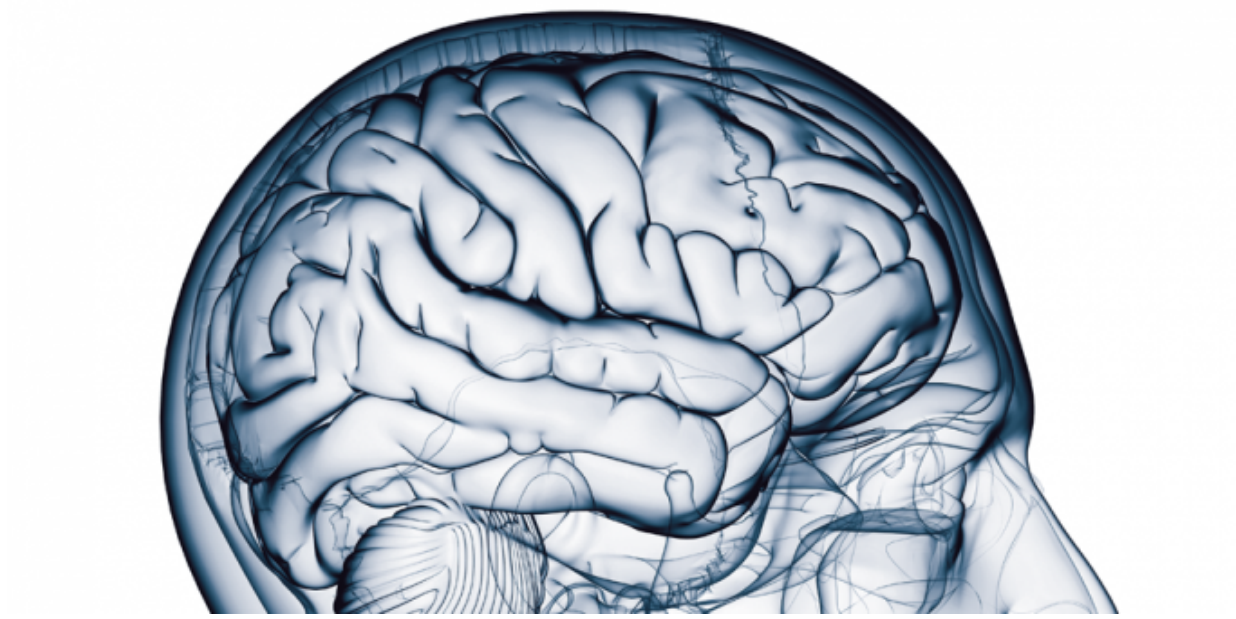
Tackling hard-to-treat cancers from every angle

June 21 2017



Improving the quality and quantity of research into cancers with the poorest survival rates remains a key priority across all aspects of our research activity – from funding breakthroughs in biology, to growing a sustainable community of world-leading researchers.

In the three years since we pledged to increase research funding in cancers of unmet need, we have increased spend in our four identified

priority cancers – lung, pancreatic, oesophageal and brain. We invested £85.8m across these four disease types in 2016/17, more than doubling our spend since 2013/14.

But our ambitions in tackling these hard-to-treat diseases go far beyond funding research, as each of these intractable diseases has its own unique challenges.

We have been working closely with the community to determine the critical scientific questions or identify gaps in infrastructure standing in the way of progress, with a view to taking proactive, bespoke approaches to each disease type. Activities have ranged from specialist symposia and conferences bringing the research community in these fields together, to looking at ways to fund large-scale international research initiatives in partnership with others. A second symposium on oesophageal cancer took place in spring 2017, followed by a workshop with key members of the international research community to identify priority areas for research. And with the long-term view of building a sustainable community working on each disease, it is encouraging that this year we have seen an increase in the number of career development awards focused on the unmet need cancers, particularly in brain tumours.

In lung cancer, a notable highlight this year is a collaboration through our partnership with the US Cancer Moonshot Initiative which will see Professor Caroline Dive at our Manchester Institute and Professor Peter Kuhn's team at the University of Southern California apply their combined expertise and technology in circulating tumour cell analysis to study the blood of patients with early-stage lung (and bowel) cancer, to see if they can identify those who will relapse.

Here, we focus on two of the toughest cancers – pancreatic and brain – and share some of the exciting investments, initiatives and new research we're funding in the UK and internationally.

Tackling pancreatic cancer

Every year around 9,500 people are diagnosed with pancreatic cancer in the UK; only 1% survive their disease for 10 years or more. Surgery can significantly extend overall survival, but only 10–15% of patients are diagnosed early enough for surgery to even be an option. Other treatments only prolong life by a matter of months. Now the 11th most common cancer in the UK, new approaches are urgently needed to combat this devastating disease.

