Cystic fibrosis airway gene therapy: towards first-in-human clinical trials

Recent estimates suggest that up to 30% of CF patients are currently ineligible to receive modulator therapies. Our primary focus at the Cystic Fibrosis Airway Research Group (CFARG) is to develop an airway gene-addition therapy, to prevent, halt, or improve lung disease in all CF patients. By introducing a correct *CFTR* (cystic fibrosis transmembrane conductance regulator) gene into the airway cells and creating functioning CFTR protein, a successful gene therapy has potential to significantly improve lung health and patient prognosis. We deliver the *CFTR* gene to the airways using a specialised delivery vehicle known as 'vector'. As pre-clinical studies progress, an important translational step for bringing airway gene-addition therapy to the clinic is producing the large volumes of gene vector required for human trials and eventual commercialisation. This project focussed on developing a large-scale gene vector production method that has the potential to be used in both pre-clinical and clinical settings.

The generous support of the Ann Maree Bosch Career Fellowship enabled me to attend two major international conferences and to visit two research laboratories in the USA to learn techniques and foster collaborations to further the progress and success of this project.

I first attended the 2019 American Society of Gene and Cell Therapy (ASGCT) Conference in Washington D.C. The ASGCT is the world's largest international gene therapy conference and brings together expert scientists, physicians, patient advocates, and industry professionals. At the conference I had the opportunity to disseminate my PhD work and presented a poster describing a novel method for large-scale gene vector production. I was also able to foster new collaborations with international conference attendees. The research presented at the ASGCT conference was very encouraging, and a pertinent reminder of the global effort currently ongoing to develop cures for inheritable diseases, including CF.

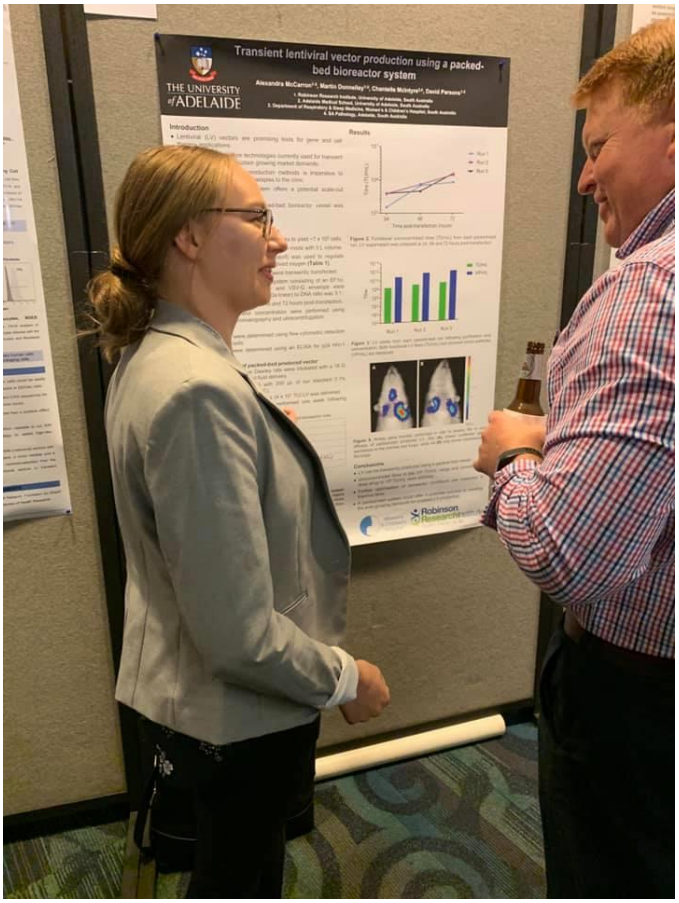
Following the conference I had the opportunity to visit two laboratories in the US that focus on vector production for gene therapies. My first visit was hosted by Dr Maria Limberis and Dr Arbansjit Sandhu at a large academic gene therapy facility at the University of Pennsylvania. During this visit I had the chance to observe and learn more about gene vector production processes ranging from pre-clinical to clinical scale. I also cultivated new connections with a number of gene therapy production experts. The second visit was in Enfield, Connecticut with Dr Ma Sha at the Eppendorf bioprocessing applications laboratory. From this meeting with Dr Ma Sha we have since collaborated together to publish an application note for large-scale production of gene vector in an Eppendorf bioreactor system (cited below).

With this generous funding I also had the opportunity to present my research at the 2019 North American Cystic Fibrosis Conference (NACFC) in Nashville, Tennessee. The theme of the 2019 meeting was laying the foundation to a "*path to a cure*" and the conference had a big focus on developing genetic-based therapies for CF, including gene-addition therapy, which was highly relevant to my work. This conference enabled me to dive deep into the many different facets of the CF field, ranging from basic mechanistic research to clinical care for CF patients. I was inspired by the huge amount of innovative research currently ongoing worldwide in the CF field. At the meeting I was able to meet with international researchers to foster relationships with big players in the CF arena and discuss project collaborations. I found the atmosphere and excitement at this meeting was hugely motivating as an early career research in the CF field, and it was extremely promising to see the huge research effort and investment in developing a cure for all CF patients with use of genetic therapies.

