DANIEL NICHOL

Experimental and Mathematical Modelling of Collateral Sensitivity in Heterogeneous Cancer Populations

Drug resistance, mediated by redundancies in signalling pathways and intra-tumour heterogeneity, is arguably the biggest problem in cancer therapy today. For cancer cells, becoming resistant to a certain agent may come at the cost of increased sensitivity to others, owing to evolutionary trade-offs. A number of preclinical studies have attempted to identify drug sequences exhibiting such collateral sensitivity with the aim to find effective follow up therapies when others inevitably fail. However, present experimental approaches have proved inadequate, as many in vitro techniques are limited to small disease populations subject to frequent re-plating, and rely on escalating drug doses to facilitate the evolution of drug resistance without driving extinction. We present a novel preclinical methodology for the prediction of collateral sensitivity in large, heterogeneous populations, subject to high drug doses, that more accurately capture the population dynamics of cancers. Through a combination of single cell barcoding, large-population cell culture, and mathematical modelling, we temporally track the evolution of polyclonal resistance to therapy in EGFR+ lung cancer. These high-resolution evolutionary trajectories are interpreted in the context of cancer therapy to outline both the difficulties and potential for sequential drug therapies to reduce heterogeneity through evolutionary herding, and to extend drug efficacy through collateral sensitivity.