UQ STRATEGIC FUNDING

PROGRESS REPORT

Recipients of Strategic Funding are required to provide a short report to the VC and/or DVC(R) on an annual basis unless they are excluded as per the advice below.

Notes:

- Payment of any subsequent year's allocation will be subject to VC / DVC(R) approval of the progress report.
- Annual Progress and Final Progress Reports are required for strategic funding allocations of $100,000 per annum or higher (i.e. after combining both VC & DVC(R) contributions).
- A Final Progress Report is required where total strategic funding allocations of $50,000 or higher are awarded across the duration of the commitment (i.e. after combining both VC & DVC(R) contributions).
- Reports are not required where the funding commitment forms part of a UQ Internal Scheme listed at http://www.uq.edu.au/research/research-management/grants-uq-internal.

1. ADMINISTRATIVE SUMMARY

Is this a Progress or a Final Report?	PROGRESS
Report Year:	2021
UniFi Project Number:	024246
Commitment IDs:	VCSF200001A DVCR19300A
Project Title:	Queensland Cystic Fibrosis Research Program (QCFRP)
Lead CI / Funding Recipient Name:	Prof Peter D Sly
Administering Unit:	CHRC
Faculty/Institute/Central Area:	Medicine
Years of Funding (YYYY - YYYY):	2020-2024
Are you intending to submit a variation request? (Yes/No)	No

Note: Dot points are acceptable for the below items

2. SUMMARY OF OBJECTIVES

100 word summary of strategic objectives (as outlined in the original proposal)

UQ's Child Health Research Centre (CHRC) hosts two internationally recognised research leaders in Cystic Fibrosis (CF), Professors Peter Sly and Claire Wainwright. They work in close collaboration with Professor Scott Bell. Their work has resulted in > 300 publications in this field and improved clinical treatment for children with CF around the world.
In recognition of their work, they were invited by the American Cystic Fibrosis Foundation (CFF) to apply for special 'out of round' funding. This was successful with more than $7.5 million (USD) awarded, across three awards, one fronted by each researcher.
This funding request is to leverage funds ($2.5 million AUD) committed by the Qld Children's Hospital Foundation (CHF) in support of this program. This will enable expansion of the project and ensure timely completion. Most importantly, it will enable the team to deliver better outcomes for patients with CF.

3. STATEMENT ON PROGRESS/OUTCOMES

How have you progressed towards your stated objectives to date?

1. Early life origins of CF Lung Disease (ELO)

i. ***The scope of work accomplished during the year***

Recruitment has progressed well with 164 children recruited. The table shows the numbers of children and number of visits conducted. An additional 30 children have been recruited but not yet attended for annual review. The original study design was for each child to be assessed in three consecutive years to allow the Advanced Longitudinal design method to be used.

Age ranges	Number recruited	Annual visits		Clinic visits	
<1	5	3	1	6	5
1-2	9	5	3	11	7
2-3	10	5	5	2	9
3-4	12	11	6	8	10
4-5	14	12	5	3	13
5-6	9	6	2	2	5
6-7	15	11	8	5	10
7-8	10	7	3	3	8
8-9	6	3	1	0	5
9-10	9	6	2	2	6
10-11	10	6	2	1	8
11-12	14	6	4	3	9
12-13	8	2	3	5	4
13-14	13	4	3	6	8
14-15	9	4	1	4	3
15-16	3	1	0	1	1
16-17	7	3	2	1	5
17-18	1	0	0	1	0
TOTAL	**164**	**95**	**52**	**64**	**116**

* Not including 38 children who had 'modified annual reviews' during the 2020 lockdowns. After overcoming Covid-related and administrative delays, MRI scanning has commenced.

ii. ***The progress of training or work in clinic***

Clinics are still being impacted by Covid-related lockdowns that prevent children travelling to Brisbane for periods when the Queensland Government imposes lockdown periods. Some clinics are still being conducted by telehealth, which limits our ability to collect biological samples.

Training: we have engaged a PhD student to include some of the ELO data in his studies. His PhD focuses on the clinical utility of intra-breath oscillometry. He will be working on the ability of intra-breath oscillometry outcome variables to reflect ventilation inhomogeneity (see below).

iii. ***Research progress***

Results:

1. ***Neutrophil respiratory burst activity in CF***

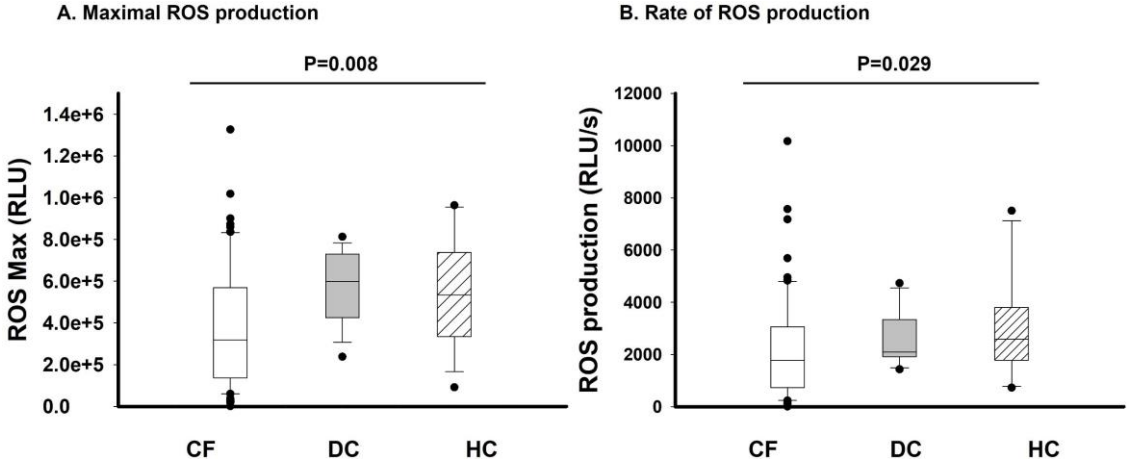
Exaggerated neutrophil-dominated inflammation underlies progressive cystic fibrosis (CF) lung disease. Older studies reported a defective respiratory burst in CF, but more recent studies suggest neutrophil function is normal.

