PIONEERING RESEARCH 2016/17
OUR ANNUAL RESEARCH PUBLICATION
OUR FRONT COVER: THE SPHERE OF INFLUENCE

The striking visualisation used on the cover of our 2016/17 publication is based on data relating to CRUK-funded research. Using Researchfish® submissions, the graphic visualises a selection of over 1000 research papers resulting from CRUK funded research and published in the last five years. Each paper is visualised through a dot surrounded by a collection of rings. These rings represent the citation links between papers - either where the paper has been cited by others or where it has cited other papers. The larger and denser the rings, the more citations. The visualisation demonstrates the influence CRUK-funded research has on the wider scientific community and the ongoing exchange of knowledge.

Note: Colours do not represent anything specific and are purely aesthetic.

16 Tackling hard-to-treat cancers

We focus on pancreatic cancer and brain tumours and share some of the exciting research going on and investments we’re making.

26 Grand Challenge

Meet the first multidisciplinary, international teams funded through our Grand Challenge.

36 A recipe for successful drug development

We take a look at the unique role CRUK plays in supporting early studies of anti-cancer therapeutics.

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The microbiome has been a buzzword for years, but what’s all the fuss about with regards to the possible link with cancer?

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This year has been another busy year for CRUK as we continue in implementing the ambitions in our Research Strategy. Our ambitions are big, and this year we have made progress towards these through strengthening our infrastructure across the UK, announcing our first Grand Challenge teams, and continuing to support novel, exciting work across our portfolio.

One of our biggest infrastructure success stories has been our Centres programme. This year we announced funding for the next five years for our CRUK Centres across the UK and, jointly with the Departments of Health for the devolved nations, for the Experimental Cancer Medicine Centres (ECMC) network. These demonstrate our commitment to the long-term support for these locations, each a hub of excellence, linking up expertise at the local level and connecting across the national network. Through our Accelerator Awards we are making it easier for researchers to collaborate between Centres, and through the expansion of these awards to include European partners, we aim to drive progress in translational research by building outstanding global networks.

Our network of ECMCs is coming into its own. Some of our biggest stories – such as TRACERx, the National Lung Matrix trial, and the newly funded PRECISION-Panc initiative – would not be happening without the ECMCs. Existing ECMCs have taken only three years to produce some really important insights – the recent Nature and New England Journal of Medicine papers resulting from the study may be transformative for lung cancer patients by predicting the likelihood of relapse and detecting it earlier.

It’s been great to see the breadth of the portfolio building on these new platforms. By giving investigators better access to clinical samples and other reagents, we’re enabling more high-quality discovery science, and whilst this is contributing greatly to our efforts across the board, it’s particularly important for our priority area of cancer of unmet need. Strong communities studying lung and oesophageal cancers are now emerging, and this year we’ll be focusing on strengthening our efforts in brain cancer, where our funded researchers are excellent, but not nearly numerous enough.

This year we have taken the next steps on our journey towards international funding, to support the best people wherever they are, with the announcement of our first Grand Challenge and Catalyst Award teams. Through Grand Challenge, the panel was overwhelmed by the high calibres of the applications, so we found a way to fund four exceptional teams, with funding awarded through the first round totalling £7.8 million. We should definitely view Grand Challenge and our other international schemes as fantastic vehicles for UK scientists to forge links with their international counterparts – something which can only be of benefit to everyone concerned.

It’s right to celebrate our successes in large scale infrastructure projects and international expansion, but we should never forget that home-grown discovery science comprises almost half our portfolio. There’s been a big growth in programmatic funding, and we’re currently supporting 5% clinical and non-clinical fellows, and around 140 programme awards. Our commitment to this core science is fundamental to our strategy and aims.

We are continually striving to do more to accelerate the translation of research, and have always encouraged our researchers to think hard about the potential of their work to benefit patients and the population at large. We’ve had some amazing successes: supporting the development of eight cancer drugs now in widespread use globally, testing over 100 new drugs in cancer patients, and taking many more anti-cancer therapies into clinical trials. In a step change in ambition, we’ve recently created a new division, Research and Innovation, with the vision of making CRUK the world-leading global cancer research and innovation organisation.

This single operation will enhance our scope and capability to go from the first funding of an idea all the way through to a fully developed or commercialised innovation. We are now in a strong position to partner with organisations that can help at the earliest stages and ensure those ideas progress as rapidly as possible.

We’ve also had some set backs this year too. We were all saddened by the news of the recent fire at the CRUK Manchester Institute. However, with no one hurt, the team in Manchester is exploring options for getting back up and running in the short-term and how to re-build for the long-term. We’ll continue to work with them and do everything we can to support our colleagues at the Manchester Institute recover from this devastating event.

I’d like to close by saying a little about the political upheaval of the past year. We live in uncertain times, and CRUK’s role as an influential scientific organisation has never been more important. Our activities will continue to support collaboration both nationally and abroad and we will always look to play our role in strengthening the UK as a world-leading destination for cancer research.

This publication celebrates some of your incredible work over the past year and outlines a few areas of current interest to the wider community and us. Thank you to everyone who contributed to the publication – we couldn’t have done it without you. We hope you enjoy reading it.

Iain Foulkes
Executive Director, Research and Innovation, CRUK
## Pioneering Research 2016/17

### FACTS & FIGURES 2016/17

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Funding (MILLION)</th>
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<tbody>
<tr>
<td><strong>Under £10m</strong></td>
<td></td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
<td>£8.8m</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>£5.0m</td>
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<tr>
<td>Bladder</td>
<td>£4.3m</td>
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<tr>
<td>Myeloma</td>
<td>£4.3m</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>£3.6m</td>
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<tr>
<td>Hodgkin’s lymphoma</td>
<td>£2.5m</td>
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<tr>
<td>Laryngeal</td>
<td>£1.9m</td>
</tr>
<tr>
<td>Small intestine</td>
<td>£1.2m</td>
</tr>
<tr>
<td>Stomach</td>
<td>£1.5m</td>
</tr>
<tr>
<td>Endometrial</td>
<td>£1.2m</td>
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<tr>
<td>Pharyngeal</td>
<td>£2.8m</td>
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<tr>
<td>Cervical</td>
<td>£3.0m</td>
</tr>
<tr>
<td>Eye</td>
<td>£0.5m</td>
</tr>
<tr>
<td>Testicular</td>
<td>£1.3m</td>
</tr>
<tr>
<td>Oral cavity &amp; lip</td>
<td>£1.3m</td>
</tr>
<tr>
<td>Skin (exc. melanoma)</td>
<td>£2.6m</td>
</tr>
<tr>
<td>Kidney</td>
<td>£3.8m</td>
</tr>
<tr>
<td>Liver</td>
<td>£4.4m</td>
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<tr>
<td><strong>£10m to £25m</strong></td>
<td></td>
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<tr>
<td>Prostate</td>
<td>£22.4m</td>
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<tr>
<td>Leukaemia</td>
<td>£18.1m</td>
</tr>
<tr>
<td>Brain</td>
<td>£13.5m</td>
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<tr>
<td>Pancreatic</td>
<td>£17.2m</td>
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<tr>
<td>Ovarian</td>
<td>£13.0m</td>
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<tr>
<td>Oesophageal</td>
<td>£11.7m</td>
</tr>
<tr>
<td>Melanoma</td>
<td>£12.0m</td>
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<tr>
<td>Colon &amp; rectal</td>
<td>£34.7m</td>
</tr>
<tr>
<td>Breast</td>
<td>£32.8m</td>
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<tr>
<td>Lung</td>
<td>£43.4m</td>
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<tr>
<td><strong>Over £100m</strong></td>
<td></td>
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<tr>
<td>Research that underpins all types of cancer</td>
<td>£112.0m</td>
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<tr>
<td><strong>£25m to £100m</strong></td>
<td></td>
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<tr>
<td>Cancer types where funding is under £0.5m</td>
<td></td>
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<tr>
<td>Other cancer types</td>
<td></td>
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</table>

### OUR PEOPLE

We are proud to support 4,000 researchers, doctors and nurses in 90 different institutions across the UK and internationally. Our progress is dependent on these outstanding individuals and teams conducting high-quality research. It is their creativity, passion and expertise that will ultimately lead us to the answers we need to beat this disease.

We are dedicated to supporting people from the start of their career through to providing programme awards for world-class group leaders. Currently we support over 550 PhD students, more than 750 post-docs, 95 Fellows, and over 700 Principal Investigators.

We have a strong tradition of excellence, having funded seven Nobel Prize winning researchers recognised for their outstanding contribution to cancer research.

### OUR PATIENTS

Our ambitious Research Strategy aims to continue our excellence in discovery research while also accelerating the translation of scientific discoveries into benefits for patients and the public. We support over 250 clinical trials, with more than 22,000 people joining our trials each year. More than 1 in 5 adult cancer patients in the UK take part in a clinical trial – a higher proportion than anywhere else in the world.

### OUR IMPACT

CRI UK has been at the forefront of advances in cancer research for over 100 years, including helping to fund milestone work that defined the way tamoxifen is used in cancer treatment today. We are also extremely proud to have helped support the development of eight new cancer drugs, including Temozolomide, Zoladex and Erbitux, that have contributed to this progress.

We have a uniquely broad portfolio of cancer-focused projects with more than 30 partnered agents in pre-clinical and clinical development. We are committed to funding curiosity-driven research as well as investing in pioneering new approaches and bringing new disciplines to bear on the cancer problem.
**FUNDING ACROSS LOCATIONS BY DISEASE TYPE**

We support research in over 90 institutions, with focus in key locations. This chart shows the distribution of 2016/17 funding for the top disease types across locations receiving at least £1 million. The shading represents the percentage of disease type funding at each location, so whilst the shading is comparable between columns, the underlying £ totals are not.

**FUNDING ACROSS THE RESEARCH PIPELINE**

The distribution of our funding across the research pipeline.
Funding allocated through our committees in 2016/17

**£187 million**

Our Funding Decisions

Every year we invest around £350 million into cancer research, made possible entirely through the generosity of our supporters and the public. They give generously in the expectation that we will deliver benefits to patients and the public, and we take that responsibility seriously.

It is incumbent on us to fund research of the highest calibre, and much of this funding is awarded through our committees, each with a specific remit, enabling us to support a breadth of discovery science, translational, clinical, population and behavioural research.

We are proud of our funding structures and processes which allow us to evaluate applications across the spectrum of research our researchers want to undertake. Our committees are split across different funding mechanisms, supporting the best research in the most effective ways, from our core-funded institutes, to funding grants and awards through our committees, and the UK-wide infrastructure network that exists for our whole community to benefit from.

Our funding committees are comprised of UK and international experts, ensuring that our decisions are well informed and that we continue to support pioneering research across a wide range of disciplines. The rigorous process for reviewing funding proposals involves many people across the community, from those who give their time to sit on our funding committees and panels, to peer reviewers who provide expert evaluation of individual applications. It is only through the hard work, enthusiasm and commitment of these many individuals that we can continue to support research that will have the biggest impact and bring significant progress to the field.

The distribution of £187m funding awarded through our committees in 2016/17, showing amount awarded, number of awards made, and success rate.

<table>
<thead>
<tr>
<th>Committee</th>
<th>2016/17 funding</th>
<th>Number of awards</th>
<th>Success rate % *</th>
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</thead>
<tbody>
<tr>
<td>Clinical Careers Committee (CCC) supports early-career clinical academic researchers, funding fellowships and bursaries supporting clinicians and health professionals working in areas spanning basic and translational cancer research.</td>
<td>Fellowships £14.2m</td>
<td>61%</td>
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<td></td>
<td>Bursaries £0.7m</td>
<td>33%</td>
<td></td>
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<td>Clinical Research Committee (CRC) oversees funding and endorsement of peer-reviewed investigator-led clinical trials, and other research supporting or enabling clinical trials.</td>
<td>Experimental Medicine Programmes £5.2m</td>
<td>33%</td>
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<td></td>
<td>Sample Collections £0.8m</td>
<td>10%</td>
<td></td>
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<tr>
<td></td>
<td>Biomarker Projects £0.6m</td>
<td>8%</td>
<td></td>
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<tr>
<td></td>
<td>Fellowships £0.3m</td>
<td>43%</td>
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<td>Drug Discovery Committee (DDC) advises on and implements our strategy in the area of drug discovery, funding biotherapeutic and small molecule drug discovery and our drug discovery infrastructure.</td>
<td>Programmes £1.6m</td>
<td>100%</td>
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<td></td>
<td>Projects £2.4m</td>
<td>48%</td>
<td></td>
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<tr>
<td></td>
<td>Projects £0.6m</td>
<td>45%</td>
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<td></td>
<td>Grand Challenge Awards £73.3m</td>
<td>44%</td>
<td></td>
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<td></td>
<td>Trial Grants £0.5m</td>
<td>67%</td>
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<tr>
<td>New Agents Committee (NAC) reviews proposals for the preclinical development and early phase clinical trials of new anti-cancer treatments and diagnostics.</td>
<td>Preclinical Grants £0.3m</td>
<td>46%</td>
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<td></td>
<td>Drug Development Projects £1.9m</td>
<td>57%</td>
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<tr>
<td>New Investigator Committee (NIC) supports early-career cancer researchers as they develop their independent research groups.</td>
<td>Fellowships £16.1m</td>
<td>29%</td>
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<tr>
<td></td>
<td>Projects £9.3m</td>
<td>45%</td>
<td></td>
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<tr>
<td>Population Research Committee (PRC) supports clinical and public health epidemiology and educational and behavioural research on cancer prevention, screening and early diagnosis.</td>
<td>Catalyst Awards £4.4m</td>
<td>17%</td>
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<tr>
<td></td>
<td>Programmes £6.7m</td>
<td>40%</td>
<td></td>
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<tr>
<td></td>
<td>Projects £2.3m</td>
<td>20%</td>
<td></td>
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<tr>
<td></td>
<td>Fellowships £1.3m</td>
<td>36%</td>
<td></td>
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<tr>
<td></td>
<td>Programme Foundation Awards £8.3m</td>
<td>46%</td>
<td></td>
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<tr>
<td></td>
<td>Projects £6.8m</td>
<td>15%</td>
<td></td>
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<tr>
<td></td>
<td>Tobacco Advisory Group (TAG) reviews applications for policy research and policy advocacy activities in tobacco control.</td>
<td>Programmes £0.3m</td>
<td>100%</td>
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<tr>
<td></td>
<td>Projects £1.1m</td>
<td>77%</td>
<td></td>
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*Success rate is from full application. Where a scheme has an outline stage, this has not been included in the rate calculations.
People affected by cancer drive everything we do. By sharing their experiences, they provide vital insights that help us develop our work. As part of assessing our progress against our Research Strategy, in January 2017 we ran a workshop with 12 patients and people affected by cancer to draw in the perspective of patients to our strategy work.

