Final Report for David Millar Giles Innovation Grant 2019

An Australian Alliance of personalised lab grown mini-organs to save the rarest of them all

Overview: This application represent an alliance of 11 CF clinics across Australia to create a nation wide stem cell based cell biobank for use in predictive drug discovery and efficacy platform (CF Avatar) created by miCF research centre (UNSW) from patients with rare CFTR mutations.

We recently established the *miCF AVATAR Platform* at Sydney Children's Hospital (SCH) and UNSW. We have developed a framework to culture CF patient derived cells from two major organs impacted in patients with CF (lung and gut). We assign a predictive value to the ranked modulator drugs based on their outcome in two functional laboratory assays designed to assess drug efficacy the created cell models; the ion flux using chamber electrophysiology assay in the respiratory model (patient's nose and airway cells) and the forskolin induced swelling (FIS) assay in the patient's intestinal gut organoids. The modulator drug with highest score represents the most effective therapy for that individual.

David Millar Gilles Innovation Grant provided financial support towards our research to expand our precision medicine predictive platform and create an Australian wide network to cover majority of CF patients with rare CFTR mutations.
Following objectives of the study were achived:

1) Ascertain governance and establish operating procedures in 11 participating CF centers for biospecimen acquisition and transport to the lead site laboratory (miCF-UNSW).

All 11 centres have received ethics approval to be added to the miCF avatar study. Site specific governance has been received from five sites.

2) Processing biospecimens received from across Australia to create a biobank of cultured airway and gut organoids from children and adults with rare CFTR mutations.

42 individuals (twice as many as proposed in the application) have been recruited, nasal organoids and gut organoids created and biobanked.

3) Test response to a drug product candidate (3 drugs currently approved for treatment of common CFTR mutation and 3 experimental phase compounds) in three of the cell models

Nasal cell models from 42 individuals with rare CF have been tested against CFTR modulator compounds. In addition, three individuals have had their intestinal organoids tested

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200 word project description written for educated non-specialists

Some individuals with rare CFTR mutations have been shown to benefit from the available modulator therapies. Sadly, most will have no opportunity to access these breakthrough treatments. Currently no clinical test exists to predict patient's response to a modulator drug. We are using a new technology in the field of personalised medicine. Stem cell derived mini-organs are generated from small biopsies serving as a personal CF model or an AVATAR. They are tested in the lab to predict an individual CF patients' responses to therapeutic agents. Should one or more therapies prove effective in the lab, these can be recommended for use as targeted therapies for the patient.

In the last 2 years we have created Avatars from the kids with CF that visit the Sydney Children's Hospital and have predicted outcome of modulator therapies. In this application we propose to extend our platform to create an Australian wide alliance for people with rare CF by extending to 11 (6 paediatric and 5 adult) CF clinics. This project will provide a novel therapeutic opportunity, ultimately enabling 'managed' off-label access to the CFTR modulator therapies for individuals with rare CFTR mutations who show response to the therapy in a prospective mini-organ test.