

# CANCER FUTURES

Issue 2

A TESTBED CITY  
**DRIVING CHANGES  
IN EARLY DETECTION**

Cancer

GLOBAL CHALLENGES  
MANCHESTER SOLUTIONS

DRUG DISCOVERY  
AND NANO ONCOLOGY  
**PIONEERING INNOVATION  
THROUGH TEAM SCIENCE**

# BREAK THROUGH

The University of Manchester's research beacons are answering some of the biggest questions facing the planet.

Research beacons

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**GLOBAL CHALLENGES**  
**MANCHESTER SOLUTIONS**

# CONTENTS

04 Introduction – Professor Graham Lord

06 Introducing Team Science – Professor Rob Bristow

08 Multidisciplinary Manchester

## **12 Prevention and Early Detection**

14 A Testbed City – Professor Ian Bruce

18 Driving Changes in Cervical Screening – Professor Emma Crosbie

22 Risk Stratification – Professor Gareth Evans

26 Transforming Cancer Survival Through Early Detection

## **30 Immunology and Team Science**

32 The Lydia Becker Institute – Professor Tracy Hussell

36 An Immunology Revolution – Dr Santiago Zelenay

## **40 Nano Oncology**

42 A Marriage of Giants – Professor Sarah Cartmell

46 Targeted Delivery – Professor Kaye Williams

50 Graphene and Cancer – Professor Kostas Kostarelos

## **54 Drug Discovery and Team Science**

56 Excellence in Basic Science – Professor Caroline Springer

60 Back to Basics – Professor Stephen Taylor



Cancer continues to be one of the world's biggest killers and as our understanding of the disease grows, so too do the multiple of ways to treat, detect and cure it. Technologies, treatments and ways of working are advancing and our researchers and clinicians in Greater Manchester are at the forefront of many of the discoveries that are shaping approaches to the disease.

Greater Manchester is one of only two biomedical clusters in the UK and The University of Manchester is the UK's largest clinical academic campus. There is a growing need to address multi-morbidity in the 2.8 million GM population; the Government's unique devolution of the £6 billion health and social care budget is unlocking fresh thinking and breaking down silos between public services; our cancer research is supporting the NHS Long Term Plan, the Life Sciences Sector Deal and local industrial strategy; we have a key partner in Health Innovation Manchester that brings together our research, education and clinical excellence with the NHS Trusts and social care providers; and the National Institute for Health Research has invested millions in Greater Manchester in the largest Biomedical Research Centre outside the South East, and the new Applied Research Collaboration, which are central catalysts in what we refer to as the Greater Manchester health eco-system.

Against this background, this edition of Cancer Futures shares a snapshot of our research discoveries and the people behind them that reflect the breadth and cutting-edge nature of the research taking place.

The stories featured here share one commonality; they all require a multidisciplinary approach and are exemplars of a cancer team science focus which we embody in our collective desire to find solutions and push through the next set of challenges.

I strongly believe that partnership working gives us one of the most exciting opportunities to improve population health anywhere in the developed world and work is continuing apace on a £150m redevelopment of our Paterson cancer research building, funded in part by UK Research Partnership Investment. As well as housing the Cancer Research UK Manchester Institute, the new building will facilitate a ground-breaking approach to the way research partnerships work together by embedding the facility within a cancer hospital.

# INTROD

Having patients, researchers and scientists in one place will help us drive a new model of integration of basic discovery, translational and clinical research, drawing on our strengths in biomarker development, early-phase clinical trials with novel agents and real-world clinical informatics – with a strong commercialisation drive towards delivering new clinical pathways to benefit patients. The project is being led by The Christie NHS Foundation Trust on behalf of The Manchester Cancer Research Centre (MCRC) which is a partnership between the University of Manchester, CRUK and The Christie. There is nothing comparable in the UK to the Paterson project that will house several hundred researchers and clinicians when it is complete.

**Professor Graham Lord is Vice-President and Dean of the Faculty of Biology, Medicine and Health, The University of Manchester.**





# UCTION



# INTRODUCING

Team Science is a key contributing factor to the increasing academic and clinical successes that the Manchester research community is enjoying. Here we look at what is 'Team Science' and why it's so important to ensuring research success.