We measured the amount and rate of reactive oxygen species (ROS) production during PMA-stimulatedrespiratory burst activity in children [70 CF, 13 disease controls, 19 health controls]

and adults [31 CF, 14 healthcontrols] in neutrophils harvested from peripheral blood. Blood was collected from participants with CF when clinically stable (60 children, 9 adults) and on hospital admission (38 children, 24 adults) and discharge (18 children, 21 adults) for acute pulmonary exacerbations.

When clinically stable, children with CF had lower ROS production [median 318,633, 25% 136,810 - 75% 569,523 RLU] than disease controls [median 599,459, 25% 425,566 - 75% 730,527 RLU] and healthy controls
[median 534,073, 25% 334,057 - 75% 738,593 RLU] (p=0.008) (Figure 1).

Figure 1: Maximal production and rate of production (slope) of reactive oxygen species (ROS) by the neutrophilrespiratory burst in children with cystic fibrosis (CF) when clinically stable (open bars), disease controls (DC) (filled bars), and healthy children (HC)(hatched bars).

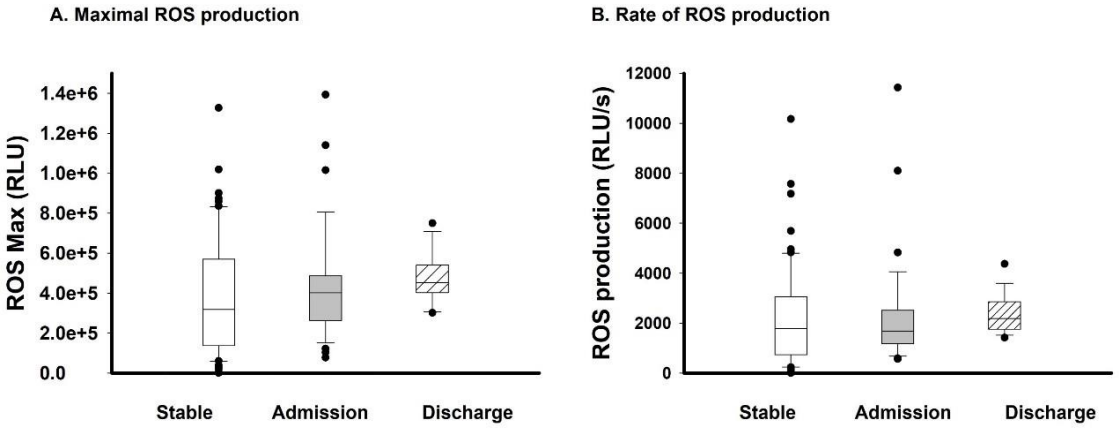


Maximal ROS production was similar in children with CF on admission for an acute pulmonary exacerbation [median 400,974 (25% 262,750 - 75% 487,429) RLU] compared to on discharge [median 452,345 (25% 403,174
- 75% 540,104) RLU] or when clinically stable [median 318,633, 25% 136,810 - 75% 569,523 RLU] (p=<0.098)(Figure 2A). No differences in maximal ROS production were seen when analyses were restricted to those children with paired admission and discharge data (n=14, p=0.75).

When clinically stable, children with CF had slightly, but statistically significantly, lower ROS production slope[median, 1,786 (25% 734 - 75% 3,061) RLU/s] than disease controls [median 2,094 (25% 1,917 - 75% 3,337) RLU/s] and healthy controls [median 2,588 (25% 1,777 - 75% 3,802) RLU/s] (p=0.029) (Figure 1B). There wasno difference in ROS production slope between males [median 2,099 (25% 832 - 75% 3,487) RLU/s] and females[median 1,464 (25% 666 - 75% 2,453) RLU/s] with CF (p=0.18).

There were no differences in ROS production slope when children with CF were clinically stable [median 1,786, 25% 735 - 75% 3,061 RLU/s] on admission from an acute pulmonary exacerbation [median 1,680, 25% 1,164 -
75% 2,515 RLU/s] or on discharge [median 2,187, 25% 1,656 - 75% 2,845 RLU/s] (p=0.15) (Figure 2B). No differences in ROS production slope were seen when analyses were restricted to those children with paired admission and discharge data (p=0.27).

Figure 2: Maximal production and rate of production (slope) of reactive oxygen species (ROS) by the neutrophil respiratory burst in children with cystic fibrosis when clinically stable (open bars), on admission to hospital for acute pulmonary exacerbation (filled bars), and on discharge (hatched bars).



ROS production in adults, both maximal levels and the rate of production followed similar patterns to those seen in children (Table 2). There were no differences between maximal ROS production between adults with CF and healthy controls (p=0.74) or between levels when clinically stable, on admission for acute pulmonary exacerbations, or on discharge from hospital (p=0.66). Similarly, there were no differences between ROS production slope between adults with CF and healthy controls (p=0.37) or between levels when clinically stable, on admission for acute pulmonary exacerbations, or on discharge from hospital (p=0.41).

Table 2: Reactive oxygen species (ROS) production by neutrophils from adults. Maximal production and rate of production are shown for healthy controls and patients with cystic fibrosis (CF) when clinically stable, on admission for acute pulmonary exacerbation and on discharge from hospital.

	Number	Median	25%	75%	Max	Min
Maximal ROS production (RLU)						
Healthy controls	14	387,860	316,245	465,768	577,991	117,900
CF Stable	9	329,515	278,860	342,308	662,833	227,413
CF Admission	24	376,855	188,835	585,812	1,984,545	20,165
CF Discharge	21	424,583	229,064	544,296	833,214	63,037
Rate of ROS production (RLU/s)						
Healthy controls	14	1,916	1,608	2,399	2,716	545
CF Stable	9	1,419	1,075	1,703	2,760	795
CF Admission	24	1,713	657	2,446	14,208	148
CF Discharge	21	2,165	1,273	3,269	4,481	221

Conclusions: Our data do not support a role for exaggerated respiratory burst activity contributing to the exaggerated neutrophil-dominated inflammation seen with CF lung disease.

