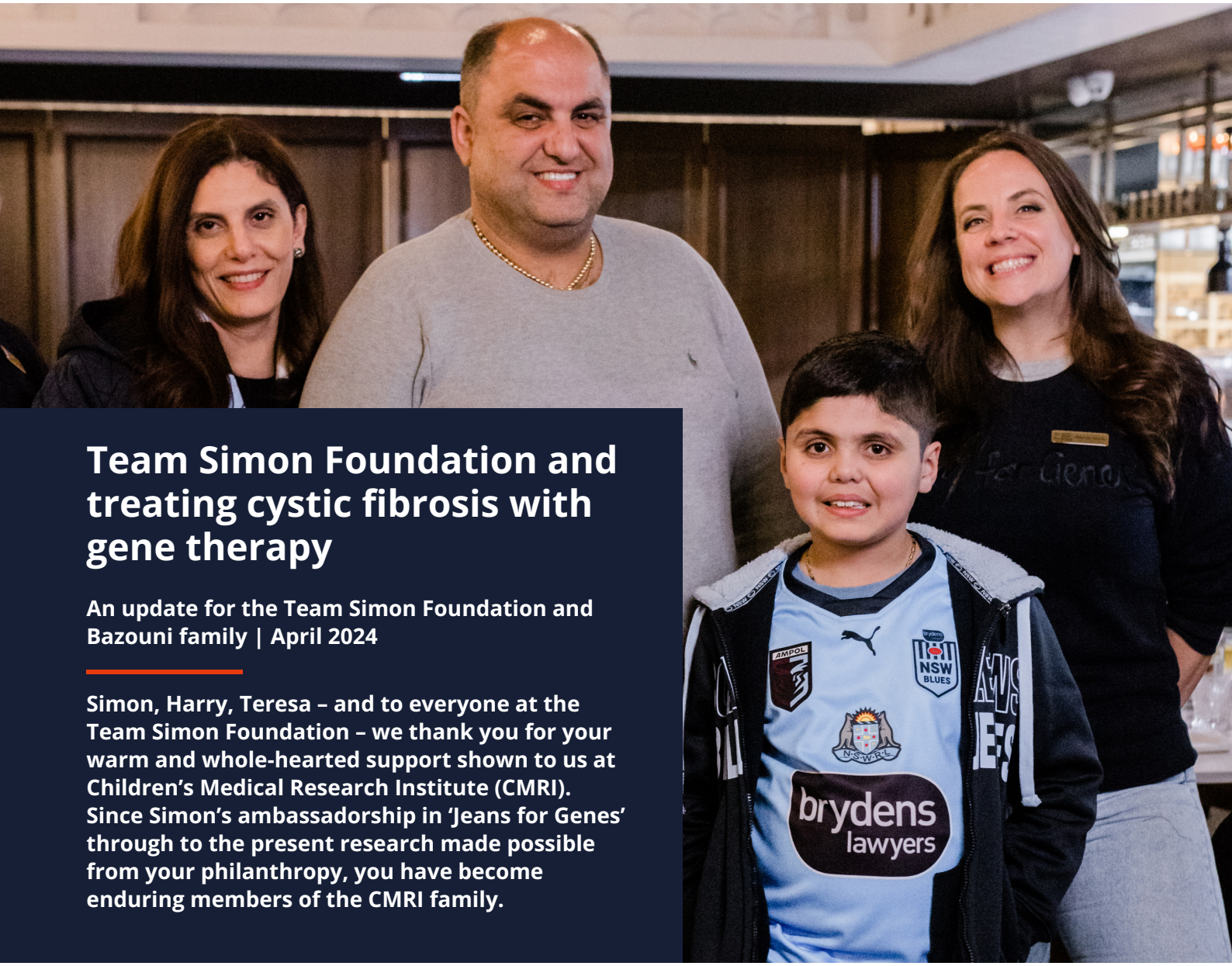
CHILDREN'S MEDICAL RESEARCH INSTITUTE

Jeans for Genes®

Finding cures for children's genetic diseases



Team Simon Foundation and treating cystic fibrosis with gene therapy

An update for the Team Simon Foundation and Bazouni family | April 2024

Simon, Harry, Teresa – and to everyone at the Team Simon Foundation – we thank you for your warm and whole-hearted support shown to us at Children's Medical Research Institute (CMRI). Since Simon's ambassadorship in 'Jeans for Genes' through to the present research made possible from your philanthropy, you have become enduring members of the CMRI family.

