

25th of January 2023

CFA Innovation Award 2021 – 12 months report

Project: Safety and effectiveness of triple -caftor combinations in cystic fibrosis during pregnancy

I was awarded the CFA Innovation Award to investigate transfer of -caftor triple combinations across placenta and entry into different fetal tissues to assess the risks these drugs might pose for non-CF babies and potential benefits they could have to improve survival and outcomes for CF babies. To date, present understanding of -caftor permeability at placental and blood-brain barriers during development is poor and a major concern for clinicians in prescribing -caftors to pregnant women with CF is the unknown risk these drugs might pose to developing fetuses and neonates.

My research background is in pharmacology where I use advanced techniques in drug transfer studies and animal models.

Despite difficulties in breeding the F508del-CFTR rats and survival of pups, the project is on track. We currently have one Honours student working on this and have a second Honours student starting in February 2023. The results to date have been exciting: WE have completed the following studies in 2 animals, and are in the process of completing 2 more. 1) Drug permeability: Wildtype Sprague Dawley rats at embryonic day (E) 19 and adult rats were administered an intraperitoneal injection of ETI (40mg/kg/d ivacaftor + 6.7mg/kg/d/elexacaftor + 3.5mg/kg/d tezacaftor) traced with [3H] ivacaftor. Lung, gut and pancreas were collected 30 minutes later, and [3H] radioactivity was measured using liquid scintillation counting.

2) Placental and Milk Transfer: CF and wildtype pups were exposed via placental or milk transfer from dams orally treated with ETI for 6 days. ETI concentrations in pup & maternal plasma were determined by liquid chromatography–mass spectrometry.

3) Histological assessments using H&E staining of tissues were completed and untreated vs treated as well as heterozygous vs homozygous vs wildtype were compared.

This work is being presented at the annual TSANZRS meeting in NZ in 2023 and we have submitted another abstract to ECFS 2023. Furthermore, we are wrapping the current work up for a publication in a high impact journal.

Furthermore, we have acquired a further \$25k of seed funding to look at factors contributing to the development of cystic fibrosis associated cataracts in pregnant rats treated with trikafta. Furthermore, a US CFF grant has been submitted in 12/2022 containing preliminary data which was conducted using this grant.



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I am very grateful for the opportunity to conduct this research, which could not be possible without CFA.

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