



Group Leader
Martin Drysdale

The Drug Discovery team has established fragment-based hit identification and structure driven design capabilities in an integrated drug discovery platform. We interact closely with research groups within the Beatson Institute and beyond to identify novel and exciting targets for translation into the drug discovery paradigm. Many of our targets are challenging and complex, however if we can de-risk them by providing tool compounds and clinical development candidates this will ultimately deliver new medicines with clear benefit for patients.

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Fascin is an actin bundling protein whose upregulation is known to correlate with advanced cancers and poor outcome, and is involved in cell movement and migration. In collaboration with Laura Machesky, we continue to make significant breakthroughs in this project increasing potency of our fascin small molecule inhibitors.

We have started a collaboration with Ahmed Ahmed (University of Oxford) and have obtained funding from the Medical Research Council Developmental Pathway Funding Scheme to develop selective SIK2 inhibitors for the treatment of ovarian cancer.

In ovarian cancer initial response rates of >70% are seen with platinum and taxane-based treatments (Muggia et al, 2000) but tumour recurrence is also observed in more than 70% of patients within a median of 12 months. These recurrences are typically resistant to chemotherapy and prove not to be amenable for surgical resection. Inhibition of salt-inducible kinase 2 (SIK2) may be an effective approach to overcoming the resistance seen to paclitaxel (Ahmed et al, 2010).

Fascin

Fascin is a pro-migratory protein whose expression is frequently upregulated when

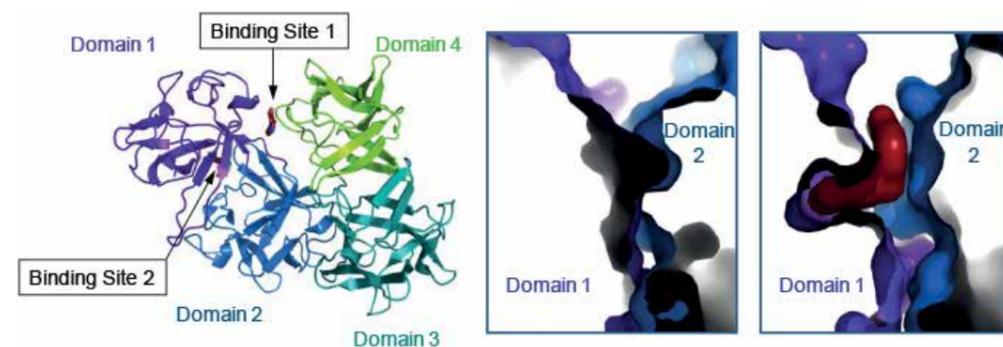


Figure 1
Structure of fascin showing the two ligand binding sites (left). A cut-through of *apo*-fascin (middle) versus ligand bound (right) shows how domain 1 moves following compound binding into a deep hydrophobic pocket within site 2.

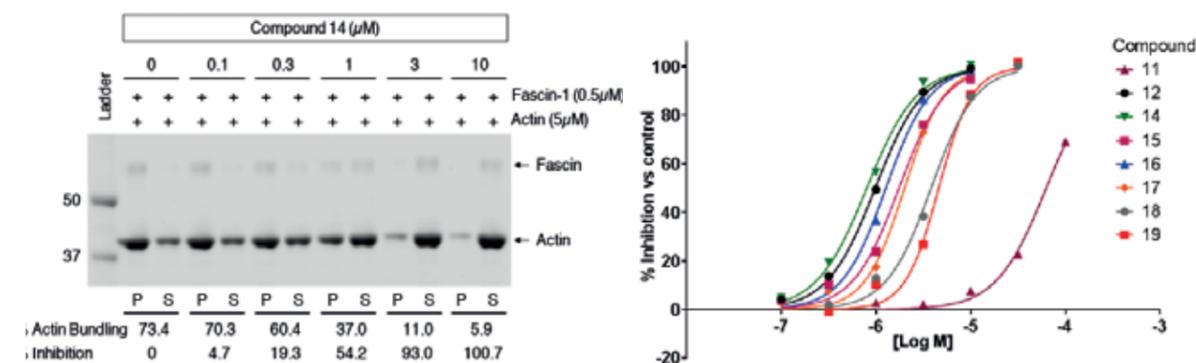


Figure 2
Inhibition of fascin-dependent actin bundling. In the absence of inhibitor, the majority of actin is bundled and in the pelleted fraction (P), with little in the supernatant (S). Addition of compound 14 inhibits actin bundling with the actin moving into the supernatant (left). Dose response curves showing the increase in potency of compounds relative to compound 11 (right).

