CHILDREN'S MEDICAL RESEARCH INSTITUTE

Jeans for Genes®

The Sydney children's Hospitals Network

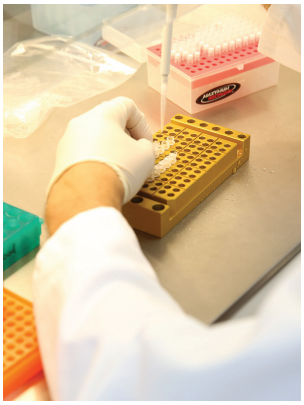
care, advocacy, research, education

Gene Therapy Program at CMRI / SCHN

AAV Vector Development & Clinical Vector Manufacturing








Introduction

Gene therapy, or the use of genes as medicine, has immense therapeutic potential in the treatment of genetic and acquired diseases that are currently difficult or impossible to treat. While progress in the development of the underpinning gene transfer technology (vectors) has been hard won, we are finally witnessing astounding successes in human clinical trials in both children and adults.

Recombinant AAV and lentiviral vectors are the technological foundation underpinning numerous exciting successes in human gene therapy clinical trials, with high-profile examples targeting diseases of the bone marrow (Orchard Therapeutics), central nervous system (Avexis), eye (Spark Therapeutics) and liver (Spark Therapeutics). These successes hinge on continuing progress in the development of AAV and lentiviral gene delivery systems and unrestricted access to clinical-grade gene transfer vector manufacturing.

To this end, CMRI, a leading Australian medical research institute, and SCHN, a world-class paediatric hospital network, have established a gene therapy program that brings together world class expertise in basic science and clinical medicine encompassing the entire translational pathway from basic science through to human clinical trials. A key enabling element of this pathway is a comprehensive Vector Development and Manufacturing Program with a strong focus on AAV-based gene delivery technology.

Problem

The current generation of rAAVs, such as AAV2 and AAV8 utilised in clinical trials today, were identified in nature. They have been adopted as gene therapy tools because they have a good safety record, the ability to transduce both dividing and non-dividing cells, and some degree of tissue specificity in preclinical animal models. However, these naturally occurring viruses have not evolved to function as gene therapy vectors, and in addition to low efficiency in clinical studies they suffer from low manufacturing efficiency.

Low efficiency and low tissue specificity can lead to decreased clinical effectiveness, increased probability of toxicity and immunological reaction and increased vector doses required to achieve clinical efficacy. This in turn increases the manufacturing challenge and cost of therapy.

Solution

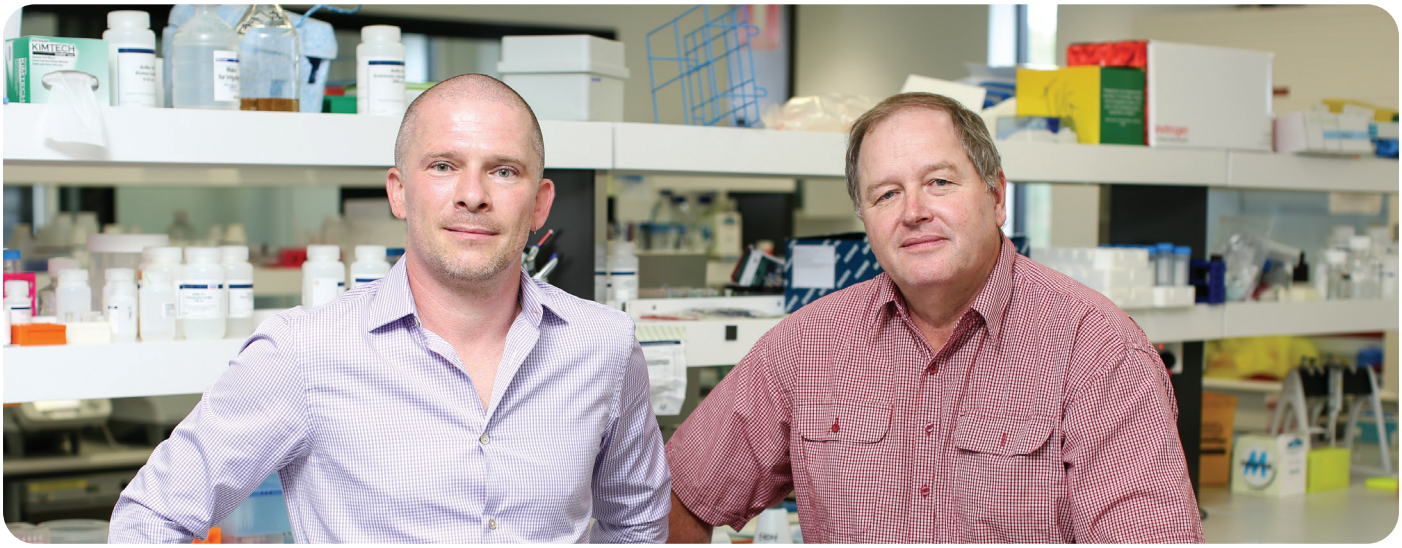
For maximal clinical effectiveness, novel vectors developed for specific clinical applications, using the most clinically-predictive models, are needed. To enhance clinical impact, our AAV Development Program employs proprietary technologies and unique expertise to address these two inter-related issues, vector functionality and manufacturing efficiency, allowing us to develop more functional vectors with improved manufacturability. This integrated approach seeks to "begin with the end in mind" and results in vectors that are optimised for clinical and commercial success