Remarkable progress thanks to you

Thanks to your generous contributions, our team at CMRI have made exciting progress towards developing a gene therapy treatment for cystic fibrosis (CF). And through your support, we were able to welcome a new scientist into the position of Team Simon Foundation Postdoctoral Researcher: Dr Andrea Pérez-Iturralde.

Andrea joins the lab of our world-leading gene therapist, Associate Professor Leszek Lisowski, and a wonderful team of PhD students, postdocs, clinicians, and other scientists, all of whom have been making great strides towards solving CF with gene therapy.

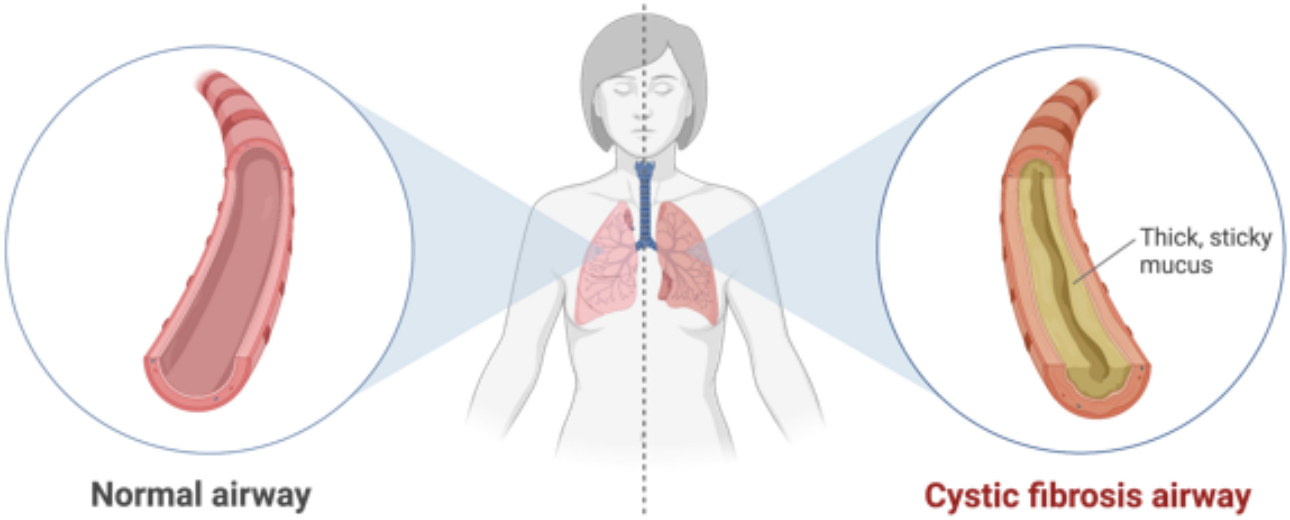
Since commencing her position, Andrea and the team have developed a number of different vectors – the 'packaging' that could eventually deliver therapeutics to the correct cells in the lungs of CF patients. They have also made progress on the genetic tools required to compensate for the faulty CFTR gene with a correctly functioning one.

We are delighted to present this report on the research your philanthropy has made possible, and the progress made by A/Prof. Lisowski, Dr Andrea and the team over the past 12 months.

The science in brief: Using gene therapy to treat cystic fibrosis

'Gene therapy' is one of the most promising strategies for treating CF, a genetic disease that is diagnosed in around 100–120 Australian newborns each year.

The symptoms of CF arise from faulty genes in our DNA, specifically the CFTR gene. When CFTR malfunctions, it causes a build-up of mucus within and around the organs, especially the lungs. With gene therapy, we could compensate for the faulty CFTR gene with a correctly functioning one – thereby allowing the lungs (and airways) to clear themselves of excess mucus.



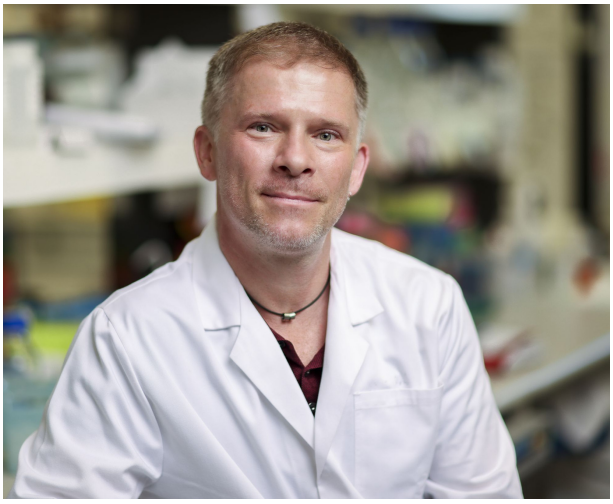
This was the goal in 2022 when Team Simon funded a new position at CMRI with an explicit objective: to use the tools of gene therapy to treat CF.

