Translating therapeutics from the bench to the bedside has proven a challenge. Focusing on cancer and rare genetic diseases, our 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 a fly-to-bedside clinical trial.

As part of an experimental fly-to-bedside clinical trial, we recently reported a clinical trial (NCT02363647), we recently reported a clinical trial. As we recently reported, we have developed 14 RASopathy fly lines on promising therapeutic leads that did work broadly and hold promise for future clinical trials.

Figure 1
Our fly-to-bedside, which led to successful treatment of adenoid cystic and colorectal cancer patients.

To model TNBC in flies, we first performed a computational analysis, identifying the most common CNVs in TNBC, then using fly genetics to create a database of functional TNBC drivers. Using this database to create a set of fly TNBC transgenic lines, we demonstrated how the additional mutations promoted resistance to the chemotherapeutic drug fluorouracil, mirroring outcomes in patients. This database of fly lines provides a novel tool in the search for more effective TNBC treatments.

RAStases: 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 Mendelian diseases. Further, accruing sufficient Rasopathy patients for clinical trials is challenging, and ideally, a trial would accept a broad cross-section of Rasopathy patients.

As we recently reported, we have developed 14 Drosophila models that express human Rasopathy isoforms of PTPN11, KRAS, HRAS, BRAF and RAF1 (Figure 2). 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 indicate these signaling differences have consequences: while several drugs worked against one or a few fly models, few drugs worked with multiple fly Rasopathy models, emphasising the unique whole-body challenge presented by the Rasopathies. We are currently working with a drug company along with our growing database of Rasopathy fly lines on promising therapeutic leads that do work broadly and hold promise for future clinical trials.

Figure 2
Platform to ‘tune’ therapeutic leads.

RAStases: Architecture of therapeutic strategies.

BIOLOGY OF THERAPEUTICS

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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 optimize efficacy and minimize liabilities including toxicity. Polypharmacology is challenging, and several laboratories including my own are working to bridge this chemistry gap. We recently reported a DREAM Challenge in which we challenged the computational chemistry community to develop innovative software to predict polypharmacology.

We have also developed a ‘drug evolution’ platform designed to attack disease networks through ‘rational polypharmacology’. 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.