Essentially, Team Science is research that involves significant work by more than one contributor within any discipline of science. This could be either the same discipline such as medicine, or it could involve two scientists with different backgrounds, for example immunology and advanced materials, working jointly together on a project.

One of the reasons for the success of the Team Science projects are the different skills and experiences that are brought together and today, collaborative research is rapidly becoming the norm. Evidence for the rise in prevalence of team science can be found in various sources. Firstly, the average number of authors on scientific papers has steadily risen from 1-2 in 1960 to 5-6 in 2015. Secondly, there are now more authors claiming first authorship on any papers produced, indicating more impactful contributions from potential collaborations.



A successful Team Science approach is dependent on multiple factors. It is about successful collaboration with different teams within an institution, or further afield. It is about identifying the right people with the skills and experiences needed to make a project work, at every step of the project's lifespan. It requires a multidisciplinary and complementary approach to research, and it sees chemists, biologists, physicists, clinicians, nurses and patients all working on the common goal of cancer research.

The co-location or collaborative spaces for the collaborating partners is also key to success as close proximity between researchers has been found to be a key factor affecting a publication's impact, as this allows for better, more productive collaboration between likeminded researchers working towards a common goal.

### Team Science at Manchester

Across the campuses in Manchester, Team Science embodies the One Manchester approach to cancer research. Spearheaded by Professor Robert Bristow, the Director of the Manchester Cancer Research Centre (MCRC), cancer researchers are encouraged to work across multiple disciplines, recruit non-traditional partners and work with clinicians and consult patients to identify new ideas and new approaches to solve problems.

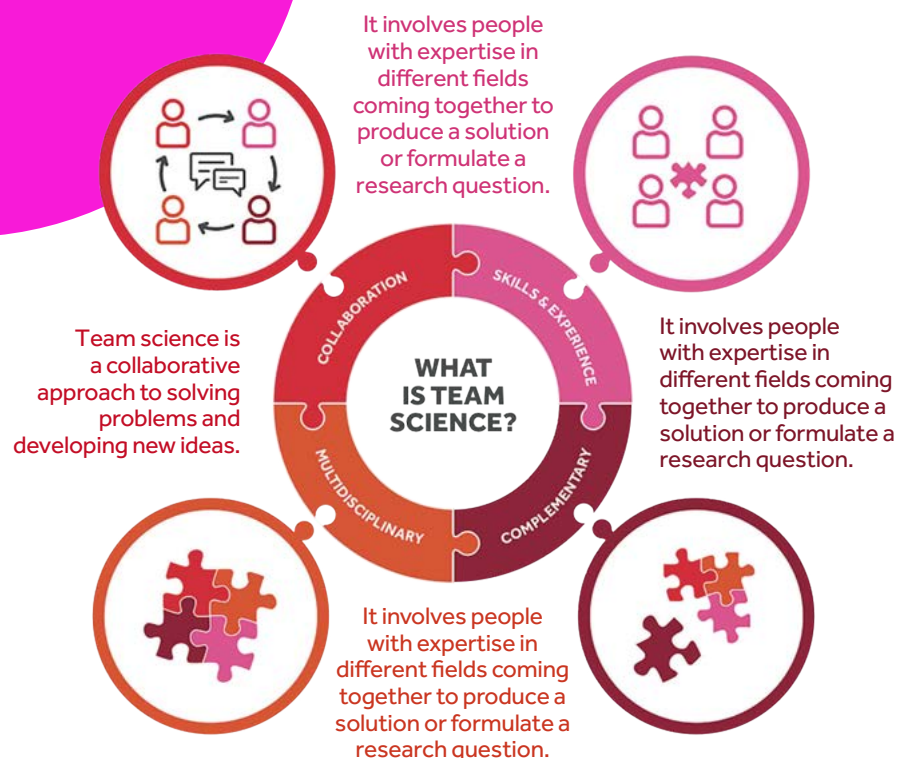
Close collaboration with our partners helps to leverage different skills and experiences from across the team. And it is through adopting a multi-disciplinary complementary knowledge approach that challenges traditional methods of thinking, helps develop new ideas and sees chemists, biologists, physicists, clinicians, nurses and patients all working on the common goal of cancer research.