The day was felt to be a positive experience, providing those present with the opportunity to get closer to CRUK’s Research Strategy. As one participant, Terry Kavanagh, noted: “This was an opportunity to share with the research community my views and opinions as a cancer patient. I felt that my comments were listened to and my input was taken on board.”

Paul Maclean was new to the scientific side of CRUK’s work, but found the workshop hugely worthwhile as he felt patient representatives were “being asked to get involved in some fundamental issues within CRUK’s core activity”. With regards to the progress being made, he reflected: “CRUK is clearly making tangible progress in many areas, but could be more focused in specific areas of need.”

Graydon Downs has been living with glioblastoma for almost five years. After the workshop he reflected: “Working with CRUK has made me realise that we need to invest in all types of cancer. Finding cures for brain tumours is personally and emotionally important to me. But every type of cancer is painful for somebody.” He added: “It felt good to be able to give my view on the charity’s progress on reaching the goals set out in their strategy.”

PROGRESS AGAINST OUR RESEARCH STRATEGY

In 2014 we launched our Research Strategy, which set out our research priorities for the next several years. We created an ambitious agenda – to develop a research programme that would accelerate progress and see three-quarters of cancer patients surviving cancer within the next 20 years. Three years in, we’re taking stock of our progress. Here we showcase some of our highlights.

Investing in the right environment for research to flourish remains a priority. We have continued our investment in our institutes, with the Francis Crick Institute opening its doors in 2016, and strengthened our investment in our UK-wide CRUK Centres and Experimental Cancer Medicine Centres (ECMC) network, with £266 million to be invested over the next five years.

Our research funding has increased to £386 million in 2016/17, enabling us to fund more research across all areas of our portfolio and supporting high-calibre science.

Since 2014 we’ve launched eight new funding schemes, allocating £140 million to date. These schemes include our Grand Challenge awards bringing international multidisciplinary teams together to tackle the biggest challenges in cancer, our Catalyst Award supporting capacity building and collaboration in population health and our Pioneer Award which backs higher-risk, novel ideas that have the potential to be transformative in tackling cancer.

We’ve increased our spend in lung, pancreatic and oesophageal cancers and brain tumours, spending a total of £86 million in these four cancer types in 2016/17. These targeted investments are helping to build leadership, train the next generation of researchers and facilitate enhanced collaboration.

Read more about the progress we’re making at cruk.org/progress-report
At CRUK we recognise the importance of creating a dynamic and responsive research environment. Our long-term investment has helped to create a thriving network of research at 90 different institutions and in more than 40 towns and cities across the UK and internationally. Our network of researchers and infrastructure includes capabilities ranging from basic biology research all the way through to the delivery of late-phase clinical trials.
We have an established history of successful drug discovery, having contributed to the discovery or clinical trials of nearly 50 drugs now in clinical development. Our work in therapeutic discovery is supported by four highly equipped small molecule Drug Discovery Units (DDUs) and our Therapeutic Discovery Labs. Our DDUs exploit biological insights derived from CRUK-funded research across the UK, in addition to identifying and validating targets derived from the published literature. These units have a proven track record in small molecule drug discovery, with many clinical candidates now under investigation in patients. Our Therapeutic Discovery Labs focus on biologically-themed multi-project alliances with academia and commercial partners. The team has established successful alliances with AstaZeneca, Tuss Pharmaceuticals, Forma Therapeutics, MRCT and Hercik IGAA. In addition to small molecule development, CRUK has partnered with MedImmune to support facilities focused on accelerating the discovery and development of novel antibodies. The Cancer Research UK-MedImmune Alliance Laboratory brings together CRUK’s cancer biology expertise with MedImmune’s world-class antibody engineering technology, enabling researchers with access to a myriad of new insights from novel antibody, to access MedImmune’s capabilities and technology in antibody engineering. The research opportunity provided by the laboratory is open to scientists based both in the UK and internationally.

THERAPEUTIC DISCOVERY

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THERAPEUTIC DISCOVERY

Our Centre for Drug Development (CDD) provides a complete pre-clinical and first-in-human capability in both small-molecule and biological therapeutic development. It spans of expertise includes therapeutic manufacturing and pre-clinical phase to the full clinical trial operations needed to demonstrate the clinical potential of new medicines. The CDD also operates its own state of the art manufacturing facilities, with the expertise to produce clinical formulations for small-molecule and biologicals including monoclonal antibodies, recombinant proteins and DNA.

Ximbio is a platform for researchers to exchange knowledge and trade reagents, enabling the sharing of research tools with a global community. It acts as a marketplace for scientists and inventors, allowing them to deposit reagents, thus maximising commercial opportunities for these tools.

TRANSLATIONAL AND CLINICAL RESEARCH

Our Centre form a unique national network facilitating multidisciplinary translational research of the highest international quality and training the next generation of clinicians and researchers. They drive local partnerships between universities and hospitals, cancer networks and other research charities, to accelerate the translation of research into the clinic.

Our network of Experimental Cancer Medicine Centres provides a unique service for early-phase clinical trials, not only for the treatments that we develop and optimise ourselves, but also to industry and other funders whose trials we are able to endorse. We also support Clinical Trials Units (CTUs) which provide the academic cancer research community with expertise to design and run clinical trials at all phases. Our CTUs provide support covering all aspects of clinical trial design, management, database provision and data analysis and publication. They coordinate national and international clinical trials, and other studies which aim to directly influence routine clinical practice.

Additionally, our translational research is enhanced by the Cancer Imaging Centres, a partnership with the Engineering and Physical Sciences Research Council, which integrate pre-clinical and clinical research to facilitate the improved detection, diagnosis and treatment of cancer.

POPULATION RESEARCH

In partnership with other agencies, we fund the UK’s outstanding infrastructure for population research, including epidemiology and behavioural sciences. We provide the core-funding for the UCL Health Behaviour Research Centre, a pioneering centre for advancing our understanding of behaviours that impact on health and the design and evaluation of behavioural interventions. We are a part of the UK Clinical Research Collaboration which funds the Public Health Research Centres of Excellence, including the Centre for Diet and Activity Research (CEDAR) in Cambridge and the UK Centre for Tobacco Control and Alcohol Studies (UCLHTS), a network of 13 universities (12 in the UK and 1 in New Zealand). We are also a key partner providing capacity in health informatics research through the Fan Institute, which comprises four nodes across the UK.

BUILDING GLOBAL NETWORKS

To support our ambition to accelerate translational research at our Centres and increase the reach of our network, we have entered into a new funding partnership with the Spanish Association Against Cancer Scientific Foundation (FC AECC), the principal cancer research charity in Spain, and the Italian Association for Cancer Research (AIRC), the principal cancer research charity in Italy. This partnership will capitalise on shared priorities across our research communities and will support our ambition to drive progress in translational research by building outstanding global networks.

Our Accelerator Award will support development of high-quality resources – including training programmes – that could not be achieved in isolation, bringing together the best teams and resources to facilitate translational research and train the next generation of clinicians and researchers.

OPENING OUR DOORS TO THOUSANDS

Imagine you’re not seen inside a research laboratory since school. Last year, thanks to CRUK, we hosted over 200 lab tours at our institutes and research hubs up and down the country. Welcoming the public to visit provides vital opportunities to engage with supporters, local communities and politicians about CRUK’s world-class science.

In October 2016, scientists at our Manchester Institute and colleagues in our Policy and Public Affairs team hosted a lab tour for members of Manchester City Council. The visitors learned about the city’s leading role in lung cancer research and CRUK’s policy work in tobacco control, both of which are important areas to help reduce the number of people dying from the disease in the future.

Council Leader, Sir Richard Leese, commented, “We are incredibly proud that Manchester researchers are leading the way in the fight against this awful disease. Manchester City Council is committed to playing its role in helping residents to reduce their risk of getting cancer.”

Hosting tours is a rewarding experience for our researchers. Dr Allan Jordan from the CRUK Manchester Institute said, “Having the opportunity to share our important work with our supporters, show how their donations are making a difference in our labs and in the wider community, was a fantastic experience.”

A recent guest remark highlights the impact of tours: “What amazing work you do! Don’t stop! What hope you’re giving. Thank you doesn’t seem sufficient – but thank you anyway.”
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, with particular success in lung and pancreatic cancer. We invested £85.8 million 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. 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 Caroline Dive at our Manchester Institute and Peter Rubin’s team at the University of Southern California apply their combined expertise and technology in circulating tumour cell analysis to study the biodata 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 developments, 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 10% survive the 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.

Continued on next page
Who have you met so far? We’re collaborating with Ron Evans and Tony Hunter at the Salk Institute and Gero Schneider at Princeton University. I have met or discussed with students and postdocs from both places and it has been a delight working together.

Meeting our patient advocates, cancer survivors from the US and the UK, has affected me the most. It is fascinating to hear the personal perspectives on what we do. I was touched by one of our patients fighting a cancer when she was diagnosed using state-of-the-art techniques, and I was humbled to hear their perspectives.

How did you two meet? We first met at the Translational Pancreatic Cancer Dream Team. We asked each other what was the common goal and a common interest, and I’m very excited for the future.

Real collaboration is where you work with each other – if you don’t get on with each other you will never do anything useful. What next generation of collaborators should you have in the clinic?
A FAMILY UNITING AGAINST CANCER

There are so many areas of CRUK research which rely on the involvement of patients in studies and trials. Here, one family share their story of why and how they got involved.

Mark Sims was 15 when he was first diagnosed with melanoma in 2003. When it came back 12 years later, it spread and became incurable. A doctor from near Bristol, Mark signed up to be part of our PEACE study, which will help us understand more about the late stages of cancer. He was an enthusiastic volunteer for CRUK, and was given a Flame of Hope award for his work. Mark died in January 2017. His twin Dave, 29, a doctor living in London, shares Mark’s story on behalf of their parents, Chris and Sue, brothers Matt and Paul and Mark’s fiancée, Georgie.

‘Mark always thought about others more than himself. Even in his last days, he was worried about not being able to reply to people who’d messaged him on Facebook. Everyone liked Mark. He was very easy to get on with and had a lot of friends. He realised that his experience of getting cancer so young, and the fact he was a doctor, would resonate with people. When Mark’s doctors asked him about taking part in the PEACE study, we knew it would be something he’d want to do. The study gave him another opportunity to help people. The tissue he donated, before and after he died, will help scientists learn about how cancer develops particularly in the later stages. It’s a great contribution to research. He wanted to do as much as he possibly could to make sure that, in 20 years’ time, another Mark Sims doesn’t have to go through the same thing that he did.

When Mark found out how serious his diagnosis was, he accepted it. He remained hopeful, but realistic. He wanted to do the best he could in the time he had.

As well as raising money for research, it’s really important to my family to raise awareness of melanoma. One of my main motivations for sharing Mark’s story is to encourage people to take care of their skin. We are all really proud of everything Mark did. We inspired us. It’s always going to be difficult without him, but the difference he’s made to other people does make it a little bit easier.’

DAVE SIMS
A FAMILY UNITING AGAINST CANCER

A NATIONAL POST-MORTEM TISSUE COLLECTION PROTOCOL (THE PEACE STUDY)

This Award, led by Professor Charles Swanton at the CRUK UCL Centre and the Francis Crick Institute, will support the longitudinal collection of biological samples from patients with primary brain or metastatic cancer across the UK, including after their death. Sample collection will comprise tissue, blood, cell-free DNA and circulating tumour cells.

The consortium will:
• Coordinate and standardise sample collection across the network
• Create a digital pathology hub from the samples
• Train clinical researchers in autopy pathology

This will create a unique resource of samples, supported by clinical annotation, to investigate through research initiatives such as understanding the evolution of cancer, intratumour heterogeneity, mechanisms of resistance, as well as identification of prognostic and diagnostic markers.

There are two questions in biology – how and why? Both are important. The ‘how’ addresses how the nuts and bolts of a biological process are hooked up with each other. The ‘why’ question is the one that the British scientist has always been very good at addressing – why are things the way they are and why do they work the way they do? As a cancer biologist, my version of this question is simple: why is it that cancers of a particular tissue or cell type show a remarkable consistency in their histological phenotype – so consistent, in fact, that we use it as a primary diagnostic tool?

I always tried to understand biology for what it is: a set of evolved processes rather than a purposefully constructed machine. Thinking this way sheds a very different light on cancer because cancer is generally a late-life, post-reproductive disease. Hence, its impact on our reproductive ‘fitness’ is negligible. We therefore have to view the properties and behaviour of cancers, and of our bodies’ responses to it, as a subversion of a process that is important for survival and reproduction – namely, our amazing ability to repair our bodies when they get damaged.

Viewed through this lens, it makes perfect sense that cancer is a way for other problems that arise immediately that, from the outset, have the potential to harm the individual. Cancer is driven by a corrupted version of the regenerative programme, which prunes the excess and aberrant tissue in the cancer and remodels it to pump the damaged region with lymphocytes and other protective cells. After the damage has been contained, the lung tissue needs to be rebuilt, so in a different way to the pancreas. At its structure and functions are totally different. Hence, if we postulate that lung cancers are driven by a corrupted version of the regenerative process specific to lungs, we end up with a coherent explanation for why lung and pancreatic cancers look so different, despite showing many oncogenic driver mutations.

Using transgenic mouse models in which we can reversibly switch on and off the oncogenic RAS and MYC oncogenes in the lung or pancreas, we’ve shown two really important things that support our hypothesis. First, as soon as you switch on RAS and MYC in each tissue, you see tumours arise immediately that, from the outset, have the signature characteristics of each cancer type. In the lung, the tumours explode with blood vessels but little desmoplasia. In the pancreas, the tumours immediately resemble highly invasive pancreatic adenocarcinomas in which 90% of the mass is not even tumour cells but desmoplasia. The same drivers but different outcomes.

Second, and most encouragingly, because we build-off-switches in our driving mouse models available. Here, Gerard discusses a new way of viewing cancer that has major implications for our understanding of the disease, and how to treat it.
We know that cancer is easier to treat, and causes patients to suffer less and live longer, when it is detected early. Yet for decades, whilst treatments for cancer have made revolutionary steps forward, early detection research has made limited progress, presenting a persistent scientific and clinical challenge. As a result, most cancers are still diagnosed at stage 3 or 4, when the prognosis is poorer and the treatment is often more severe. Now, with advances in technology starting to open up new research paths, our investment and commitment can help push this important field forward. We recognise that cracking this area could be a major player in achieving our aim to see 3 in 4 patients survive cancer within the next 20 years.

WHAT IS EARLY DETECTION?

We define ‘early detection’ as the detection of cancer, or pre-cancerous states, at the earliest possible point at which an intervention might be made in order to lead to a better patient outcome. As Dr Ian Walker, Director of Clinical, Population and Early Detection Research at CRUK, states, “In terms of survival, early detection science is one of the biggest things you can do. Take the example of bowel cancer – caught at stage 1, it has a 95% survival rate at five years. But once you have a tumour, you can’t catch cancers earlier, it will have a significant impact on survival rates – on a scale that is very difficult to achieve through drugs alone.”

