ICR The Institute of Cancer Research

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Project title: Mechanisms of non-genetic evolution to therapy in solid paediatric cancer

Project Summary:

Recently, the role of genetic evolution as a sole driver of cancer progression is intensely debated with new evidence indicating a major role for cell plasticity and epigenetic rewiring in therapeutic resistance, bringing into sharp focus non-genetic mechanisms of evolution. We hypothesize that non-genetic evolutionary processes are particularly relevant in paediatric cancer, where tumours are developmentally imprinted restricting genomic evolution and most alterations occur in the context of lineage-derived programmatic epigenetic events reminiscent of their cell of origin. However, little is known about how evolutionary and selective mechanisms operate within/interact with and/or replay developmental programmes to drive progression of malignancy or treatment resistance. Significantly, this (restricted) cell plasticity is likely to limit the spectrum of evolutionary pathways tolerated within progressing childhood cancers. Therefore, identifying the molecular mechanisms shaping evolution may present a recipe for therapeutic susceptibilities which could turn into superior therapeutic responses and these could more easily be predicted/anticipated. This highlights a potential by which single-cell-omics and lineage tracing experiments could be used to identify and target mechanisms driving evolution and adaptation in progressing childhood tumours. We aim to; O1/ explore the evolutionary principles driving the evolution to treatment at a single cell read-out in novel organoid systems from patient's derived embryonic paediatric cancers (hepatoblastoma and neuroblastoma). We will use single-cell barcoded organoid culture systems to identify cell state-cell fate decisions and choices of evolutionary trajectories activated during the onset of therapy resistance; O2/ identify epigenetic mechanisms driving evolution under similar therapy stress. We will use chromatin landscape configurations and functional approaches, including screens, to identify and validate the events regulating non-genetic evolutionary processes; O3/ validation of improved combination therapies. We will evaluate promising mechanistically targeting evolution strategies obtained from O1-2 in genetically-defined, PDXs and implanted organoid systems in vivo to develop robust data on the efficacy of approaches

Supervisory Team:

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