One of the approaches used by Professor Bristow and colleagues to develop new cancer research teams were regular Town Hall meetings held over the past two years. These meetings have brought together experts in different fields to identify and shape novel research projects in disease specific tumour sites. The only stipulation for the project focus is that the project must be multi-disciplinary, high-risk, highly important and completely unique to the Manchester-based facilities and population test beds found in Manchester.

To date, seven meetings have been held and where projects to tackle breast, prostate, haematological, lung, gynaecological, blood and hepato-pancreato-biliary cancers have been identified. Stressing the importance of Team Science, these meetings call together clinicians, scientists and patients to identify the key challenges in particular disease sites and how Manchester research expertise can best be utilised to be best suited to overcome them.

"Team Science embodies the One Manchester approach to cancer research. Researchers are encouraged to work across multiple disciplines."

## TEAM SCIENCE



### Next steps

A number of the town hall ideas have led to larger programme grants, including one in breast cancer that led to a successful bid for a CRUK Alliance for Early Detection programme grant with UK and USA partners. The research project will focus on "Reaching the Unreached", will unite radiologists, clinicians and psychologists with experts in genetics, imaging and artificial intelligence to build and develop a platform to detect breast cancer in at-risk young women in the Greater Manchester area. Pump-priming team science will no doubt step-change cancer science with increasing grant income into Manchester.



# MULTI-DISCIPLINARY MAN

Under his stewardship, Professor Rob Bristow has been championing a team science approach to all research activity taking place across the Manchester cancer landscape. This approach, which sees teams of experts working across a research question, is yielding exciting results. Here the Director of the MCRC tells us why he sees this approach as transformative to the cancer research environment.

"Multi-disciplinary science is a key aspect of team science and brings the best ideas from different scientific areas, all focused on one specific cancer question. That's exciting because in

our busy day to day approaches to our own research, we don't necessarily have time to think about what are the big questions or developments occurring in other disciplines. These include the best new ideas coming in from engineering, physics or chemistry and creating the opportunity to work together with these experts to bring the best solutions to some of the most complex questions in cancer research. These new ideas positively disrupt out thinking in the cancer realm. It allows us to look at old problems through a new and exciting lens. Its an invitation to other disciplines to say, 'You are one of the new disciplines that we need to be working with closely in order to pull this problem off with pace and scale-come and help solve this question with us'. That's a new way of doing things. The best teams will always be multi-disciplinary because the best ideas will come from that mix of different expertise and accepting that others may have solutions to your problems that you have not yet thought of".



# CHESTER

## Setting the question

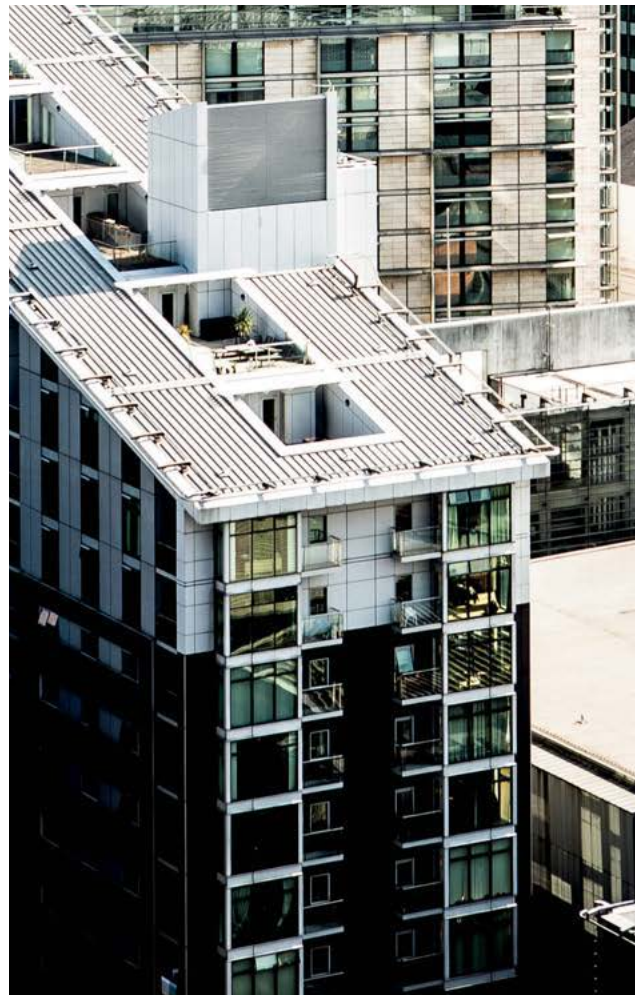
"Ensuring the questions are set appropriately is at the heart of good multi-disciplinary science. When we think about setting up the multi-disciplinary science teams, it's crucial that we identify the clinical need. The clinical need must be spelt out for the tumour type, and what the specific need is to be explicitly understood from the outset to ensure that you properly identify the disciplines that you need to bring in and collaborate with you. That level of granularity is needed to ensure successful collaborations.