However, there are big challenges. Currently, we don’t understand the cellular and molecular biology that occurs as cells become dysregulated and then cancerous. We don’t know what we need to detect, how to avoid overtreatment, or how to distinguish lethal and non-lethal disease. We don’t have adequate models of early disease, which has delayed the progress. We need better combinations of ‘omic’ and analytic platforms to identify and validate biomarkers of early disease. We need improved systems technology approaches to bring data into biological context. We need novel technology, including sensors, biosips and nanotechnology, to improve how we image and detect cancer, and we need multidisciplinary teams to develop the technology and ultimately to implement it in the appropriate clinical context.

These are all big issues, and CRUK is making a significant commitment to early detection research to start to unravel them. We are working across our UK network to drive new activity in the area, as well as establishing international partnerships to start building a wider early detection community. And in 2017 we will announce major new funding specifically dedicated to supporting early detection research.

CAMBRIDGE EARLY DETECTION PROGRAMME

One current major area of investment is the CRUK Cambridge Centre Early Detection Programme, launched in 2016. This multidisciplinary programme brings together world-class researchers from a wide range of areas, and is co-led by clinician scientist Professor Rebecca Fitzgerald and physicist Dr Sarah Bohndiek.

Rebecca’s own work in the field of oesophago-gastral cancer is a flagship example of early detection research. Her team developed a tiny sponge on a string, the ‘Cytosponge’, which can be used to sample cells from the whole oesophagus, and a simple lab test to analyse this. The cells are analysed with an antibody to check for Barrett’s oesophagus, a condition that can be a pre-cursor to oesophago-gastral cancer. As Rebecca says, “We are now at the exciting stage of starting a large clinical trial in GP surgeries, the BEST3 trial, which is the final step in determining whether the Cytosponge antibody (TFF3) test is effective enough to be introduced into mainstream practice. As most oesophago-gastral cancer is currently diagnosed at a late stage, the Cytosponge could provide a powerful new tool to improve early detection at the stage of Barrett’s, offering GPs a cost-effective and minimally invasive first step of investigation. Rebecca’s team is now working to develop the lab tests further, so that they not only diagnose Barrett’s, but also distinguish between those Barrett’s patients at low and high risk of cancer progression.”

Rebecca’s close colleague and co-director of the Early Detection Programme, Sarah, comes from a very different field. “I’m a physicist by background, but now focus on how we can improve imaging techniques for early detection and evaluating cancer progression. For example, standard endoscopy replicates only what our eye could see if we were able to look inside the body. This struggles to pick up early abnormalities, so we’re developing novel endoscopic devices that bring additional contrast for subtle early changes. One example is applying coherent light – where the waves travel in unison as this is distorted when it hits tumour tissue compared to normal tissue. Studying the light distribution may prove to be a valuable tool in assisting earlier detection.”

Thanks to CRUK funding for early detection, the Cambridge team is expanding. As Rebecca explains, “We now have three dedicated early detection research labs, with two more planned this year. It’s an incredibly exciting time.” Recent(y set up in its new home, Dr Daniel Munoz-Espin joined the department last September, having moved from the Spanish National Lung Cancer Research Centre in Madrid. His work is another example of the multidisciplinary nature of the field. “My research focuses on developing nanotechnological tools to target pre-malignant tumours, both for early detection and early therapy.”

NANOTECHNOLOGY

Daniel’s work is looking at the origin of lung cancer and, in particular, the role of senescent cells, damaged or stressed cells that can no longer replicate. In the long term, it’s thought that accumulated senescent cells could act as a source of malignancy in the nearby cellular environment. Interestingly, cellular senescence is emerging as a feature of pre-malignant lung tumours and so could be a property with potential use in early detection.

Daniel is working with silicon nanoparticles 100nm in size, and has developed the technology to load these up with active substances that can specifically target senescent cells. “It works because in normal cells, the nanoparticles are internalised and then simply secreted. But in senescent cells, the coating is digested inside the cell, releasing the active substance.” Using a fluorescent tracer as the active substance means any senescent cells light up, providing a powerful tool for early detection. Excitingly, the same technique also has potential in early therapy, because the nanoparticles can be loaded with active substances that target and kill the senescent cells.

As Daniel explains, “We’ve now validated the tools in mouse models of pulmonary fibrosis and tumour models, showing that we can use nanoparticles to both detect and eliminate senescent cells. Our innovative treatment results in the photodynamic activity, including reduction of tumour size. The next steps are to take this technology to mouse models of lookout for any new developments in the field.”

“I hope that, in the long term, this research could lead patients to a smoking history having a test for senescent cells. If they show accumulation in one area, early therapy could treat this, eliminating damaged cells and stopping lung cancer before it even develops.”

LIQUID BIOPROFILES

At the CRUK Manchester Institute, Professor Caroline Dix is also working on lung cancer, and has become internationally renowned for her work on ‘liquid biopsies’ – detecting cancer cells or particles in the bloodstream that could act as reliable signals for cancer. As Caroline says, “Until very recently, our work has been looking at circulating tumour cells (CTCs) as agents of metastasis, causing cancer to spread around the body in patients with more advanced disease. But now, we are turning our attention to how useful this technology could be for early detection.”
multidisciplinary fields, in the UK and globally, An improved understanding of early tumour interactions within cells, between cells and academia, clinicians, industry, patients and with the early tumour microenvironment.  

**OUR AREAS OF FOCUS IN EARLY DETECTION**

**EARLY & PRE-CANCER BIOLOGY**
Innovative technologies will help solve our biggest problems.

**GLOBAL COLLABORATION**

The ambitous nature of the Early Diagnosis Consortium led CRUK to seek out expertise globally and form new alliances. This need for a global approach will be crucial to advance the early detection field. Following the launch of our Research Strategy in 2014, we formed a partnership with the Knight Cancer Institute at Oregon Health and Science University (OHSU), a first of a kind collaboration for early detection.

The Knight Cancer Institute is an ideal partner because it has been a pioneer of precision cancer therapy and, thanks to a philanthropic investment of $1 billion, is now establishing a new, large-scale early detection programme. Dr Sadik Sarsar and his team, by background, have recently taken the helm as the new Director of the Center for Early Detection Research. He’s brought together US-based researchers. Sadik agrees that a multinational team, led by Dr Jelle Breuker, is hopeful this area holds huge promise, “There is incredible promise. From devising nanoparticle red flag for early detection. In an exciting new venture, Caroline is joining forces with Oxford and US-based researchers. Sadik agrees that a multinational team, led by Dr Jelle Breuker, and, thanks to a philanthropic investment of $1 billion, is now establishing a new, large-scale early detection programme. Dr Sadik Sarsar and his team, by background, have recently taken the helm as the new Director of the Center for Early Detection Research. He’s bringing together US-based researchers. Sadik agrees that a multinational team, led by Dr Jelle Breuker, is hopeful this area holds huge promise, “There is incredible promise. From devising nanoparticles that can flag up and kill pre-cancerous cells, to harnessing the physics of light for better imaging, early detection research is a diverse, multidisciplinary field, with ground breaking potential. It is an issue with global challenges, but also a reward-rich field that could bring real impact to cancer prognosis and mortality. The announcement of new funding specifically for early detection, which will build to an investment of £20 million per year, is designed to set us firmly on the path to success. Ian Weller, “This is new funding, specifically for early detection. We are showing our commitment to this important new area of cancer research, which we hope will bring rewards that change the field forever.”

**RAISING A GLASS TO EARLY DETECTION**

In December 2015, The British Museum opened its doors to an exclusive evening of glamour in aid of CRUK. Dr Sarah Bohndiek and her team were at the event to showcase their work into early detection.

Transforming the museum to host a chic soiree, Sarah and her group used fun activities to engage the guests. But while the cocktails they were serving may have looked like drinks you’d find at a swanky bar, they were in fact science demonstrations disguised as cocktails.

One activity involved sherving a laser beam through a glass of water, gradually adding milk to show guests how it increases the scattering of light. This simple demonstration helped explain how they are developing cutting-edge new technologies using light scattering to detect oesophageal cancer sooner. All the early-stage, changes in the tissue microstructure that are invisible to the naked eye can be detected with their new methods.

These cocktail-style activities provide a tangible insight into the research of Sarah's lab, helping to bring to life the incredible breakthroughs in early detection.

**COSTUMES BLACK TIES**

Our guests, who are supporting the Early Detection Research Programme, enjoyed the chance to dress up and get their picture taken for the camera.

In December 2015, The British Museum opened its doors to an exclusive evening of glamour in aid of CRUK. Dr Sarah Bohndiek and her team were at the event to showcase their work into early detection.

**THE KEY TAKEAWAY**

A multinational team, led by Dr Jelle Breuker, and, thanks to a philanthropic investment of $1 billion, is now establishing a new, large-scale early detection programme. Dr Sadik Sarsar and his team, by background, have recently taken the helm as the new Director of the Center for Early Detection Research. He’s bringing together US-based researchers.

Global collaboration is key to making progress in early detection research. As Ian Weller, CEO of CRUK, says: “This is new funding, specifically for early detection. We are showing our commitment to this important new area of cancer research, which we hope will bring rewards that change the field forever.”

Find out more about our opportunities in early detection research, including funding available, at cruk.org/early-detection.
In October 2015, CRUK launched a completely new and different type of funding scheme – Grand Challenge – with the aim of bringing together the world’s greatest scientific minds to catalyse a revolution in how we prevent, diagnose and treat cancer. Here we celebrate our four exceptional teams that, having spent almost £70 million, have been able to fund four teams this year, investing more than £70 million in the first round of the initiative.

“Grand Challenge was set up to stimulate and inspire teams around the world to try and tackle some of the most persistent, intractable problems that face the entire cancer community,” explains Dr Rick Klausner, Former Director of the US National Cancer Institute, and Chair of the CRUK Grand Challenge Advisory Panel.

“And the response was a triumph,” recalls Rick. Applications came in from 57 teams across 25 countries and the panel had the unenviable job of scrutinising every proposal. “And the response was a triumph” recalls Rick. “This is just the beginning. We want this flexibility of Grand Challenge funding to be the hallmark of ambition,” she recalls. “I heard the problem people are really excited about, and I thought ‘That’s something we really need to do’. And I was excited to hear the scale of ambition,” explains Professor Ed Harlow, Professor of Cancer Biology at Harvard.

“A FLEXIBLE APPROACH

The flexible nature of Grand Challenge funding is hugely important for tackling challenges of this scale, and is certainly true for the second 3D tumour map team, led by Professor Greg Hannon from the CRUK Cambridge Institute. His team will be developing entirely new technologies and pushing the capability of existing ones. At this point it’s impossible to know which will be the frontrunners and how the team will need to spend funds towards the latter stages of the grant. “We’ve structured our project a little differently from others,” explains Greg. “It’s a big project, and you can’t predict its course over the next six or seven years, so we’ve built in a year where we ramp up, and we hire the right people, which is probably the most important determinant of success. Then we’ll wait until we get further down the line to decide how to scale up.”

Our funded teams are now embarking on the first of, or more, of making their Grand Challenge vision a reality. In February 2017, we brought them together in London, where they had the chance to share their plans, exchange knowledge and discuss synergies and opportunities for collaboration.

“We thoroughly enjoyed meeting the other teams at the launch and hearing about their plans,” says Josephine. “We have started thinking about how we could work with the other teams and have already had some early conversations to start planning some joint work.”

“These awards aim to stimulate people to think about problems differently, get together, discuss ideas and, as teams, be able to achieve more than the sum of their individual parts,” says Rick. “This is just the beginning. We want this to be the start of a global approach, a unique community, which will collectively redefine the way we think about cancer.”

Meet the teams on the next page...
MEET THE WINNING TEAMS

CREATING A ‘GOOGLE EARTH’ FOR CANCER

Dr. Josephine Bunch is based at the National Physical Laboratory (NPL), the UK’s National Measurement Institute, which is also home to the National Centre of Excellence in Mass Spectrometry, the technological firepower behind the team’s approach.

They plan to generate a map of a tumour at the metabolic level, by layering information obtained using a range of multiscale molecular imaging technologies.

“No single method can measure everything that you want to within a tumour, so we need to bring in a whole host of different techniques,” Josephine explains. “Some operate under vacuum conditions, others at atmospheric pressure, some use lasers, some use ion beams, some use charge solvents and some use surgeons’ knives.” The team will need to find a way to bring these to bear on the same sample to build up the levels of molecular detail needed, and then accurately register this information spatially back to the tumour sample.

“It’s very important that this work, and particularly this level of investment, delivers methods that are reliable and can be used by other laboratories and so we will be making efforts to standardise our work flow,” Josephine explains.

But it’s not just about technology development. By building a team that includes co-investigators from AstraZeneca as well as renowned academic cancer biologists, Josephine wants to ensure that the technology answers several biologically and clinically relevant questions: How does metabolism relate to key cell types, tumour types, genotypes? How does metabolism relate to activation of key pathways? What are the pre-clinical models teaching us? How do our new generation of metabolism-targeting therapeutics impact the tumour?

“There is still much we don’t know about how metabolism is altered in tumours versus normal cells,” she says. “Our team is a collective force of physicists, chemists and biologists, all coming together to gain new insight into these fundamental processes and develop new and better ways to diagnose and treat cancer.”

IMAXT: IMAGING AND MOLECULAR ANNOTATION OF XENOGRAFTS AND TUMOURS

For Professor Greg Hannon, Grand Challenge gave him the opportunity to take an idea he had been mulling over and investigate it further.

“No single method can measure everything that you want to within a tumour, so we need to bring in a whole host of different techniques,” Josephine explains. “Some operate under vacuum conditions, others at atmospheric pressure, some use lasers, some use ion beams, some use charge solvents and some use surgeons’ knives.” The team will need to find a way to bring these to bear on the same sample to build up the levels of molecular detail needed, and then accurately register this information spatially back to the tumour sample.

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“There is still much we don’t know about how metabolism is altered in tumours versus normal cells,” she says. “Our team is a collective force of physicists, chemists and biologists, all coming together to gain new insight into these fundamental processes and develop new and better ways to diagnose and treat cancer.”

The team’s approach involves taking alternating physical and image sections of cancers using serial two-photon tomography which can be ‘stitched’ back together to create 3D renderings of a tumour. Then, using a combination of analyses – single-cell sequencing, imaging mass cytometry and multiplexed error robust fluorescent in situ hybridisation (MERFISH) – they will identify and molecularly annotate each cell.