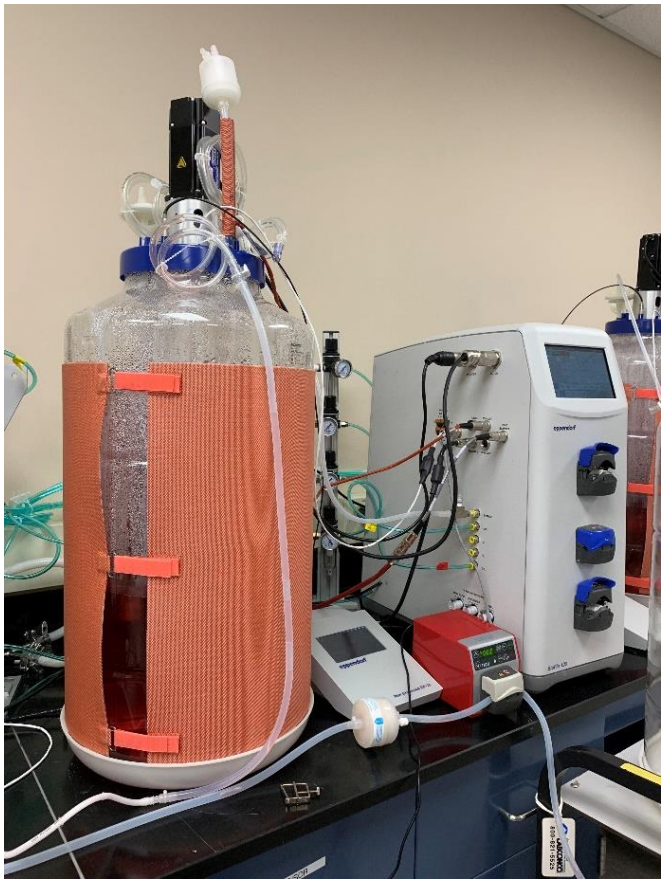
Publications arising from this work include:

A. McCarron, M. Donnelley, C. McIntyre, D. Parsons. Transient lentiviral vector production using a packed-bed bioreactor system. Human Gene Therapy Methods, 2019, 30(3): 93-101. DOI: 10.1089/hgtb.2019.038

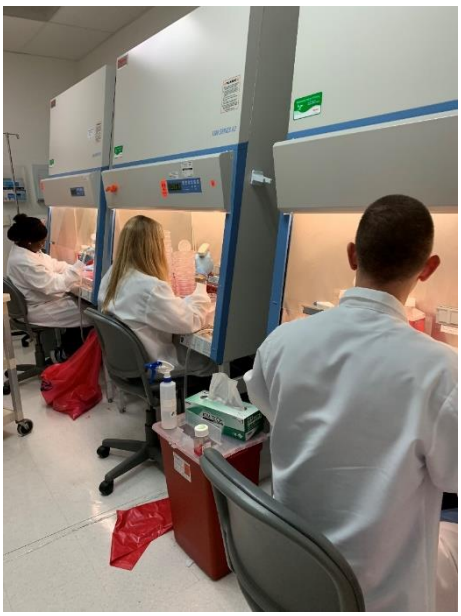
Product application note published by Eppendorf. A. McCarron, M. Donnelley, C. McIntyre, D. Parsons. Transient Lentiviral Vector Production in HEK 293T Cells Using the BioFlo® 320 Control Station with a BioBLU® 5p Single-Use Packed-Bed Vessel.

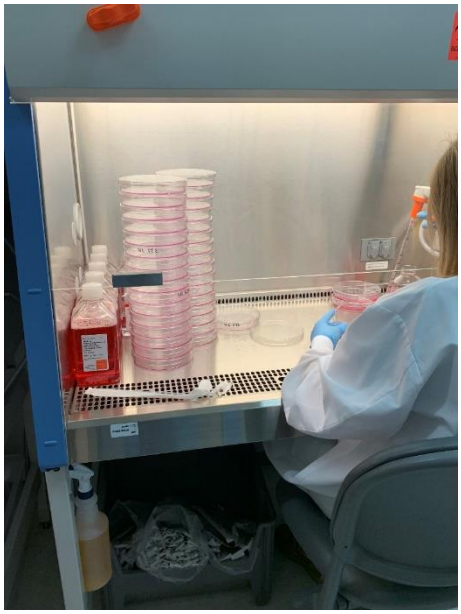


Presenting my work on up-scaling gene vector production at the American Society of Gene and Cell Therapy Conference in Washington D.C.



Visiting the Eppendorf applications lab in Enfield, Connecticut with Dr Ma Sha. This piece of equipment (a bioreactor) can be used for large-scale gene vector production for clinical and commercial use.





Visiting the gene vector production facility at the University of Pennsylvania with Dr Maria Limberis and Dr Arbansjit Sandhu. Images show pre-clinical scale manufacturing of vector for gene therapy studies.