SRC 2 – Mike Gray

Cystic fibrosis is caused by a faulty CFTR protein, which leads to dehydrated, acidic secretions in the lungs, which makes them more prone to infection. This SRC is using a novel approach to help correct the fluid, pH and bacterial-killing defect in all CF patients by switching on/off non-CFTR 'bypass' channels/transporters, such as the anoctamins (ANOs), to compensate for the lack of CFTR in affected lung cells.

The groups from Lisbon and Regensburg have focussed on ANO1, which is normally activated by increases in calcium within the cells. They have recently identified nine novel small molecules (chemicals) that have positive effects on ANO1 Cl^- (calcium) transport. They have also set up an automated 'screening assay' that will help identify proteins inside airway cells that can alter the number of ANO1 channels in the membrane. This approach could help identify new drug targets that would improve ANO1 activity in the airway cells of someone with cystic fibrosis.

The group from Chapel Hill (USA) has been looking at the way acid pH affects a protein called SPLUNC1 which makes many natural antimicrobial proteins better at killing bacteria. Results show that when the pH falls below neutral (pH 7.0), SPLUNC1 loses its ability to help these antimicrobial proteins work, so they are less able to kill bacteria. However, they have made changes to the structure of SPLUNC1 that makes them pH-independent and, importantly, these altered versions now work at the acid pH found in CF lungs. This is very exciting as these 'pH-independent' versions of SPLUNC1 could potentially be inhaled to help improve bacterial killing in CF lungs.

The groups from Newcastle have begun developing a method to produce F508del CFTR airway cells from a non-CF human embryonic stem cell line, to help reduce the need for cells from CF patients. For this they need to first introduce the F508del mutation into the normal CFTR gene cells using a process called 'gene editing', which involves cutting the gene at a specific location and then inserting a small piece of DNA that contains the F508del mutation. The group has now designed the gene editing 'tools' and shown that these cut the gene at the right location. They are now ready to develop methods to insert the DNA template. After this they will then use a mixture of hormones and growth factors that will make these CF cells turn into lung epithelial cells that can then be studied in a range of different ways.