Translating therapeutic strategies from the bench to the bedside has proven challenging. Focusing on cancer and rare genetic diseases, my laboratory explores the ‘biology of therapeutics’, why some therapies make the successful leap from pre-clinical to clinical, while others fail? We use Drosophila as our lead tool to explore these questions, focusing on developing genetically complex models and using these to develop lead therapeutics.

My laboratory uses Drosophila along with a variety of complementary tools to explore why some therapies succeed and others fail. We then use this information to develop networked drug targeting. We have been testing these ideas in experimental fly-to-bedside clinical trials as well as building a new generation of lead therapeutic compounds for cancer and Rasopathies.

Colorectal cancer
A key unmet need in the cancer field is effective, durable treatments for solid tumours, the major focus of my laboratory. A particular challenge is tumours with oncogenic RAS isoforms, contributing to ~30% of all solid tumours and tumours with oncogenic RAS isoforms, focus of my laboratory. A particular challenge is tumours with oncogenic RAS isoforms, contributing to ~30% of all solid tumours and perhaps 30,000 cancer deaths annually in the UK alone. KRAS mutations are associated with poor patient outcome, and RAS pathway inhibitors have proven ineffective for most solid tumours.

As part of an experimental fly-to-bedside clinical trial (NC7/02363647), we recently reported a fly-based treatment of a CPCT patient with an advanced KRAS-mutant treatment-resistant colon adenocarcinoma. Building a patient-matched 9-hit ‘personalised fly avatar’, we identified a combination of trametinib plus azolodronate as effective in rescuing avatar viability (Figure 1) and a strong partial response in the patient (Figure 1) that exceeded 11 months.

To compare different Rasopathy isoforms, we reported treatment of an ACC patient presenting with treatment-resistant metastatic disease to trametinib- plus vemurafenib (Figure 1). We used a full genomic tumour analysis to develop a 5-hit ‘personalised fly avatar’, the resulting fly exhibited multiple aspects of transformation. Our robotics-based approach identified the novel three-drug combination trametinib-plus-vorinostat-plus-panobinostat, which proved effective: the patient displayed partial response for 12 months on treatment, with tumour burden reduced by 49% across all lung and bone marker lesions (Figure 1). Similar to our colorectal cancer work, we are now exploring why this drug combination was effective in this patient, and whether it has promise to enter clinical trials for other ACC patients.

Rasopathies
Rasopathies are a family of rare Mendelian diseases characterised by mutations that activate RAS pathway signalling. There are currently no treatments approved for Rasopathies, a common situation for inherited diseases. Further, accruing sufficient Rasopathy patients for clinical trials is challenging and, ideally, a trial would accept a broad cross-section of Rasopathy patients.

To compare different Rasopathy isoforms, we collaborated with Bruce Gell’s laboratory to develop 29 Drosophila models that express human Rasopathy isoforms including PTPN11, KRAS, HRAS, BRAF, RAF1, and MEK1. Some isoforms showed distinct phenotypes as well as different levels of RAS activity as assessed with phosphorylated ERK (pERK), mirroring differences in Rasopathy patients. Our models indicate these signaling differences have consequences: while several drugs worked against one or a few fly models, few drugs worked against multiple fly Rasopathy models, emphasising the unique whole-body challenge presented by the Rasopathies. We are currently working with Maria Kontarides to explore these compounds in mouse Rasopathy models, as well as a drug company to help advance our most promising leads towards clinical trials.

Drug development
Despite exciting new advances, targeted therapies are effective in less than 30% of solid tumours. A particularly vexing problem is the identification of an effective and durable drug for Ras-mutant solid tumours. One approach is ‘polypharmacology’: single agents that target multiple points along a disease network to optimise efficacy and minimise liabilities including toxicity. Polypharmacology is challenging, and several laboratories including my own are working to bridge this chemistry gap. For example, we have established a ‘drug evolution’ platform designed to attack disease networks through rational polypharmacology, a whole animal version of Quantitative Structure/Activity Relationship (QSAR). We combine fly genetics with medicinal and computational chemistry, ‘evolving’ leads that are tuned for whole body efficacy (Figure 2). The results can be striking when tested in standard mammalian models. To date we have used our platform to evolve lead compounds for RET-dependent thyroid and lung cancers, RAS-mutant colorectal cancer, hepatocellular carcinoma, and Rasopathies. We are currently working with Lee Cronin’s laboratory to further advance this technology through advanced automation.

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