Our strategy

CMRI / SCHN has developed a unique iterative development and evaluation pipeline that allows us to develop bespoke vectors for clinical applications targeting a wide-range of clinically relevant tissue targets.

Our Team

Prof. Alexander and A/Prof. Lisowski have over 35 years of collective experience across a range of viral vector systems, including lentiviral vectors, gamma-retroviral vectors, adenoviral vectors, rabies vectors, with primary expertise in AAV vectors. They lead independent, but highly synergistic research teams, that include over 30 members with expertise in molecular biology, cell biology, stem cell biology, genome engineering, immunology and bioinformatics. They have world class expertise in gene therapy applications targeting the liver and the haematopoietic compartments. The team has strong, established expertise in viral vector development and manufacturing, and a proven record in commercialisation and clinical development.



A/Prof. Leszek Lisowski, PhD MBA

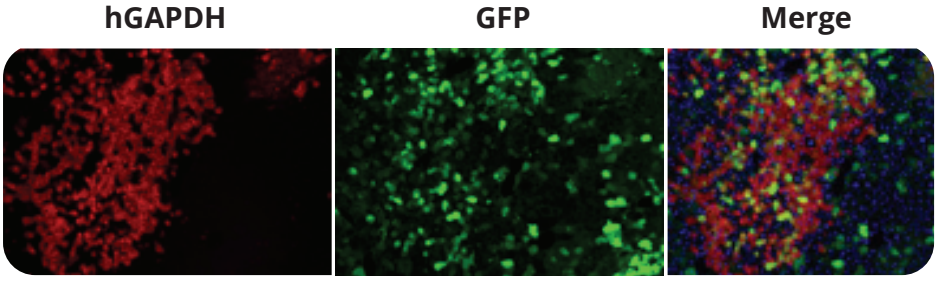
- Head of CMRI Vector and Genome Engineering Facility
- Group Leader of CMRI Translational Vectorology Group
- Co-founder of LogicBio Therapeutics (NASDAQ: LOGC)
- World expert in vectorology, including vector bioengineering and manufacturing
- Previously Director of Gene Transfer, Targeting and Therapeutics (GT3) facility at Salk Institute for Biological Studies, CA
- PhD from Cornell University & MSKCC; Post-doctoral fellow at Stanford University, School of Medicine
- MBA from Rady School of Management, UC San Diego, CA

