Catching cancer earlier—a new frontier for early detection research

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Credit: Cancer Research UK

In our 2014 Research Strategy we included an intention to facilitate a major shift in early detection and diagnosis research. We made an ambitious commitment to invigorate this field, stimulating research interest, building capacity, forging new partnerships, and actively supporting a community for early detection research.

2017 sees a further increase in our investment, with significant new

funds being made available by CRUK specifically for early detection science. What are the developments so far in this area, and what promise do they hold for the future?

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 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, yet at stage 4 this is this is around 8%. If we can 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 over-detection, 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 'omics' and analytic platforms to identify and validate biomarkers of early disease. We need improved systems biology approaches to bring data into biological context. We need novel technology, including sensors, biochips 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 oesophageal cancer is a flagship example of early detection research. Her team developed a tiny sponge on a string, the 'Cytosponge', which is swallowed 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 oesophageal 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 oesophageal 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."

Recently setting up his new lab, Dr Daniel Munoz-Espin joined the department last September, having moved from the Spanish National Cancer Research Centre in Madrid. His work is another example of the multidisciplinary nature of the field:

"My research focuses on developing nanotechnologies able 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 can lead to 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 also in tumour models, showing that we can use nanoparticles to both detect and eliminate senescent cells. Our innovative

treatment results in therapeutic activity, including reduction of tumour size. Now the next steps are to take this technology to mouse models of lung cancer and to human tissues. We will first be checking for a correlation between levels of accumulated senescent cells and stage of pre-malignancy in human lung cancer."

If this is established, it is hoped that, in the long term, this research could lead to patients with 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 so stopping lung cancer before it even develops.

Liquid biopsies

At the CRUK Manchester Institute, Professor Caroline Dive is also working on lung cancer, and has become internationally renowned for her work on 'liquid biopsies' – detecting cells or particles in the bloodstream that could act as reliable signals for cancer. As Caroline says, "Up 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. The big question is how early on CTCs are sent out, and the hope is that they could be a very useful red flag for early detection."

In an exciting new venture, Caroline is joining forces with Dr Phil Crosbie, Consultant in Respiratory Medicine at the University Hospital of South Manchester (UHSM). Phil has been part of the team that conducted the first ever UK-pilot to bring mobile computed tomography (CT) scanners to the public, allowing smokers and former smokers to receive free lung checks in shopping centre car parks. Funded by Macmillan Cancer Support, and led by clinician Dr Phil Barber at UHSM, the Manchester Lung Health Check pilot showed a dramatic

benefit for early diagnosis: 80% of lung cancers picked up through mobile screening were at the potentially curable stage 1 or 2, compared with less than 20% of normal lung cancer diagnoses.

The next stage of the pilot aims to assess 1,000 people in summer 2017, and Caroline's collaboration will now add another element to the study. Running in parallel to the CT scans, her team will take blood samples, which will be searched for CTCs and other particles such as nucleic acids and microRNA. "If CTCs are present as an early sign of cancer, they are going to be extremely rare, so we'll use high definition single cell analysis to ensure we don't lose any. We'll also sequence what we find, which enables us to distinguish cancers."

If the blood tests show positive markers, they could provide a powerful, non-invasive tool for early detection. Caroline is hopeful this area holds huge promise, "I think there are times in your career when you take stock and think where can my research make the biggest impact? This is a big turning point for me now, shifting to really focus on early detection, with the aim to develop a minimally invasive test for early cancer detection."

The idea of a simple test that could reliably pick up signs of cancer before it takes hold is a clear goal of early detection research.

Taking this further, the ultimate aim for early detection would be to identify biomarkers that warn a cancer is first starting to develop, catching it at a pre-cursor stage.

One avenue of our research that may take us a step closer is using the huge biobank originally built up for the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). This was a CRUK funded study that assessed screening tests for ovarian cancer, and involved a huge cohort of 200,000 healthy volunteers, collecting longitudinal blood

samples from a quarter of them, and following up which volunteers went on to develop cancer. To have annual blood samples leading up to the clinical presentation of cancer is an incredibly valuable resource, and these data are now being combed for biomarkers. The priority cancers in this study are colorectal, lung, oesophageal and pancreatic. CRUK, Cancer Research Technology, and the biotech company Abcodia joined forces to form the Early Diagnosis Consortium to achieve this. They enlisted the help of three leading 'omics' companies, with specific expertise in proteomics, microRNA, and tumour auto-antibodies. The aim is to identify biomarkers that have consistently altered expression prior to cancer diagnosis. The results from years of this work are expected in 2017, with the best biomarkers then being taken forward.

Global collaboration

The ambitious 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 to join forces with: It has been a pioneer of precision cancer therapy and thanks to a philanthropic investment of $1 billion in 2015, is now establishing a new, large-scale early detection programme. Dr Sadik Esener, a nanoengineer by background, has recently taken the helm as the new Director of the Center for Early Detection Research. He's enthusiastic about the partnership with CRUK. "Early detection research holds huge promise, but it is still at a very embryonic stage, and it is such a big and complex problem that collaborations between institutions are going to be of crucial importance."

With the aim of building a new community for the field and invigorating ideas, the partnership includes an annual joint conference, the second of which will take place in Cambridge in September 2017. This will draw researchers together and aid the development of a global, multi-disciplinary network of early detection experts. To support and encourage collaborative research, we are developing schemes, in partnership with OHSU, to fund collaborative research between UK researchers and US-based researchers. Sadik agrees that one major area ripe for collaboration will be the hunt for biomarkers, but he doesn't underestimate the challenge.

As Sadik identifies, "One of the greatest challenges for early detection research is not only finding early warning signs that cancer is starting to develop, but identifying which of those alarms need following up with more tests and treatment – and which we can safely ignore."

This is the flipside of the early detection coin: the risk of causing overdiagnosis and unnecessary worry and intervention.

The risk of overdiagnosis

To really make progress in early detection, we need to understand how to tell apart early benign changes from lethal ones. This question is so crucial that we made it one of our Grand Challenges for 2016, with a multi-million pound award available to advance research that would "distinguish between lethal cancers that need treating and non-lethal cancers that don't". A multinational team, led by Dr Jelle Wesseling of the Netherlands Cancer Institute in Amsterdam, were successful in securing this award, co-funded with the Dutch Cancer Society, and will address this challenge in the context of breast cancer.

Breast lesions, known as ductal carcinoma in situ (DCIS), can sometimes develop into cancer, but a large proportion of DCIS never develop into

the disease, and we currently can't tell the difference. The Grand Challenge team aim to find biomarkers that identify which DCIS patients are at high risk of developing cancer, and which are not. By combining tissue samples and clinical data from thousands of patients, the team hopes to come up with the answer that will help women with DCIS avoid the burden of unnecessary treatment. This award is another sign of our commitment to early detection research, and the progress that we hope will be made in the coming years.

A new frontier

Whilst the journey into early detection research is just at its beginnings, it holds incredible promise. From devising nanoparticles that can flag up and kill pre-cancerous cells, to hunting through millions of blood samples for biomarkers, to harnessing the physics of light for better imaging, early detection is a diverse, multi-disciplinary field, with ground breaking potential.

It is an area with significant 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 remarks: "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."

Provided by Cancer Research UK