FINDING A CURE FOR PARALYSIS

Cell Transplantation and Rehabilitation Human Clinical Trial Project Summary

November 2022

Perry Cross Spinal Research Foundation

To Cure Paralysis For All™

Context

What is the challenge?

A spinal cord injury can happen to anyone at any time. In fact, in Australia, on average one person sustains a spinal cord injury (SCI) and is paralysed every day. The are currently over 20,800 Australians living with a spinal cord injury and millions globally.

- Men account for 70% of SCI
- The main cause for injuries includes falls (42%), vehicle accidents (40%) and sporting injuries (11%)
- 40% of people with a SCI are likely to suffer PTSD

Paralysis is the loss of voluntary movement and often results in being confined to a wheelchair as well as the loss of function and feeling.

About the Perry Cross Spinal Research Foundation

People with a spinal cord injury are at the heart of everything we do.

The Perry Cross Spinal Research Foundation aims to facilitate, collaborate and initiate the connections and research required to find a cure for paralysis. We are driven by a commitment to our vision and mission and guided by our organisational values.

VISION

Cure paralysis for all

MISSION

The Foundation is dedicated to facilitating and funding world class research aimed at curing paralysis caused by spinal cord injury and supporting better outcomes for those living with paralysis.

In 2010, Perry Cross AM founded the Perry Cross Spinal Research Foundation with the mission to cure paralysis for all. Over the ensuing decade, with the support of incredible donors and the Queensland State Government, we have raised over $13.2M for research focusing on a cure.

We support and fund the Spinal Injury Project (SIP), which is based at the Menzies Health Institute Queensland (MHIQ) and the Griffith Institute for Drug Discovery (GRIDD) at Griffith University. This ground-breaking, world first project was pioneered by 2017 Australian of the Year, Emeritus Professor Alan Mackay-Sim and involves the transplantation of the patient's own Olfactory Ensheathing cells (OECs) from the nose into the spinal cord.

By combining advanced cell purification techniques and engineering, the research team is designing three-dimensional nerve bridges that will help regenerate the spinal cord. These 3D cell constructs use newly invented, award winning technology involving 3D printed templates. After transplantation into the spinal injury site, the nerve bridges create a permissive glial bridge which enables the endogenous neurons to grow across the injury site, leading to restoration of neural connectivity.

This incredible approach has the potential to result in the first widely available treatment for spinal cord injury and it is being developed here in Australia.

Curing Paralysis

Our ultimate goal is to conduct a Cell Transplantation and Rehabilitation Human Clinical Trial using this transplantation treatment to restore movement in people suffering with paralysis.

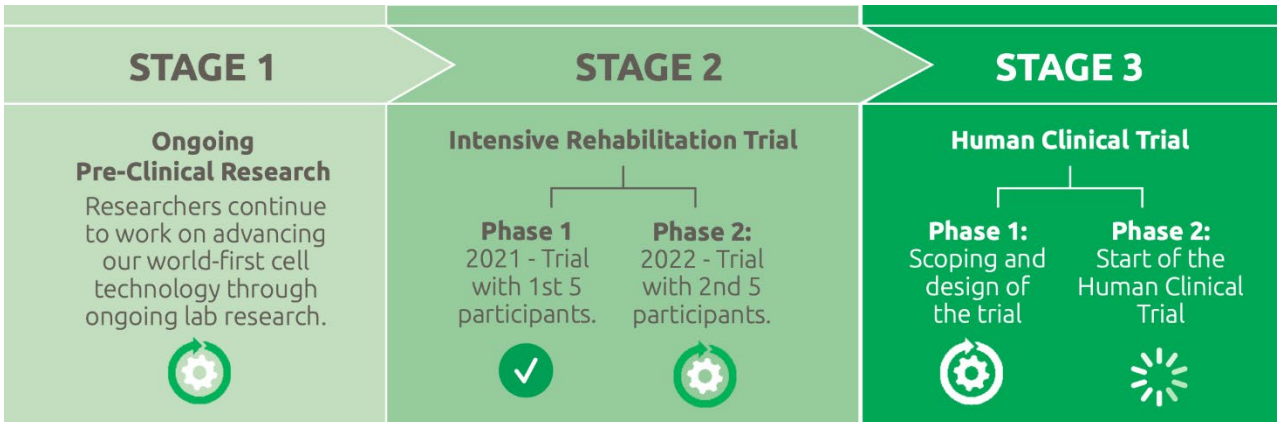
Before we can do this, the program requires the patient to undertake intensive rehabilitation to prepare the body to move again. Without long-term activity-based rehabilitation, cell transplantation alone will not be successful.

With this in mind, we have worked to combine research with rehabilitation in pursuit of recovery. Recently, through the generous support of donors, the first five participants have completed a six-month Intensive Rehabilitation Trial (phase 1 in diagram).

The biostatistician is currently analysing the data from this Trial and over the coming few months, the research team will collate all the findings. Whilst the official results have not been formally shared, the preliminary findings have indicated life changing outcomes for the participants.

We have funded and are now moving forward with the next five participants (phase 2 in diagram). This will ensure a robust set of data and it is hoped that this work will help change the way rehabilitation is administered in Australia, post injury.

