



Project Title “How disseminating melanoma cells seed secondary organs and shape the local immune landscape”
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This 4-year PhD studentship will be based in the Oglesby Cancer Research Building, Manchester Cancer Research Centre, adjacent to the Christie NHS Foundation Trust, Withington, Manchester.

Background

Recent studies reveal that tissue-specific cues in the tumour microenvironment (TME) emit signals that shape the transcriptomic and metabolic cancer and immune cell phenotypes; and specific cancer cell phenotypes dictate tumorigenic competence and metastatic behaviour. In distant organs, metastases arise from disseminated tumour cells (DTCs) that reach the organs early in the course of disease. DTCs that seed distant sites can evade therapies by entering into dormant or quiescent states, and residual, dormant cells have unique properties. Importantly, once cells grow at metastatic sites, tissue specific TME signals are linked to the heterogeneous response across organs in response to immunotherapy.

Our lab works on the TME nutrient substrates (specifically lipids) that are taken up by melanoma cells and sustain cancer cell growth. We have found specific nutrients in the skin confer unique properties to melanoma cells. The acquisition of new properties is reflected in the melanoma transcriptome and metabolic dependencies, which leads to enhanced invasion and accelerates the time to organ metastasis. Importantly, the availability of nutrients in the TME varies by age, and melanoma cells growing in an aged TME are more metastatic. Furthermore, the aged melanoma TME has a distinct immune cell landscape compared to the young TME.

Aims and approach

In this project we will study whether primary TME factors *i)* determine the rate of growth of DTCs at metastatic organs following early dissemination; and *ii)* shape the immune landscape and therapy response at the metastatic site.

i) To study whether TME primary cues restrict DTC growth at secondary sites, we will use *in vivo* models of melanoma metastasis. We will track the temporal and spatial patterns of dissemination, seeding and rate of growth of DTCs exposed to specific primary tumour signals. We will challenge the hypothesis that unique primary TME signals confer transcriptomic, metabolic properties to DTCs that will determine the rate of growth of early metastatic deposits, impacting the time to symptomatic metastasis development. We will validate our findings in human melanoma tissue.

ii) We will study whether the TME imposed transcriptomic and metabolic states impact immunity at the site of metastasis. Preclinical models show dissemination occurs early in the course of disease, and disseminated cells remain non-proliferative for extended periods of time until cells re-enter proliferative programmes, grow and develop symptomatic disease. Importantly, adjuvant and neoadjuvant immune checkpoint blockade (ICB) for melanoma at early stages of disease (stage II and III) leads to better outcomes. Thus, we will test *in vivo* how early seeding cells at distant organs, with distinct transcriptional programmes, shape local immunity and respond to ICB.

The expected outcome of this work is to understand the TME factors allowing melanoma cells to seed distant organs in early disseminating disease; and to then test *in vivo* the efficacy of ICB by anatomic site in adjuvant therapy regimes targeting clinically asymptomatic early disseminated disease.