BIOLOGY OF THERAPEUTICS

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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 models to clinical success while others fail? We use Drosophila, mouse, human, and chemputer based tools to explore these questions, focusing on genetically complex models and building on our experience in bringing therapies to the clinics.

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 whole animal- based candidate therapies. We recently tested these ideas in an experimental fly-to-bedside clinical trial and are using this information to build a new generation of lead therapeutic compounds for cancer and rare genetic diseases.

Colorectal cancer: A key unmet need in the cancer field is effective, durable treatments for solid tumours. 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.

In an experimental fly-to-bedside clinical trial (*NCT02363647*), we generated a 9-hit 'personalised fly avatar' for an advanced, KRAS-mutant, treatment-resistant colon adenocarcinoma patient (Figure 1). Screening identified a trametinib–zoledronate combination that rescued avatar viability and produced a strong partial response in the patient lasting over 11 months (Figure 1). In a broader set of patient-based 'personalised fly avatar' lines, we have found that increasing genetic complexity drives multiple mechanisms of drug resistance, notably through upregulation of detoxification pathways when specific cancer genes co-occur. Inhibiting these detox networks reinstated drug activity and restored tumour shrinkage. We are pursuing multi-drug and medicinal chemistry strategies to bypass these resistance networks in flies and mouse/human organoids. These efforts help clarify how complex mutation profiles can directly influence drug response in colon cancer.

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 therapies.

As part of our fly-to-bedside clinical trial, we reported treatment of an ACC patient presenting with treatment-resistant metastatic disease (Figure 1). We used a bespoke 5-hit 'personalised fly ACC avatar' along with our robotics-based approach to identify the novel three-drug combination tofacitinib-vorinostat-pindolol: the patient displayed partial response for ~year on treatment, with tumour burden reduced by 49% across all lung and bone marker lesions (Figure 1). Constructing an expanding set of fly ACC avatars plus a new murine model, we now have evidence for a drug that can reduce tumours in a broad palette of preclinical models. We are now working to bring this candidate lead into clinical trials, while expanding our understanding of ACC networks through spatial omics.

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—or other rare disease—patients for clinical trials is challenging and, ideally, a trial would test a single drug that works across a broad cross-section of patients.

To compare different RASopathy isoforms, we collaborated with Bruce Gelb's laboratory to develop 29 Drosophila models that express human RASopathy isoforms including *PTPN11*, *KRAS*, *HRAS*, *BRAF*, *RAF1*, and *MEK1*. Different isoforms showed distinct phenotypes, distinct levels of RAS activity, and distinct response to drugs. We identified a promising, clinics-relevant lead that can act broadly; this compound has also shown promise in a moue RASopathy model.

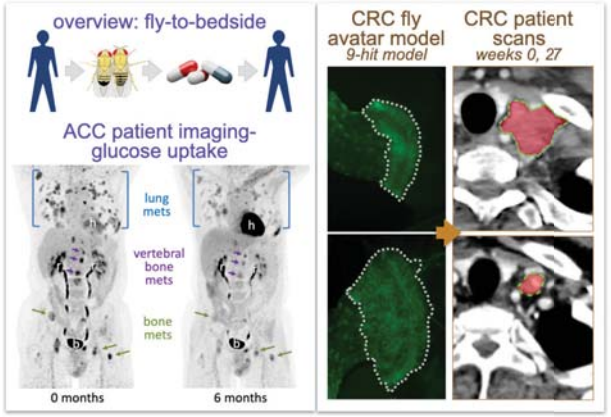

Figure 1. Our fly-to-bedside clinical trial, which led to successful treatment of adenoid cystic and colorectal cancer patients.

We are currently expanding our RASopathy efforts to neurofibromas in NF1 patients, both to understand the unique aspects of the disease and to identify promising new therapeutic approaches. Our genetic screening studies have identified new candidate targets to promote neurofibromas. These targets also represent potential therapeutic targets, a point we are exploring.

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 whole body disease networks through 'rational polypharmacology' by combining fly genetics with medicinal and computational chemistry (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 specific types of thyroid, lung, and colorectal cancers, as well as RASopathies. We are currently working with Lee Cronin's laboratory to further advance this technology through advanced automation, merging chemical evolution and 'chemputer' technologies. Our efforts have yielded interesting new 'network-targeted' therapeutic leads for colorectal cancer that are designed to act in the context of the whole body. We are now extending this unique platform to other diseases as well as to create unique chemical genetic tools to explore complex biology.

Publications listed on page 118

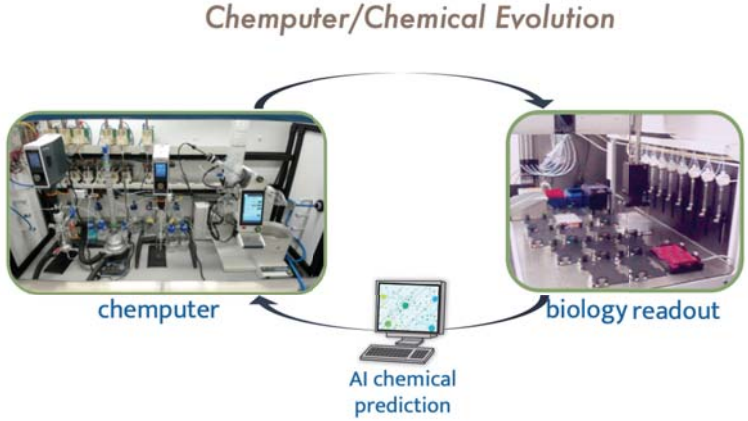

Figure 2. We are working with the Cronin lab to develop a closed-loop system designed to build chemical tools and therapeutic leads.