2. Ability of intra-breath oscillometry to reflect ventilation inhomogeneity in CF

Patients with CF continue to experience poor lung function outcomes and there is growing concern that changes occurring in the early years of life are being missed. Early assessment of lung disease is

required to improve clinical outcomes. Lung clearance index (LCI) calculated from multiple breath washout (MBW) reflects ventilation inhomogeneity and is a more sensitive indicator of peripheral lung disease than spirometry. LCI indicates early peripheral lung disease, especially in CF. However, MBW is time-consuming and challenging for young children to achieve (feasibility reported ~50%) and does not fit well into a routine clinic setting.

Specific Aim 1 of the ELO program is to improve clinical outcome measures across the lifespan and disease severity spectrum in CF. Improving our ability to detect the onset of CF lung disease and to predict acute exacerbations would fulfil this aim. New techniques, such as oscillometry (conventional-OSC), that can measure lung function safely and accurately in very young patients in a short time, are attractive additions to clinical practice. OSC measures the mechanical impedance of the respiratory system by superimposing small pressure waves on top of tidal breathing. As such, no special breathing maneuvers are required, each data epoch typically lasts 20-30 seconds and testing session can usually be completed in 10-15 minutes in preschool-aged children and reliable data can be collected at much younger ages using OSC than when using spirometry. Several reference equations for children (3-18 years) have been validated for this test. The main variables measured by OSC are resistance (R) and reactance (X). R is a measure of the energy dissipation in the respiratory system, specifically, the friction of gases moving through the airways. Measurements of R also include contributions from energy dissipation in the lung and chest wall tissues. In practice R reflects the resistive properties of airways where gas moves by bulk flow. X measures energy conservation in the respiratory system which includes elastic energy stored in components of the lung as well as inertive forces related to the acceleration and deceleration of the air as it moves through the airways. X also includes the resistive properties of airways where gas moves by facilitated diffusion and Brownian motion. As such, the resistive properties of small airway are reflected in X. Combined, R and X measurements provide unique information regarding airway resistance and obstruction, compliance and ventilation inhomogeneity that cannot easily be achieved using other lung function tests.

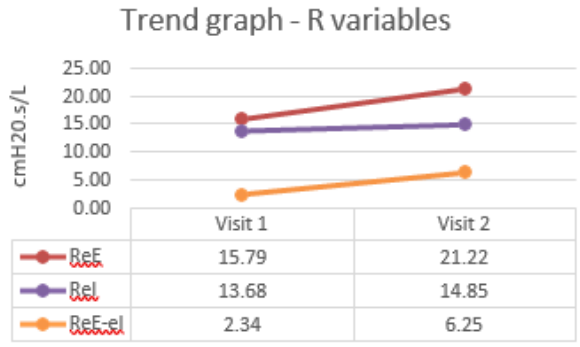
A limitation to current conventional-OSC measurements is that data are averaged across several breathing cycles, reporting a single R and X value for each frequency contained in the oscillation signal. The mechanical properties of the respiratory system however are not constant, with R and X varying with both volume and flow during tidal breathing. In response to this, we have developed a modification of OSC that tracks changes in impedance over time during tidal breathing (Temporal or T-OSC) with improved detection of airway obstruction over conventional-OSC and ventilation inhomogeneity. Similar to conventional-OSC, each data epoch is collected over 30-60 seconds, testing sessions generally last 15-30 minutes in preschool-aged children. The changes in R and X occurring during tidal breathing are influenced by dynamic properties of the airways and influence ventilation distribution. Variations in resistance and elastance of individual lung units result in variations in regional time-constants. This means that lung units fill and empty at differing rates during tidal breathing, resulting in ventilation inhomogeneity. We hypothesize that intra-breath changes in X should mirror LCI, as both measurements are influenced by the same physiological principles, namely regional time-constant differences. No study has been reported using T-OSC in the CF population and few have collected data from infants and very young children however, feasibility in two studies that collected measurements on infants aged between 6-10 weeks have been reported to be between 78-94%.

Sensitivity of T-OSC measurements to exacerbations and interventions

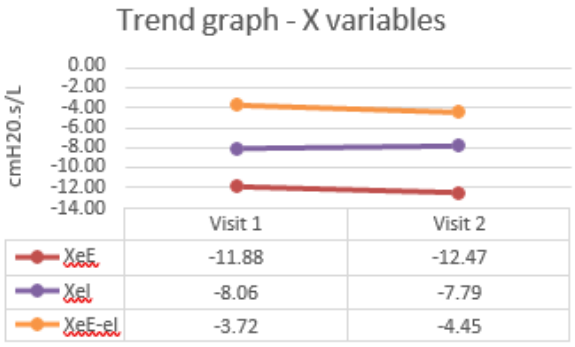
Figure 3 shows results from a 4.5-year-old male who has a history of exacerbations generally requiring at least one admission a year. He was asymptomatic and clinically stable and performed T-OSC as part of his annual review (Visit 1). T-OSC showed evidence of airway obstruction (R variables) and peripheral inhomogeneity (X variables). At his next clinic visit (Visit 2; four months later), his parent reported that he was becoming unwell and had URTI symptoms. T-OSC was again performed which showed increased airway obstruction (more positive R variables) and peripheral inhomogeneity (more negative X variables). MBW was performed at this time which unsurprisingly was elevated (LCI 2.5% = 10.16 units). The patient was discharged home with antibiotics however was admitted 2 weeks later as his cough had not resolved with antibiotics and become productive. These data suggest that T-OSC may be able to

predict the onset of an acute pulmonary exacerbation as abnormal results were seen before the onset of clinical symptoms.

Figure 3: Trend data depicting resistance and reactance measured at patients' baseline (Visit 1) and at the beginning of an acute pulmonary exacerbation (Visit 2).