“We hope to collect 20,000 plus pieces of information on every cell in a tumour,” explains Greg, “so we needed to invent an entirely different way for people to interact with the information. Using virtual reality we can present many more dimensions of information than you can on a piece of paper, and it’s immersive, so it creates a level of focus that is otherwise difficult to achieve.”

In addition to technological innovators Greg’s team includes leading cancer biologists and clinicians who are hungry to learn more about tumour behaviour and tumour-host interactions. “We don’t want to just build the map, we’re also seeking to derive some new basic biological insights.”

TEAM MEMBERS

National Physical Laboratory: Josephine Bunch, Ian Gilmore, John F. Marshall
CRUK Cambridge Institute: Kevin Brindle
CRUK Cambridge Institute: Alvin Bindle, Francis Crick Institute: Zoltan Takats
Queen Mary University of London: John F. Marshall
The Institute of Cancer Research: George Pougios, Patient advocates: Kelly Gissin, Harry C. Hall, Lead PI: Josephine Bunch

CRUK Cambridge Institute: Greg Hannon, Shankar Balasubramanian, Dario Bressan, Carlos Caldas, Simon Tavare
Harvard University: Xiaowei Zhuang
Massachusetts Institute of Technology: Ed Boyden
Technology: Owen Harris
Súil Design: Owen Harris
University of British Columbia: Sam Aparicio
University of Zurich: Johanna Joyce
University of Lausanne: Nicholas Walton
Columbia: Jan Aparicio
University of Lausanne: Bernd Bodenmiller
Patient advocates: Elaine Chapman, Lynn Dundas
Lead PI: Greg Hannon
Dr Jelle Wesseling’s team is tackling an urgent unmet clinical need – the significant overtreatment of ductal in situ carcinoma (DCIS) – and requires a large collaborative effort to do so: “There are only three large cohorts of DCIS in the world right now,” Jelle explains, “and they are from the Netherlands Cancer Institute (NKI), Birmingham in the UK, and MD Anderson in Texas.”

One of the first questions the team will address is the genomics of DCIS. As Jelle states: “This is something that no other study has had the power to do.” They brought in the expertise of Dr Serena Nik-Zainal from the Wellcome Trust Sanger Institute to see if they can unveil a genetic clue about which cases of DCIS go on to become invasive breast cancer, and which cases of DCIS recur.

The team will take the insights generated from this stage into functional studies, with Dr Andrew Futreal at MD Anderson investigating the tumour microenvironment and the immune profile, and Professor Jos Jonkers at the NKI taking on the challenge of developing a mouse model of DCIS – something that has never been achieved before.

“CRUK and the Dutch Cancer Society have essentially bought DCIS globally under one umbrella. It’s going to lead to joined-up thinking around the world,” says Jelle. “The biggest challenge is this high risk, high impact in vitro and in vivo validation work we’re planning to do” says Jelle. “If we can find markers that distinguish DCIS that invades from DCIS that doesn’t, and can validate these, then we have an opportunity to intervene in aggressive DCIS. Our goal is to change clinical practice but to do so very much based on understanding the biology.”
Population research has a fundamental role to play in CRUK’s ambition of 3 in 4 people surviving cancer by 2034, particularly in the areas of early diagnosis and prevention. To make sure we help drive the population research we need, there’s been a quiet revolution taking place in our approach to funding it.

Over many years, we have funded some of the world’s best population researchers, leading to changes in prescribing regimens and clinical practice, and the introduction of screening programmes. But our researchers told us that there is still huge untapped potential if they had the time, space and flexibility to come together and collaborate, they could make the UK a global hub for population research. The snag? There was no recognised funding mechanism they could use to develop the necessary infrastructure to run big, collaborative, international projects and cut existing population research ‘Centre of excellence’.

Last year, to meet this challenge, we launched the Catalyst Award. Competing for a grant of up to £5 million over five years, teams had to show that their proposals, as well as being novel and innovative, were collaborative and sustainable, with a commitment to training and mentoring early career researchers, the research leaders of the future.

As Professor Robert Strausberg, Chair of the Catalyst Award Panel, says, “It’s a great opportunity for international scientists from diverse disciplines, such as surveillance, early detection, prevention, and clinical research, to build connectivity with those they would not ordinarily interact with, in order to facilitate big-impact research.”

Unsurprisingly, the scheme is attracting huge amounts of interest: for the first round, 56 different groups and institutions applied from 10 countries. In 2015, two shortlisted teams, comprising 22 groups from seven countries, are currently preparing their final applications, with a decision due in November.

As well as providing a unique way of meeting a substantial research need, the Catalyst Award offers applicants a very different experience from the norm. If their Expressions of Interest are shortlisted, four members of each team are invited to a Joint Applicant Meeting, before submitting their full proposals. It’s a great opportunity to meet up and do some face-to-face planning, but there’s more: instead of using the occasion to check out the competition and work out how to beat them, participants are invited to discuss each other’s proposals with a view to improving them all. They also give an opportunity to meet the CRUK staff who’ve shepherded their applications towards the award plate, to ensure that everyone knows how to present their ideas in the best possible way.

For those accustomed to keeping their cards close to their chest, the idea of spilling the beans to the competition may be disturbing, but Dr Fiona Reddington, Head of Population, Prevention and Behavioural Research at CRUK, thinks that fears of being scooped are groundless: “The ideas are so ambitious that the expertise needed can’t be replicated elsewhere,” she says, “so nobody’s going to get their project pinched!” Even if people are critical, it’s helpful, she adds: “Some of the brightest minds in population research are there, and you have an opportunity to pick their brains. They’ll take the potential weaknesses in your proposal that the committee will inevitably grill you on.”

The long-term aim of the Catalyst Award, to create the nucleus of a virtual centre for population research, will allow the many cohort studies in the UK, and eventually internationally, to be rationally combined and shared. Traditional cohort studies, where participants typically complete lifestyle-based questionnaires over a number of years, are changing drastically. Nowadays, biological and phenotypic data are also collected, and cohort studies represent a rich data resource to generate and test hypotheses, and to identify and validate biomarkers.

Backed up by the revolution in big data collection and processing, such studies mean that population research can be better integrated into discovery and clinical research, creating a genuine two-way flow of information: data from normal and patient cohorts will inform our understanding of the molecular basis of diseases and health, which can then be used to develop early detection and prevention measures. Bob Strausberg thinks that the Catalyst Award will be influential in driving this change: “I envisage that the Catalyst Award will one day be looked back on as a transformational scientific endeavour that made a difference for people everywhere.”

Find out more at cruk.org/catalyst-award.

IN THIS ARTICLE
Fiona Reddington
Head of Population, Prevention and Behavioural Research, CRUK
Robert Strausberg
Executive Vice President for Research, Ludwig Institute for Cancer Research and Chair of CRUK Catalyst Award Panel

Find out about the first team funded through our Catalyst Award on the next page. ——
Pioneering Research 2016/17

AND THE WINNER IS ...

CANTEST: OFFERING THE RIGHT PATIENT THE RIGHT TEST, AT THE RIGHT TIME, AND IN THE RIGHT SETTING

The Catalyst Award asked for a paradigm shift. For us as GP cancer researchers, the paradigm shift is to gather the evidence that’s currently lacking to change the way diagnostics are delivered in primary care, so that patients will either have a more timely provisional diagnosis of cancer, or an exclusion of cancer. As an example of why this needs to happen, for colorectal cancer, only about 66% of people getting a rapid specialist referral are diagnosed with colorectal cancer. Therefore, the vast majority of these patients may have been unduly worried about possibly having cancer, and many colonoscopies are undertaken with a negative result. Against the backdrop of the financial concerns of the NHS, we need to use our specialist and GP care much more cleverly.

The first part of the project is providing a solid evidence base about which diagnostic tests can be used safely, accurately and cost-effectively for patients in a community setting. We want to build up our multidisciplinary evaluation expertise to form a ‘corridor’ so we have sustainable, methodological approaches for evaluating not just current tests, but future tests as they come out.

When exciting discoveries are made, we need to ensure there are researchers, to translate and evaluate them so they can be used accurately and safely in primary care diagnosis. So our second objective is to nurture the workforce of the future by establishing an international School for Cancer Detection Training in Primary Care. We’ll train and support a new generation of scientists from a variety of backgrounds – it’ll be an educational melting-pot to rapidly expand the field internationally.

WHAT DOES IT MEAN FOR PATIENTS?

This is about more diagnostic tests for patients so they can be quickly reassured if they haven’t got cancer, and have the appropriate tests and referrals if there is a high chance that they do. Ultimately we will very quickly, in 3 to 5 years, be able to reduce later diagnosis and poorer outcomes for patients with some cancers.

It’s the biggest investment there’s ever been in primary care cancer diagnosis and treatment, and in effecting change for the patient. And of course we’re not just talking about cancer. A patient usually presents with one of between 50 and 100 common symptoms – yet there are around 8,000 diseases which we have to identify. We’ll be helping our patients with any of these diseases if we can do more diagnostics in primary care.

WHO DO YOU HAVE IN THE CANTEST TEAM?

We are lucky to have a group of people who bring specialist understanding to our team of GP cancer researchers. We’ve got behavioural scientists, health economists and statisticians involved, and they’ll help us understand more about the patient safety and cost effectiveness aspects.

We can also learn a great deal from others around the world. In Europe, we will be working with colleagues from Denmark and Holland who have healthcare systems similar to ours, but we’re also working with GP colleagues from Australia and the US, both of which have very different healthcare systems to the UK; we can learn a great deal from them about some of the tests that will be of use in the NHS, as they are already widely used in those countries where GPs don’t act as gatekeepers for specialist care.

Our international colleagues are equally keen to develop the evidence base for some of the tests they use, as some can result in overdiagnosis and overtreatment. This is one of our major concerns – that you might diagnose people who are not at risk of dying of their disease. An important example comes from thyroid cancer, where there’s increasing evidence that tests are picking up cancers that don’t need treatment.

I’VE BEEN A GP FOR ABOUT 30 YEARS. CANTEST ARISES FROM THAT EXPERIENCE – FEELING THAT WE CAN ALWAYS IMPROVE THE WAY TO BEST MANAGE OUR PATIENTS

Fiona Walter

Fiona Walter, Principal Researcher in Primary Care Cancer Research at the University of Cambridge, and Willie Hamilton, Professor of Primary Care Diagnostics at the University of Exeter, are joint PIs on the first Catalyst Award project: CanTest – a £5 million venture aimed at investigating ways of bringing new and improved cancer diagnostic tests to GPs. Here, Fiona tells us about the CanTest team’s plans.

WHAT IS CANTEST?

In partnership with Channel 4, we showed the removal of two bowel polyps from Philip McSparron, under the expert care and guidance of Dr Sunil Dolwani, live from University Hospital Llandough in Cardiff. Colonoscopies involve inserting a flexible tube with a camera and small loop into the bowel to remove the polyps, a vital procedure as it can prevent the disease from developing.

The advert was viewed by over 1.6 million people, and obtained huge media coverage, reaching 54% of the UK public.

Sunil played an instrumental role, from initial conversations with Philip, to guidance on the messaging and shaping of the live TV broadcast. He explains: “This project was the combination of a wonderful patient, a great team and an important message. If it relieves anxiety around colonoscopies, then we have achieved something.”

And he has a note of encouragement to others: “As cancer researchers we always want to share our passion with the public and patients – I would encourage any researchers to get involved in similar projects so we can help the public understand better what we do and its importance.”

Diagnosing cancer early can save lives. So it’s crucial we use new ways to demonstrate its power to the public. In a world first, in January 2017, we broadcast a live 90 second TV advert from inside the human body to demystify a common procedure to find and remove early signs of bowel cancer: the colonoscopy.

In partnership with Channel 4, we showed the removal of two bowel polyps from Philip McSparron, under the expert care and guidance of Dr Sunil Dolwani, live from University Hospital Llandough in Cardiff. Colonoscopies involve inserting a flexible tube with a camera and small loop into the bowel to remove the polyps, a vital procedure as it can prevent the disease from developing.

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Fiona Walter

AND THE WINNER IS ...

CANTEST: OFFERING THE RIGHT PATIENT THE RIGHT TEST, AT THE RIGHT TIME, AND IN THE RIGHT SETTING

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only take for a few months before they died. The first steps towards understanding the molecular basis of cancer were being taken, but the era when drugs targeted against particular molecules could become billion-dollar blockbusters was yet to dawn. **BREAKING DOWN BARRIERS BETWEEN BENCH AND BEDSIDE**

Many of the classic cytotoxic chemotherapy drugs, such as vincristine and cisplatin, had been discovered in academic labs, and in the UK the Cancer Research Campaign (CRC, one of the precursor charities to CRUK) funded three major drug discovery labs – at the Institute of Cancer Research in London, the Paterson labs in Manchester, and Aston University in Birmingham. However, there was a big barrier between the lab bench and the clinic: promising candidates had to get from pre-clinical studies into Phase I and II trials designed to demonstrate safety, dose, and efficacy before most drug companies would be interested, and the logistics – the facilities for bulk synthesis, toxicology, formulation and early clinical trials management – were missing. To address these challenges, a funding committee was set up in 1982, the Phase I/II Clinical Trials Committee. Chaired by the dynamic and inspirational medicinal chemist Professor Tom Connors, the committee comprised key players involved in anti-cancer drug design, together with the clinicians who sought to use the new agents. Once the committee approved a project, our Formulation Unit, established by CRUK at the University of Strathclyde, got the drug into a form suitable for clinical use and manufactured supplies; the CRC-funded Clinical Trials Data Centre at Charing Cross Hospital helped develop and manage the Phase I/II trial protocol and collect the trial data, and pre-clinical toxicology testing was undertaken. Potential drugs, many of which, as first-in-human compounds, would have been considered too risky a commercial proposition for a drug company, sped through the programme.

**A BLEAK HISTORY**

For anyone unlucky enough to have been diagnosed with cancer in 1980, prognosis and treatment were very different from today. Cancer therapy relied on surgery, radiotherapy, and adjuvant chemotherapy with cytotoxic drugs, and whilst some of these treatments were very effective and are still in use today, their side effects could be horribly toxic. The commercial arguments for making new anti-cancer drugs weren’t very strong; cancer was a terminal illness, and there wasn’t much profit in making drugs that patients would only take for a few months before they died. The first steps towards understanding the molecular basis of cancer were being taken, but the era when drugs targeted against particular molecules could become billion-dollar blockbusters was yet to dawn.

**IN THIS ARTICLE**

Kevin Lee
CEO, Bicycle Therapeutics

Herbie Newell
Emeritus Professor, Newcastle University

Ruth Plummer
Clinical Professor of Experimental Cancer Medicine, Newcastle University

Malcolm Stevens
Emeritus Professor, University of Nottingham

Heike Lentfer
Head of CRUK Biotherapeutics Development Unit, CRUK

**COMPLEX, INNOVATIVE AND NOVEL: A RECIPE FOR SUCCESSFUL DRUG DEVELOPMENT**

As our Centre for Drug Development celebrates its 25th birthday, we recognise the unique role CRUK plays in supporting early studies of anti-cancer therapeutics.