## Making it work

"By increasing the focus on a particular problem, say "Why do certain patients get certain inflammatory side effects following radiotherapy whilst others don't?" then that self-selects specific researchers that are interested in the problem from their own unique perspective such as the different physics pertaining to photon versus proton radiotherapy, or experts in germline genetics that might wonder whether a radiotherapy sensitivity gene is involved or a non-cancer expert in immune biology or inflammation who may see their work mirrored in a cancer side-effect By placing the questions that are important to patients out to the science community, this allows a much more granular approach and brings multiple disciplines to bear on specific questions.

## Ambitious projects

"A project which typifies our multi-disciplinary team science approach is our ambition to understand which patients, when undergoing bone marrow transplant, are going to acquire acute graft versus host disease which develops after the transplant. Here, the body starts to see itself as something foreign and creates an inflammation against itself which can affect kidney and liver function and the acquired blood cells after transplant and ultimately, it can lead to a 50% chance of death. If we knew therefore which patients were more likely to develop this, we could start to think about novel treatments to reverse the effects. Using state-of-the-art approaches with CyTOF and SWATH-MS proteomics, our team of clinicians and basic researchers are trying to develop an assay to detect this side effect early and offer new treatments to improve survival after transplant."



## Graphene

"One of the exciting multi-disciplinary projects with engineers are those we're working on with Professor Kostas Kostarelos from the prestigious Graphene Institute. He is a world leader in nano-technologies and is collaborating with our early cancer detection researchers to develop new cancer risk signatures.

"Kostas and his team have created nanoparticles that can trap proteins as they circulate through the body. In patients with the earliest beginnings of cancer, these nanoparticles may detect novel cancer-specific proteins to herald the development of certain types of cancer. The specific proteins detected within the blood might then give us an early signal as to who is most at risk for an aggressive cancer and provide earlier treatment to attain better cure rates.

"This is a much more sensitive technique for picking up circulating proteins than other approaches, so it's literally small nano particles mopping up novel proteins from people who are, or are not, at risk from cancer and comparing those signatures by shaking out the protein mop at the end of the day. We hope these technologies will grow to involve multi-disciplinary scientists within the UK and USA within the next two years.

## Manchester

"Manchester is already an exemplar of team work with the MCRC itself. The MCRC represents the "cancer beacon" and is a research cancer centre bringing together the strengths of our University, The Christie and other Manchester trusts, and CRUK (including the CRUK Manchester Institute and Major Centre). This unique partner collaboration doesn't exist anywhere else in the world and its ethos trickles down into the creation of our unique research projects."

"What's exciting about the "One Manchester" approach is the success in developing new multi-disciplinary science teams with more than £25M new research funds accrued in the last year alone. Providing a research environment for team science is added value to the individual research program. This recent track record of success has led other researchers and patients to think, 'how can I be part of a team?' We've been using our Town Hall meetings to provide the opportunity for people to think about the ideas early on and then to develop them. What's been impressed clearly upon me are the numbers of people wanting to take part in team science."

## Change

"At the beginning of a Town Hall, we state our goal: to step-change the outcomes for patients in Manchester through best research that is activated within the NHS.