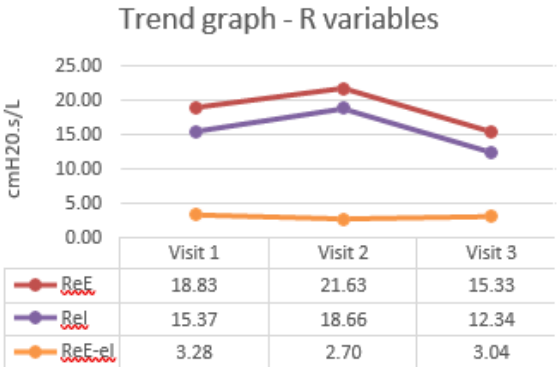
	Visit 1	Visit 2
ReE	15.79	21.22
Rel	13.68	14.85
ReE-el	2.34	6.25



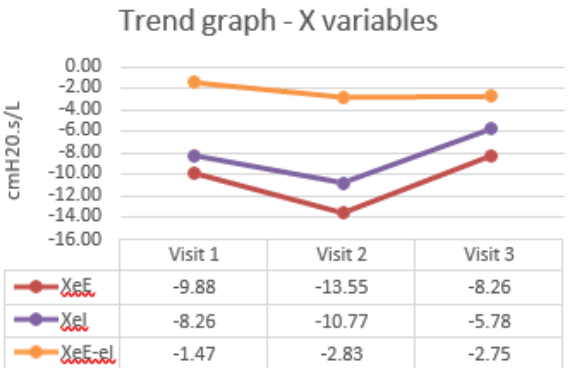
	Visit 1	Visit 2
XeE	-11.88	-12.47
Xel	-8.06	-7.79
XeE-el	-3.72	-4.45

Figure 4 shows results from a 3-year-old male who was well, with no respiratory symptoms and no regular respiratory medication use. He had no growth on respiratory swabs/cultures and had never been admitted for a pulmonary exacerbation. He performed T-OSC and MBW as part of his annual review (Visit 1). His T-OSC results showed evidence of airway obstruction (R variables) and peripheral inhomogeneity (X variables) which was also evident on LCI. After consultation with his physician, the patient was scheduled for a CT, bronchoalveolar lavage, and 2-week admission for optimization (Visit 2). BAL culture grew normal respiratory flora however his CT showed early changes suggestive of bronchiectasis. The patient now takes Dornase Alpha and Seretide daily. At his next clinic visit (Visit 3; two months later), T-OSC was again performed. His results still showed evidence of airway obstruction (R variables) and ventilation inhomogeneity (X variables), however both variables had improved in severity from the previous visit.

Figure 4: Trend data depicting resistance and reactance data measured at baseline (Visit 1), during an admission (Visit 2) and after 2-months post admission (Visit 3). Note the more positive R variables and more negative X variables which normalized after admission.



	Visit 1	Visit 2	Visit 3
ReE	18.83	21.63	15.33
Rel	15.37	18.66	12.34
ReE-el	3.28	2.70	3.04



	Visit 1	Visit 2	Visit 3
XeE	-9.88	-13.55	-8.26
Xel	-8.26	-10.77	-5.78
XeE-el	-1.47	-2.83	-2.75

Comparison between T-OSC variables and MBW

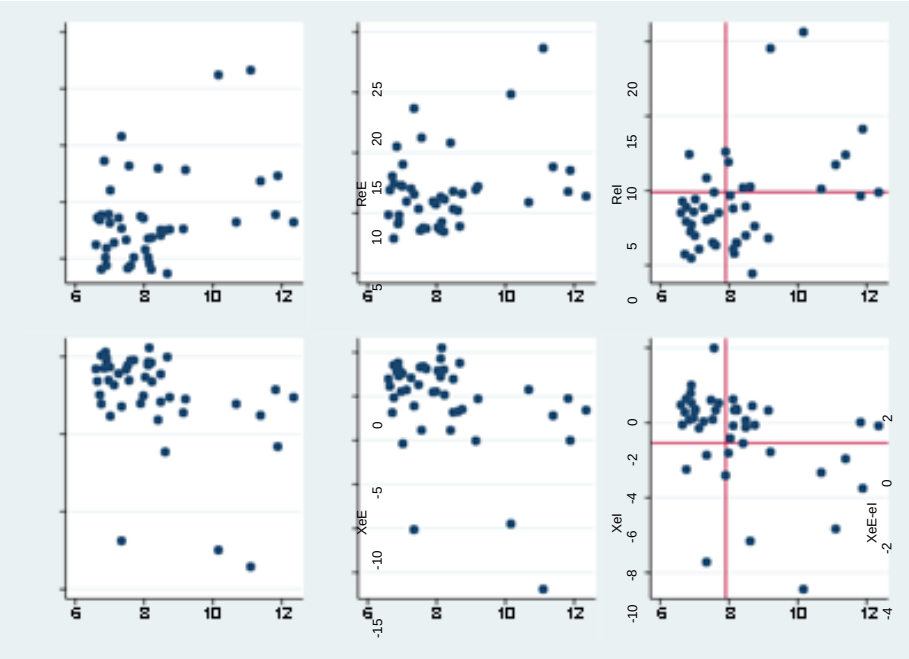
Paired T-OSC and MBW measurements have been attempted on 53 children at their annual review visit. Acceptable T-OSC and MBW measurements have been achieved by 44 children (59% male), median age 6.5 yrs (IQR 4.5-8.4) and height 120.6 cm (IQR 106.1-130.7). Of the 9 children not included in this analysis, 6 were unable to achieve acceptable MBW and 3 were unable to achieve either MBW or OSC. Abnormal LCI values (defined as an LCI 2.5% >7.937) were found in 22 patients (50%). There were no differences in sex, age, or height parameters between children who had normal vs. abnormal LCI results. Children with abnormal LCI results had decreased (more negative) Xrs variables when compared

to children with normal LCI (Table 1). When corrected for height, these differences reached significance for XeE and XeE-eI. When applying the lower limit of normal from normative data collected from preschool-aged children previously by our team, 11 patients (50%) with abnormal LCI measurements also had abnormal T-OSC (Figure 3).