We look at some of the major achievements over the last 25 years, how the landscape of drug development has evolved and the impact our work is making internationally. As we enter the next quarter century of the charity’s support for drug development, we’re well placed to support the increasing breadth of therapeutics and are excited about the future potential for developing new treatments to improve the outlook for cancer patients.
TEMZOLOMIDE: THE BRAIN TUMOUR SUPERSTAR

TEMZOLOMIDE was synthesised by Professor Malcolm Stevens and his team at the University of Aston, and was an early success for the Phase I/II Clinical Trials Committee. Now the international standard of care for treatment of glioblastomas, in 2008 sales figures exceeded £31 billion. Malcolm reflects on the work that led to his team’s discovery.

“We didn’t have any particular idea where we were going to work. After all, we’re scientists, we expect that something very worthwhile will come, but we didn’t know what that ‘worthwhile’ was going to be when we gathered at Aston in the 1970s.

There was no particular moment in time when temzolomide was discovered – there was nothing that we did that was unrelated to our apprenticeship, and my early days as a lecturer in Edinburgh where we investigated the properties of molecules that were rich in nitrogen. That was the secret of our ultimate success – making compounds with multiple nitrogen atoms. They tend to be rather easy to make, which is a good thing, and they have interesting properties from a chemical and from a biological perspective.

We realised when we’d made the family of compounds that eventually became temzolomide that they were likely to have some exciting biological properties. Until then, all the compounds we’d made were biologically inert, and it was only around that time – the early 1980s – when we were making interesting molecules.

And because of funding from the CRC (a predecessor charity to CRUK), we had the ability to test the compounds. We were able to do the synthetic chemistry, the toxicology work, and could manufacture formulations of the drug.

When we were researching temzolomide, we weren’t supported by any major pharmaceutical companies, so the obvious place to go was the CRC’s Phase I/II Trials Committee. Exciting early work convinced the committee of the potential for the treatment, so they decided to fund the clinical trials on temzolomide.

I don’t think there was ever a ‘eureka’ hats-in-the-air moment, but I guess we expected that something was going to happen. After all, we’re scientists, we think that we’ve done our side of the bargain – the preclinical work – and why should we be surprised if something beneficial is found in the clinic?”

The number of new drugs tested by the CDD in cancer patients

Continued from page 37

BIRTH OF THE CRUK CENTRE FOR DRUG DEVELOPMENT

By 1992, the Phase I/II Clinical Trials Committee had acquired a reputation for fast-tracking compounds into the clinic, with 32 drugs tested and, one, temzolomide, exciting activity against glioma. The nature of the drugs was changing too: targeted therapy was now the buzzword, and the committee was considering proposals to test biological agents such as monoclonal antibodies, as well as rationally designed small-molecule drugs.

So that drugs could be taken into commercial development with as little delay as possible, a new expert resource was set up to ensure that all trials met the international standards of Good Clinical Practice. Under its first director, Dr David Secher, the Drug Development Office (DDO) – the precursor to today’s CRUK Centre for Drug Development (CDD) – undertook to manage and coordinate development of all the drugs approved by the Phase I/II Clinical Trials Committee, and the data management team was moved from Charing Cross Hospital to the DDO. In 1998 the DDO established the New Agents Committee, which took over the role of the Phase I/II Clinical Trials Committee in considering new applications.

In 2004, with the arrival of the EU Clinical Trials Directive, the DDO’s role became even more critical. Prior to 2004, academic clinical trials were conducted under light touch DDO (Doctors’ and Dentists’ Exemption) rules, which allowed these two groups of doctors to conduct trials that were in the best interests of their patients, with few research costs and little oversight, which could increase if new patients were far more stringent. Whilst the DDO was already complying with established good clinical practice (GCP) quality standards, the requirement for the preparation of detailed scientific information in the form of investigational Medicinal Product Dossiers (IMPDs) signalled a need to increase the scientific expertise in the DDO. The DDO was now the Centre for Drug Development (CDD) in 2005, and stands as a fully integrated, multidisciplinary development process that is globally unique in the non-commercial sector.

EXPERT NAVIGATION IN A COMPLEX LANDSCAPE

Today, led by Dr Nigel Blackburn, the CDD, staffed by 120 people, has a portfolio of around 25 drugs in development. The CDD works in close collaboration with the researchers, scientists and clinicians in our UK-wide Experimental Cancer Medicine Centre (ECMC) Network, providing specialist expertise on every aspect of preclinical and clinical development for a portfolio of increasingly complex drug candidates. Once new projects pass the stringent scientific review of the New Agents Committee, which also factors in assessment of novelty and likelihood to deliver a benefit to patients in the future, a multidisciplinary CDD team assembles to design and deliver pre-clinical and clinical trials in close collaboration with experts in our ECMC Network. It’s the CDD’s proud boast that they’ve never failed to deliver regulatory approval for any single molecule to the UK’s regulator, the Medicines and Healthcare Products Regulatory Agency (MHRA).

RUCAPARIB: TARGETING DNA REPAIR

Inhibitors of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) kill BRCA-deficient tumours, and have significant activity in single agent and combination therapy. Professor Herbie Newell, of Newcastle University (with Hilary Calvert, Nicola Curtin, Barbara Druce, Bernard Golding, Roger Gooding and Ruth Plummer), was part of the team responsible for making the PARP inhibitor rucaparib. In December 2016, the FDA fast-tracked rucaparib (Rubraca®) into the clinic to treat women with advanced ovarian cancer who have received two or more prior chemotherapy regimens and whose tumours have a BRCA1 or BRCA2 mutation. Here Herbie explains the start of the story.

“...in the late 1980s, temzolomide, a DNA-methylating agent, was the drug of the moment. We reasoned that a PARP inhibitor should make temzolomide, as well as some other drugs and ionising radiation, more active by inhibiting DNA repair. There was lots of scepticism from pharma as they said a PARP inhibitor wouldn’t be a stand-alone drug and would increase toxicity, consequently there was no major commercial interest. Nevertheless, in a collaboration between the Cancer Research Unit and the School of Chemistry, we established a drug discovery group in Newcastle in 1990 to make and test PARP inhibitors. Rucaparib was subsequently identified in collaboration with Agouron and Pfizer, and is now being developed and marketed by Clovis Oncology.

The critical breakthrough for PARP inhibitors was the recognition of single agent activity in cells deficient for homologous recombination repair, as found for the BRCA-deficient tumours (reported independently in Nature in 2005 by two UK teams). With the help of the CRUK New Agents Committee (NAC), rucaparib went through the DDO trials in 2003, and went on to the levels that were of high interest in PARP inhibitors in multiple companies. The FDA approved rucaparib in December 2016, having previously identified it as a breakthrough drug.”

In 2003, Professor Ruth Plummer, now the chair of the NAC, wrote the prescription for the first patient in the world to receive rucaparib, the first ever cancer patient to be treated by a PARP inhibitor. “It was always clear we had a drug that did something. We have some patients whose scans are currently clear and have been for some years now. It’s fantastic – really great. The patient from our first trial doesn’t even come to clinic now – he’s been discharged!”

A PATIENT’S PERSPECTIVE ON RUCAPARIB

Susan Ross was first diagnosed with ovarian cancer with a BRCA1 gene mutation 10 years ago. Here she explains her experience of being part of a clinical trial of rucaparib (Rubraca®) at the Northern Centre for Cancer Care in Newcastle.

“Early in 2015 I was told the ovarian cancer had returned and unfortunately an operation was not possible. I was facing the prospect of having chemotherapy again. Previously I had three rounds of chemotherapy and four operations, so knowing what treatment was going to entail, my heart sank. ‘I thought I really want to go through this again?’

My consultant organised a BRCA gene mutation test, which showed I was a BRCA1/2 mutation carrier. I was then offered the opportunity to go on a clinical trial of this new treatment rucaparib, and I grabbed it with both hands. My care is overseen by Dr Yvette Drew, and I attend the unit every three weeks to be monitored, and discuss any worries with the nurses and doctors. I’ve been taking rucaparib as part of this trial since December 2015 and it’s the best I’ve felt in ages, both physically and mentally. With the help and support of all the staff, it feels like I’ve got my life back.

Being part of a clinical trial means I’m monitored very closely. I am so grateful for all those who have been involved in the development of rucaparib and for making this clinical trial possible. Being part of a clinical trial is an opportunity to help a difference, to help cancer patients in the future and hopefully find a cure for this awful disease. I’d do it again in an instant.”
BT1718:
FIRST-IN-CLASS THERAPY
FOR SOLID TUMOURS

In December 2016, CRUK, Cancer Research Technology (CRT), and Bicycle Therapeutics announced their collaboration to trial a first-in-class drug in patients with advanced solid tumours. Together with Dr Uday Banerjee, Chief Investigator for the trial, our CDD is sponsoring and funding the first-in-human Phase I and Phase IIa clinical trial for BT1718, a bicyclic peptide conjugated to DML, an existing anti-cancer therapeutic that kills cells by inhibiting microtubule formation. Bicyclic peptides are small molecule drugs which have pharmacology similar to monoclonal antibodies providing targeted delivery of highly potent cytotoxic drugs, but their low molecular weight allows them to penetrate tumours far more efficiently. In this case, the peptide portion of BT1718 binds with high affinity to Membrane-Typic Matrix Metalloproteinase (MT1-MMP) which is highly expressed in many solid tumours, including triple negative breast cancer, sarcoma and non-small cell lung cancer.

Bicycle Therapeutics has the right to license the exclusive BT1718 CRUK trial in return for success-based milestone and royalty payments to CRUK as well as an equity stake in the company to refinance CRUK’s value-add to the broader Bicycle platform. “This relationship is an example of a situation where one plus one is greater than two,” says Dr Kevin Lee, CEO of Bicycle Therapeutics. “Our excitement for our lead molecule BT1718, our technology platform, and its potential to transform the treatment of solid tumours is shared by CRUK. It is clear that by combining forces we can deliver potential benefit to patients more rapidly than we could by working alone.”

“We greatly value our relationship with CRUK for many reasons,” Kevin continues, “especially the access the partnership gives us to CRUK’s in-depth and complementary expertise and to its clinical network and infrastructure. CRUK’s investment, as well as the breadth of data we expect will be generated, is beyond what we would have been able to accomplish on our own.”

Continued from page 39

A RECIPE FOR PRESENT AND FUTURE SUCCESS

Not surprisingly, the portfolio managed by the CDD has changed considerably over the years. Nowadays, the majority of CDD projects are collaborations with industry, forged through the innovative Clinical Development Partnerships scheme. The agents under investigation have also changed drastically. Now, more than half of the CDD portfolio are biological drugs – vaccines, antibodies, radiopharmaceuticals, cell therapies, viruses and recombinant proteins – a development that would have astounded the pioneers in the 1980s. The CRUK Biotherapeutics Development Unit, now located in a new state-of-the-art building opened in 2010, undertakes the manufacture of these highly complex biological drugs for early phase clinical trials.

At CRUK we are also tackling the challenge of how to run trials of combination therapies.

Frequently, ideal drug partners belong to different companies, and there has been little appetite for joint testing. Commercially-sponsored trials involving drugs paired with radiotherapy have also been a rarity. “Through the Combinations Alliance, a joint initiative between CRUK, the ECMCs and a growing number of pharmaceutical collaborators, combination trials involving novel or marketed drugs, radiotherapy and/or chemotherapy are trialed in the ECMC Network. Currently, 14 trials are open with six more being set up – five of these trials are radiotherapy combinations and one an immunotherapy combination.”

Throughout all this change, the underlying philosophy of the CDD has remained the same – to bring drugs that otherwise might not have been developed into clinical trials, to bring benefit to patients in need of new medicines.

AST-VAC2: A FIRST-IN-CLASS MANUFACTURING CHALLENGE

Isolation and in vitro loading of dendritic cells with cancer antigens is a promising concept for immunotherapy. Dendritic cells can elicit an immune response by presenting cancer antigens such as telomerase (expressed by nearly all cancer cells but very rarely by normal cells) to the adaptive immune system, kick-starting a focused attack on the tumour. To date, this approach has been limited by the requirement to individualize patient therapy.

In a Clinical Development Partnership with Asterias Biotherapeutics, our CDD has developed an innovative laboratory-scale process to make it possible to manufacture a Good Manufacturing Practice (GMP) clinical drug product of this kind for the first time ever. The process employs human embryonic stem (ES) cells that are more than patient blood as the starting material, which are expanded in number and differentiated into mature dendritic cells by adding various growth factors at key development stages. The dendritic cells are loaded with modified telomerase (hTERT) mRNA so that the cells express suitably-short telomerase fragments, shuffled by the cell onto its surface for presentation to the immune system. The resulting vaccine is being made in the CRUK Biotherapeutics Development Unit, here Dr Heike Lentfer, the Unit’s manager, explains some of the challenges. “The journey starts from a single cryovial containing 10^7 human ES cells, which are expanded and differentiated into dendritic cells over a period of 65 days and electroporated with hTERT mRNA. By the end of the process, approximately 120 vials of drug product have been made, each containing 20 million cells – enough to dose many patients.”

“The manufacturing processes for creating living cell therapies at sufficient scale to supply clinical trials are still in their infancy. Our team has addressed many challenges, including maintaining rigorous cell culture and stability standards during the two month manufacturing process, through to the development of new assays to make sure that dendritic cells are present in abundance. There were similar challenges for monoclonal antibody production 10 years ago, so we’re optimistic that improvements will be made in scale-up and productivity.”

Asterias has helped solve problems throughout the technology transfer and manufacturing campaign, no matter what time of day it was – in California – a great example of a productive collaboration with an industry partner.”
The Francis Crick Institute is huge, but it’s also beautiful: sweeping curved roofs cover an imposing structure of glass, steel and concrete, with a facade whose vast cathedral-like stained glass windows reflect a rainbow of colours into the high-tech atrium. Inside, things only get more impressive. Standing in the entrance area feels like stepping into the space between two ocean-going liners; the five above-ground floors (a further four lie below) rise up on either side, joined by walkways floating across the gulf of the atrium. But walk up the central spiral staircase, or ride the high-tech lifts, and the impression of grandeur disappears. Collaborative spaces and work pods featuring comfy sofas and coffee machines give each floor a far more intimate feel. The labs and offices, laid out on either side of the atrium, are open-plan, with sight-lines extending across the whole breadth of the building, but they house familiar equipment, and are already gathering the reassuring clutter of scientific workspaces the world over.