We've been given a major challenge with the devolved healthcare system in Manchester. Already a systems healthcare approach exists to bringing together all the Trusts in Manchester to streamline and harmonise our NHS clinical pathways for every cancer type. As researchers, we ask ourselves, 'how can we develop research methods to impact on more than three million people in the aligned clinical care pathways of the Greater Manchester Cancer Plan?'

"When we take this attitude and collaborate with the commissioners in the NHS this then becomes one of the most powerful ways of touching the greater population with our research programmes and technologies."



## Together

"That we have an MCRC sets the stage for powerful partnerships to direct against the increasing incidence and complexity of cancer detection and treatment in our populations. We aim to drive very best science from our CRUK and other science funders across the whole of the University and link this with the very best state of the art treatments at The Christie.

"This provides us an opportunity to conduct research in early detection or personalised treatments at a pace and scale unlike that in any other healthcare system".

"The collaborative and multidisciplinary Town Halls provide a new and exciting way to conduct added-value research. For those who've always done research on their own, it's an opportunity to be involved in bigger projects and projects that move more quickly towards their clinical ambitions. The Town Halls are really designed for impact in this unique way".

**Robert Bristow is University Professor of Cancer Studies in the Division of Cancer Sciences (The University of Manchester), Chief Academic Officer at The Christie and Director, Manchester Cancer Research Centre.**



CANCER  
RESEARCH  
UK

MANCHESTER  
CENTRE

**MCRC**



# WORK WITH US TO CONQUER CANCER

At the Manchester Cancer Research Centre (MCRC) we aim to attract the best cancer researchers at all stages of their career.

With a strong legacy of innovation, and an ambitious vision for the future, we offer an environment where you can make your name in world-leading research and investigation.

## TRAINING OPPORTUNITIES

- We offer a rigorous and highly competitive PhD training programme within an intellectually challenging, innovative and supportive environment
- To join us as a Clinical Research Training Fellow, you will be a post-registration clinician, ideally with a specialist training post
- For non-clinical studentships, a first or an upper second honours degree or the overseas equivalent will be vital

For more information or to discuss current or future vacancies, please contact:

**[MCRCtraining@manchester.ac.uk](mailto:MCRCtraining@manchester.ac.uk)**  
**[www.mcrc.manchester.ac.uk](http://www.mcrc.manchester.ac.uk)**



A partnership founded by



Early diagnosis is key to cancer survival.

When diagnosed in its early stages, the survival rates of cancers are much higher, before it has potentially metastasised or advanced beyond current treatments and therapies.

For some cancers, this effect can be quite profound, for instance in colorectal cancers where the 10-year survival rate decreases from 94% when diagnosed in Stage 1 to just 4% if the disease is diagnosed at Stage 4.

## Prevention

- 4 in 10 UK cancer cases can be prevented through lifestyle changes
- Lifestyle changes such as increasing exercise, reducing alcohol intake or being smoke free help reduce cancer risk
- Being overweight or obese is the second biggest preventable cause of cancer in the UK after smoking, and contributes to around 18,100 cases of cancer every year
- Over 60% of the UK population are classified as overweight
- Manchester researchers were the first to prove a link between weight gain and cancer, identifying that obesity is directly linked to 20 different types of the disease

# PREVENTI

Cancer prevention and earlier detection of cancer are two different strands of research which are aiming to increase survival rates. While early detection focuses on identifying the hallmarks of cancer in an effort to treat cancer sooner, prevention involves identifying causes of cancer. Preventing cancer often revolves around adopting lifestyle changes to avoid the risks associated with smoking, obesity, and alcohol. In fact, it is thought that two in every five cancers diagnosed could be preventable through individual changes.

In our endeavour to identify cancers sooner, Manchester-based researchers are actively investigating the molecules known as biomarkers that indicate the early stages of cancer. These molecular biomarkers can also help to provide a genetic profile of the cancer type, allowing precision treatments and therapies to be selected that are tailored to the patient and cancer type. Basic and translational research is being performed to identify these new biomarkers to detect cancer sooner through the Stoller Biomarker Discovery Centre - the largest biomarker centre in Europe - and the Cancer Research UK Manchester Institute Cancer Biomarker Centre. This research is also being translated into the clinic, with novel clinical trials seeking to identify how this research can be used to benefit patients.

