PCL/18/06 - Manipulating the immune microenvironment in Malignant Pleural Mesothelioma (MPM)

MPM is caused by asbestos exposure, usually through work in trade industries such as shipbuilding. Asbestos exposure causes chronic inflammation which promotes tumour formation. The UK has the highest death rate from Mesothelioma in the world- it is resistant to all chemo and radiotherapy. Research until now has focused largely on the cancer cell but it is becoming clear that the surrounding cells and the immune system are crucial in allowing tumour initiation and progression. New treatments called immunotherapies reveal previously hidden cancers to the immune system, or activate immune cells directly to fight cancer. For example, drugs that disrupt the PD1 “immune checkpoint” system have shown great promise, but only work in around 20% of patients with MPM. Macrophages are an immune cell which initiate and establish inflammation in the lining of the lung, which precedes MPM in most patients. They make up 20-30% of all the cells present in human MPM tumours and studies show that macrophage programming is important in influencing the immune response to cancer and may be involved in resistance to standard treatments. As a result, new drugs which directly target macrophages are in clinical trials for other cancers. We believe that targeted treatment of macrophages in MPM may result in new and highly effective MPM therapies. In particular, based on previous studies, we anticipate that macrophage treatment may be effective as a single agent and increase the number of responders to standard chemotherapy and/or anti-PD1 immunotherapy. We will have the opportunity to interrogate a new, unique, mouse model of MPM. This means we can test these questions before any patients are exposed to new drugs in clinical trials. Our model combines asbestos-driven inflammation with state-of-the-art genetic engineering. Importantly, our mice have normally functioning immune systems. In this study we will inject macrophage treatments (CSF-1R or CD98 inhibitors) directly into the pleural cavity of MPM-bearing mice. We will then measure the effect of these treatments on the activity and death rate of the tumour cells, and the length of time the mice survive.