Recruiting the talented team for Children's Medical Research Institute

Team Simon placed its trust in world-leading gene therapy expert Associate Professor Leszek Lisowski to be the project champion. Before a therapeutic gene can be used as a therapeutic, a vector must be created. A vector is a delivery vehicle that will be used to deliver the therapeutic gene to the target cells. It is in the creation of these vectors that A/Prof. Lisowski excels.

One of A/Prof. Lisowski's first duties was to recruit a researcher dedicated to the study of gene therapy for cystic fibrosis and the design of a vector for that therapy's delivery.

The standards were high, and finding the right person with the right experience and expertise was a stringent process that took almost six months. Then, after a call out to the research community and after two rounds of interviews, the right candidate was found.



"For the position of Team Simon researcher, I knew the search would be difficult," said A/Prof. Lisowski. "Our expectations were high and so, too, were our aspirations for the role. We needed someone who not only understood CF and the challenges particular to this disease, but someone who had the experience and applied skillset for overcoming them. This is a big job."

Introducing the Team Simon Foundation Postdoctoral Researcher: Dr Andrea Pérez-Iturralde

By April 2023, a scientist was identified and granted a contract to become the Team Simon Foundation Postdoctoral Researcher: Dr Andrea Pérez-Iturralde.

- Andrea is from Pamplona, Spain, where she obtained her bachelor's degree in Biochemistry from University of Navarra. She subsequently completed a master's degree in Drug Research, Development & Innovation and earned her PhD in Applied Medicine and Biomedicine.

- During these years, Andrea had the chance to study in detail the transduction mechanism of adeno-associated viral (AAV) vectors. This area of research (of whether and how a viral vector can enter certain types of tissues) would come to be of great relevance when being considered for the Team Simon researcher position.

> *"I've always wanted to work in gene therapy for diseases that are incurable so – for me – it is super motivating to work towards something. At CMRI we are interested in the families, the recipients of the treatment, so for me it's a calling, working on this. It's fulfilling for my self."*
> *– Andrea Pérez-Iturralde*

- Since joining CMRI, Andrea has worked in the Translational Vectorology Research Unit with A/Prof. Lisowski and his team where she has developed numerous methods for engineering variants of AAV vectors for the therapeutic treatment of cystic fibrosis.

Designing a gene therapy solution for cystic fibrosis

Once appointed, Andrea concentrated and channelled her expertise towards the challenge of solving CF through gene therapy. Gene therapy is a relatively new area of biomedical and translational research, and its use for treating genetic disorders is an unfolding and ever-instructive story. Across the broader scientific community, there are several challenges that have delayed a universal treatment for CF. Three are:

i) We know that CF is caused by a faulty CFTR gene, but there are over 700 different mutations that might render that gene faulty.
ii) One of the main targets for a treatment of cystic fibrosis is the lungs – but the human body has evolved many defences to prevent foreign objects (like gene therapy treatment) from entering our lungs.
iii) Any potential treatment must be tested, and it is highly impractical, if not hazardous, to test treatments on an individual with CF; alternative models must, therefore, be found and used instead.

Any true search to solve cystic fibrosis will be slow, costly, and unpredictable. Hence any true treatment will be the result of patience, ingenuity, and dedication.

In the past year, Dr Andrea and A/Prof. Lisowski have added to the search for a treatment through these three broad goals:

1. Designing the viral vector to deliver the treatment:

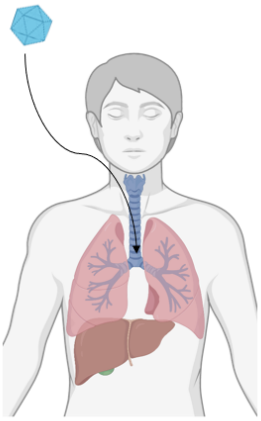
First, the team have worked on designing the actual viral vector – the packaging – that will contain and deliver the therapeutic material to the lungs.