A new era of precision

As for all cancers, molecular stratification of tumours is key to our basic understanding of pancreatic ductal adenocarcinoma (PDAC), and its prognosis and treatment. Professor Andrew Biankin, at the University of Glasgow, is a leader in molecular analysis and next generation sequencing of pancreatic cancers: besides confirming known mutations, his work has uncovered new genes and pathways mutated at lower frequencies, some of which are potential therapeutic targets. He is lead investigator on PRECISION-Panc, an ambitious programme of research that seeks to uncover the molecular profile of individual patients with pancreatic cancer, to learn more about the disease and to facilitate patients entering clinical trials for treatments that match their tumour biology. CRUK is investing £10m in this flagship initiative, to date our largest stand-alone investment in pancreatic cancer research. He also co-chairs Precision Promise, a sister programme to PRECISION-Panc, that will bring precision medicine to pancreatic cancer patients in the US.

Andrew's aim is to pull together a knowledge bank about PDAC, taking in information not just from the US and the UK, but from many other partners around the world. His hope is that, eventually, a newly-diagnosed patient's tumour characteristics can be run against the

knowledge bank database, enabling the best treatment option to be offered as part of a clinical trial: "There'll be a day in the future, if we harmonise and align our methodology, that we can address specific issues through running international multicentre studies", he says, "but for that, we'll have to better integrate research with the clinic. We want a patient to know when experimental medicine is the best option for them, and make sure that they have trials to enter."

Targeting the molecular basis of pancreatic cancer

From the work of Andrew and others, we know that the KRAS oncogene is mutated in 80–100% of PDACs, and has a frequent partner in crime: the MYC oncogene. Amplification of MYC in PDAC makes the tumours more aggressive, and, as in many other tumour types, MYC expression is critical for KRAS-driven tumour maintenance. Recently, it's been shown that MYC regulates so-called super-enhancers – clusters of DNA–protein complexes that coordinate the expression of large banks of genes critical for specifying cell identity and behaviour. This may be how MYC can reprogramme cells at the flick of a switch. Because of its importance, MYC is one of the lead molecules being studied by the Pancreatic Cancer Dream Team, funded through a partnership between CRUK, Stand Up To Cancer (SU2C) and the US Lustgarten Foundation.

Led by Professor Gerard Evan at the University of Cambridge, Professor Daniel von Hoff at the Translational Genomics Research Institute in Arizona and Professor Ronald Evans at the Salk Institute for Biological Sciences in California, the Pancreatic Cancer Dream Team aims to map super-enhancer 'hotspots' in pancreatic cancers. They hope to understand how MYC 'hacks' into the normal regenerative programme of the pancreas, driving relentless proliferation and, eventually, pancreatic cancer. In particular, they are studying how MYC engages with the super-enhancers in pancreas cancer cells and how disabling that interaction

triggers regression of pancreatic cancers. This knowledge will inform the use of super-enhancer-targeted drugs, some of which are already available, and has the potential to enhance responses to chemo- and immunotherapy.

One year in, Gerard has found the collaboration immensely rewarding: "The notion of looking at transcriptional changes would probably not have been something we'd have gone for in our own lab, as we didn't have the necessary expertise," he says, "so this was, and is, a game-changing opportunity for us and, we hope, for pancreatic cancer patients."

Targeting the microenvironment

One of the hallmarks of PDAC is extensive desmoplasia – the formation of rigid fibrotic tissue or extracellular matrix, wrapped like a corset around the tumour. In some PDACs, as much as 90% of the tumour mass comprises non-tumour cells, and this stromal tissue shapes the tumour, both literally and metaphorically, toughening it up by starving it of oxygen and nutrients, and impeding treatment by reducing the access of drugs and immune cells.

These stromal and tumour cells talk extensively to each other. Dr Claus Jørgensen, at the CRUK Manchester Institute, made the crucial discovery last year that oncogenic KRAS ramps up tumour cell signalling by coercing the stroma into feeding paracrine signals back to the tumour. And this communication extends into 'mechanotransduction' too – where cells sense their rigidity and that of their surroundings and convert that information into signals that control behaviours such as proliferation and invasion.

Building on this, Claus has set up a collaboration with Professor Martin Humphries at the University of Manchester, who has made fundamental

discoveries about the basic mechanisms of cell adhesion, to determine how stromal rigidity drives proliferation. "Adhesion has evolved over hundreds of millions of years to control cell fate – it's not simply a way of sticking cells together," says Martin. They will be studying how the adhesion nexus – a cluster of receptors, extracellular matrix fibres and cytoskeletal polymers – works as a sensor of stromal rigidity in PDAC, and hope to unpick exactly how desmoplasia forces proliferation under unfavourable circumstances, thereby accelerating tumour progression.

Tackling brain cancers

CRUK's spend on brain tumour research has more than doubled in the last five years. But growth since the launch of the Research Strategy in 2014 has been modest, suggesting more needs to be done. Brain cancer remains a challenging area in which there is limited research activity. To address this we held an international workshop in 2016 with a panel of expert leaders in the field. The meeting identified key research areas seen as crucial for the progress of brain tumour research and improving patient outcomes. We are now looking at ways to highlight these questions to the research community and to fund research to address them.

