Deconstructing Solid Tumour Heterogeneity: The Stromal Matrix Perspective

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Homeostasis of the extracellular matrix (ECM) is critical for correct organ and tissue function. Both the biochemical and biomechanical properties of the matrix contribute to modulating the behaviour of resident cells and are more than just passive bystanders. In tissue diseases such as cancer, we have shown that the matrix undergoes significant change. These changes, driven by both tumour and local and recruited stromal cells, feed into the pathological progression of the disease[1].

Our studies have shown that the matrix and matrix remodelling can both promote and restrict tumour progression. Through deploying multiple approaches to characterise tumour matrix remodelling, including the development of new technologies to visualise and catalogue the matrix over both time and space, and subsequently recapitulate these microenvironments *in vitro*, we are gaining insight into the factors that shape the development, evolution and cellular heterogeneity of a tumour, as well as its response to a particular therapy.

The non-selective depletion of the matrix has yielded paradoxical results, often accelerating progression. Instead, we have shown that more nuanced approaches to normalising biochemistry and biomechanics, rather than depleting the matrix results in favourable outcomes. As such, co-targeting the changing matrix in cancer, as well as the cellular response to the remodelled tumour matrix offer powerful approaches to improve therapy outcome for patients.

[1] Cox, TR. *Nature Reviews Cancer* **2021**, *21*, 217–238. '*The Matrix in Cancer'*