The SIP Team is currently working on scoping and designing the ultimate goal; a Cell Transplantation and Rehabilitation Human Clinical Trial (stage 3 in diagram). <u>It is estimated to cost $8.5M for the first 10 participants</u> with a spinal cord injury. The funding and development of future Trials will be dependent on these outcomes.



$3.7 billion cost to society

Without an effective cure, the emotional and financial costs to individuals, their families and to our community as a result of a spinal cord injury are life-long.

Aside from the devastating personal trauma, the cost to our society to care for people living with a spinal cord injury is over $3.7 billion a year. This is not sustainable and must change.

Finding a cure of this magnitude takes universal force and collective power. Every time someone links arms with us, our global movement strengthens our voice gets louder, our presence more visible and a cure becomes a reality.

What are the stats?

The Perry Cross Spinal Research Foundation has one main goal, to find a cure for paralysis for all, by funding world class spinal injury research.

1 person injured every day

Over **20,000** Australians are living with a SCI.

Men account for 70% of SCI's

The main cause for injuries

42% falls

40% vehicle accidents

11% sporting injuries

7% other

Quadriplegia
42% of injuries

Paraplegia
58% of injuries

Paralysis is the loss or impairment of voluntary movement and the loss of function and feeling.

Spinal cord injuries cost the Australian economy more than **$10M** per day.

Since 2010, the Perry Cross Spinal Research Foundation has invested over **$13.7 million dollars** into ground-breaking Australian research.

70%
of people with a SCI suffer from chronic pain for more than 6 months

80%
of people with a SCI are affected by a lack of bladder /bowel control

40%
of hospitalised people with SCIs have respiratory failure

40% of people with a SCI are likely to suffer PTSD

30% of people with a SCI are at risk of depression

Statistics from; AlphaBeta. Spinal Cord Injury in Australia. 2020

Cell Transplantation and Rehabilitation Human Clinical Trial Project Summary

The Perry Cross Spinal Research Foundation supports and funds The Spinal Injury Project (SIP), which is based at the Menzies Health Institute Queensland (MHIQ) and the Griffith Institute for Drug Discovery (GRIDD) at Griffith University.

The Spinal Injury Project is translating a long-established scientific discovery into a clinical product to treat spinal cord injury. Specialised cells called olfactory ensheathing cells are obtained from a simple biopsy inside the nose, and then isolated, expanded and activated. These cells are then formulated into a three-dimensional (3D) cellular nerve bridge for transplantation into the site of injury to repair the spinal cord.

The translational research project is on track to commence a clinical trial in 2023 to treat the chronically injured spinal cord. The Spinal Injury Project is led by Professor James St John and involves a diverse team of thirty five researchers including bioengineers, cell biologists, molecular biologists, who use discovery and translational research to fast-track the progression to clinical trial.

Translating a treatment to the clinic

Griffith University and the Spinal Injury Project are translating a cell transplantation therapy that has been extensively tested in preclinical animal models and comes off the back of work conducted by scientists around the world including here in Queensland. The first human trial of olfactory cells for treating spinal cord injury was conducted in Brisbane and led by the 2017 Australian of the Year and Griffith University Professor Emeritus Alan Mackay-Sim. This trial demonstrated that the use of olfactory cells for treating spinal cord injury was safe for use in humans.

Following this clinical trial researchers around the world then continued to improve the therapy and in 2014 a human trial by British and Polish researchers demonstrated that restoration of function is possible. Within 6-12 months after transplantation the patient, who had been paralysed for several years prior to the treatment, regained some motor, sensory and autonomic function. This work demonstrated that the therapy could work, but that improvements were needed to make it more effective.

The critical advantage of olfactory cells

The olfactory system is responsible for our sense of smell. Nerve cells within the lining of the nasal cavity detect odours within the air and send the signal via olfactory nerves up into the brain. As we know from covid, when

we breathe in air, we also breathe in toxic chemicals, bacteria and viruses which can destroy the olfactory nerve cells. Luckily, the olfactory nerve cells constantly regenerate due to stem cells that can rapidly replace the lost nerve cells. Every day, 1-3% of the olfactory nerve cells die and are replaced by stem cells. The olfactory system is the only part of the nervous that continually regenerates every day as part of its normal process.

Central to the regenerative capacity are a crucial cell type called olfactory ensheathing cells. These cells ensheathe, or wrap up and protect, the nerve cells. The olfactory ensheathing cells remove the dead cells, guide the new nerve cells to their targets in the brain, and they provide ongoing support to the nerve cells. Due to these special properties, transplanting olfactory ensheathing cells into the spinal cord can help repair the injury and lead to effective regeneration.

Olfactory ensheathing cell transplantation is very safe as these cells are not stem cells which could grow into other cell types or causes tumours. Instead, they are a fully mature cell type that is already in the desired state for repair. In our preclinical animal research we have not detected any inappropriate cell growth after transplantation of our purified cell preparation into the injured spinal cord.

