Longitudinal profiling of the molecular features of mesothelioma – a fatal malignancy causally linked to asbestos exposure

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Mesothelioma is a uniformly fatal malignancy of the lining of the chest cavity and lungs that is causally linked to inhalation of asbestos fibres. The UK currently endures the highest incidence of Mesothelioma worldwide: 45 fatalities/million population; 1/212 male lifetime risk, making asbestos exposure the leading cause of occupation-related mortality in the UK. Worldwide, mining and use of asbestos continues in many counties with inadequate labour protection and Mesothelioma rates are rising rapidly. The disease does not respond to conventional therapy and lacks obviously druggable driver mutations. Due to a prolonged latency period and difficulty in distinguishing pre-malignant from benign lesions, the molecular features of early stage disease are presently uncharacterised. Chronic inflammation, arising from frustrated fibre phagocytosis, is an established risk factor in disease initiation and predictor of poor outcome but its role in progression and maintenance remains unclear. A much deeper understanding of the basic biology underpinning disease progression in vivo is needed in order to develop new strategies for prophylaxis and treatment. The late onset of clinically symptomatic pleural disease that precedes Mesothelioma (typically several decades after asbestos exposure), combined with very short survival from time of diagnosis, has limited studies in human subjects to the analysis of very advanced disease. Besides the established link to inhalation of asbestos fibres, we know very little about how this cancer develops prior to the late emergence of clinical symptoms. We have pioneered longitudinal in vivo analysis of asbestos-exposed wildtype mouse models and uncovered asbestos-driven molecular changes that occur prior to Mesothelioma development. Furthermore, we have shown that biopersistent synthetic fibres (Carbon Nanotubes) that physically resemble asbestos can drive Mesothelioma in mice via a near-identical sequence of molecular events, potentially heralding future outbreaks of synthetic fibre-driven MPM. Our future work focusses on longitudinal analysis of genetically-defined mouse models with predictable outcomes t0 provide mechanistic insight into pre-malignant cancer emergence & progression, linking disease-relevant mutations to evolving tumour phenotypes and their bi-directional interactions with the immune microenvironment. Our goal is to use these platforms i) to determine mechanisms of progression to Mesothelioma and ii) to identify strategies to improve responses to immunotherapy.