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DRUG DISCOVERY UNIT

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The Drug Discovery Unit bridges the gap between bench science and clinical development, providing a mechanism to deliver urgently needed treatments for cancer patients where there is a clear unmet medical need. Through our focus on exciting science coupled with a collaborative mindset, we have worked with our Beatson colleagues to develop an exciting portfolio of targets that has gained considerable attention from the drug discovery community. Our flagship project seeks to generate reversible inhibitors of KRAS^{G12D}, a highly challenging target with profound importance in cancer biology. In 2019 we partnered with Novartis to take forward this innovative and exciting KRAS project.

Identifying new therapeutic targets from basic research fuels the pipeline for future medicines. In 2020, we implemented our Working Group strategy to bring together like-minded researchers with a focus on therapeutic discovery. With drug discovery staff working side by side with institute researchers, we can foster a closer framework for collaborative research and more effectively progress novel therapeutic opportunities into clinical development.

KRAS
KRAS is one of the most heavily pursued targets in cancer therapeutics, but despite decades of research, little progress 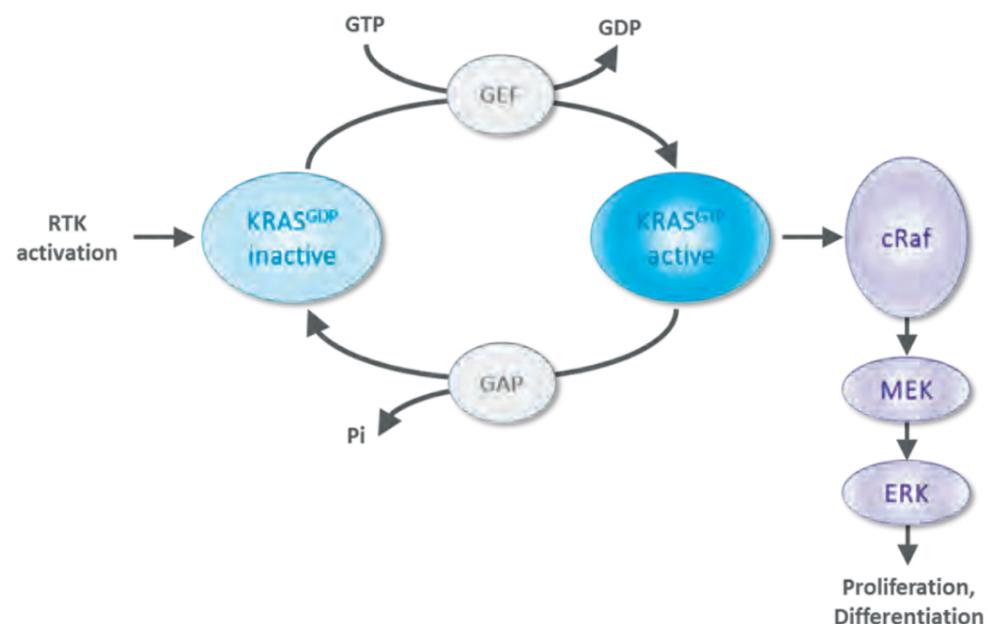has been made. Missense gain-of-function mutations of the three RAS isoforms are found in 27% of all human cancers, with KRAS being the most mutated isoform: 85% of all RAS mutations are in KRAS, 11% in NRAS and 4% in HRAS. There are clear cancer-type specific mutational profiles for RAS. KRAS mutations dominate over NRAS and HRAS in PDAC (100%), colorectal (86%) and lung adenocarcinoma (LuAd) (96%), whereas NRAS is highest in melanoma (94%) and HRAS in head and neck squamous cell carcinoma (86%). Whilst there are >130 missense mutations of RAS in cancer, hotspot mutations at G12, G13 and Q61 account for 98% of these. G12 mutations are by far the most prolific of all KRAS mutations (83%), and of these G12D dominates (41%). Interestingly, substitutions are cancer-type specific with G12D followed by G12V being more frequent in PDAC whilst G12C is the highest substitution in lung adenocarcinoma (LuAd). The most tractable approach to directly inhibit KRAS has been via covalent binding to KRAS^{G12C} mutant protein, and there has recently been great progress in this area with Amgen (AMG 510/Sotorasib) and Mirati (MRTX849) now in clinical trials. However, this approach is clearly limited to KRAS^{G12C} mutant cancers and is pre-disposed to resistance mechanisms. We have taken a more challenging approach but one that is likely to have a more profound impact on patient treatment if successful, by targeting KRAS^{G12D} with non-covalent inhibitors. We initiated our KRAS project in 2010 and from the initial fragment screen we have made significant progress, putting us in a very competitive position within the RAS inhibitor field.