Award-winning cellular nerve bridges

The Spinal Injury Project team has invented a powerful technology to rapidly produced three-dimensional cellular nerve bridges. The potentially transformative power of this technology has been recognised by two major national awards:

(1) The NHMRC Marshall and Warren Innovation Award 2019 to Professor James St John, A/Prof Jenny Ekberg, Dr Matt Barton, Dr Brent McMonagle

(2) The Research Australia Discovery Award 2020-2021 to Dr Mo Chen

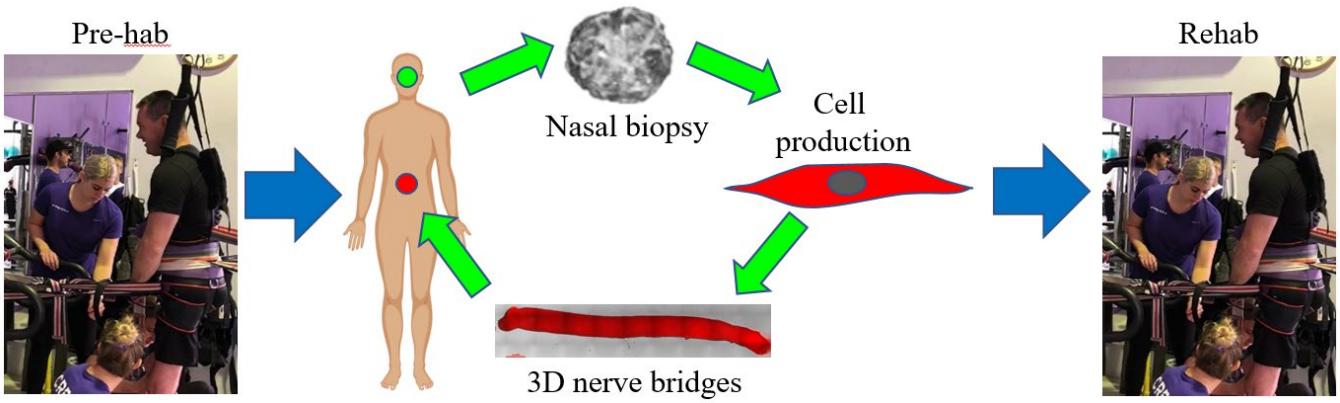
The nerve bridges dramatically improve the integration and survival of the transplanted cells and lead to improved outcomes in preclinical research.

Co-design with the community

The therapy has been co-designed with the spinal cord injury community to ensure that it meets their expectations and needs. The Spinal Cord Injury National Consumer Research Panel consisting of ten people from around Australia living with spinal cord injury regularly advises the team about the research direction and provides input into the therapy design. Griffith University frequently hosts tours of the research laboratories where the community gets to experience the research activities and to see the nerve bridges that are used for transplantation. Continual input and co-design from the community ensures the therapy has the best chance of success.

Ready for Clinical Trial

The Spinal Injury Project therapy is now ready to be tested in a Phase I human clinical trial. In addition to the cell transplantation, the participants will undergo intensive exercise rehabilitation to help stimulate the nerve cells to find their appropriate targets to re-establish functioning neural connections.



The Phase I clinical trial will be conducted on the Gold Coast, Queensland and will have 10 participants who live with chronic spinal cord injury. Participants will undergo 12 weeks of rehabilitation exercise therapy before the cell transplantation and then a further eight months of rehabilitation after the cell transplantation.

The olfactory cell therapy trial has six stages:

1. Nasal biopsy to obtain olfactory cells
2. Purification and separation of olfactory cells
3. Construction of the 3D nerve bridges for cell transplantation
4. Long-term intensive exercise therapy to prime the body prior to transplantation
5. Surgical transplantation into the injury site
6. Long-term intensive exercise therapy to maximise chances of forming functional connections

Clinical Trial Stage I - $8.5 million – for a Phase I human clinical trial to test the safety and efficacy of the therapy in 10 patients over one year.

Budget

We recently met with the team at Griffith University and confirmed that the Perry Cross Spinal Research Foundation have quarantined $2M of our retained fundraising dollars as a seed contribution to this trial.

In response, Griffith University have offered their commitment to contribute a further $1M of in-kind support. As a result, contributions committed are as follows;

$8,560,000 total estimated funds required for the trial

- $2,000,000 Contribution from PCSRF
- $1,000,000 Contribution from Griffith University
- $1,000,000 Contribution from Nicola and Andrew Forrest
- $1,000,000 Matching Contribution to Nicola and Andrew Forrest (to be sourced)

<u>$3,560,000 further funding required</u>

The Foundation's current fundraising purpose is to work with Griffith University to ensure we secure the dollars to make this trial happen as soon as 2023.

The main purpose and objective of the trial (Phase I) is to test the safety and efficacy of the therapy in 10 patients, each of whom will have previously sustained a spinal cord injury, over a one-year testing period.