Beyond the grand exterior, what is life like at the Crick? Talking to the new inhabitants gives a flavour for how it feels to work in this amazing building. Whilst there are some of the inevitable teething problems that are to be expected when settling into a brand new facility – there are issues with the glassware washing and ultrapure water, and the category 3 labs have yet to be commissioned – things are running remarkably well given that the last groups moved from their legacy institutes [CRUK’s National Institute of Medical Research (NIMR)] less than six months ago.

The Crick was designed in concert with its future occupants, and the strategies for encouraging collaboration and mingling of the scientists are working well. All the offices are deliberately small, so everyone, including Director Sir Paul Nurse, meets in the communal areas. Monica Rodrigo, a staff scientist in Professor Steve West’s group, thinks the Crick’s layout is changing how individual labs function: “On each floor there are booths and LCD screens so you can have impromptu meetings. Steve doesn’t have meetings in his office anymore, he’s just got a booth,” she says.

Dr Narin Hengrung, a postdoc with Dr Steve Gamblin, agrees: “The NHM in Mill Hill had very small and cut-off labs, and they were very crowded,” he says. “Here, the views and openness make it feel like you can wander over to another lab and see what they’re up to.” He’s looking forward to finding out what everyone else is doing. Peter Cheeseman’s lab works on something very similar to what I’m trying to do, so it’s really nice to have their expertise next to us, I don’t know what most of the other permanent scientists who are acknowledged experts in that field, the Crick is tremendously lucky. As Monica endorses: “Not everyone can be an expert in everything. Now, if you have an idea for, for example, a screen, you don’t have to figure out how you’re going to do it on your own, you can talk to someone in the screening facility. That really accelerates research because you just deal with the results and look at what it interesting.”

It’s too early to demonstrate the impact of the Crick, all the ingredients for success are in place: great people, amazing facilities, and a diverse talent pool will mean that the Institute attracts talent from all areas.

The Francis Crick Institute

After years of meticulous planning and design, in late 2016 Her Majesty The Queen officially opened the brand new Francis Crick Institute in London, the biggest biomedical research facility in Europe under one roof. Bringing scientists together from different disciplines to tackle some of the pressing health concerns of the 21st century, the new institute is now home to 1,250 scientists and a further 250 support staff. Here, we take a glimpse behind its doors and meet some of its new inhabitants.

The Francis Crick Institute

For IN THIS ARTICLE

Narin Hengrung
Postdoctoral researcher, Francis Crick Institute

Monica Rodrigo
Principal Laboratory Research Scientist, Francis Crick Institute

Esther Wershof
PhD student, Francis Crick Institute

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A MIXING POT OF IMMUNOLOGY

One way that tumours evade the immune system is by producing prostaglandin E2. It reduces the role of dendritic cells in kick-starting antigen presentation, and so can’t be activated. That’s because naive T cells aren’t encountering tumour antigens, and so can’t be activated. That’s why it’s so important that we activate dendritic cells to process and present tumour antigens, the T cells are blind to the tumour.

We already know that tumours infiltrated by dendritic cells have a better prognosis – data from mouse and man show that dendritic cell presence elicits a good immune response, and correlates with survival across different cancers. Now we’re trying to work out how to increase dendritic cell numbers in tumours; we think there’s an exciting opportunity for therapeutic intervention.

Previously at the LRI, there was understandably a strong emphasis on using cancer as a model, so there are a lot of people at the Crick who are interested in cancer. But we’re also finding people who’ve come from NIMR, who weren’t necessarily looking at cancer before, but are now identifying synergies with their research, and vice versa. There are so many interesting parallels between different diseases, for example cancer and infections, and we now have more opportunity to explore these options. It’s not just hope that being more integrated brings benefits – it really does. From CRUK’s perspective, the Crick is a very worthwhile investment: they’re getting the expertise of the whole institute.

A lot of that is due to the pro-active legislation, which provides a protected space where you can focus on developing tools that enable you to address really important questions in human biology.

Being in the Crick has significantly increased our ability to collaborate. We’re working with nearby clinics much more directly and rapidly than we could in the past. It’s a two-way learning process: they have embryologists interested in basic research who we can learn from as they’re experts in certain aspects like embryogenesis. And this can only mean one thing – faster progress.

My interest is in how we start, of a cell–cell interaction and the subsequent events that drive all the cells from each other as they multiply. Increasing our understanding of this fundamental area of biology will, we hope, help us to uncover pioneering new ways to tackle infertility, miscarriages and developmental disorders, as well as support the development of new therapies using stem cells.

We know a little about the molecular mechanisms in the mouse, but in the human we know very little – the more we compare the two, the more we see how different they are. The classic developmental regulators abundant in the mouse zygotes are absent in humans, and vice versa. It would have been so easy if molecularly they had been similar, but they’re fundamentally different at this stage.

Unfortunately, we don’t always have the technology available to test out what we think, and we need to test whether insights found in model organisms translate as well. Another problem is that we can’t be clear whether CRISPR, which we successfully use to edit genomes in mice embryos, could be used in a human embryo. There were no optimised protocols, so we’ve spent almost a year optimising every single one of the parameters and developing new technologies. We’ve been testing them in any cellular context we can, so before we do anything with even one human embryo, we’ve developed the best methods we can.

Overcoming technical challenges will hopefully enable us to use this technology to address fundamental biological question. The idea is that naive T cells aren’t encountering tumour antigens, and so can’t be activated. That’s what led to a resurgence of interest in exploring the role of dendritic cells in kick-starting the anti-tumour immune response.

One way that tumours evade the immune system is by producing prostaglandin E2 (PGE2), quite different from other routes that target immune checkpoints. We’ve found that PGE2 can decrease dendritic-cell infiltration of tumours, which might help explain how the T cell response is impaired if there are no dendritic cells to process and present tumour antigens, the T cells are blind to the tumour.

My lab’s work is going very well, particularly considering that we’ve only been here for six months. My research is centred around the role of dendritic cells in early embryonic development. It’s a really critical stage of development. It’s a really satisfying experience; you get to work with flies, so you see a lot more of other people, you bump into them and talk about all sorts of things, including science. Most importantly, people in different labs are talking to one another more.

The fact we have so many great people doing so many things in the building is facilitating research – somehow information just gets transmitted. Someone in my lab doing Drosophila work who wants to do some clever mutants involving conditional knockouts found that Jean-Paul Vincent is working on flies, so she’s gone to talk to someone in his lab.

People always say that there are too many good people. We’d love to get more people into them and talk about all sorts of things, but I’ve started injecting DNA constructs into early cells diverge in their fate and function at this critical stage of development. It’s a really hard choice for fly technicians to decide what to do with excess embryos, so it would be disrespectful to them to not use that precious material in absolutely the best way we can.

My lab is working very well, particularly considering that we’ve only been here for six months. My research is centred around dendritic cells, the body’s professional antigen-presenting cells – we study their ontology and function. We’re currently excited about PGE2, which is an anti-inflammatory, and it’s a really friendly atmosphere. Everyone working with flies, so they’re all really friendly.
The microbiome has been a buzz word for years because of its association with a number of diseases, from obesity to Crohn’s disease. Now some researchers from around the world believe there may be a link between cancer and the microorganisms that call our body home – which, if true, will open up a host of new opportunities to understand and tackle the disease. We take a look at what’s happening within this rapidly developing field and ask some of its leading figures if they think it will live up to the hype.

The microbiome

The microbiome is becoming a buzzword in cancer research. But the theory that gut bacteria might play a role in the development of cancer, and in the response of patients to immunotherapies, is not a new one. It was first proposed over 30 years ago, but since then the potential of the microbiome has been explored in a number of studies, and the evidence is becoming more compelling.

Jennifer Wargo, Assistant Professor of Medicine, MD Anderson Cancer Center, was closing the National Cancer Research Institute’s conference by presenting results from her study examining the connection between the microbiome and skin cancer. The study focused on patients who had undergone immunotherapy, a treatment that alters the immune system to fight cancer. The results showed that patients who had a higher diversity of gut bacteria were more likely to respond to immunotherapy than those with less diversity.

The microbiome can influence the effectiveness of cancer treatments in a number of ways. For example, some studies have suggested that altering the microbiome can improve the body’s immune response to cancer, while others have shown that certain types of bacteria can inhibit the growth of cancer cells.

Jennifer calls the science “potentially game changing” for cancer. “We have made tremendous advances in cancer treatment over the decades, with personalised medicine and immunotherapy that target components of the human immune system. The next era we are entering is to understand not only the tumour but other parts of the individual, such as interactions with the immune system and the scaffolding in the surrounding tissues that counts towards the development of cancer and how it responds to treatment,” she says. “This is a whole new aspect of cancer therapy. Could we predict responses? Could we treat cancer more effectively by modulating the microbiome? Or prevent it altogether? That’s why it’s exciting.”

But looking beyond the scenes, a number of important challenges still remain for research into the microbiome. The relationship is complex, with studies suggesting certain bacteria can promote tumour growth while others appear to inhibit it – and, in some cases, they might even switch roles in different cancers. At the moment, there are simply too many moving parts to understand enough about which species is doing what, how they change over time and how they interact to know what role they play in disease and what we might be able to target. And we need to relate any results seen in laboratory animals with what actually happens in patients. Despite the challenges, the potential is enormous and is continuing to fuel the current flurry of interest. As Paul O’Toole, Professor of Microbial Genomics at the APC Microbiome Institute at University College Cork, notes, “The microbiome is a plastic environmental factor. It’s found to be an additional determinant of cancer that we can modulate.”

IN THIS ARTICLE

Mark Bodmeier
Biotherapeutics Officer, Evelo Biosciences

Michael Burns
Assistant Professor, Department of Biology, Loyola University Chicago

Hani El-Nezami
Assistant Professor, School of Biological Sciences, University of Hong Kong

IN THIS ARTICLE

Jennifer Wargo
Associate Professor, University of Texas MD Anderson Cancer Centre

Emery Zuroske
Assistant Professor of Oncology, Roswell Park Cancer Institute

AN EXPLOSION OF INTEREST

Attention on cancer and the microbiome is coming from several directions: first, from the research community – clearly demonstrated by the fact that between 2005 and 2015 the number of published articles on the topic increased by nearly 2,000%. The media have also latched on to the bandwagon, capturing the public’s imagination with reports of its potential for preventing and treating various diseases by targeting and “rebalancing” our microbiome. And results from early studies like Jennifer’s have spurred industry to back research into live biotherapeutics (or probiotics), with several start-ups backed by heavy investment. Even some big pharma companies, such as Bristol-Myers Squibb and Roche, are moving into the microbiome-immuno-oncology space.

Researchers are also actively exploring what role the microbiome might play in the development of cancer, and their early findings make interesting reading. The microbiome appears to differ between people with cancer and those without, and the disease can develop in a healthy mouse after transferring the microbiome via a faecal transplant, from another with colorectal cancer. Several species of bacteria are also potentially connected with cancer, with researchers finding them in higher proportions in people with the disease. This opens up intriguing possibilities that a certain microbiome may be a risk factor in developing cancer or could be used as a new diagnostic tool.

An explosion of interest

But many others within the community are becoming more confident that there is indeed a connection. A 2013 opinion piece in Nature Reviews Genetics states: “Increasing evidence indicates a key role for the bacterial microbiota in carcinogenesis” (see: 10.1038/nrg3610).

And while the evidence continues to stack up, many researchers believe the potential mechanism is through our resident microbes’ influence on the immune system, with their abilities to dial up or dampen down inflammation as well as to manipulate the capabilities of our immune cells. For instance, it has been known for years that inflammation is central to the development of colorectal cancer, but there have been question marks over its source – and now fingers are pointing towards the microbiota.

But the relationship is complex, with studies suggesting certain bacteria can promote tumour growth while others appear to inhibit it – and, in some cases, they might even switch roles in different cancers. At the moment, there are simply too many moving parts to understand enough about which species is doing what, how they change over time and how they interact to know what role they play in disease and what we might be able to target. And we need to relate any results seen in laboratory animals with what actually happens in patients. Despite the challenges, the potential is enormous and is continuing to fuel the current flurry of interest. As Paul O’Toole, Professor of Microbial Genomics at the APC Microbiome Institute at University College Cork, notes, “The microbiome is a plastic environmental factor. If it is found to be an additional determinant of cancer then we can modulate it. That’s exciting.”

Continued on next page
Studies identify that Fusobacterium is found more often in colon cancer tissues than healthy tissue.

University of Michigan researchers show that transferring the gut microbes from a mouse with colon cancer to those with no microbiome causes them to develop two times more tumours than mice receiving microbes from a healthy mouse.

Researchers from Kumamoto University in Japan find that people whose oral microbiome includes Fusobacterium nucleatum have poorer oesophageal tumours test positive for this bacteria. Researchers at the European Molecular Biology Laboratory predict the presence of bacterial species in stool samples, with an increased risk of colorectal cancer from the abundance of these microbes.

Researchers at the University of Michigan show that transferring the gut microbes from a mouse with colon cancer to those who do not treated mice were reduced by 40% compared with control mice without the probiotic, with those who received Prohep head start to the disease. On top of that, mice with a microbial cocktail called Prohep in their guts modulated systemic immunity for an anti-tumour effect, says Mark. “It’s still early days,” he adds, “but the new tools and a new appreciation of the microbiome has opened up a massive area of biology with scope to develop new types of therapeutics for patients.”

EXCITING RESEARCH

...Continued from page 47

OPPORTUNITIES ABOUND

Indeed, the opportunities are considerable, with the scope to change our approach to cancer treatment sparking a lot of interest. At the end of 2016, a new Phase II clinical study started at Roswell Park Cancer Institute in the US, with backing from Merck & Co. This is one of the first human trials looking for links between the microbiome and response to immunotherapies. The team will evaluate how well 40 ovarian cancer patients respond to a combination treatment of the immunotherapy drug pembrolizumab (Keytruda®) and two other cancer drugs, bevacizumab (Avastin®) and oral cyclophosphamide (Cytoxan®). Then, the researchers will analyse their blood, tumour, stool, vaginal and skin microbiomes to identify any associations with clinical outcomes and tumour response.

“The study will extend the work that has already been carried out looking at the influence of the gut microbiome and highlights the variety of research angles being investigated to improve immune defences against cancer,” says the study’s principal investigator, Dr Emece Ziros of Roswell Park Cancer Institute. Indeed, for scientists exploring drug responses, this opens up a possible new treatment paradigm whereby patients’ microbiomes are checked before treatment — and then modulated, if needed, to enable the best drug response.

Benefits could also come through using live medicines or probiotics to modify a person’s resident microbiome. Uncovering this tantalising possibility, last year a team in Finland and China carried out a study feeding mice with a microbial cocktail called Prohep for a week before injecting them with liver cancer. Their results were astonishing — the weight and size of tumours in the microbiobically treated mice were reduced by 40% compared with control mice without the probiotic. With the team showing that it works by promoting an anti-inflammatory environment for gut and liver, Dr Han-El-Nezami, associate professor of biological sciences at the University of Hong Kong and lead author of the study, is excited by their results. He says, “We had not expected such a significant impact and we are now exploring even better cocktails for study. We now also want to investigate how humans will respond to this bacterial cocktail.”

