Translating therapeutics from the bench to the bedside has proven a challenge. Focusing on cancer and rare genetic diseases, my laboratory explores the ‘biology of therapeutics’: why do 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 including fly-to-bedside clinical trials.

Our 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 network- and medicinal chemistry approaches to circumvent these resistance networks in flies and organisms. Leaning into our bioinformatics tools, we are further connecting these resistance networks to fundamental biological processes such as ‘cell competition’, broadening our understanding of the relationships between complex mutation profiles, cell competition, and drug response.

**Adenoid cystic carcinoma**

Adenoid Cystic Carcinoma (ACC) is the most common malignant tumour of the minor salivary glands and the second most common of the major salivary glands. Unfortunately, once disseminated there are currently no effective treatments. For example, we have identified upregulation of detoxification pathways when specific cancer genes were paired. Blocking these emergent networks is sufficient to reveal a drug’s full activity, leading to tumour shrinkage. We are taking both multi-drug and medicinal chemistry approaches to evolve lead compounds for RET-dependent metastatic disease.

**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 Gelb’s laboratory to develop 29 Drosophila models that express human RASopathy isoforms including PTEN, KRAS, HRAS, BRAF, RAF1, and MEK1. Different 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 indicated that these signaling differences have consequences: while several drugs worked against one or a few fly models, few drugs worked with multiple fly RASopathy models, emphasizing the unique whole-body challenge presented by the RASopathies. We have identified promising lead therapeutics that act broadly across our models; 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 RAS-negative 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, merging chemical evolution and ‘chemputer’ technologies.

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