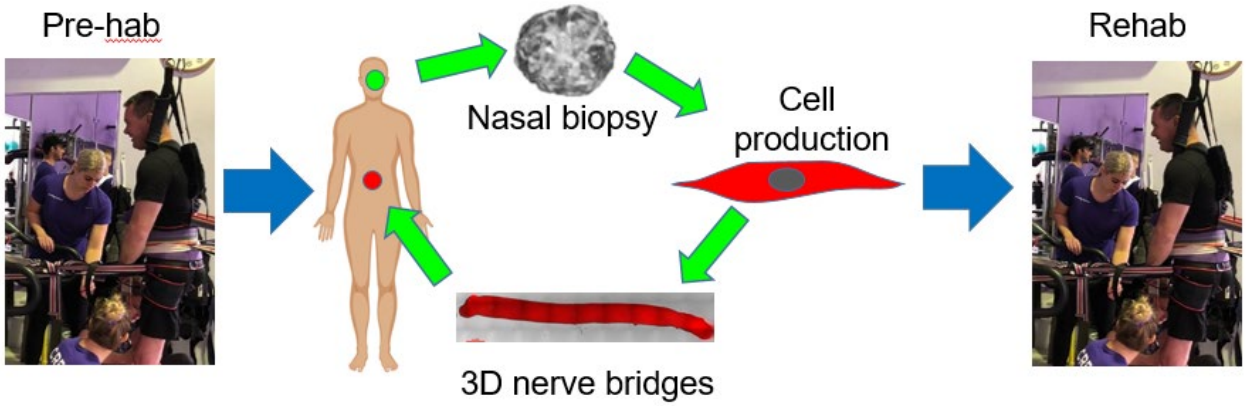
Budget Breakdown: total cost $8.56M

Item	Reason	Cost
Griffith University specialist researchers	High skilled researchers are required for the isolation of the cells and production of the cell nerve bridges for transplantation. They also lead the investigation and analyses of the results throughout the clinical trial.	$1 million
Contract Research Organisation	Independent professional clinical trial management at world standard – includes stats and data management and full report.	$3.2 million
Nerve bridge production and quality control	Cells for human transplantation must be produced in a Good Manufacturing Practice facility.	$550,000
Transplantation surgery	The nerve bridges will be transplanted by specialist neurosurgeons at the Gold Coast University Hospital. Participants will need at least five days hospital stay in intensive care.	$750,000
Comprehensive medical assessments	A large range of medical assessments will be performed throughout the trial including medical imaging, pathology, electrophysiology and physiotherapy	$375,000
Exercise rehabilitation (including travel allowance)	Participants will undergo intensive rehabilitation for 11 months, 12 weeks before the transplantation and 8 months after the surgery. Rehabilitation will be provided by the specialist rehabilitation centre, Making Strides.	$2.5 million
Data management and analysis	In accordance with best practice, data management and reporting, and statistical analyses will be performed by principal investigator and assistant	$187,000
Total human trial cost		**$8.56 million**

Project Plan

Title: Olfactory cell transplantation and intensive rehabilitation to repair chronic spinal cord injury

Estimated Cost: $8.56M



- **Sponsor:** Griffith University
- **Lead investigator:** Professor James St John, Head, Clem Jones Centre for Neurobiology and Stem Cell Research, Griffith University, j.stjohn@griffith.edu.au
- **Principal investigator:** Dr Brent McMonagle, brent_mcmonagle@me.com
- **Sub principal investigator:** Dr Dinesh Palipana, d.palipana@griffith.edu.au
- **Site.** Single site: Gold Coast University Hospital (GCUH), Queensland.
- **ENT surgeon for obtaining nasal biopsies:** Dr Brent McMonagle, Pindara Qld.
- **Cell production:** Performed at Q-Gen Cell Therapeutics, QIMR-Berghofer
- **Radiology:** QScan
- **Transplantation:** Gold Coast University Hospital.
- **Surgical team:** Lead surgeon: Dr Wayne Ng. Supporting neurosurgeons: Dr Ellison Stephenson, Dr Chris Daly.
- **Neurologist:** to be confirmed.
- **Rehabilitation:** Making Strides, Burleigh
- **Independent physiotherapist:** Charmion Bevan
- **Independent Medical Monitor:** Dr Ben Gerhardy
- **Contract Research Organisation and biostatistics:** to be appointed via tender

The patient profile

Patients will have:

- chronic (>12 months since injury) spinal cord injury
- complete motor and/or sensory loss of function below the injury site (ASIA A/B)
- thoracic or low cervical (C5-C7) injury
- exclusion/inclusion criteria – see synopsis.

Number of participants

Ten people will be enrolled. The first patient (sentinel patient) will start 4-6 weeks prior to the others. The remaining nine patients will commence in two groups (4 patients and then 5 patients) separated by one-two weeks.

The cell treatment

The treatment uses a three-dimensional nerve bridge produced with glial cells. The glial cells are obtained from a biopsy of the olfactory epithelium within the nose. The cells are autologous, fully differentiated and minimally manipulated. After isolation from the biopsy, the cells are expanded using routine cell culture techniques and GMP-compliant media.

The nerve bridges are generated using a newly invented in-house production technique. The nerve bridges can be produced to any dimension including (i) large nerve bridges (centrimetres long) which are suitable for transplantation using open surgery, or (ii) small nerve bridges (< 1 mm) which are suitable for deposition via CT-guided injection.

After transplantation into the injury site, the nerve bridges create a permissive glial bridge which enables the endogenous neurons to grow across the injury site, leading to restoration of neural connectivity.

Dose: 2 – 20 million cells will be transplanted.

Cell transplantation

The initial transplantation will be performed with open surgery so the surgical team can visually inspect the injury site and can minimally remove scar tissue to gain access and improve transplantation. Removing scar tissue may re-initiate the “acute” injury responses which may aid regenerative capacity.

Safety

In over 500 transplantations in mice, we have not detected any adverse cellular events.

Within their endogenous environment of the olfactory nerve, and when cultured in vitro, the olfactory glia have a low immune profile which make them suitable for transplantation as they will not initiate an inflammatory response.