Start-up companies are also getting in on the microbiome immuno-oncology trend.

Some recent findings exploring the role of the microbiome in cancer

This is an intriguing area of research which offers a lot of promise but also many uncertainties. This is why we’ve identified it as one of the questions in the next round of our Grand Challenge Award.
INVESTING IN THE FUTURE

HOW OUR FELLOWSHIPS MAKE A DIFFERENCE

Our fellowships support home-grown talent as well as attract promising scientists from around the world. We fund across a wide range of research areas and at all career levels, supporting renowned researchers at the top of their fields, as well as helping promising early career researchers to become the leaders of the future. We believe this early career support is crucial in cultivating the next generation of scientists who will bring real impact to the field.

In the last 10 years, CRUK has Centre Development Fellow, Cambridge

Dr David Adams, a world-renowned researcher at the Wellcome Trust Sanger Institute, started his early research on a Career Development Fellowship (CDF). "I think the ability that first CRUK fellowship gave to work on a long-term vision was what really appealed to me. The six-year fellowship is different to a normal three-year cycle of grant funding. It gives you the support and freedom to chase the big ideas, and have the time and resources to evolve that."

Our strong community is a big part of why our fellows testify that our career support is invaluable. We host networking events that allow our junior fellows to rub shoulders with world-leading researchers. Our scientific meetings provide opportunities to share ideas and learn from the best, and we actively help our fellows to forge new connections and collaborations. As David puts it, "the network of researchers CRUK draws together and the interactions they encourage is just incredible."

We also provide mentoring opportunities to enable our fellows to gain advice from more experienced researchers, and we assist all our fellows to do a lab management course to improve skills needed to set up and run a lab. Dr Noor Gammoh currently holds a CRUK CDF, having moved to the UK in 2014 to pursue her research career and emphasises this important aspect of CRUK fellowships. "I get invaluable support and advice from my mentor No matter how much training you've had before, starting your own lab is a big step, and I think having that outside window -- someone who knows the challenges, but is not closely related to your work -- can have a really positive effect. I can reflect with them on how my research is progressing, and the areas I need to develop, as well as get practical advice on new areas like managing finances."

Our fellowship schemes offer flexibility, with funding designed to support a range of career pathways, including both clinical and non-clinical careers, and over long-term career progression. Our early career options for non-clinicians include the Career Development Fellowship (CDF), open to postdocs and early career researchers, and the Career Establishment Award (CEA), to help researchers who already have a tenured position to set up as new group leaders. Both awards provide six years of funding to help researchers establish themselves and their science.

For clinicians, the Clinician Scientist Fellowship is available to researchers with less than three years’ postdoctoral experience, and the Advanced Clinician Scientist Fellowship for those with more than three years’ experience. Both schemes offer funding over five years.

Our two awards for the most senior researchers -- the Programme Foundation Award and Senior Cancer Research Fellowship -- are open to both clinicians and non-clinicians. The Programme Foundation Award is for researchers already salaried at a host institution, and the Senior Cancer Research Fellowship for those without existing salary support. These awards support the most experienced researchers to establish or further develop their own independent research group.

As David testifies, "With CRUK it is about long-term funding that allows you to pursue your own long-term vision. My initial CDF really allowed me to establish myself, I then went on to be awarded a Senior Fellowship and in 2016 I was awarded a CRUK Programme Award. It’s that long-term support that really allows you to meet your goals and produce research with real impact."

Our fellowships are different, and provide support in ambitious ways to achieve real results in cancer research. I’m so proud to be a part of that."

Here three researchers from different fields and at different stages of their careers recount their experiences of CRUK fellowships.

Dr Serena Nik-Zainal qualified in medicine, trained as a medic, and then specialised in clinical genetics. She has recently been awarded a CRUK Advanced Clinician Scientist Fellowship (ACSF) to further her research into the mutational signatures of primary cancers.

My interest in research led me to pursue a PhD and postdoc, which by chance took me into the area of cancer genetics. I started looking at patterns of mutational signatures that arise as cells become cancerous, caused by factors such as smoking, ultraviolet light, or DNA repair defects.

CRUK is extremely supportive, welcoming and positive. They take the time and effort to understand you and your science and what it needs to progress, and they really listen to you.

The five-year award gives me the ability to spread my research wings and explore a much more sophisticated understanding of mutational signatures. One of my aims is to try to understand the mechanisms that actually cause these signatures. At the moment it’s like having a photo of a landscape, where you can see the mountains and rivers, but can’t tell how they were formed. We can see the mutations, but don’t know how they’ve arisen, such as by sunlight, smoking or a genetic defect, so we want to gain a better knowledge of this.

The fellowships provide a great level of autonomy and flexibility, which is very powerful to advance research. I’m now also part of a team funded by the incredible CRUK Grand Challenge -- it’s another example of how CRUK is prepared to think differently, fund differently, and provide support in ambitious ways, to achieve real results in cancer research. I’m so proud to be a part of that."

Continued on page 53

Dr Noor Gammoh
CRUK Career Development Fellow,
CRUK Edinburgh Centre

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<thead>
<tr>
<th>CAREER LEVEL</th>
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<td>Research Training Fellowship £100k (flexible length)</td>
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**For clinical academics only**

**For clinical and non-clinical researchers with salaried positions**

**For clinical and non-clinical researchers with salaried positions and private sector**

**Other support / positions available**

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**FUNDING AVAILABLE**

**CRUK CAREERS AND FELLOWSHIPS**

**Pioneering Research 2016/17**

**PRE-casePhD**

**RESEARCHER**

**POSTDOCTORAL**

**EARLY STAGE**

**POSTDOCTORAL**

**EXPERIENCED**

**RESEARCHER**

**LEADER**

**RESEARCHER / SENIOR**

**GROU**

**GROUP LEAD**

**in Institutes & Studentships**

**Bursary**

~£25k

~£35k

~£1.7m

~£1.2m

~£50k/yr

~£1.5m

~£1m

<£10k

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The results of this level of support can be seen in the science. My proudest achievement, besides balancing my career with being a new mum, is uncovering how an immune pore called the Membrane Attack Complex is formed. These pores can punch holes in cancer cells and only now, with work done in my lab, can we see this complex in 3D and determine at a molecular level how it works.

The award from CRUK has enabled me to take up a postdoc at Oxford University. She now leads a group at Imperial College London, supported by a CRUK Career Establishment Award. Her research merges cryo-electron microscopy and x-ray crystallography to investigate membrane proteins.

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Originally from New York, Dr Doryan Blumberg completed her PhD in biophysics at Harvard, before coming to the UK as a postdoc at Oxford University. She now leads a group at Imperial College London, supported by a CRUK Career Establishment Award. Her research merges cryo-electron microscopy and x-ray crystallography to investigate membrane proteins.

She has also been awarded a Senior Cancer Research Fellowship and has a growing worldwide reputation for her cellular and molecular work in the field of immunotherapy.

Applying for the CRUK Career Development Fellowship was definitely the best decision I ever made. I was drawn to it initially because it offered six years of funding and I wanted that level of security to follow my own path of research.

For me, the fellowship is about so much more than just the funding. From the very beginning CRUK takes great care of you. The amazing community of scientists, collaborators, and support it offers seems unmatched to me.

The fellowship: allows you the freedom to innovate, explore your research and take it in new directions. I believe the best scientific results come from having that freedom.

I have now been awarded a Senior Cancer Research Fellowship to pursue my work in lung cancer. These fellowships are different to funding just for a specific piece of research or an individual. They allow you to build a team that all start at the same time, hiring postdocs and technicians, and building that team over the long-term, giving continuity to the whole research group.

None of this would have been possible without that first CRUK fellowship. It allowed me to settle and establish myself, with the six years of absolute support and freedom that produced real results. I’ve become very attached to CRUK now. They have given me a level of support and funding that means I am achieving everything I ever wanted to do.
WINNERS

Our Future Leaders in Cancer Research Prize recognises those with great potential at the early stages of their research careers. Winners must have produced research of international importance within 10 years of receiving their doctorate. In 2016 the quality of nominations was incredibly high, and so the panel took the decision to award the maximum three prizes for this category.

Dr Georgios Lyratzopoulos, a CRUK Clinician Scientist Fellow working at University College London, has produced world-class outputs in key areas of population health research. His research has provided large-scale evidence for the influence of psychosocial factors in early diagnosis, highlighting the importance of ongoing community campaigns about cancer symptoms. His work has allowed a better appreciation for diagnostic timeliness in cancer patients presenting to their GPs with symptoms, and his discoveries have been highly influential, providing a roadmap to guide future early diagnosis strategies and investment.

Dr Florian Markowetz, a senior group leader at our CRUK Cambridge Institute, has, over the last seven years of his career, been on a quest to integrate genomics and imaging. His research is giving us unprecedented insights into the evolution of the cancer genome and his interaction with the tumour microenvironment. Florian has collaborated closely with clinicians to create novel, quantitative assessments of histopathological images, whilst jointly analysing genomic aberrations in tumours. He has pioneered approaches to link genetic heterogeneity of tumours to clinical outcomes and has demonstrated how rigorous analysis of evolutionary patterns can predict progression-free survival in ovarian cancer. Florian is a true champion for research reproducibility and data sharing. He is leading the way by making the software developed in the lab freely available as a research tool for others – many having been downloaded thousands of times.

Dr Andrea Sottolina, a Group Leader at The Institute of Cancer Research, has a passion for applying mathematical and computational methods to solve biological problems. He has pioneered the development of novel models based on understanding cancer evolution from a solid mathematical perspective, and his models have the potential to forecast the future course of disease in individual patients. His fresh perspective has revolutionised our understanding of carcinogenesis, revealing new opportunities for early intervention.

We were extremely saddened by the passing of Jane Wardle in 2015, a pioneer in the fields of prevention and early diagnosis. In recognition of Jane’s outstanding research career and lifelong devotion to the field, we launched the Jane Wardle Prevention and Early Diagnosis Prize. This prize recognises a researcher at any stage of their career who has produced world-leading research in the fields of prevention and early diagnosis.

We were delighted to award the first prize to Dr Jo Walker, a CRUK Career Development Fellow working in the fields of epidemiology and public health at University College London. Jo trained and worked with Jane between 1998 and 2015, and she has mentored Jo’s commitment to training junior colleagues, and has a reputation for being approachable and generous with her time. Jo has made substantial advances in understanding of women’s attitudes to cervical screening and HPV vaccination – identifying the psychological factors that influence women who receive a positive HPV result through screening. Jo works to ensure that her findings lead to a real impact on cervical cancer prevention and early diagnosis in the UK and beyond. In particular, Jo’s research has directly influenced the Cervical Screening Programme in England.

Our Pontecorvo prize is awarded to CRUK-funded students who have produced outstanding PhD theses and made the greatest contribution to scientific knowledge in their field. In 2016 the prize was awarded to Dr Nicholas McGranahan, an outstanding young scientist at University College London and the Francis Crick Institute. Nicholas is now a postdoc at the University of Cambridge Cancer Research Centre and the Francis Crick Institute. Nicholas is a true champion for research reproducibility and data sharing. He is leading the way by making the software developed in his lab freely available as a research tool for others – many having been downloaded thousands of times.

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We were delighted to award the first prize to Dr Jo Walker, a CRUK Career Development Fellow working in the fields of epidemiology and public health at University College London. Jo trained and worked with Jane between 1998 and 2015, and she has mentored Jo’s commitment to training junior colleagues, and has a reputation for being approachable and generous with her time. Jo has made substantial advances in understanding of women’s attitudes to cervical screening and HPV vaccination – identifying the psychological factors that influence women who receive a positive HPV result through screening. Jo works to ensure that her findings lead to a real impact on cervical cancer prevention and early diagnosis in the UK and beyond. In particular, Jo’s research has directly influenced the Cervical Screening Programme in England.

Our Pontecorvo prize is awarded to CRUK-funded students who have produced outstanding PhD theses and made the greatest contribution to scientific knowledge in their field. In 2016 the prize was awarded to Dr Nicholas McGranahan, an outstanding young scientist at University College London and the Francis Crick Institute. Nicholas is now a postdoc at the University of Cambridge Cancer Research Centre and the Francis Crick Institute. Nicholas is a true champion for research reproducibility and data sharing. He is leading the way by making the software developed in his lab freely available as a research tool for others – many having been downloaded thousands of times.

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A LIFELONG PASSION

Stan’s interest in oncology was sparked while training as a doctor at Charing Cross Hospital in the 1970s, working with Ken Bagshawe who he describes as ‘one of the godfathers of medical oncology’. He witnessed the astonishing curability of the advanced cancer choriocarcinoma in young women and feels privileged to have been there at such an exciting time when many of the key drugs, such as platinum, were being used for the first time. He says, “There were young men with testicular cancer, which was usually fatal, and all of a sudden we were curing them too.”

In 1985 he moved to the University of Glasgow, where he set up a new state-of-the-art early stage clinical trials unit. Embedding his specialist interest in ovarian cancers, he founded the Scottish Gynaecological Cancer Trials Group, with some key results highlighting another of his career themes – tackling the challenge of drug resistance. Stan explains, “Before it became fashionable, we were collecting blood samples to understand why some people do better than others. That is now widely appreciated – and almost all trials will now have some sampling of blood or tumours to understand why subgroups do better or worse.”

KEY INGREDIENTS FOR SUCCESS

In Scotland, Stan was one of the first clinical cancer researchers to demonstrate the importance in translational research of the link between the laboratory and the clinic. He believes that to succeed you need a critical mass of people, hospital support, and support from an academic institute. He was one of the really high-quality cancer research that will make a difference to patients you have to have top class lab bench scientists working alongside doctors,” and he cites examples of Paul Workman and Allan Balmain from his time in Glasgow. He also emphasises, “It really does matter that scientists work with doctors who closely interact with lab scientists, and that it is a whole community of UK medical oncologists in cities all across the UK.”

In 2000 he moved to The Institute of Cancer Research in London, where he established the Drug Development Unit – now one of the largest and most successful in the world. One of his group’s most notable achievements was their pioneering work to develop the new PARP inhibitor, olaparib, which they demonstrated as an effective treatment for women with BRCA mutation-associated ovarian cancers. Stan says, “Once every 10 years or so something comes along that really changes treatment for a subgroup of cancer patients. Within a few months of taking it into the clinic, it was clear that it was making a difference – you could see the cancer shrinking.” The drug was approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in 2014, with recent results suggesting that doubling the number of patients may benefit than originally thought. Led by its eventual successor as Head of the Drug Development Unit, Johann de Bono, his team was also the first to show the potential of albralixine for prostate cancer patients and it is now sought after approval.

