31 August 2021 **Zara Sheikh**

Final Report for ACFRT Post Graduate Student Grant 2018

'Unlocking the mechanisms of interactions between anti-inflammatories and antibiotics for optimal cystic fibrosis treatment'

Overview

The main objective of the research was to investigate the interactions between anti-inflammatories and the most widely prescribed inhaled antibiotics used for cystic fibrosis (CF) treatment and explore other anti-inflammatory options for CF treatment using different *in vitro* models of bronchiolar epithelial cell lines - NuLi-1 (healthy) and CuFi-1 (CF) cell lines.

Australian Cystic Fibrosis Research Trust (ACFRT) Post Graduate Student Grant provided financial assistance towards my PhD research to understand the potential interactions between anti-inflammatories and antibiotics for optimal cystic fibrosis treatment.

Outcomes of the research

The following objectives were achieved:

1. A literature review of the current anti-inflammatory agents available for CF treatment and the potential role of inhaled anti-inflammatory drugs as treatment options for CF, with a particular focus on ibuprofen, was performed and is published as 'Is there a role for inhaled anti-inflammatory drugs in cystic fibrosis treatment?' in *Expert Opinion on Orphan Drugs*, 2018. 6 (1): 69 - 84.

   Sheikh, Z., Ong, H.X., Pozzoli, M., Young, PM., Traini, D. (2018). Is there a role for inhaled anti-inflammatory drugs in Cystic Fibrosis treatment? Expert Opinion on Orphan Drugs, 6, 1:69-84.

2. A novel *in vitro* model of the cystic fibrosis cell line CuFi-1 with characteristic features of the CF airways and its healthy counterpart NuLi-1 was developed and characterized for assessing drug transport of inhaled therapies used in CF treatment and is published in *European Journal of Pharmaceutics and Biopharmaceutics*, 2020. 156: 121 - 130

   Sheikh, Z., Bradbury P, Pozzoli M, Young P.M, Ong H.X, Traini D (2020). An in vitro model for assessing drug transport in cystic fibrosis treatment: Characterisation of the CuFi-1 cell line. European Journal of Pharmaceutics and Biopharmaceutics, 156: 121 - 130.

3. Diclofenac, a widely prescribed anti-inflammatory drug was explored as a novel anti-inflammatory treatment option for CF. A low dose diclofenac inhaled formulation was developed that showed an anti-inflammatory effect in both the healthy and CF *in vitro* models, thus highlighting its potential as a promising inhaled anti-inflammatory therapy for CF treatment. The research work is published in the *International Journal of Pharmaceutics*, Volume 596: 12031

   Sheikh, Z., Reis L.G.D, Bradbury P, Meneguzzo M, Scalia S, Young P.M, Ong H.X, Traini D (2021). Development and in vitro characterization of a novel pMDI diclofenac formulation as an inhalable anti-inflammatory therapy for cystic fibrosis. International Journal of Pharmaceutics, Volume 596: 12031

4. The mechanisms of interactions between the anti-inflammatory drug ibuprofen with each of the CF-approved inhaled antibiotics (Tobramycin, Colistin and the Colistin prodrug Tadim) was elucidated, including their anti-bacterial and anti-inflammatory effects and is published in *European Journal of Pharmacology*, 2021. Volume 902: 174098.

   Sheikh, Z., Bradbury P, Reekie T.A, Pozzoli M, Robinson P.D, Kassiou M, Young P.M, Ong H.X, Traini D (2021). Tobramycin and Colistin display anti-inflammatory properties in CuFi-1 cystic fibrosis cell line. European Journal of Pharmacology, Volume 902: 174098

Research Summary

The inhaled route allows targeted drug delivery to the lungs at low doses, overcoming decreased bioavailability issues and other systemic side-effects associated with high oral doses. Owing to these numerous advantages of inhaled delivery, the role of potential inhaled anti-inflammatory drugs used in CF treatment with a particular focus on ibuprofen has been investigated. The mechanisms of interactions between the two primary modalities of CF treatment – anti-inflammatory drugs (ibuprofen) and antibiotics was further elucidated to determine if a combination therapy could be more beneficial. Surprisingly, ibuprofen in combination with the antibiotics did not significantly decrease inflammation in a CF model when compared to the drugs alone, suggesting that new anti-inflammatory drugs must be explored to identify a more effective combination treatment. However, to study the drug delivery of novel therapies, an *in vitro* model simulating the CF lung and suitable to assess drug transport is required. Hence, an *in vitro* CF bronchial epithelium model to study drug transport was developed and characterized to recapitulate the CF airways and compared to a healthy epithelial model. Finally, a low dose inhalation formulation of novel anti-inflammatory drug diclofenac was successfully developed and characterized in terms of transport and anti-inflammatory activity using these established models. Future studies will focus on investigating the interactions of diclofenac with the CF-approved antibiotics on the developed models and correlate these findings *in vivo* to comprehend its clinical relevance to optimize CF treatment and reduce the treatment burden of CF patients.

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