Key to this success is the Structure-Based Drug Design capability within the Drug Discovery Unit. Using state-of-the-art biophysical techniques such as Nuclear Magnetic Resonance (NMR) and Surface Plasmon Resonance (SPR), alongside an 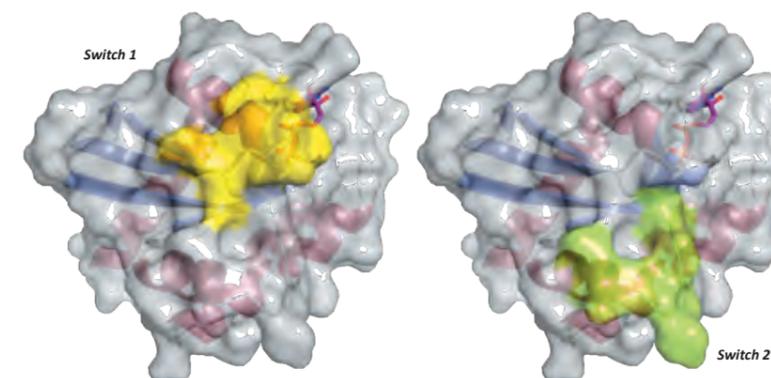in-house crystallography platform and substantial expertise in computational chemistry and modelling, we have successfully evolved small fragment molecules into high-affinity cell active compounds.

Establishing strong and productive collaborations is a key approach that the Unit adopt for all projects, to ensure the best chance of success in delivering new treatments for patients, in the shortest possible timeframe. Within the Institute, we work closely with Owen Sansom's group, who have a research focus on mutant KRAS–driven models of colorectal cancer. We have also collaborated with the National Cancer Institute's RAS Initiative programme in the USA thanks to funding from Sixth Element capital via the CRT Pioneer Fund, and in 2019 we signed a collaboration deal with Novartis to further optimise our KRAS inhibitors and potentially identify a clinical development candidate.

Translational Science
Translating breakthroughs in cancer biology into new therapeutics is the foundation of drug discovery research. Our location at the heart of the Institute enables us to work closely with researchers to identify the most promising opportunities as they emerge, and importantly, to work together to take these forward into drug discovery projects. This year we have initiated our Working Group strategy, building on a model of collaboration to put in place a framework for closer integration between research groups and drug discovery staff. This approach not only fosters a culture of translational research, including training of early-stage researchers, but also creates a portfolio of therapeutic assets and capability, as a foundation for building alliances with pharmaceutical partners.

Publications listed on page 101

Figure 1
KRAS acts as a molecular switch, rapidly converting to an active state upon receptor tyrosine kinase (RTK) stimulation, by exchanging GDP for GTP via a guanine nucleotide exchange factor (GEF). Active KRAS binds to effectors such as cRaf and activates downstream signalling through the MEK/ERK pathway, driving proliferation and differentiation. KRAS is rapidly de-activated by a GTPase activating protein (GAP), switching back to the inactive GDP form. However, mutant KRAS is resistant to GAP-mediated hydrolysis, resulting in prolonged activation of downstream pathways.

Figure 2
KRAS protein structure showing Switch 1 and Switch 2 which undergo conformational change upon activation to enable binding of effectors such as Raf1
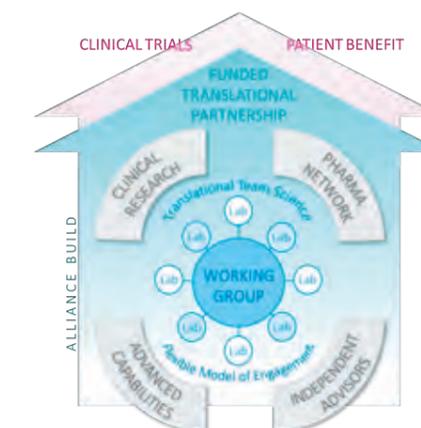

Figure 3
Working group model as a foundation for building translational partnerships that drive novel therapies into clinical trials for patient benefit.