portfolio established
- Qualified, scalable GMP process
- Proprietary clinical-grade producer cell line (CTX), giving high yields
- Stable and consistent product
- Established analytics
- Broad anti-cancer properties identified in lead candidate (ExoPr0)
- Scope to tailor endogenous exosomes to specific targets via loading and/or producer cell modification

Stable and consistent product

Nanoparticle Tracking Analysis (NTA):



Proteomic Fingerprint - Capillary Electrophoresis (CE):



Next-Generation miRNA Sequencing (NGS):

	Batch 1	Batch 2	Batch 3	Batch 4
hsa-miR-A	1	2	1	1
hsa-miR-B	2	1	3	3
hsa-miR-C	3	3	4	4
hsa-miR-D	4	5	2	2
hsa-miR-E	5	7	6	7
hsa-miR-F	6	6	5	5
hsa-miR-G	7	12	9	10
hsa-miR-H	8	8	8	8
hsa-miR-I	9	11	12	15

ReNeuron's exosome candidates

ReNeuron are developing three distinct exosome product candidates:

1
ExoPr0

2
ExoPr0+

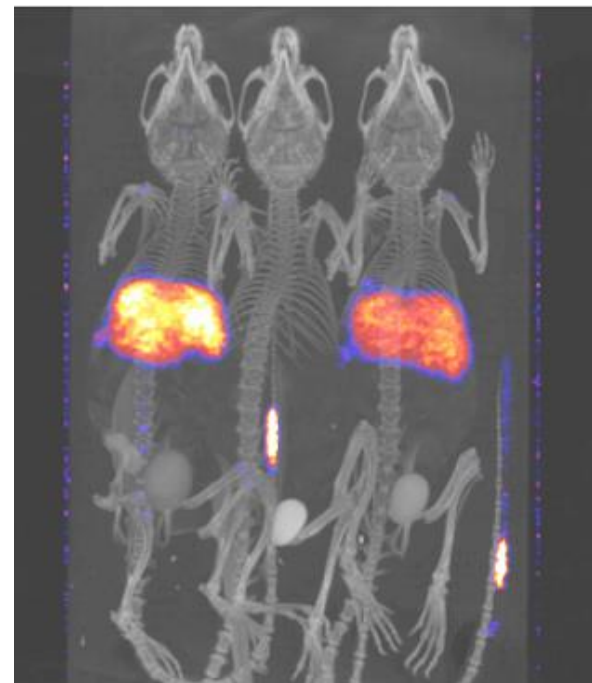
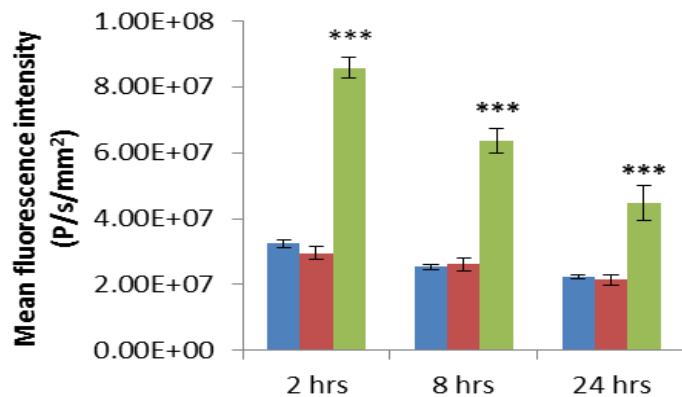
3
ExoDiff

Source:	Derived from Proliferating neural stem cell cultures at scale		Derived from 6+ weeks differentiated culture (small scale)
Type:	Native	Exogenously Loaded	Native
Isolation:	Defined and optimised processing method (DSP) in place		
Additional processing:	N/A	Active loading with select cargo	N/A
Target Indication(s):	Cancer (GBM, Ovarian, hepatocellular carcinoma)	Cancer (subtype TBD) Specific targeting for gene modulation	Neurodegenerative disease, stroke, fibrosis Anti-inflammatory, Liver cirrhosis

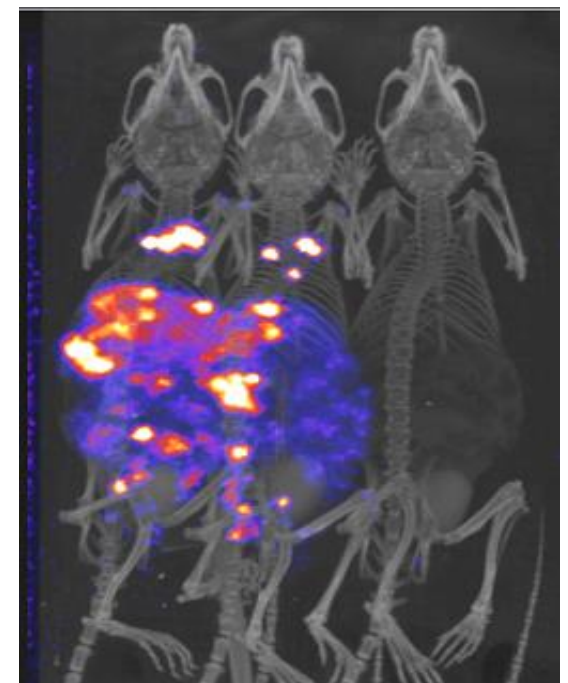
ExoPr0 exhibits brain-specific tropism

- Assessment of ExoPr0 in vivo bio-distribution using two distinct labelling methods (fluorescence and radiolabel) indicated favourable distribution across the blood-brain barrier and distinct distribution profiles based on route-of-administration.