Table 1: Height corrected R and X variables measured using the T-OSC technique separated according to LCI result. ReE: resistance at end-expiration; ReI: resistance at end-inspiration; XeE: reactance at end-expiration; XeI: reactance at end-inspiration; LCI: lung clearance index *: p-value calculated using the Mann-Whitney U test; #: defined as LCI 2.5% >7.9

Parameter	*Normal LCI*	*Abnormal LCI #*	*p-value**
ReE	0.062	0.068	0.4219
ReI	0.052	0.053	0.5847
ReE-eI	1.333	1.867	0.1867
XeE	-0.008	-0.022	0.0493
XeI	-0.010	-0.020	0.1714
XeE-eI	0.303	-0.101	0.0161

Figure 5: Two-way plot of height corrected R and X variables measured using the T-OSC technique against LCI. Panels A-C display resistance variables, panels D-F display reactance variables. Red vertical line depicts the LCI 2.5% upper limit of normal of 7.9 units. Red horizontal lines depict the upper limit of normal for ReE-eI (difference between resistance at end-expiration and end-inspiration) of 1.96 hPa.s.L-1 (panel C) and lower limit of normal for XeE-eI (difference between reactance at end-expiration and end-inspiration) of -0.54 hPa.s.L-1 (panel F) previously identified by our team.



Conclusion: These data show the promise of T-OSC to reflect ventilation inhomogeneity and to track disease activity in the lungs.

3. Use of urinary glutathione sulphonamide to tract lung disease activity

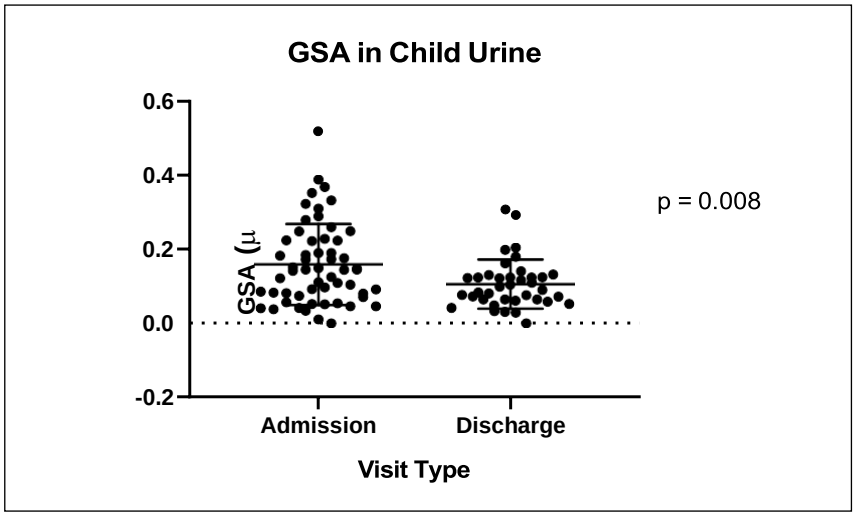
The airway epithelium provides an immunologically active physical barrier to inhaled microbes, but once airway epithelial cells detect bacterial invaders, they signal for assistance from neutrophils, the front-line troops of the innate immune system. Neutrophils migrate into the airway from the peripheral

blood and as they do so they become activated and primed to phagocytose and kill bacteria. Activated neutrophils in the lungs release a variety of destructive enzymes and oxidants associated with CF lung disease. Neutrophils generate superoxide and hydrogen peroxide, then use the enzyme myeloperoxidase (MPO) to convert hydrogen peroxide to an array of ROS, including hypochlorous acid (HOCl), hypothiocyanous acid, and radicals such as those from urate and tyrosine. MPO is the predominate peroxidase present in the CF lung and the protein is 100% activated in young children with mild disease. The lung needs an efficient antioxidant defense to cope with these oxidant stimuli. The reduced form of glutathione, GSH, is a major part of this defense, reaching high levels in ELF of healthy individuals. GSH is sacrificially oxidized to GSSG to neutralize oxidants. This reaction is reversible and GSSG can be reduced to GSH by glutathione reductase to preserve antioxidant defense. However, levels of GSH are lower in CF ASL; contributed to by reduced transport via mutated CFTR. We and others have shown increased oxidative stress (OS) in the lungs of infants and young children with CF, with evidence of protein damage through chlorination and glutathionylation. With neutrophil-dominated inflammation the main reactive species is HOCl. When GSH is oxidized by HOCl, glutathione sulfonamide (GSA) is formed via an irreversible reaction providing a specific biomarker of neutrophil-induced OS.

As a preliminary investigation into the ability of urinary GSA to reflect lung disease activity, we collected urine from children on admission for an acute pulmonary exacerbation and prior to discharge on resolution of the exacerbation. In total, we collected 56 samples on admission and 39 on discharge. GSA was measured using the techniques described in the application.

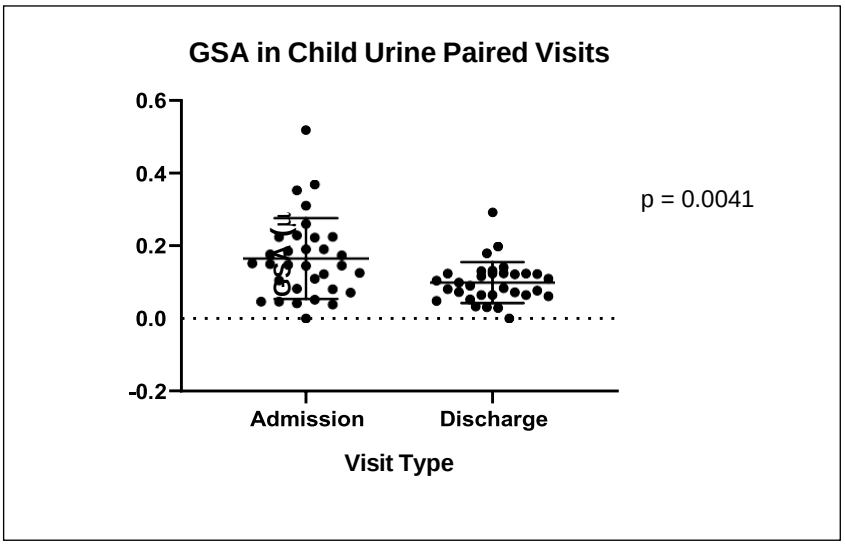
GSA was significantly higher on admission than on discharge (Figure 6).