Within Manchester, there is great potential for treating patients earlier and preventing many of the most common cancers. The Greater Manchester area has a larger population of smokers, and fewer who take part in screening programmes than the national average. Our prevention and early detection projects are therefore crucial for the benefit of the public locally and across the world.

## AND EARLY DETECTION



ON

### Early detection

- 10 year relative survival rate for colorectal cancers decreases from 94% at Stage 1, 73% at Stage 2, 50% at Stage 3 and 4 % at Stage 4
- 1 in every 2 people will be diagnosed with cancer during their lifetime but more than 50% are surviving treatment
- Manchester-based 'Lung health check pilot' study detected 1 lung cancer in every 23 patients screened with 80% being at the early stage
- A patient diagnosed with Stage 1 lung cancer has over 70% chance of survival beyond one year. This drops to less than 15% if diagnosed at Stage 4

The National Institute for Health Research (NIHR) is the research arm of the NHS and Europe's largest national clinical research funder. One of its key objectives is to support research across the UK in areas that are internationally leading - research that will deliver tangible benefits and that will have the critical mass both to drive improvements in patient care and develop the next generation of researchers.

# A TESTBED CITY



It's therefore little surprise that the NIHR chose to fund research in Manchester. A combination of proven research excellence, established partnership working via Health Innovation Manchester (HInM) and a devolved healthcare budget means that the city's Biomedical Research Centre (BRC) is well placed to bring together multiple research themes relatively easily - ultimately to develop better healthcare for the 2.9 million citizens of Greater Manchester.

The Manchester BRC, which is hosted by the University and Manchester University NHS Foundation Trust (MFT) in partnership with The Christie, and Salford Royal NHS Foundation Trust, focuses on research for which the city is already well recognised – including three cancer themes, one of which is Prevention and Earlier Detection (PED). Its role is to be a central catalyst in the Greater Manchester health eco-system, with a strategy that focuses on integrating research power and translational excellence, mapping our strongest clinical areas with the best enabling sciences.

As Director of the NIHR Manchester Biomedical Research Centre, Professor Ian Bruce explains why the NIHR chose to invest in Manchester and provides unique insights into the pivotal impact the PED cancer theme is playing across the city region.

### Why cancer?

"When it came to identifying the best clinical research in Manchester, the NIHR looked around and found that cancer is clearly at the forefront. It's got Research Beacon status at the University; Cancer Research UK has a massive presence; and by working in partnership with the University and the local NHS Trusts, there is a real opportunity to reach across the entire Manchester clinical infrastructure to undertake cancer research that will have a positive impact on patients' lives.

"What's more, if you can address cancer risk here in Manchester, not only will the local population benefit, but it's also a fantastic way of selling what you do, or examples of best practise, to the world because you've got a large population to work with.

"We tried to identify areas of cancer research which are relatively underfunded, in comparison to other areas, and prevention and early detection (PED) didn't have a huge prominence so we thought, if we could invest in cancer PED, that would be a real USP for Manchester as we've got huge strengths in that area. Some of the other BRC themes - Respiratory Disease and Dermatology for example - play into the cancer theme as well, because cancer risk is increased in such chronic inflammatory diseases. So there's a lot of cross-theme working."

### Research with impact

Research coming out of the NIHR Manchester Biomedical Research Centre is already making a difference.

Professor Gareth Evans' research into developing multiple genetic markers for breast cancer screening has led to a better understanding of predicting breast cancer risk and knowing when to offer preventative treatments or screening to people who need it. It is also helping to reduce the amount of unnecessary screening and radiation exposure.

Manchester has also developed pioneering work in the area of lung cancer screening. Dr Philip Crosbie's research into the early detection of the disease has seen the screening process being delivered in more convenient and accessible locations, including supermarket car parks. This is an example of how Greater Manchester, with its devolved health system, can lead the way by devising and executing research locally without the need for approvals by national authorities. The project has been so successful that it is now being rolled out by the NHS across the country.

