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 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 KRASG12D, 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 translational drug 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 (85%) and lung adenocarcinoma (LuAD) (96%), whereas NRAS is highest in melanoma (94%) and HRAS in head and neck squamous cell carcinoma (86%).

While there are >130 missense mutations of RAS in cancer, hotspot mutations at G12, G13 and Q61 account for 96% of these. G12D mutations are by far the most prolific of all RAS 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 KRASG12C 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 KRASG12C 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 KRASG12D 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 collaborative discovery in place 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**