Figure 6: Urinary GSA measured on hospital admission for acute pulmonary exacerbation of CF and on discharge. Dots represent individual data points. Mean and SD are shown.



When analyses were restricted to children with paired admission and discharge sample (n=32) a similar result was obtained (Figure 7).

Figure 7: Urinary GSA measured using paired samples collected on hospital admission for acute pulmonary exacerbation of CF and on discharge. Dots represent individual data points. Mean and SD are shown.



4. Problems/issues encountered and actions taken

The main problems encountered during the past 12 months related to Covid-19 induced changes in clinic practice. More visits have been conducted by Telehealth, restricting our ability to collect biological samples. As more of the Queensland population are vaccinated, lockdowns are less likely, and more children will return to face-to-face clinic visits.

The problems have been most extreme at the TPCH adult CF clinic. The CF ward was re-allocated to treat patients with Covid-19, CF nursing staff were diverted to Covid-19 care and few adults with CF attended in person for clinic visits. To overcome this difficulty, we are turning to the second adult CF clinic in Brisbane, at the Mater Hospital. This clinic has approximately 70 adults with CF in the ELO target age. These adults were previously treated at the QCH pediatric clinic and data from their childhood will be available to us.

Commencing MRI scanning has been difficult, due to Covid-19 and to equipment problems. However, these issues have been overcome and the first children in the ELO program have had MRI scans. While our initial plan was to prioritize MRI scans for children with a current chest CT scan, we will now “take all comers”. Paired CT-MRI scans will still be a priority where possible.

5. **Plans for the coming project year, as related to future training**: No changes to the research proposal are anticipated for the coming year

6. FORMaT Trial:

CFF PROGRESS REPORT

A. Detailed Progress Report for the year (or period)

(1) The scope of work accomplished during the year

Contracts with two countries have been executed. The United Kingdom Coordinating Centre, the University of Nottingham, was executed January 18th, 2021 and includes seven UK study sites:

- Alder Hey Children's Hospital
- Bristol Children's Hospital
- Edinburgh Children's Hospital
- Royal Brompton Hospital
- Southampton
- Manchester Wythenshaw
- Queen's Medical Centre (Nottingham University Hospitals NHS Trust)

The contract with Rigshospitalet, Denmark was executed January 13th, 2021. Additional work with the site has commenced to assist with preparing the submission documents to the Danish Medicines Agency and the Institutional Review Board. The submission of these documents is expected to occur in August 2021.

Three trials sites are now activated in Queensland, Australia – The Prince Charles Hospital, (adults) (Queensland), Queensland Children's Hospital (pediatrics) and the Gallipoli Medical Research Foundation (adult Observational Cohort participants only). A further six Australian sites have been approved by the relevant IRB/s to be added as sites to the FOR*Ma*T Trial:

- Mater Misericordeae (adults and pediatrics), Queensland
- Gold Coast University Hospital (adults and pediatrics), Queensland
- Sunshine Coast University Hospital (adults), Queensland
- Princess Alexandra Hospital (adults), Queensland
- John Hunter Hospital (adults), New South Wales
- Royal Melbourne Hospital (adults), Victoria

The above sites are currently developing submissions for their local institution which is required before sites can be activated in Australia. Additionally, the John Hunter Hospital, New South Wales, and Perth Children's Hospital, Western Australia, are in the process of being submitted to be added as pediatric trial sites to the pediatric IRB.

A total of ten participants have been recruited to the FOR*Ma*T Trial: seven participants to the Intervention Program and three participants to the Observational Cohort.

New international collaborators (Singapore and Florida, USA) have contacted the FOR*Ma*T Principal Investigator to express interest in joining the FOR*Ma*T Trial.

During this time, the FOR*Ma*T Project Team has refined many of the documents, including improving the useability of the case report forms (both paper and electronic) based on feedback from the recruiting trial sites. The FOR*Ma*T Project Team has also purchased licenses for a clinical trial management system, SiteDocs. SiteDocs will host the Trial Master File and the Investigator Site File and also has a remote monitoring function which will assist where on-site monitoring is not available.

Published February 2021

(2) The progress of training or work in clinic

We anticipate discussions to occur with other countries in the second half of 2021.

(3) Problems/issues encountered, and actions taken

The COVID-19 pandemic has continued to affect the proposed plans for the FOR*Ma*T Trial. While the contract with the United Kingdom Coordinating Centre, the University of Nottingham, was executed early in 2021, the UK Coordinating Centre has advised that the recruitment of a project manager is expected to commence in November 2021. This is due to a stepwise plan to re-open trials which were paused due to the pandemic before commencing new trials. Other international sites have been unable to re-start the discussions at this time.

Additionally, in Australia, the management of the COVID-19 pandemic is challenging as sites non-essential services are limited temporarily during periods of lockdown. This has significantly affected the ability of the FOR*Ma*T Trial project team to activate sites.

(4) Plans for the coming project year, as related to future training:

In response to the significant challenges faced by the COVID-19 pandemic, the FOR*Ma*T Master Protocol is being changed to assist in improving the number of trial sites able to participate and therefore improve the recruitment rates. While the changes to the FOR*Ma*T Master Protocol are significant, the changes do not change the main aims of the research proposal approved by the Cystic Fibrosis Foundation.