Like pancreatic cancer, glioblastoma, the most aggressive form of brain cancer, is intractable and rapidly lethal. Though thankfully rare, with around 2,300 cases in England each year, survival is low with less than 5% surviving for at least five years.

Clinician scientist Dr Paul Brennan, a recent Pioneer Award recipient, works on the frontline of glioblastoma, combining his work as a consultant neurosurgeon at Edinburgh's Western General Hospital with research at the CRUK Edinburgh Centre. When it comes to brain cancer, being a surgeon is peculiarly frustrating: "This is a disease that can't be cured surgically. In the brain, there's no natural containment barrier;

glioblastomas spread quickly along the normal white matter tracts, so removing the mass isn't curative," he explains. "Eventually I'd hope only to offer surgery to people with no alternative. Frustratingly, at the moment, that's everyone."

Paul's Pioneer Award relies on a collaboration with two colleagues at the CRUK Edinburgh Centre – Dr Dirk Sieger, who models brain cancer in zebrafish, and Dr Asier Unciti-Broceta, a medicinal chemist. Asier's work on palladium catalysts drives the project, and came to Paul's notice during a thesis committee meeting for one of Asier's students: "I remember thinking that although this is a pure chemistry PhD and I don't understand the aromatic chemistry, I do understand how this would be applicable to brain tumours", Paul says.

Glioblastomas tend to recur at their original site, implying that, post-surgery, residual cells remain. The Pioneer Award will be used to study the potential of implanting inert palladium beads at the time of surgery, and then treating patients with a prodrug that the palladium catalyst will activate. "We should be able to give people a higher concentration of the drug and avoid some of the side effects," Paul says. They hope to develop prodrugs that work in Dirk's zebrafish glioma model, providing proof-of-principle evidence needed to scale up the project and take it into pre-clinical development.

Developing research resources

Moving the brain cancer field forward will require the development of communal research resources to mine the knowledge gleaned from patient cell lines and samples, something that Dr Steve Pollard, also at the CRUK Edinburgh Centre, is passionate about. As well as having his own glioblastoma research programme, Steve is the principal investigator for the Glioma Cellular Genetics Resource (GCGR), funded by CRUK in 2016 through an Accelerator Award. The GCGR will be a

centralised resource for the generation, cataloguing and curation of glioblastoma cell lines, accessed via an open source database. Genome editing tools and novel engineered patient-derived cellular models will also be on offer – Steve's already receiving plenty of requests for the CRISPR tools he's developed in the last year for modifying target genes of interest.

There's a training and recruitment component too: a new generation of scientists will be nurtured via the PhD programme associated with the award, and the participation of the developmental neurobiologists at the Francis Crick Institute is a route for bringing some excellent basic scientists into the glioblastoma field: "We hope to tempt them in with the unique resources we can offer," he says, "Our cell lines, for example, contain a whole spectrum of glioblastoma mutations, many of which may have profound implications for normal neural development."

Taking a global view

International cooperation is vital for rare cancers, where national patient numbers are frequently too low to permit meaningful studies, and this is especially so in the challenging field of paediatric brain tumours. Professor Richard Gilbertson, at our Cambridge Centre, believes that the availability of big data means that the global community can now work together in a more purposeful way: "Next generation sequencing has allowed us to look into the biology of childhood cancer in a way we've never done before," he says. "It's like looking for keys in a dark room. What next generation sequencing has done is switched the light on so you can see the keys. You don't necessarily know what lock the keys fit but at least you've found them."

The tumour transcriptome has meant that paediatric brain cancers are now beginning to be stratified, but Richard says the challenge is to transfer this knowledge into the clinic: "We now know, for example, that

in medulloblastoma there are four distinct subgroups, one of which does really well and should probably be spared radiotherapy. There are things we're armed with now that will make an impact, and I have a lot of hope for the next five years."

Major advances

In his own lab, Richard has had a long-standing preoccupation with the paradox that tissues grow faster during childhood than at any other time, and yet childhood cancers are so rare: "If you have a tissue with this massive mitotic process going on there has to be a mechanism in there to stop it becoming malignant," In what he believes is the most significant work of his career, CRUK-funded work from his lab published last year in *Cell* showed this to be true: stem cells that give rise to adult cancers are about seven-fold more sensitive to generating cancer than paediatric stem cells.

The results have profound implications: "Because we know precisely what those cells are, we can interrogate them at the molecular level in adults and neonates across all organs to find whether there is a particular biological cassette in a neonatal cell that is protecting it from cancer," Richard says. "And if you could pharmacologically activate that in adults, you'd have a system that was no longer susceptible to cancer."

Major discoveries draw people and resources into a field, and cause a build-up of momentum that pushes the field forward. Up until now, such advances have been few and far between in the cancers identified by CRUK as unmet needs. Now, though, thanks to the influx of new blood synergising with the expertise and dedication of long-term researchers, those discoveries are starting to come; and as some of the work profiled here shows, the consequences may be profound, not just for single cancers, but for the whole spectrum of disease.