Prof. Ian Alexander, MD PhD

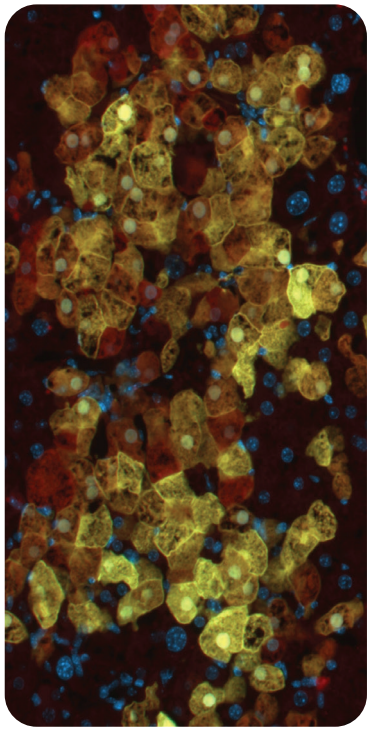
- Head of the Gene Therapy Research Unit, Children's Medical Research Institute & Sydney Children's Hospitals Network
- Clinical geneticist at The Children's Hospital at Westmead
- Professor in Paediatrics and Molecular Medicine at the University of Sydney
- Fellow of Australian Academy of Health and Medical Sciences (FAHMS)
- Specific expertise in virus-mediated gene transfer with a focus on target organs including the liver and bone marrow
- Led the first team in Australia to treat a genetic disease (SCID-X1) by gene therapy and are recognised leaders in the establishment of this exciting field in Australia

Our Technology

- Comprehensive portfolio of ten (10) filed patents covering a range of vector selection and manufacturing technologies, and novel AAV variants for clinical application.
- Access to biologically-predictive *in vitro* and *in vivo* models of human liver.
- Access to primary human tissues (retina, skeletal and cardiac muscle, HSC, kidney, liver, etc) for vector development and evaluation studies.
- Ability to develop dual xenograft models (liver & muscle, liver & lung, etc for enhanced vector bioengineering).
- Collaborative access to a range of organoid systems (eye, CNS, liver, etc) and 3D model systems (CNS, liver, etc) and iPSC derived models.



Novel bioengineered AAV variant capable of efficient functional transduction of mouse and human primary hepatocytes



Superior transduction of primary human hepatocytes with next generation bioengineered AAV capsid

Our Facilities

The CMRI / SCHN Gene Therapy Program occupies two custom designed floors (550m^2) in the newly constructed CMRI Tower and custom designed clean rooms in SCHN's Kids Research building.

The facilities include two separate laboratories, five standard tissue culture rooms, custom designed to facilitate work related to 1) vectorology, 2) genome engineering, 3) vector manufacturing and 4) GLP/GMP process development as well as three newly updated clean rooms (GMP rooms).

Dedicated specialised equipment, including qPCR/TaqMan, Droplet Digital PCR (ddPCR), ÄKTA Pure and Pilot FLPC chromatography systems, 25L and 50L WAVE bioreactor, ÄKTA Flux-S and Flux 6 TFF systems, Amaxa electroporation system, and more.

Unrestricted access to state-of-the-art facilities, including a cell analysis and sorting facility (FACS), sequencing facility, Genome Engineering Facility, Stem Cell and Organoids Facility, Next-Generation Sequencing (NGS) facility, electron microscopy facility, mass spectrometry (MS) facility, confocal microscopy facility, bioinformatics, Cell Bank Australia and Drug Screening Facility.

Clinical Vector Manufacturing

- We are funded to establish a pilot (up to 25 L) and medium (up to 200 L) scale GMP vector manufacturing
- Pilot scale operational by February 2020 and medium scale by February 2021
- Dedicated team including QA, QC, Production Manager, AAV and LV manufacturing team
- Dedicated CMC Process Development team specialising in the unique requirements of bioengineered vectors

The Opportunity

Technology licensing, cross-training, academic collaborations, sponsored research arrangements, fee-for-service, short-term research projects, consulting and technology training

Collaborations

Strong established collaborations with leading academic institutions, including:

Stanford University, CA
Memorial Sloan Kettering Cancer Center, New York, NY
University College London (UCL), UK
Salk Institute for Biological Studies, CA
UC San Diego, CA
UC San Francisco, CA
TLV University, TVL, Israel
Harvard University, Boston, MA
University of Florida, FL
University of Texas, Dallas, TX
University of Washington, Seattle, WA
University of Nantes, France
University of Sydney
University of Melbourne

Market Size

Globally there are over 300 active AAV programs between 114 AAV companies

The global market for gene therapy is projected to exceed US$11 billion by 2025

The vector manufacturing market is expected to exceed US$800m in 2023, representing a 5 year CAGR of 20%

Please contact

Laura Hourigan,
IP & Commercialisation Manager
Children's Medical Research Institute
p: +61 2 8865 2800
m: +61 414 559 072
e: lhourigan@cmri.org.au

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NSW GOVERNMENT Health

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