B. Staffing.

Investigator Emmanuelle Fantino has been unable to continue on the FOR*Ma*T Trial and the allocation of money has been re-directed to project management costs as per approval email from CFF (August 2020). Tiffany Jong, Senior Research Pharmacist, is on maternity leave and Daniel Hicks is acting in her position during this time. No further staffing changes have occurred during this reporting period.

C. Publications/Presentations.

- Pulmonary *Mycobacterium abscessus*: to treat or not to treat, and how should we treat?
  - May 26th, 2021 Scottish Lung in Childhood Meeting
- NTM and cystic fibrosis: epidemiology and management of an old enemy
  - July 2nd, 2021, Keynote lecture for 2nd European NTM and Bronchiectasis Workshop

The revised version of the FOR*Ma*T Master Protocol (currently being drafted) is expected to be submitted for publishing late 2021 and the statistical analysis plan (SAP) will also be made available on open access in early 2022 once the protocol is published.

D. Invention Disclosures/Patents.

Nil.

E. For research projects supported by multiple awards, please indicate the **estimated percentage of CFF support** to the total.

Approximately 50%. We request to roll forward the unspent funds from the Year 2 budget to Year 3 provided this is acceptable to CFF.

Published February 2021

7. Publications

- Chakma S, Osmani MG, Akwar H, Hasan Z, Nasrin T, Rezaul Karim M, Abdus Samad M, Giasuddin M, Sly P, Islam Z, Debnath NC, Brum E, Soares Magalhães R. *Risk Areas for Influenza A(H5) Environmental Contamination in Live Bird Markets, Dhaka, Bangladesh.* Emerg Infect Dis. 2021 Sep;27(9):2399-2408. doi: 10.3201/eid2709.204447.
- Chacko A, Sly PD, Ware RS, Begum N, Deegan S, Thomas N, Gauld LM. *Effect of Nusinersen On Respiratory Function in Pediatric Spinal Muscular Atrophy Types 1-3.* Thorax. 2021 May 7;thoraxjnl-2020-216564. doi: 10.1136/thoraxjnl-2020-216564. Online ahead of print.
- Vilcins D, Scarth P, Sly PD, Jagals P, Knibbs LD, Baker P. *The association of fractional cover, foliage projective cover and biodiversity with birthweight*. Sci Total Environ. 2021 Apr 1;763:143051. doi: 10.1016/j.scitotenv.2020.143051. Epub 2020 Oct 17. PMID: 33127150
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- Yeo AJ, Subramanian GN, Chang KL, Gatei M, Parton RG, Coman D, Lavin MF. *An anaplerotic approach to correct the mitochondrial dysfunction in ataxia-telangiectasia (A-T).* Mol Metab. 2021 Oct 9;101354. doi: 10.1016/j.molmet.2021.101354. Online ahead of print.
- Li SX, Li C, Pang XR, Zhang J, Yu GC, Yeo AJ, Lavin MF, Shao H, Jia Q, Peng C. *Metformin Attenuates Silica-Induced Pulmonary Fibrosis by Activating Autophagy via the AMPK-mTOR Signaling Pathway. Front Pharmacol. 2021 Aug 9;12:719589. doi: 10.3389/fphar.2021.719589. eCollection 2021.*
- Gao Y, Nanan R, Macia L, Tan J, Sominsky L, Quinn TP, O'Hely M, Ponsonby AL, Tang MLK, Collier F, Strickland DH, Dhar P, Brix S, Phipps S, Sly PD, Ranganathan S, Stokholm J, Kristiansen K, Gray LEK, Vuillermin P. *The maternal gut microbiome during pregnancy and offspring allergy and asthma.* J Allergy Clin Immunol. 2021 Sep;148(3):669-678. doi: 10.1016/j.jaci.2021.07.011. Epub 2021 Jul 24. PMID: 34310928
- Li S, Shao L, Fang J, Zhang J, Chen Y, Yeo AJ, Lavin MF, Yu G, Shao H. *Hesperetin attenuates silica-induced lung injury by reducing oxidative damage and inflammatory response.* Exp Ther Med. 2021 Apr;21(4):297. doi: 10.3892/etm.2021.9728. Epub 2021 Jan 28.
- Pang X, Shao L, Nie X, Yan H, Li C, Yeo AJ, Lavin MF, Xia Q, Shao H, Yu G, Jia Q, Peng C. *Emodin attenuates silica-induced lung injury by inhibition of inflammation, apoptosis and epithelial-mesenchymal transition.* Int Immunopharmacol. 2021 Feb;91:107277. doi: 10.1016/j.intimp.2020.107277. Epub 2020 Dec 23
- Cortes-Ramirez J, Wilches-Vega JD, Paris-Pineda OM, Rod JE, Ayurzana L, Sly PD. *Environmental risk factors associated with respiratory diseases in children with socioeconomic disadvantage*. Heliyon. 2021 Apr 22;7(4):e06820. doi: 10.1016/j.heliyon.2021.e06820. eCollection 2021 Apr. PMID: 33997379
- Brereton CF, Jagals P. *Applications of Systems Science to Understand and Manage Multiple Influences within Children's Environmental Health in Least Developed Countries: A Causal Loop Diagram Approach.* Int J Environ Res Public Health. 2021 Mar 15;18(6):3010. doi: 10.3390/ijerph18063010.

- Brereton CF, Pedercini M. *COVID-19 Case Rates in the UK: Modelling Uncertainties as Lockdown Lifts.* MDPI Systems 2021, 9, 60. https://doi.org/10.3390/systems9030060

Accepted for publication

- Pang X, Shao L, Nie X, Yan H, Li C, Yeo AJ, Lavin MF, Xia Q, Shao H, Yu G, Jia Q, Peng C. *Microcrystalline Silica Particles Induce Inflammatory Response via Pyroptosis in Primary Human Respiratory Epithelial Cells.* Environmental Toxicology

Submitted

- Kelk D, Logan J, Andersen A, Bell SC, Wainwright CE, Sly PD, Fantino E. *Neutrophil respiratory burst activity in cystic fibrosis.* Submitted to Journal of Cystic Fibrosis
- Tarique AA, Tuladhar N, Kelk D, Begum N, Lucas RM, Lou L, Stow JL, Wainwright CE, Bell SC, Sly PD, Fantino E. *Azithromycin augments bacterial killing and anti-inflammatory phenotypes in macrophages from patients with cystic fibrosis via ERK1/2-mediated pathway.* Submitted to Journal of Clinical Investigation.

