CF Innovation Grant 2019 – Final Report

From Gerard Kaiko

April 2022

Optimising patient-derived stem cell technology in cystic fibrosis to predict CFTR modulator response

Due to COVID19 we had to delay the completion of this study as COVID19 slowed and then completely stopped cystic fibrosis (CF) patient recruitment for significant periods in 2020-2021.

General Report

We have been able to develop an optimised new personalised CFTR functional test and apply this test to stem cell organoids from over 40 CF patients receiving treatment to predict their response to multiple CFTR modulator therapies (the drug combinations used in Kalydeco, Orkambi, Symdeko, and Trikafta) in the clinic. We have followed up these *in vitro* testing results in the clinic with lung function measurements and response while receiving modulators and found that our test is highly predictive of the clinical response of patients receiving Kalydeco and Orkambi and a number of patients receiving Trikafta under extended clinical trial settings and compassionate access. We will be publishing this work in 2022 after Trikafta enters the Australian market following its recent PBS listing. This will allow us to compare the predictive personalised test results we already have assessed to the clinical outcome for many more patients who will now receive Trikafta in the clinic under the PBS over the coming 1-3 months. This will add greater statistical rigour to the test evaluation. We have also identified multiple patients in the clinic that have rarer non-F508del mutations in the CFTR that will not qualify for Trikafta and will miss out on access, but for whom our personalised test indicates that the triple combination therapy could potentially provide significant benefit to their CFTR function. We have also looked to the future, and determined the applicability of using this test for newer drug candidates both in preclinical and early clinical trial stages including new drugs from US biotech entering clinical trials in Australia in 2022. This is an exciting finding that opens the opportunity for many uses with this test, including 1) tailoring CFTR modulator therapies to match the right drug to the right patient as more therapies become available in the future, 2) using precision medicine to ensure that therapies are being optimally utilised especially given the substantial cost of modulators on the PBS, and 3) using this personalised test to determine which CF patients with rarer non-F508del mutations may respond to existing CFTR modulators and therefore in the future (with regulatory changes) could benefit from these medications. To assess this people with rarer CF mutations would need to enter 'n of 1' clinical trials, based on a positive result from their personalised lab test, so that their outcome while receiving the modulator could be assessed in the clinic. The latter is the only way in which we are likely to get Trikafta access to patients without a copy of F508del (~10% of people living with CF). We have already identified multiple such patients in the clinic, and it is our current goal to make this happen based on the outcomes of this work. This work has also helped establish a collaborative network within multiple centres within Australia and in particular with UNSW/Sydney Children's Hospital. We have setup systems to enable this collaboration at other centres and successfully assessed the ability to test samples in NSW and interstate.