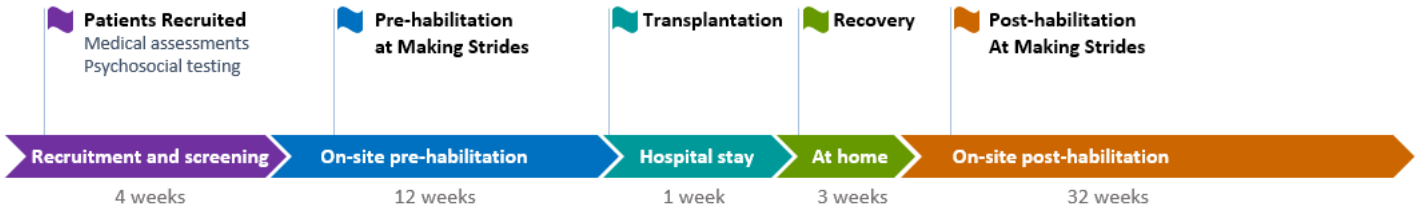
Unlike other glia which can lead to tumours in their endogenous environment, there are around only six reports in the entire medical literature of olfactory glia potentially forming cancer in humans, but the evidence of their identity in those six reports is weak. Therefore, the likelihood of adverse cell growth/tumour growth is low.

The transplantation of olfactory glia into human spinal cord has been tested previously in Australia (2002 Phase I study by Australian of the Year Prof Alan Mackay-Sim). This trial used an injection of a suspension of olfactory glia and demonstrated that the transplantation o of these cells was safe.

The prehabilitation and rehabilitation component

To promote neural plasticity and connectivity, participants will undergo an intensive rehabilitation program both prior to transplantation and after transplantation. The rehab program includes 2 hours of exercise physiology plus 30 minutes of functional electrical stimulation per day, 5 days per week. The “prehab” program will be for 12 weeks, while the post-transplantation rehab program will continue for another 32-week program.

Timeline Summary



(1) the safety testing and approvals will commence in 2023
(2) the active trial will start in late 2023 with recruitment and screening
(3) then the prehab/surgery/posthab will be in 2024 (or start late 2023) for 12 months
(4) then analyses will be in 2025.

Milestones Include

(i) safety testing
(ii) approvals for ethics, therapeutic goods administration, research governance office
(iii) advertising, recruitment and screening of trial participants
(iv) prehabilitation and cell production
(v) cell transplantation
(vi) post-surgery rehabilitation
(vii) active trial completion
(viii) data analyses and report

Outputs and Success Criteria

What success looks like for the Project?

The Phase I trial's primary objective is to test safety. Success will therefore be that the cell transplantation or the rehabilitation program did not lead to any serious adverse events. Secondary objectives are to assess changes in motor, sensory and autonomic function. If any of these are detected to have improved, it will be an indication of efficacy, but due to the Phase I small participant numbers it will not be possible to show significant differences.

Key outputs, targets, results, milestones and deliverables;

- Full detailed trial report to international standards (for example, to satisfy USA Food and Drug Administration reporting)
- Publications in scientific journals
- Reports for community distribution

Milestones achieved: (i) safety testing - cell analyses demonstrate safety across a range of measures including cell characterisation, microbiological status, growth characteristics, (ii) all relevant approvals obtained and full detailed trial protocol; (iii) successful recruitment of 10 participants (iv) production of cells and nerve bridges (v) cell transplantation at Gold Coast University Hospital (vi)completion of rehabilitation program (vii) completion of data analyses and delivery of trial report.

Meet The Research Team

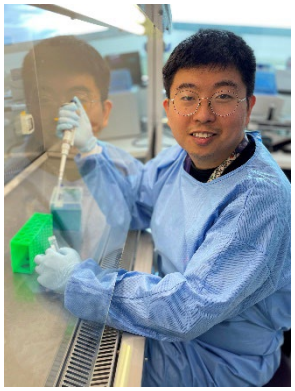
The Spinal Injury Project is directed by Prof James St John and Associate Prof Jenny Ekberg and they lead the following team of internationally recognised researchers, including the key researchers:

- Dr Mo Chen – bioengineer and inventor of the nerve bridge production technology
- Dr Mariyam Murtaza – an expert in human cell production
- Dr Ali Delbaz – an expert in molecular and cellular biology
- Dr Ronak Reshamwala – a medically trained doctor and world class spinal surgeon
- Dr Marie-Laure Vial – a translational clinical trial manager

This exceptional research team are based in state-of-the-art laboratories at MHIQ and GRIDD and have an impressive track record securing high value collaborative grants. They have received previous philanthropic support from the Perry Cross Research Foundation, the Motor Accident Insurance Commission and the Clem Jones Foundation.