HOPE FOR THE FUTURE

Stan officially retired from his role at the ICR in 2014, but he’s not stopping yet. He says, “I’m now involved in health services research. We can make a difference by changing pathways and finding ways to diagnose cancer earlier.” He also remains an active advisor to many organisations.

Stan’s many outstanding contributions to the care and treatment of cancer patients and to the conduct of cancer research in the UK and internationally makes him an worthy winner of our Lifetime Achievement Prize. Describing how he felt when he heard he had won, he says, “I was flattered, but a little anxious as I didn’t feel I deserved it. I know people who have won this Award before – they are genuine terms of science, people who have made great contributions.”

Reflecting back over his career, Stan says: “If I had my time again, there is nothing else I’d rather have done.”

Stan Kaye
At CRUK we run more than 40 funding schemes in a wide range of different disciplines, each with a specific purpose and remit and, as a result, requiring different application processes – from those that ask for an anonymous outline, to those that require a preliminary interview with an expert review panel. But although the application process might vary, all our schemes have one thing in common – they are designed to ensure we fund the highest quality, internationally competitive science, judged through a fair, robust and transparent process. This is no easy task, given the diversity and breadth of scientific applications we receive. And we couldn’t achieve this without the expertise and commitment of our research community, who sit on our panels and committees and participate in our independent peer-review. Here are the perspectives of three people with a different behind-the-scenes view of our funding process.

**DOORS**

**AN INSIGHT INTO OUR FUNDING COMMITTEES**

**THE APPLICANT**

Postdoctoral fellow Dr Alice Forster successfully applied for a Cancer Prevention Fellowship in 2014.

“This was the first grant I had applied for so I had to learn a lot about the process. I started thinking about my application about six months before the submission deadline, and had a supportive group of collaborators who reviewed early drafts. As an early career researcher it can be intimidating sharing your ideas with senior staff, but their input was so important to shaping the application. I felt that the more I could address the comments of internal reviewers, the more I would be prepared to deal with peer reviewers’ comments.

After submitting my application, it was sent for peer review. The next stage was my interview with an expert review panel, made up of four senior cancer prevention scientists alongside three CRUK staff observers. My interview was a relatively pleasant experience. The panel were friendly, and interested in my research. And thanks to having two mock interviews in advance, I felt prepared and able to respond to their questions.

The most helpful part of the process was having a single point of contact at CRUK. I felt comfortable asking any questions – they were very supportive, and I got the impression that they wanted to facilitate funding researchers. I would encourage anyone applying to get in touch with the relevant CRUK contact to discuss their proposed project with them.

Since being awarded the Fellowship, I’ve been involved in cancer prevention conferences, and even spent some time seconded to the CRUK Policy Research Centre to learn about how research is translated into policy.

**THE SCIENTIFIC COMMITTEE MEMBER**

Medical oncologist Professor Ruth Plummer sits on CRUK’s Science Committee and Clinical Research Committee and is Chair of CRUK’s New Agents Committee (NAC), which selects new anti-cancer treatments for early clinical trials.

“It’s a huge honour to be asked to chair a CRUK committee, and it’s a fascinating role. My day job means I see patients who don’t have any treatment options and are prepared to take an experimental agent – and these are the patients we recruit to the Phase I studies funded through NAC. It’s a good grounding for me, seeing novel agents coming through and knowing that, by also sitting on Science Committee, I’ve got an idea of the science that’s ongoing in the background and some of the new developments that might come through.

NAC is a good-humoured committee, and as Chair I try and make sure that people who come in to present their trials – ideas they’ve worked incredibly hard on – feel comfortable, even if there are probing questions.

We’re very involved with the Centre for Drug Development (CDD) staff. This is the team that will ultimately take the projects forward, as many of the studies are run through the CDD, and there’s a world of experience and advice available there. Often the proposals that don’t do well at the committee are those where the applicants haven’t talked to CDD first.

There are often situations where you think a proposal is good but there’s a critical part missing. With NAC we have the option of giving a preliminary score and providing feedback to support applicants submitting a revised application. Or if a project’s really exciting, we may be able to fund an initial stage, and review progress.

**THE PATIENT REPRESENTATIVE**

Mat Baker is a member of CRUK’s Prevention Expert Review Panel. After many active years at the consumer-research interface, following his wife’s death from cancer, he became interested in helping to develop a research portfolio that engages with the challenges of cancer prevention and health inequalities.

Most of the research proposals that come before the panel are exciting in one way or another, and I am continually impressed by the weight and quality of thought that is being applied to reducing cancer risk at a population level.

I have a background in social sciences, which means I’m aware of some of the methodological challenges that a successful proposal must overcome, but I’m careful not to get preoccupied with methodological detail. The other panelists are all world-class experts in this area. My role is to establish the public and community benefit that would flow from a proposed study, and to gauge whether a study is placing realistic expectations on its participants.

Studies are often flawed if there has been little or no consultation with representatives of the relevant population. I see public involvement of this nature as being necessary for a well-grounded and viable study.

The panel discussions are particularly stimulating – I’m always impressed by the expertise, care and thoroughness with which applications are considered and the thought that goes into the provision of feedback to applicants. Most of all, I appreciate the opportunity to assist in the development of an important research portfolio, and to contribute points that may be of concern to patients and other lay people. The patient voice, I believe, is invaluable.
Evaluating the broader societal impact of research is increasingly important for research funders. But what is the best way to do this? And how should we work with the research community to ensure we know our research is bringing the greatest possible impact to cancer patients?

**A BRIEF HISTORY OF RESEARCH IMPACT ASSESSMENT**

Impact assessment involves plotting a path from input (right through to patient impact (see diagram)). The concept is not new, but is increasingly important for funders. There is a need for society to hold research funders and organisations undertaking research to account,” says Professor Jonathan Grant, Assistant Principal for Strategic Initiatives and Public Policy at King's College London. “We have a duty to make research effective if we are using taxpayers’ and donors’ money.”

Research impact and its assessment has moved up the science policy agenda, Jonathan says, and now plays a strong role in the UK’s Research Excellence Framework (REF), which determines institutional level impact case studies to better showcase interdisciplinary research.

**LAYING THE FOUNDATIONS**

In 2014, we joined Researchfish®, an online platform that enables us to capture research outputs and outcomes directly from researchers and link them with inputs. Andrew describes Researchfish® as a tool that helps collect a “wealth of information that allows us to review our funds. Aware of the risk of creating more admin for researchers, we worked closely with many funders, including Research Councils UK, to agree a shared set of questions for the platform. “We’ve still learning what works,” Andrew says. “But lessons from REF and Researchfish® have evolved our thinking on impact assessment.”

As Dr George Santangelo, Director of the Office of Portfolio Analysis at the US National Institutes of Health (NIH) points out, impact assessment is “evolved our thinking on impact assessment.” In 2015 in Health Research Policy and Systems (doi:10.1186/s12961-015-0201-1), and each has its own benefits and downsides. And understanding what to measure is critical. This is where working with the research community and learning from others is paramount. As Rachel notes, there is still a lot of work needed to develop the right metrics, but she points to the work being done by experts in the field that will help frame CRUK’s thinking.

The NIH’s George Santangelo is one such expert. He is of the mind that traditional impact gauges – used mainly because they are easy to measure, such as publications, citations and journal impact factors – are flawed metrics, and he believes a more effective metric is needed. George and his team have developed the Relative Citation Ratio, which looks at the citations of individual papers and the rise those are accrued, adjusted and measured for different research disciplines, as a proxy of influence rather than impact. He is pleased with the buy-in from the community, but “no one metric will capture impact,” he notes. Instead, these need to be a diversity of metrics – which could include measuring translation into treatment, media mentions, patents, data sharing, reproducibility and quality based on human judgement – and these need to be developed collaboratively with the research community.

**FINDING THE RIGHT MEASURES**

But figuring out what to do, and what not to do, is complicated. For starters, there are 16 different frameworks and models that already exist for assessing impact, according to a review published in 2015 in Health Research Policy and Systems (doi:10.1186/s12961-015-0201-1), and each has its own benefits and downsides. And understanding what to measure is critical. This is where working with the research community and learning from others is paramount. As Rachel notes, there is still a lot of work needed to develop the right metrics, but she points to the work being done by experts in the field that will help frame CRUK’s thinking.

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**STRIKING A BALANCE**

Hundreds of scientists and research organisations also hold this view, critiquing the balance on the journal impact factor and signing the Declaration on Research Assessment (DORA). As a signatory of this Declaration, CRUK committed to accurately measuring output and improving the ways research is evaluated. As Andrew explains, “CRUK doesn’t want to focus too much on publications. “We want to take a wide-ranging approach, incorporating lots of data sources and a whole host of existing information, to develop a broad suite of metrics that work for CRUK at each stage of the impact pathway.”

Furthermore, Andrew and Rachel both confirm that expert review will stay as part of the suite because it remains key to ensuring that we continue to fund world-class research.

We want to make sure our reporting is as simple and efficient as possible while still achieving high-quality data necessary for analysis. Sharing data between systems, universities and funders is one way to enable this. Andrew believes Researchfish® is aiming to improve interoperability between systems, with work so far focusing on publication records between institutions and funders – a recent pilot study showed significantly reduced reporting times for researchers, with this increased sharing of data. Researchers can also share information between their Researchfish® account and their ORCID® profile.

Keeping on track

Measuring impact – and doing it well – is a necessity for CRUK. “To be able to understand where we’ve had impact, and where we could help to drive impact if we applied funding, has been incredibly important for us,” Andrew says. We will continue to fund high-quality research, and building on learnings and collaborations today, we will establish an appropriate suite of metrics for CRUK. Our supporters increasingly expect to understand how their money is helping to solve the cancer problem as part of their reason to donate; ultimately, our aim is to use our supporters’ money in the most effective and efficient way, helping the researchers we fund generate the greatest impact for cancer patients.

Impact assessment pathway from input to patient impact. Adapted from CSIRO (Commonwealth Scientific and Industrial Research Organisation).
WHAT’S NEW AND EXCITING THIS YEAR?
In terms of science, immunology and immunotherapy continue to produce very exciting results, but the other thing I’m really interested in is the microbiome. It is yet another layer of complexity that we’re just beginning to understand: how the microorganisms that we live with can change the body’s internal environment to help or hinder the growth of cancer, and how we might be able to manipulate this through alterations in diet. Our knowledge is still at a very early stage, but it is clearly an area that we need to explore, now that the tools for doing so are becoming readily available. Read more about the microbiome and cancer in our hot topic article on page 46.

In our own research portfolio, I’m keen to see how the PRECISION-Panc programme develops: there’s a lot of expectation riding on it for patients with pancreatic cancer, an area where we badly need to speed up progress. Read more about this programme in our article on tackling pancreatic cancer and brain tumours on page 16. I’m looking forward to seeing how we can maximise the value of this great project for cancer research in the coming years. We must ensure that we continue to attract the brightest minds to the UK, now more than ever, and the Crick is just the kind of magnet we need for this.

YOU’VE PREVIOUSLY MENTIONED THE CHALLENGES OF CLINICAL ACADEMIC CAREERS – WHAT DEVELOPMENTS ARE YOU SEEING IN THIS AREA?
I am encouraged by the progress we’re making in supporting clinical academics; despite many and varied challenges. We funded a record number of Clinician Scientist Fellows in the last year – they are such an impressive group of people, brilliant minds, and so motivated to make a difference to patients at the same time as pursuing the best science. I hope we can keep up the pace and really put the UK at the forefront with the work that our clinical academics are doing at the interface of science and medicine. This is so important for patients and the good of the healthcare system. We know that the NHS is under more pressure than ever before, but this is just the moment when we should invest in the next generation to lead the cancer treatment workforce of the future.

WHAT DO YOU THINK THE IMPACT OF THE CRICK WILL BE?
The Crick is a world-class institute that’s going to be a great asset, not just to discovery science but to many fields of medicine, both in London and across the UK. I am looking forward to seeing how we can maximise the value of this great project for cancer research in the coming years. We must ensure that we continue to attract the brightest minds to the UK, now more than ever, and the Crick is just the kind of magnet we need for this.

THE CRICK IS JUST THE KIND OF MAGNET WE NEED TO ATTRACT THE BRIGHTEST MINDS
Peter Johnson

YOU’VE BEEN IN THIS CRUK ROLE FOR A YEAR NOW, COULD YOU EXPLAIN HOW YOU THING OF YOUR ROLE?
My job is not to drive research in a particular direction, but rather to try to ensure the scientists doing the most innovative and impactful research are supported, enabling them to tackle big ideas and ambitious projects. Whilst such research spans the whole spectrum from bench to bedside, a large part of our commitment at CRUK, and a personal passion, is to continue to fund the best discovery science and blue skies research, to make sure we have a strong base on which to build our translational ambitions.

WHAT DO YOU THINK THE IMPACT OF THE CRUK ROLE FOR A YEAR NOW, COULD YOU EXPLAIN HOW YOU THINK OF YOUR ROLE?

In my travels round the country meeting our funded researchers and clinicians, I’ve been pleased to discover that, on the whole, they feel we’re doing a pretty good job. We’ve built a community where people feel they’re listened to, if they have concerns or suggestions, or simply need a little flexibility in the system, and where they feel confident that our scientific objectives are shaped after consultation with them. Scientifically, there’s enthusiasm for our Centres and Institutes, and for the way in which we’re networking them to leverage our resources, both human and technical.

IT’S IMPORTANT THAT CRUK REMAINS A CONVENOR OF THE BEST RESEARCH
Karen Vousden

In cancer research, we’re seeing more and more opportunities for really meaningful international collaboration, and I’m very excited by the possibilities we’ve uncovered for funding schemes of people worldwide. I believe CRUK has the vision, flexibility of approach and resources to make a real difference in an area where grant schemes are difficult to find. In order to get to grips with the big, complicated problems in cancer we’ve begun funding researchers worldwide, through initiatives such as our Grand Challenge, the Stand Up To Cancer/CRUK/Lustgarten Foundation Pancreatic Cancer Dream Team and our Catalyst Awards. We’re also working with international partners, tackling the problem of early detection with the Knight Cancer Institute in Oregon, and working closely with the Dutch Cancer Society (NWO) to jointly fund one of our Grand Challenge awards and collaborate across other activities.

In the years ahead, we will deepen our existing partnerships and are committed to exploring more opportunities for joint initiatives, both nationally and internationally. For example, one area of priority for cancer research is machine learning, and we are exploring interactions with the Farr and Tuning Institutes in London to develop capacity in this area.

WHAT DO YOU HOPE THE FUTURE HOLDS?
I am confident that CRUK will continue to support the best work, strengthening its capabilities in emerging areas such as inflammation, metabolism and the microbiome, and taking smart risks to fund potentially transformative ideas. It will be my great privilege and responsibility as Chief Scientist to try and make sure that this happens.