IR800CW-labelled ExoPr0 i.v. administration Brain



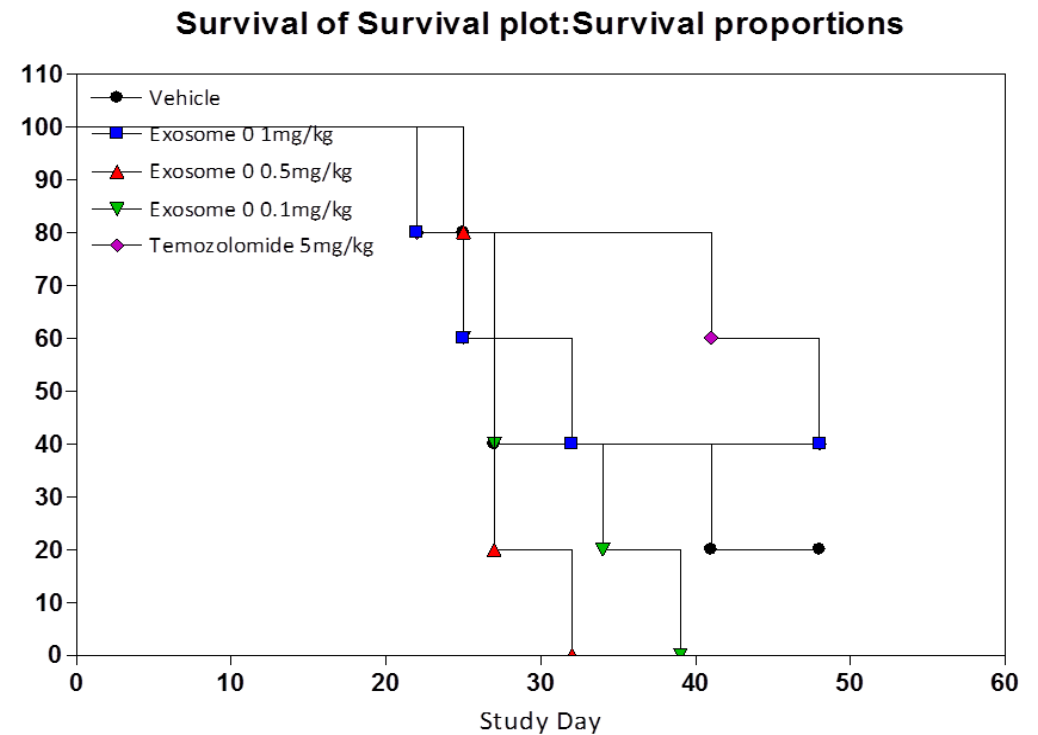
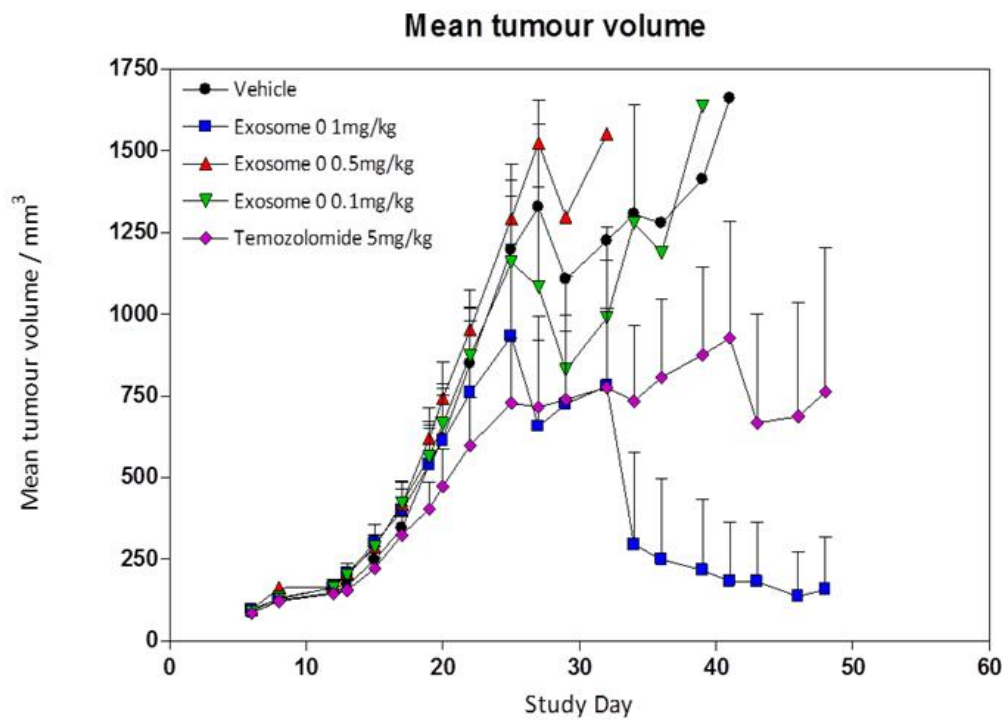
⁸⁹Zr-labelled ExoPr0
i.v. administration
48 hours post-dose