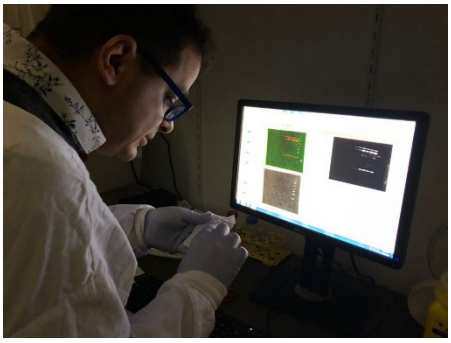
Prof James St John is Head of the Clem Jones Centre for Neurobiology and Stem Cell Research. James is a Life Technologist specialising in the creation and translation of therapies to repair injuries and diseases of the nervous system. He has a particular interest in understanding the biology of the olfactory system (sense of smell) and the role of glial cells in the functioning and repair of the nervous system. He leads the translational research to bring the spinal cord injury therapy to the clinic. **James was awarded the prestigious National Health and Medical Research Council Marshall and Warren Innovation Award 2019 for the application of nerve bridges for repairing the nervous system.**

Associate Prof Jenny Ekberg is Associate Prof of Neurophysiology at Menzies Health Institute Qld and has 20 years' experience in neuroscience research. Her current research aim is to create therapies for nervous system injuries and diseases, such as spinal cord and peripheral nerve injury. She brings in-depth experience of the biology and function of the cells used for transplantation to repair spinal cord injury. **Jenny was also the recipient of the prestigious National Health and Medical Research Council Marshall and Warren Innovation Award 2019 for the application of nerve bridges for repairing the nervous system.**



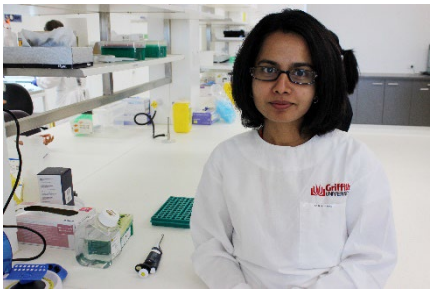
Dr Mo Chen is a Research Fellow with the Clem Jones Centre for Neurobiology and Stem Cell Research. His expertise is in 3D cell culture and his research is focused on the identification of natural products that enhance spinal cord regeneration. Mo has developed a novel 3D cell culturing system and is an inventor for two patent applications for systems that allow cells to self-assemble and form 3D constructs suitable for surgical applications. He also recently invented an additional organoid 3D culture technique with several patent applications currently being finalised. **Mo was awarded the prestigious Research Australia Discovery Award 2020-2021 in recognition for the potential impact of his inventions.**

Dr Ali Delbaz is a Research Fellow with the Clem Jones Centre at the Menzies Health Institute Queensland. He obtained his PhD at Griffith University and specialises in the understanding how gene and protein expression by the transplanted cells can be manipulated to improve their regenerative capacity. He has identified key functions of the cells that now offer exciting new avenues to further improve the efficacy of the cell transplantation therapy.



Dr Ronak Reshamwala is a Research Fellow with the Clem Jones Centre for Neurobiology and Stem Cell Research at Menzies Health Institute Queensland. He is a medical doctor trained in India and has received his PhD from the Griffith University. Dr Reshamwala's research focuses on improving the surgical transplantation of nerve bridges to repair spinal cord injury to improve regeneration.

Dr Mariyam Murtaza is a Senior Research Fellow with the Clem Jones Centre for Neurobiology and Stem Cell Research. Mariyam is a neurobiologist with expertise in the purification and profiling of primary olfactory cells and stem cells. Mariyam completed her PhD and her MSc in Stem Cell Research and Regenerative Medicine at the University of Sheffield. Mariyam specialises in the production of high quality human cells for the transplantation therapy.



Dr Marie-Laure Vial is a Senior Research Fellow with the Clem Jones Centre for Neurobiology and Stem Cell Research. Marie leads the clinical trial team and is an expert in requirements for clinical trial regulations, approvals and governance. She manages the complex partnerships amongst all the stakeholders for the clinical trials. She leads the analytical team that interprets the outcomes of the clinical trials.

Risks

What are the key Project risks? How will they be mitigated?

The capability requirements to deliver the Project (personnel, equipment, and expertise);

SIP team is large with over 30 people, providing duplication of skills. All critical clinical trial members have been appointed.

Any regulatory approvals that may be required;

Human ethics and research governance approvals will be obtained as part of the project. We have already conducted one rehabilitation trial and have a second trial commencing using the full trial partners, so it is anticipated that approvals will be without complication.

Funding profile and security;

Partners for the Human Clinical Trial are actively being sought. We have worked with a number of partners to date;

- Motor Accident Insurance Commission (MAIC) has funded the majority of the preclinical research with an investment of $5M in 2017 and a further $5.7M in 2020. Application for future funding is in process.
- The Perry Cross Spinal Research Foundation has contributed a total of $1,974,125 to the Spinal Injury Project. This funding has supported a number of projects including, most recently;
    - the scoping and design of the Cell Transplantation and Rehabilitation Human Clinical Trial
    - an Intensive Long Term Rehabilitation Clinical Trial (five participants)
    - a Pre-habilitation Clinical Trial (five participants)
- Griffith University in kind support (people and infrastructure) has totalled $4M to date. A further $1M in support for the trial has been agreed.
- The Clem Jones Foundation has contributed $2.4 million for the preclinical research since 2016.
- The National Health and Medical Research Council has contributed $715,000 for the nerve bridge development.

Support from the community

- The Perry Cross Spinal Research Foundation fully support this project and is a community-based organisation.
- It is important to note, the therapy has been co-designed with the spinal cord injury community to ensure that it meets their expectations and needs. The Spinal Cord Injury National Consumer Research Panel consisting of ten people from around Australia living with spinal cord injury regularly advises the team about the research direction and provides input into the therapy design.