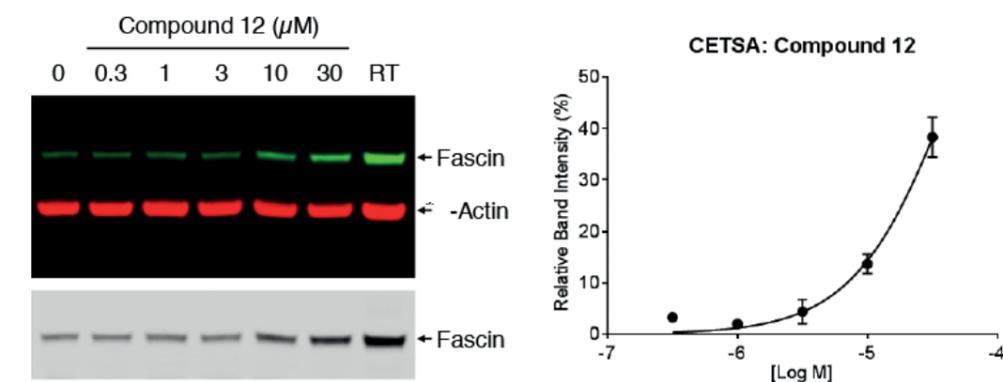
normal epithelial tissues become malignant. Its main cellular function is to crosslink filamentous actin into tightly packed bundles that drive the formation of cell surface protrusions involved in cancer cell migration and degradative invasion into the tumour extracellular matrix. Elevated fascin expression is strongly correlated with tumour invasiveness and poor clinical outcome in a variety of cancer types, therefore making fascin a compelling drug discovery target.

We have used a fragment-based screening approach incorporating surface plasmon resonance (SPR) to identify novel compounds that bind to fascin. X-ray co-crystallography of these hit compounds highlighted two distinct compound binding sites within the fascin protein (Fig. 1). We have concentrated our recent

efforts on one site; a deeply enclosed pocket situated between domains 1 and 2 of the fascin protein. Fascin-compound complex crystal structures show that compound binding at this site forces significant conformational change between these two domains (Fig. 1B).

We have developed a fluorescence polarisation competition assay as an alternative to primary screening by SPR, thereby allowing the fast identification of compounds at binding site 2. A robust and reproducible actin bundling assay has allowed us to routinely determine the inhibitory effect of compounds on functional activity (Fig. 2). The combination of biochemical data with crystallography structures has helped to guide structure-based hit-to-lead chemistry, and furthered our understanding of the

Figure 3
CETSA showing ligand engagement of fascin in cells. Compound binds and stabilises fascin 1 in the MDA-MB-231 D3H2LN breast tumour cell line.



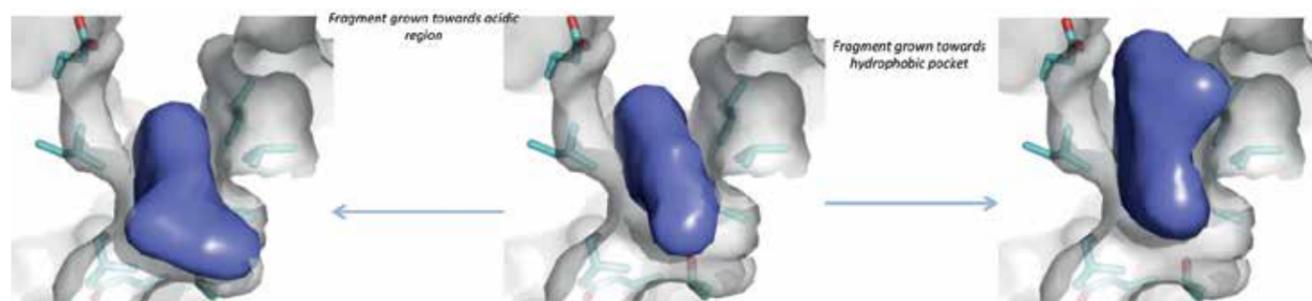


Figure 4
X-ray crystallography of fragment exemplars bound to SIK2 surrogate highlighting fragment 'growth'.

functional implications of different compound binding modalities. This has allowed us to develop a series of sub-micromolar compounds that inhibit fascin functional activity and also show compound engagement of fascin in a cellular environment using CETSA (cellular thermal shift assay) (Fig. 3).

Salt-inducible kinase 2

Ovarian cancer is diagnosed in more than 7000 women per year in the UK. Despite greater than 70% of patients responding to initial surgery followed by treatment with carboplatin and/or paclitaxel, tumour recurrence remains a problem, with a significant number of patients (70%) experiencing recurrence within 12 months.

Despite circulating in the blood, ovarian cancer cells metastasise specifically to the adipocyte-rich regions in the abdominal cavity (omentum and peritoneum) where the metastatic tumour can lead to bowel obstruction and subsequent malnutrition. This project is run in collaboration with Ahmed Ahmed (University of Oxford), who has shown recently that the serine/threonine protein kinase, SIK2 plays an important role in survival and proliferation of ovarian cancer cells and is upregulated in ovarian metastatic tumours. We are currently designing small molecule inhibitors of SIK2 to test the

hypothesis that this approach will reduce proliferation and metastasis of ovarian cancer cells.

A recent fragment screen of our in-house fragment library identified a number of attractive chemical starting points for the SIK2 drug discovery project. Currently, the project is in the early stages of fragment evaluation and optimisation (hit-to-lead). To guide our medicinal chemistry approach, we are employing structure-based drug design. X-ray crystallography of our fragments bound to a SIK2 surrogate, derived from structurally related MARK2 (Fig. 4), is being employed to prioritise medicinal chemistry plans. Preliminary results are exciting, demonstrating that we can successfully 'grow' the initial hit fragment (SIK2 K_i $7\mu\text{M}$ in SIK2 biochemical assay) and improve the SIK2 potency (elaborated fragments show SIK2 K_i $< 10\text{nM}$ in SIK2 biochemical assay). Work is continuing within the group to further improve the SIK2 potency of the elaborated fragments in preparation for cellular screening, whilst also evaluating their wider kinase selectivity and scope for optimisation.

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