**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Ameliorating ageing, age-related diseases and cancer by targeting senescence and the p53 pathway. |
| **Project Summary** | |
| Ageing is a process defined by the accumulation of old (senescent) cells in tissues.  It has been shown that senescent cells interfere with the normal functions of tissues and thus lead to the phenotypic changes associated with ageing as well as the establishment of age-related diseases. Together, these are responsible for loss in quality of life and the eventual reduction of lifespan of an organism. The genetic factors involved in triggering and maintaining senescence have not been fully characterized. Our main goal is to take advantage of novel markers and effectors of senescence, particularly those related to the p53 pathway, in order to:  i) better understand the molecular processes involved in human ageing.  ii) define new therapies that target senescence, which should:  -ameliorate age-related diseases, such as cancer, fibrosis and neurodegenerative diseases.  -delay and/or ameliorate the symptoms of ageing, with the final goal of slowing/reverting the process in humans.  Through an initial proteomics screening, we identified several novel potential components of the senescent pathway1, and we showed that inhibition of one of them delays ageing in a mouse model2 due to its control of p533.  We propose to study the role of these proteins in senescence and ageing. Our research plan will include:   1. Assessing the effects of potential effectors of senescence by inhibiting/overexpressing them in different cellular models (such as fibroblasts aged in culture or derived from premature ageing syndromes, or stress-induced senescent normal and cancer cells). By doing this, we will also study the changes in gene expression that define the senescent phenotype. Preliminary data suggests that certain chemical inhibitors of these proteins can block senescence. We will test their effect on cell ageing.   b) Defining novel markers of senescence. The methods currently available to detect senescent cells need to be improved. We plan to characterize several novel membrane proteins upregulated in senescence to be used as new and more efficient markers. We have recently shown that such markers could have prognostic potential in diseases such as cancer. With the help of our collaborators, we will develop systems to detect senescent cells in tissues and in culture. This has therapeutic potential (see below) but could also be useful to determine the percentage of senescent cells in tissues and thus its biological ageing. Comparisons to chronological ageing could have diagnostic and prognostic value.  c) Establishing new protocols for clearing senescence cells. It has been shown in mouse models that eliminating senescent cells from tissues suppresses the symptoms of ageing and prolongs lifespan4. We will use our newly identified markers to selectively target senescent cells using tools such as peptides, nanotechnology, monoclonal antibodies, etc. This aim will also be performed with our collaborators at the Department of Chemistry and commercial partners, which will provide targeted compounds that could selectively detect and kill senescent cells. We will also test them in in vivo models if possible.  We expect our experiments to clarify the mechanisms involved in the senescence pathway, which are still poorly defined, as well as to provide new tools for the study of senescent cells and possible diagnostic/therapeutic interventions that could increase health and quality of life in older populations in the future.  Techniques that will be undertaken during the project:  The student will use techniques such as protein/DNA/RNA extraction, microscopy, immunofluorescence, immunohistochemistry, subcellular fractionation, gradient separation, cloning, transfection, RNA interference, flow cytometry, Western blots, luciferase assays, quantitative Real Time PCR, microarrays and mass spectrometry. The student will also be taught to process data, including image editing with Photoshop and advanced statistical analysis of data with R, using quantitative tools such as Excel, GrahPad’s Prism and Image J, among other specific software regularly used in the lab.  BBSRC Strategic Research Priority: Integrated Understanding of Health - Ageing | |
| **References** | |
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