2. Designing the package's contents:

The team have also been working on the genetic tools that would 'cut out' the faulty region of the CF gene and 'insert' the healthy, functional gene.

3. Identifying the ideal test subjects:

During their research progress, the team have arrived on a suite of different test subjects and model systems for testing the effectiveness of their tools.

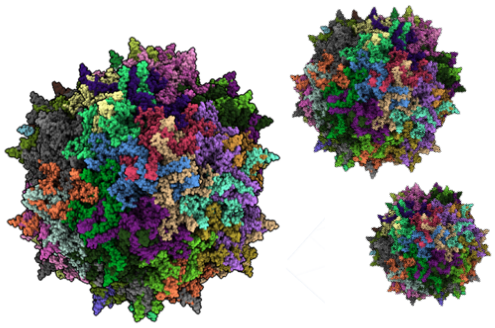


Development of vectors able to specifically target the human lung

Successes and setbacks, and the future of gene therapy for CF at CMRI

Finding the vector

To deliver the treatment, the team needed to find a 'vector' that could infiltrate the defences of the lungs like the Trojan Horse. They enjoyed an early win when they discovered three novel vectors, in human lungs, which showed promise for the delivery role of a future therapeutic.



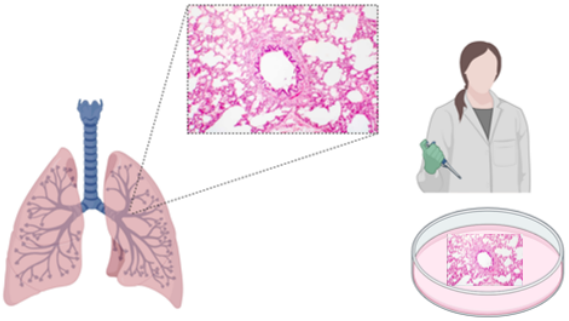
"Thanks to the work of Kim [Dilworth – the project's PhD student], we found three naturally occurring vectors. This was quite exciting, but then we tested them on a model [lung]..." says Andrea.

Though the three vectors appeared effective in mouse models, the team discovered that they did not work the same on human tissue. When tested on samples of human lung, the three novel vectors were no more effective at entering the lungs than any of the known vectors. An alternative strategy needed to be sought.

A new collaborator provides model lungs for testing

Fortunately, through this setback the team formed a valuable partnership with Associate Professor Jane Bourke from Monash University who has provided ongoing access to samples of human lungs – in addition to the mice the team were already using.

The team started using these samples in their studies last year and will continue using them to test the effectiveness of potential vectors at entering lungs – with promising results, as detailed below.

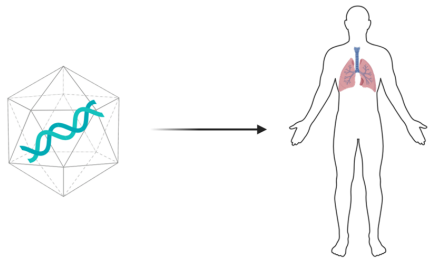


Samples of human lungs are an invaluable model for testing CF treatments

Successes and setbacks, and the future of gene therapy for CF at CMRI (cont.)

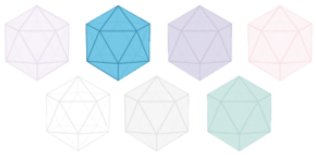
Designing the vector

After verifying that the three naturally-occurring vectors were not the best candidates for clinical development, Dr Andrea, A/Prof. Lisowski, and the team have been trialling methods for engineering bespoke vectors for safe and efficient therapeutic delivery to the lungs.



They have used two methods to engineer these vectors and the results are promising.

The first method mimics natural evolution, where the team generates a large number (millions) of vector variants that aim to capture all the various possibilities the nature may have created itself. These are then tested for efficacy.



