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RACP Foundation Research Awards

YEAR 2 PROGRESS REPORT

Project / Program Title		Long term outcomes following early infection and inflammation in cystic fibrosis lung disease
Name		Dr Katherine Frayman
Award Received		2018 RACP P&CHD NHMRC Award for Excellence
Report Date		12 December 2019
Chief Investigator / Supervisor		Supervisor - Prof Sarath Ranganathan
Administering Institution		Murdoch Children's Research Institute
Funding Period	Start Date:	1 January 2018
	Finish Date:	5 February 2020

PROJECT SUMMARY

Cystic fibrosis (CF) is the most common life-limiting genetic condition amongst Caucasians, affecting approximately 3300 Australians. Most people with CF die as a result of respiratory failure due to progressive bronchiectasis (scarred and dilated airways), in mid-adulthood.

Infection and inflammation are critical to the developmental of CF lung disease, and both can begin very early in life. Over the past three decades, there have been significant changes in our understanding and management of CF lung disease, including the introduction of newborn screening (which occurred in Victoria in 1989), evidence that improved health in infancy and early childhood affects lung function when first measured at age 6-years, and an understanding, from molecular analysis of adult sputum samples, that there is a diverse bacterial community (microbiota) in the airways of adults with CF. The lower airway microbiota of children with CF has not been characterised.

This PhD follows a birth cohort of 100 infants with CF that was established in Victoria in 1992, soon after the introduction of newborn screening. Infection and inflammation was initially explored in multiple lower airway samples obtained under general anaesthesia. These samples have been re-analysed to describe the microbiota in early CF lung disease. This study will then describe the very long-term impact of early lower airway infection, inflammation and microbiota composition on survival and the development of lung disease over a 25-year period.

PROJECT AIMS / OBJECTIVES

This project aims to explore the very long-term outcomes following early infection and inflammation CF lung disease.

It will first explore the development of the lower airway micro biota (bacterial community) in infants and young children with CF, including differences in the lower airway microbiota of infants with and without CF; the evolution of the CF lower airway microbiota through infancy and early childhood and its relationship to disease status, including airway inflammation; and spatial differences in the micro biota of the right middle lobe and lingula airways of young children with CF.

The project will then evaluate the influence of lower airway infection, inflammation and microbiota composition on survival, need for lung transplant, rate of decline of lung function, and progression of structural lung disease over a 25-year period.

A birth cohort of 100 infants with CF was established at the Royal Children's Hospital, Victoria, in 1992. These infants were recruited soon after diagnosis (predominantly by newborn screening, introduced in Victoria in 1989), into a study designed to explore infection and inflammation in early CF lung disease. Infants underwent bronchoscopy and bronchoalveolar lavage (lung washings; BAL) at recruitment and annually thereafter. Infants undergoing bronchoscopy for investigation of chronic strider were recruited as controls. Quantitative cultures were performed and inflammatory markers were measured contemporaneously. The BAL fluid was then frozen and stored, and 16S rRNA gene sequencing has been performed on stored samples.

SIGNIFICANCE AND OUTCOMES

To date, this research project has demonstrated that differences in the CF lower airway microbiota are evident by 6-months of age, and are most pronounced in symptomatic infants. There are ongoing age-related changes in its composition and structure, but it appears that the lower airway microbiota is dynamic. In childhood, lower airway microbiota composition is associated with airway inflammation; the next part of this project will evaluate the long term impact of this.

Substantial future research will follow on from this project, including an evaluation of the adult airway microbiome and its relationship to current disease status and early life factors, with the aim of improving our understanding of the development of CF lung disease and identifying potentially modifiable factors in that process.

PUBLICATIONS / PRESENTATIONS

Original publications:

Frayman KB, Armstrong OS, Grimwood K, Ranganathan SC. The airway microbiota in early cystic fibrosis lung disease. Pediatr Pu/mono! 2017; 52(11):1384-1404.

Frayman KB, Armstrong OS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. The lower airway microbiota in early cystic fibrosis lung disease: a longitudinal analysis. Thorax 2017; 72:1104-1112.

Frayman KB, Wylie KM, Armstrong OS, Carzino R, Davis SD, Ferkel TW, Grimwood K, Storch GA, Ranganathan SC. Differences in the lower airway microbiota of infants with and without cystic fibrosis. J Cyst Fibros 2019; 18(5):646-52.

Abstracts:

Frayman KB, Armstrong OS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. The microbiome in early cystic fibrosis lung disease: a longitudinal analysis. European Cystic Fibrosis Conference 2015, Brussels - poster abstract.

Frayman KB, Armstrong OS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. Comparison of the right and left lower airway microbiota in infants with cystic fibrosis. Australasian Cystic Fibrosis Conference 2015, Sydney - poster abstract.

Frayman KB, Armstrong OS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. The microbiome in early cystic fibrosis lung disease: a longitudinal analysis. Australiasian Cystic Fibrosis Conference 2015, Sydney - oral abstract.

Frayman KB, Armstrong OS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. Differences in the lower airway microbiota of infants with and without cystic fibrosis. Thoracic Society of Australia and New Zealand Annual Scientific Meeting 2017, Canberra - oral abstract.

Frayman KB, Armstrong OS, Carzino R, Ferkol TW, Grimwood K, Storch GA, Teo SM, Wylie KM, Ranganathan SC. Differences in the lower airway microbiota of infants with and without cystic fibrosis. Australasian Cystic Fibrosis Conference 2017, Melbourne - e-poster abstract.

Frayman KB. Early lung microbiome. Australasian Cystic Fibrosis Conference 2017, Melbourne - invited speaker, concurrent session.

Frayman KB. The lower airway microbiota in early cystic fibrosis lung disease. Australian Paediatric Respiratory Meeting, 2018, Adelaide - invited speaker.

ACKNOWLEDGEMENTS

Frayman KB, Wylie KM, Armstrong OS, Carzino R, Davis SD, Ferkol TW, Grimwood K, Storch GA, Ranganathan SC. Differences in the lower airway microbiota of infants with and without cystic fibrosis. J Cyst Fibros 2019; 18(5):646-52.

Carzino R, Frayman KB, King L, Vidmar S, Ranganathan SC on behalf of AREST CF. Regional differences in infection and structural lung disease in infants and vounQ children with cystic fibrosis. J Cyst Fibros [in press].