**iCase Project / AY 2023 -2024**

# Antibody-drug conjugates for targeted treatment of cellular senescence in lung cancer and respiratory disease

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**Department/Institute:** Chemical Engineering and Biotechnology

**Industrial Partner:** AstraZeneca

**Research area:** Cellular Senescence in Lung Cancer and Respiratory Disease

**Project outline:**

Cellular senescence is characterised by a stable cell cycle arrest in response to damage or oncogenic stress. When senescent cells accumulate in damaged tissues, they can drive cancer progression and the pathophysiology of a wide range of diseases.

Selective removal of senescent cells with help of small molecule drugs (senolytics) is an emerging therapeutic approach that can restore a pro-regenerative environment and reverse senescence-associated pathologies in the lung (Cottage, Comm. Biol., 2019). For example, removal of senescent cells in lung precancerous lesions in advanced non-small cell lung cancer (NSCLC) resulted in tumour eradication, and reduced scarring and recovery of lung function was observed in bleomycin-induced pulmonary fibrosis (Muñoz-Espín, EMBO Mol. Med., 2018;).

However, currently available senolytics suffer from low specificity resulting in numerous off- and on-target effects. We have recently demonstrated improved senolytic action by introduction of galactose modification to exploit increased intracellular level of galactosidase enzyme (Gonzales-Gualda, Age.Cell 2020). Even higher level of specificity can be achieved by exploiting surface biomarkers, and we have recently made significant progress in identifying membrane proteins that are differentially overexpressed in chemotherapy-induced senescent cancer cells.

Building on these findings we propose development of antibody-drug conjugates (ADCs) targeting the senescent surfaceome as a novel therapeutic tool for the treatment of lung cancer and senescence-associated respiratory diseases. ADCs will be designed using enzyme-sensitive linkers and small molecule warheads (Fruk), and validated in our in vitro and in vivo modles of NSCLS (Munoz Espin) and respiratory disease (AZ)

**BBSRC DTP main strategic theme:** Transformative technologies

**BBSRC DTP secondary strategic theme:** Bioscience for an integrated understanding of health