⁸⁹Zr-labelled ExoPr0
i.p. administration
48 hours post-dose

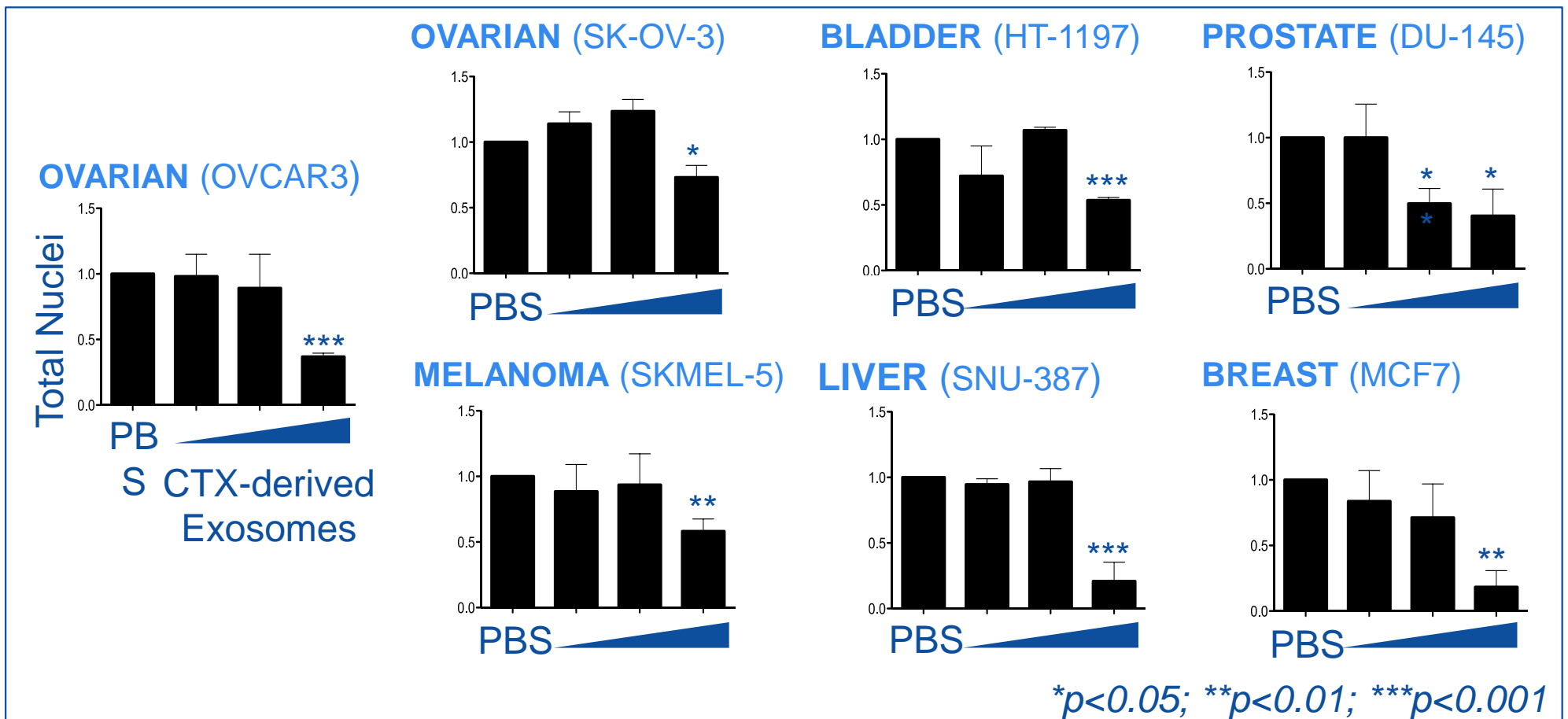
In vivo anti-cancer efficacy of ExoPr0

- Subcutaneous grafts of U87MG glioblastoma cells into athymic nude mice
- Single treatment ExoPr0, delivered directly into tumour
- Dose response (1, 0.5, 0.1 mg/kg), Temozolomide control



Broad anti-cancer efficacy of ExoPr0 *in vitro*

- *In vitro* screen for ExoPr0 efficacy in a truncated NCI60 cell line panel
- Anti-proliferative responses observed across multiple tumour types – approx. 1/3 of all lines tested showed evidence of positive response to ExoPr0



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