SCAF/17/03 - Therapeutic targeting of AMP-activated protein kinase to enhance airway bacterial clearance in bronchiectasis

The lung is the major interface between the body and the environment. A normal person breathing at a normal rate will inhale more than 1,000,000 bacteria per day. As a result, the lung needs to have an effective method of removing bacteria and other inhaled particles to prevent lung damage. This involves the action of lung immune cells which eat bacteria and other particles, as well as the action of tiny hairs called cilia, which “flick” particles that are trapped in lung mucus out of the lungs.

In patients with lung disease, these natural defences against infection fail. In a particularly severe form of chronic lung disease called bronchiectasis, the airways widen, leading to a failure to clear mucus. The cilia are damaged and slow and fail to clear infection from the lungs and we and others have shown that the immune cells in the lungs fail to eat bacteria effectively. As a result, patients suffer from frequent respiratory infections, chronic cough and poor quality of life. There are no effective treatments and as a result patients are treated mostly with frequent courses of antibiotics.

The cause of the disease is unknown but our studies are beginning to unravel what happens to cause immune and cilia dysfunction in bronchiectasis. Our studies have identified a critical energy regulator called AMP-activated protein kinase (AMPK) as an important contributor to the disease. AMPK senses when cells need more energy and responds by suppressing energy consuming process (to preserve energy). The converse is also true when energy is abundant. AMPK affects multiple cellular processes including being a very powerful regulator of how the immune system functions.

We and others have found in the laboratory that drugs that activate AMPK, some of which are already in use in the clinic, can reduce inflammation and promote the clearance of bacteria. In this project, we will test whether AMPK activators could become a new therapy for bronchiectasis and other lung conditions. We will use AMPK activator drugs to stimulate immune cells, aiming to improve their ability to clear bacterial infections. We will also study whether AMPK activators can enhance the movement of cilia, helping to clear mucus from the lungs. Finally, we will conduct studies in patients that will provide the proof of concept needed to target medications in the right way at the right time.