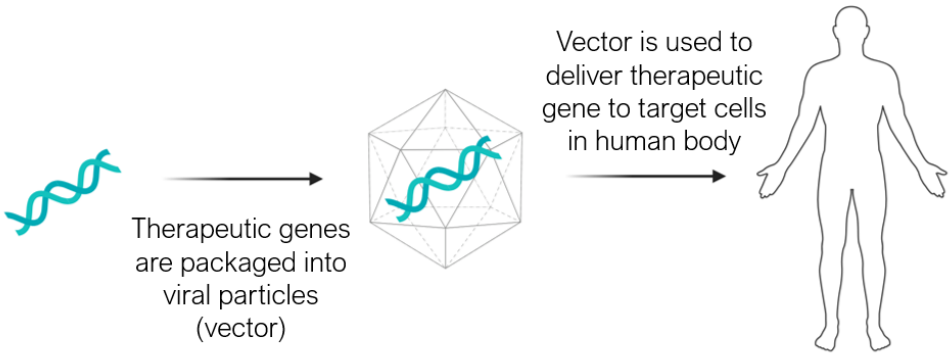
Millions of vectors like these are generated

Two methods. One goal.

In the other method, the team takes advantage of years of research published by other teams around the world, to identify specific molecules that would direct the final vector to the correct cells in the body. By the end of this process, the team will have found the ideal 'packaging' that will deliver the gene therapy medicine for cystic fibrosis.

Designing the gene therapy

While the team will use a vector to deliver the correctly-functioning CFTR gene to the lungs, a separate set of 'genetic tools' is required to actually perform the 'cutting' and inserting at the DNA-level.



Furthermore, due to the vector's limited capacity, the corrected CFTR gene and the genetic tools do not into the same vector and so the genetic tools require their own capsule for delivery. A further accomplishment of the team regards this capsule: rather than using a vector, they will use a distinct delivery method called a 'lipid nanoparticle'.

Lipid nanoparticles are tiny spherical capsules that can transport biologic compounds, such as therapeutics, into the body. They have already been used by Moderna and Pfizer–BioNTech to deliver mRNA and present a promising solution for the team's goals.

Sharing Success

'A Night of Belief' | August 2023

Associate Professor Leszek Lisowski and Dr Andrea Pérez-Iturralde were honoured to be invited to celebrate and share their progress with a special and deeply engaged community: the attendees of the second annual Team Simon Foundation Gala, 'A Night of Belief', on the 11th of August 2023. The CMRI team was delighted to support the Gala as the Foundation raised funds to support medical research into a cure for CF.

On this inspirational evening, 500 guests listened to A/Prof. Lisowski share the science of CF and gene therapy, and the progress he, Andrea and the team are making into developing a gene therapy solution for CF, thanks to the Foundation's support.

The CMRI team were also glad to support Team Simon's 'State of Origin' fundraising event on 21st June 2023, where a successful auction raised further vital funds for medical research into CF.

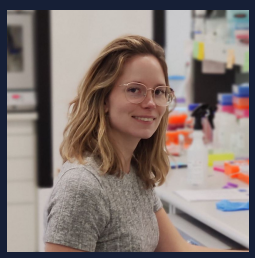
Funding success through C4CF

Thanks to a pivotal introduction from Team Simon, A/Prof. Lisowski and his team have been able to present their findings and their progress to successfully secure future funding from Cure4 Cystic Fibrosis Foundation. With this additional funding, the promising data generated from Team Simon's initial investment can be advanced through to April 2026 and to its next crucial stages.

We are extraordinarily grateful to Team Simon for your part in this collective success.

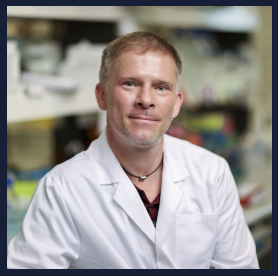
Thank You

To the Bazouni family and the Team Simon Foundation – on behalf of A/Prof. Lisowski, Dr Andrea, and everyone at Children's Medical Research Institute, thank you sincerely for the belief and trust you have placed in us as we work to create a happier, healthier future for children with CF. In the past year, the team have accomplished significant foundational work and overcome some of our earliest challenges, and are eagerly looking forward to the next stage of this important research.



"It's exciting – this work could help deliver a healthy gene for patients, and we hope to make the technology for correcting CF permanently. "Knowing that the Team Simon Foundation have made this research possible is so inspirational."

"Working in the lab and designing and testing vectors and living through these highs and lows, 'Yes they work; no they don't work,' it can be a challenging experience. What has made a great contribution to our work, for me and I know the rest of the lab, has been getting to meet Simon, Harry, Teresa – and their friends and family – and to be reminded of our purpose. We are working for something, yes, but we are also working for someone. And even more than that - we get to meet the patients, who would eventually benefit from our hard work. And that has been really important to me and my team."



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