8. Funding

- Tarique A**.** Children's Hospital Foundation. CHF Program Grant. $50,000
- Soares Magalhães R. RSP: Queensland Alliance for One Health Science. Strategic Research Investment. $905,000
- Blake T. Cystic Fibrosis Foundation. Clinical Pilot and Feasibility. Invitation to submit, outcome pending. $212,000
- Wong M. Thrasher Research Fund. Early Career Award. $35,519.22
- Wong M. Queensland Health (HIIRO). Queensland Advancing Clinical Research Fellowship (Round 3). 100,000
- Vilcins D. CHRC Small grant scheme. $4,589.00
- Yeo A. Children's Hospital Foundation. CHF Project Grant. $50,000

9. Awards and Media

- Yamamoto A. American Thoracic Society. 2021 ATS Student Scholars Award
  A select group of motivated students to benefit from a specially designed curriculum and offered free registration to the ATS International Conference
- Yamamoto A. Wonder of Science, The University of Queensland. Young Science Ambassador Award 2021.
  Promoting a STEM culture in Queensland schools.
  https://wonderofscience.com.au/young-science-ambassadors
- Vilcins D. WeAreBrisbane Twitter. Guest curator for National Science Week – 17 Aug 21

10. Conferences and Presentations

Researcher	Date	Int/Dom	Location	Conference Title	Role	Presentation title
Blake T	May-21	Dom	Virtual	TSANZSRS Annual Scientific Meeting 2021	Invited speaker	Ethnicity and its impact on prediction equations (including Aboriginal Australians)
Blake T		Dom		CF Australia Conference	Oral presentation	Comparing intra-breath oscillometry and multiple breath washout in children with CF
Brereton C	Sep-21	Int	Hybrid	PBC 2021 Focus meeting	Invited speaker	A system dynamics approach to children's health improvement in the Solomon Islands
Cortez Ramirez J	Sep-21	Int	Hybrid	PBC 2021 Focus meeting	Invited speaker	Risk factors determinant of environmentally transmitted zoonoses in Queensland: A spatial regression analysis
Lau C	Sep-21	Int	Hybrid	PBC 2021 Focus meeting	Invited speaker	Precision public health approaches to surveillance and response to infectious disease
Le Hong H.T.C	May-21	Dom	Virtual	TSANZSRS Annual Scientific Meeting 2021	Presenter (poster)	Significant lack of recognition of asthma in Vietnamese children
Sly PD	Jan 21	Int	Virtual	Master's in Allergy (MSc) course - Asthma and Allergic Airways Disease (AAAD) module	Invited presenter	Effects of environmental pollution
Sly PD	May-21	Dom	Virtual	TSANZSRS Annual Scientific Meeting 2021	Invited speaker	Projections of the effect of climate change on respiratory health in children
Sly PD	May-21	Int	Virtual	KJ Price Respiratory conference	Invited speaker	Air pollution and children's health – Where next?
Sly PD	Jun-21	Int	Virtual	44th European Cystic Fibrosis Conference	Invited speaker	Early detection of pulmonary exacerbations
Sly PD	Sep-21	Int	Hybrid	PBC 2021 Focus meeting	Invited speaker	Epidemiological evidence of air pollution increasing Covid-19
Sly PD	Nov-21	Int	Virtual	Iberoamerican Society for Environmental Health	Invited speaker	Toxic Effects of e-Waste
Sly PD	Nov-21	Int	Virtual	II World Conference on the World Pneumonia Day	Invited speaker	WHO Collaborating Centre for Children's Health and Environment.

Vilcins D	May-21	Dom	Gold Coast	The National Symposium on Herbal and Naturopathic Medicine	Invited Keynote speaker	Children's health and the environment
Vilcins D	May-21	Dom	Gold Coast	The National Symposium on Herbal and Naturopathic Medicine	Workshop presenter	Building preconception care into naturopathic practice: moving beyond fertility support
Vilcins D	Sep-21	Int	Hybrid	PBC 2021 Focus meeting	Invited speaker	Oxidative stress as a mediator of the effect of air pollution on respiratory disease
Yamamoto A	May-21	Dom	Virtual	TSANZ Annual Scientific Meeting	Presenter (Poster), awarded best poster	Effect of environmentally persistent free radicals on human airway epithelium
Yamamoto A	May-21	Int	Virtual	ATS 2021 International Conference	Presenter (poster)	The Effect of Combustion Generated Environmentally Persistent Free Radicals on Well-differentiated Human Airway Epithelial Cells
Yamamoto A	Sep-21	Int	Hybrid	PBC 2021 Focus meeting	Invited speaker	Environmentally Persistent Free Radicals increase susceptibility to SARS-CoV-2 infection

4. EXPECTATIONS FOR COMING YEAR (not applicable for Final Reports)

How do you expect to use your funding allocation for the coming year?

The funding allocation for 2022 will follow the initial proposal. This covers mainly gaps in staff funding and allows additional positions not covered by CFF or CHF funds

CERTIFICATIONS

Note: Approvals by email are acceptable.

Annual Report:

Lead CI or Funding Recipient:

Name	Signature	Date
Peter D Sly		3 Feb 2022

Head of School/Centre/Institute:

I have read and endorse the annual report.

Name	Signature	Date
Karen Barlow		

SUBMISSION OF THE REPORT

Please email the completed form to strategicfunding@uq.edu.au

Submission requirements:

- Send a separate email for each annual report submitted
- Attach a single PDF document containing all approvals
- Use descriptive subject lines to help categorise emails
  e.g. {Project number} Annual Report