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Building on the basic research themes of the Beatson Institute as well as areas of expertise in both pre-clinical models and clinical treatment, the Drug Discovery Programme has developed an initial portfolio of exciting targets. These include novel approaches to target invasion and metastasis, a hallmark of cancer that ultimately results in the vast majority of cancer deaths. In addition, we will utilise our expertise in fragment-based hit identification to target protein-protein interactions that, although challenging biological targets, have a high degree of validation as cancer targets.

Hits-to-lead programmes

Tumour metastasis requires cells to cross tissue boundaries and is a multistep process driven by remodelling of the actin cytoskeleton and extracellular contacts. Members of the Rho family of GTPases are key regulators of the actin reorganisation required for the invasive process and on this basis, the downstream effector of RhoA, Rho kinase (ROCK) has emerged as a target for anti-metastatic therapeutics. It has been shown however that tumour cell lines have differing sensitivities to ROCK inhibition, suggesting that ROCK independent pathways are also responsible for the ability of tumour cells to invade and metastasise. One such alternative pathway is via Cdc42, another member of the Rho protein family that plays roles in cytoskeletal organisation and cell migration through effector proteins that include MRCK α and MRCK β (myotonic dystrophy kinase-related Cdc42-binding kinases).

In collaboration with Mike Olson, we are proposing to develop small molecule inhibitors that target MRCK α and MRCK β and that, alone or in combination, may be used in the management of metastatic disease. Initial screens have identified several series with activity against both isoforms of MRCK as well as some selectivity over other key kinase targets. We have set up a robust screening cascade to develop these and subsequent compounds. Importantly, we have established X-ray crystallography

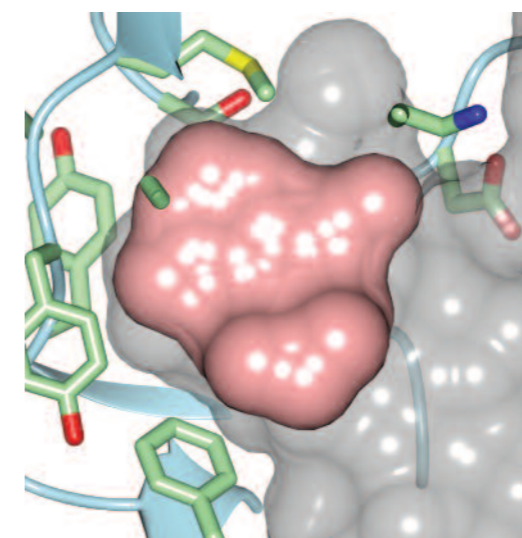
conditions that have allowed us to solve co-crystal structures of novel ligands (Fig. 1) that will enable us to utilise structure-based methodology in both our hits-to-lead and subsequent lead optimisation studies.

Exploratory programmes

Our early phase targets in hit identification are from the class of targets known as protein-protein interactions. Although considered to be amongst the most challenging class of targets, they include many of the most exciting and well-validated ones in cancer biology to date. It is recognised that agents targeting such protein-protein interactions would have a very high likelihood of providing significant patient benefit.

Fascin is an actin-bundling protein that is not expressed in normal adult epithelium but is often abundantly expressed at the leading edges of epithelial tumours. Its expression frequently correlates with advanced, aggressive and metastatic cancers. Fascin is implicated in cell migration, filopodia protrusion and more recently, by the Machesky lab, in degradative invasion of cells into extracellular matrix (Li et al., *Curr. Biol.* 2010; 20: 339). Fascin depletion by siRNA results in a reduction in the ability of cells to invade into extracellular matrix and to actively degrade matrix using invadopodia (Fig. 2).

Figure 1
BDP-002616 bound to the ATP binding site of MRCK β .



Furthermore, siRNA knockdown of fascin blocks invadopodia formation and subsequent degradation of gelatin (Fig. 2). These data highlight the importance of fascin in the invasive process and suggest its inhibition as a therapeutic strategy for the prevention of invasive disease *in vivo*. Indeed, it has subsequently been shown that inhibition of fascin function decreases metastasis

in experimental mouse models. We are collaborating with Laura Machesky to develop small molecule inhibitors of fascin, to be used as single agents or in combination with current anti-cancer therapies as treatments to manage the metastatic disease process.

We have developed additional collaborations both within the Beatson Institute (Karen Vousden, Owen Sansom and Marcos Vidal) as well as with world leaders elsewhere (Terry Rabbits, Leeds Institute for Molecular Medicine and Gerard Evan, University of Cambridge). With the Vousden laboratory we are investigating ways to reactivate wild type p53 tumours. In addition, we are targeting transcription factors and signal transduction proteins with both internal and external collaborators. Fragment-based hit identification using biophysical methods (nuclear magnetic resonance and surface plasmon resonance) and biochemical screens are being used to identify start points for all of the exploratory programmes.

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Figure 2
Fascin knockdown with siRNA blocks invadopodia formation and gelatin degradation. Wild type A375 metastatic melanoma cells (top panel) and fascin siRNA knockdown cells (oligo1 and oligo2, middle and bottom panels) are shown with red actin filament staining, green cortactin (an invadopodia marker) and fluorescent gelatin (grey) – the black spots indicate areas of degradation. Photos provided by Ang Li, a graduate student in Laura Machesky's lab.

