Progress Report to Cystic Fibrosis Australia

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Project Name: Development of new mucus-thinning drugs for CF patients

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Progress to date:

The lung is protected by a mucus lining that acts like a sticky conveyor belt to capture and remove the particles and microorganisms that we inhale with each breath. Patients with cystic fibrosis (CF) have an abnormally thicker mucus layer in their airways, resulting in complications that can even precipitate events that lead to premature death. The aim of this project is to develop more effective mucus-thinning drugs for CF patients.

Our lab has recently identified a novel mucolytic drug target called 'trefoil factors', which is a group of proteins produced by the human body to increase the stickiness of mucus. We have demonstrated that CF patients produce up to 1000-fold more trefoil factors than healthy people. We have also determined how the 'trefoil factors' thicken mucus at a molecular level – they crosslink specific sugar moieties on the polymeric mucin proteins and hence rigidify the mucus gel. We then recombinantly produced the protein responsible for installing the sugars.

With the protein-sugar-trefoil factor axis identified, we will next investigate on how the levels of sugar and trefoil factors impact on the mucus viscoelasticity respectively. Meanwhile, working in collaboration with Telethon Kids Institute (Perth), Murdoch Children's Research Institute (Melbourne) and the AREST-CF program, we are now focussing on evaluating the ability of 15 monoclonal antibodies against the trefoil factors to reduce the viscoelasticity of patient mucus samples. This will help us determine which antibodies will be progressed towards clinical studies.

Thank you to Cystic Fibrosis Australia for this scholarship.

Signed: Shiyi Xi **Date:** 24/11/2021

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