Exploiting the basic research themes of the Institute’s scientists we have made significant advances in our portfolio targeting novel approaches to modulate disease-relevant processes.

Metastasis is responsible for approximately 90% of cancer deaths, however, there are currently no therapeutic agents available to combat this process. One of the proteins we have chosen to target is fascin, an actin bundling protein that plays a key role in the movement of cancer cells and whose upregulation is known to correlate with poorer overall survival in severe cases of pancreatic ductal adenocarcinoma. We have continued to utilise our fragment-based hit identification expertise to target other protein-protein interactions since these are very challenging biological targets but with a high degree of validation as cancer targets. In particular we are targeting RAS, one of the most highly validated cancer targets that is mutated in approximately a third of all human cancers.

Fascin
Fascin is a migration promoting protein that is frequently upregulated when epithelial tissues become malignant. 80-90% of cancers are of epithelial origin and fascin is overexpressed in a variety of tumour types including bladder, colon, lung and pancreas. Thus, it is not only a prognostic marker for multiple types of cancer but is also a compelling drug target.

Fascin is a uniquely folded actin bundling protein whose regulation by PKC is tightly coupled with integrins and the extracellular matrix. It exists in equilibrium between the cytoplasm and cytoskeleton where it is bound to actin. It has at least two binding sites for filamentous actin and crosslinks these filaments into tightly packed parallel bundles, oriented with their growing ends toward the plasma membrane. Since fascin is found in actin-rich protrusive membrane structures (microspikes and filopodia) and degradative structures (invadopodia and podosome), which are all directly bind to KRAS (protein in grey).

We have taken a fragment based approach to identify novel binders of fascin. Coupled with a highly successful crystallography campaign this has enabled us to progress initial fragment hits through to compounds with low µM binding.

In order to assess the ability of our compounds to inhibit one of the functions of KRAS, we have assayed multiple examples in a nucleotide exchange assay (Fig. 5).

Of course we also target KRAS, a key RAS family member, but our focus is on KRAS-GDP exchange, as we do not feel that small molecules can effectively block GTP binding

Through the application of structural biology and medicinal chemistry the project has improved potency of the initial fragment hits, delivering compounds that bind directly to KRAS and inhibit the function of nucleotide exchange. Future strategies will build on this, utilising a combination of chemistry, structural biology and biology to generate potent KRAS binders that can inhibit the interaction between GTP-bound KRAS and its effector proteins.