- Griffith University frequently hosts tours of the research laboratories where the community gets to experience the research activities and to see the nerve bridges that are used for transplantation. Continual input and co-design from the community ensures the therapy has the best chance of success.

Provide a risk management plan if appropriate

Risk theme	Risk	Inherent Risk Rating	How risk is mitigated / managed	Residual Risk Rating
Cell product: Manufacture	Slow cell growth (from nasal biopsy) affecting production times	Low	Cell production normally takes 4-6 weeks. Production time available is 12 weeks so sufficient time is available to allow for the event of slow production.	Low
Cell product: Supply chain failure	Replacement of reagents required during production.	Low	Duplicate suppliers of all reagents have been identified and all products tested and verified.	Low
Product Labelling: Investigational Medicinal product (IMP) labelling	Chain of identity and patient privacy becoming compromised.	Medium	The act of, labelling samples and final products will be undertaken only by qualified persons at the GMP manufacturing site and cross referenced with documented evidence.	Low
Product Labelling: Logistics failure	Breach of chain of custody from production to transplantation	Medium	Clinical coordinator, GMP team and logistics team will confirm sample custody and will regularly perform sample ID checks	Low
Product Labelling: Sample tracking, temperature monitoring	Compromised cold chain, CO_2 levels, storage temperature	Medium	Document evidence of sample monitoring and acceptable hold times/hold temperatures will be defined prior to trial commencement	Low
Product Labelling: IMP packaging	Breach of packaging	Low	All IMP packaging will be checked prior to use and acceptable breach of primary versus secondary packaging will be identified and defined.	Low
Storage: Intermediate banking / cryopreservation	Frozen samples becoming compromised before surgical transplantation	Medium	The GMP facility storage uses standard operating procedures carried out by qualified persons at facility to ensure high quality of frozen samples.	Low
Storage: Sample tracking for storage	Identity or location of samples are misplaced.	Low	IMP labelling will be done by qualified persons and storage in vapour-phase liquid nitrogen will be documented.	Low
Cell product safety and	Presence of highly proliferative cells may	Low	In-process controls will be implemented to remove highly	Low

efficacy: Proliferation capacity	induce tumour formation		proliferative epithelial cells and mucous-forming cells from the initial biopsy.	
Cell product safety and efficacy: Homogeneity of cell population	Contaminating cell types in the cell population will result in a highly varied product	Medium	Define target product profile prior to trial and only products meeting acceptable product criteria will be released.	Low
Cell product safety and efficacy: Batch-to-batch consistency	Profiles for different batches of cells become very dissimilar resulting in a highly varied product	High	Carry out rigorous in process controls and checks and define acceptable variation range to maintain consistent batch cell profiles.	Medium
Cell product safety and efficacy: Acceptable safety profile	Safety standards become unsafe, and product becomes unfit for use	Low	Collect safety data for in vitro and in vivo studies prior to transplantation.	Low
Cell product safety and efficacy: Microbiological contamination of cells	Introduction of adventitious agents during biopsy or processing compromising patient safety	Medium	Well-defined and adequately controlled aseptic manufacturing process with appropriate in-process controls and release tests will be implemented when acquiring nasal biopsy.	Low
Cell product safety and efficacy: Generation of an immune reaction in patient	Transplantation of cells resulting in an immune reaction in the patient.	Low	The nature of the therapy is that the cell product is taken from the patient's own tissue, reassembled, and put back into the same patient. Should not illicit an immune response.	Low
Cell product safety and efficacy: Toxicity	Overdosing of cell could result in toxicity in the recipient.	Low	Pre-clinical animal studies have shown no indication of toxicity from large cell numbers.	Low
Operation / Procedure: Surgery: Unexpected delays	Hospital surgery availability could become impeded by other high priority surgeries	medium	As nerve bridges can be prepared very quickly (24-hour notice)	Low
People: Local Recruitment	Insufficient recruitment numbers to carry out the trial	Low	Site selection and recruitment targets are based on known, robust clinical data and patient interest. Our extensive networks, including the PCSRF network, will be used to advertise for recruitment of participants.	Low

People: satisfactory recruitment	Potential participants do not satisfy inclusion/exclusion criteria.	Medium	We anticipate that we will receive a large number of expressions of interest for the trial. We have already gauged community interest via our survey and 99% of respondents say they would be willing to participate. We have had good recruitment for both rehabilitation feasibility trials.	Low
People: Staff Experience	Site staff and research staff inexperienced at collection of clinical data for the trial resulting in poor collection methods.	Low	Site staff experienced at collection of similar data using similar collection tools as part of routine rehabilitation programs. All staff trained on completion of trial clinical report forms at trial initiation. The two rehabilitation feasibility trials have involved trial staff and all are now experienced with the proposed trial reporting.	Low
People: Response Rate	Insufficient completion / response rates to questionnaires and psychosocial tests.	Low-Medium	Data on psychosocial health will be collected via Electronic Data capture system, which may result in poor response rates; Reminders will be sent to participants to encourage completion.	Low
Management: Project Management (Contract Research Organisation, CRO)	CRO complications and management difficulties resulting in clinical trial quality becoming compromised	Low	We have previously worked with the CRO Neuroscience Trials Australia for our first two feasibility trials. CROs have extensive experience in managing clinical research and trials in Australia.	Low
Prehab / Rehabilitation: Adverse health events	Routine health complications affecting participants ability to complete the trial	Medium	People living with spinal cord injury frequently have health complications including pressure sores or autonomic dysreflexia. Adverse events during the trial will be reported in accordance with standard guidelines. Participants will continue their routine medical consultations to manage these conditions.	Low
Prehab / Rehabilitation: Adverse Events/ Serious Adverse Events during rehab	Participants acquiring injuries or medical complications as a result of the SCI therapeutics	Low	There is a risk of musculoskeletal damage in people with spinal cord injury doing new activities. The activity-based program will be designed for each individual, and overseen by a physiotherapist, to	Low

