English

The **TUNIC** project aims to better understand how neutrophils, the most abundant type of white blood cell, impact cancer immunotherapy. Immunotherapies like immune checkpoint inhibitors (ICIs) have revolutionised cancer treatment, but resistance remains a challenge. The TUNIC project will investigate whether neutrophils can be targeted to enhance immunotherapy efficacy.

Current research on neutrophil function in cancer relies heavily on mouse models, which may not accurately reflect human biology due to significant species-specific differences in neutrophil biology. For example, human neutrophils contain antimicrobial proteins that are absent in mouse neutrophils. Reliance on mouse models has resulted in several failed clinical interventions for human diseases. Similarly, large-scale sequencing datasets, while informative, do not fully elucidate human neutrophil functionality.

To overcome these limitations, the TUNIC project will utilize a "phenotype-first" approach. This involves:

- **Creating a 3D "tumor-on-a-chip" (ToC) model**: This model will incorporate primary human cells, including neutrophils, tumor cells, CD8+ T-cells, and cancer-associated fibroblasts, within a biomimetic 3D hydrogel that replicates the tumor microenvironment.
- **Observing neutrophil behaviour**: Automated image analysis algorithms will be used to assess how different neutrophil subpopulations directly and indirectly kill tumour cells, and how this behaviour is influenced by other cells in the tumor microenvironment.
- **Analysing successful phenotypes**: Once a neutrophil subtype with promising anti-tumor activity is identified, advanced techniques like spatial transcriptomics will be employed to analyse the ToC model and pinpoint the functional pathways responsible for the observed phenotype.

The TUNIC project expects to identify novel therapeutic targets in neutrophils to boost immunotherapy efficacy in a clinically relevant setting. This research could pave the way for new treatment strategies that overcome immunotherapy resistance in cancer patients.