			ensure that the activities are within reasonable limits. Evidence from our first feasibility trial has shown that few AEs occurred during intensive rehabilitation, and no SAEs.	
Delivery of trial: Costing/Funding	Delays in the trial may result in increased clinical trial costs	Medium	Trial budget has accounted for 20% of unexpected costs	Low
Delivery of trial: Inadequate staffing numbers	Insufficient site staff to perform trial duties in addition to existing rehabilitation services.	Low	Site Staff at the Gold Coast University Hospital, are employed independently from the trial, as are the staff at the rehabilitation centre, Making Strides.	Low
Delivery of trial: Staffing complications	Principal Investigator not present due to unavailability/sickness resulting in deviations to patient visits and/or assessments	Low	We have engaged a sub-PI to avoid delayed assessments due to PI unavailability/sickness	Low
Delivery of trial: Site withdrawal	Withdrawal of the site resulting in no adequate site for the trial to take place in.	Low	The trial site team was involved in the trial design and set-up, as were industry partners, Making Strides and so are aware of trial timelines and capacities.	Low
Delivery of trial: Approvals	Delay in obtaining approvals, modifications required resulting in clinical trial timelines becoming compromised.	Low	The Contract Research Organisation will manage the approvals process. The team, via a Research Fellow, will liaise closely with the CRO to ensure timely completion of all required activities.	Low
Delivery of trial: Making Strides / Industry partners	Inability of Making Strides to provide rehabilitation service	Low	Making Strides has been closely consulted during the design of the trial and are a well-established provider of rehabilitation services for people living with spinal cord injury. Making Strides has already been engaged for the first two feasibility rehabilitation trials.	Low
Delivery of trial: COVID-19 (Pandemics)	COVID-19 complications (lockdown, travel restriction, quarantine/isolation for insurance) may result in participants being unable to attend	Medium	The trial site has a COVID-safe plan in place. In addition, catchup sessions will be allowed to extend the trial if required due to COVID-19 lockdowns.	Low

	the on-site rehabilitation program			
Governance: Participant compliance	Participant dropouts may result in overall decreases in participant's activity and lower compliance averages.	High	People with spinal cord injury are frequently faced with numerous challenges, and it is possible that some participants will not be able to fully complete the prehabilitation or rehabilitation programs. Two feasibility trials to measure compliance to an intensive on-site rehabilitation programme have been completed or are in progress. Preliminary analysis of first feasibility trial shows very high compliance to the programme.	Medium
Governance: Litigation	Participant in trial is injured and may sue the trial organisers	Medium	Griffith University has insurance for clinical trials, and documentation established by Griffith Legal Team. Participants sign a Patient Information Consent Form and have contact details of the Site Staff of the Gold Coast University Hospital.	Low
Information: Data storage	Hacking of data security results in a breach in patient confidentiality.	Medium	Participant data will be collected, entered, and managed by authorised study personnel in an Electronic Data Capture application. The application will be Health Insurance Portability and Accountability Act (HIPAA)-compliant, highly secure, and intuitive to use. Only authorised and fully trained staff will access the data capture programme. All paper records will be stored in locked file cabinets with restricted access. Access will only be granted to designated staff. Patient records will be kept for 15 years post-trial.	Low
Collection of Data: Secondary outcome measures	Secondary outcome measures including vital signs, spirometry, motor function, and sensory function may result in participants experiencing discomfort due to the comprehensive nature of the examination.	Low	Site staff and research staff performing trial assessments have considerable experience with trial population as part of existing spinal cord injury rehabilitation programs; All staff will be appropriately trained and supervised on appropriate clinical methods	Low

Collection of Data: Laboratory Tests	Laboratory tests, and a part of the ASIA impairment scale exam are invasive assessments and may result in some participants feeling discomfort	Low	Blood collection will be performed by registered nurses. The ASIA impairment scale exam will be conducted by a fully trained physiotherapist to reduce the level of discomfort experienced by each individual.	Low
Collection of Data: Psychosocial Health	Psychosocial health is evaluated using several questionnaires including DASS-21, AQoL-8D, CSE, ABAS-3, Fatigue Severity Scale, and daily mood rating form. While the questionnaires have been validated, there is a small risk that some questions have the potential to cause upset/distress to people living with SCI	Low	The different questionnaires have been validated and widely used in clinical trials. A psychologist will oversee the psychosocial health evaluation to minimise potential for upset/distress to participants.	Low