Linking in with this, BRC researchers are also championing smoking cessation. The city's lung cancer screening programme has helped to raise awareness of the health risks associated with smoking, prompting more people to change their habits. And this in itself has generated huge health benefits downstream. If people stop smoking in their middle years, they reduce the risk not only of lung cancer, but also of Chronic Obstructive Pulmonary Disease (COPD), heart disease and rheumatoid arthritis.

## Research programmes within the BRC PED theme

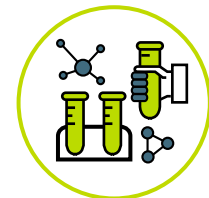
Risk Stratification



Obesity Related Research



Imaging and Molecular Biomarkers



Early Detection



### Benefits of cross-theme research

The fact that BRC researchers - whether they are focusing on Cancer, Musculoskeletal Disease, Dermatology, Respiratory Medicine or Hearing Health - work together in the same location means that they have been able to develop very close working partnerships and share ideas and research outputs across illnesses. Professor Bruce continues:

"The BRC allows researchers to work off each other and say: 'OK, if you're doing that, what are the benefits on our side of the patch?'

"For example, some of the new cancer drugs with checkpoint inhibitors have quite significant adverse effects, sometimes triggering auto-immune or inflammatory diseases. So our immunologists are now beginning to discuss with the cancer team how we can best address this.

"Many women who are treated with tamoxifen and other breast cancer drugs can get lots of joint pain, so we need to work out how they can stay on the drug and remain pain free. I think the fact that researchers sit together and discuss these issues across the BRC gives a different perspective on problems, which in turn allow us to develop new, innovative programmes of work."

### New research funding

Some of the seed funding for the PED cancer theme has supported a lot of the early projects at the BRC, but more recently the focus has turned to leverage additional funding to take forward some of the new, emerging research projects.

"One of the things we want to see at the BRC is not only improved patient outcomes, but also more generally, better health and wealth for the nation as a whole," says Professor Bruce.

"So it's about leveraging additional money to set up new funding platforms. This would involve for example two or three BRC colleagues coming together and approaching the likes of Cancer Research UK with a compelling joint bid."

"The cancer research community in Manchester is extremely forward-thinking, with researchers able to identify the next horizons."

### The Manchester approach

"Manchester has big, big strengths in partnership working and has the advantage of having a single, joined-up research community across numerous sites, including the Christie, The University of Manchester and the MFT facilities.

"This means that when you look at health informatics and data sciences for example, there are people working across Manchester on laboratory data, population data and clinical data; and via the BRC the research can line-up more effectively - so we've got a range of people thinking across the problem.

"I think the cancer research community in Manchester is extremely forward-thinking, with researchers able to identify the next horizons. There's also a great team science approach and cancer research best exemplifies this.

"Manchester research is also embedded in and addresses the needs of the local community - particularly important in a city where there is significant health deprivation and large pockets of underserved populations - so patient and public engagement and involvement in research is absolutely central to the Manchester way of doing things."

### An international reputation

Professor Bruce has little doubt about the city's growing international standing as a leading research centre.

"Personally, I think Manchester is already leading the way in many aspects of clinical research and will continue to grow as one of the leading international cancer research centres - I've no doubt that we're on that global trajectory.

"And of course the NIHR Manchester BRC has a pivotal role to play by acting as a catalyst for new ideas and bringing researchers together from across a range of disciplines to work more collaboratively.

"As Director of the Centre, one of my ambitions is that the Manchester research community continues to grow from strength to strength so that we become a truly world-leading centre for research excellence."

**Ian Bruce is Professor of Rheumatology, The University of Manchester and Director of the NIHR Manchester Biomedical Research Centre.**



## Cancer research at the NIHR Manchester Biomedical Research Centre and NIHR Manchester Clinical Research Facility

Across Greater Manchester the National Institute for Health Research (NIHR) is helping researchers, academics, healthcare professionals, and the public to revolutionise cancer research.

The NIHR Manchester Biomedical Research Centre (BRC) brings together leading researchers from across the NHS (Manchester University NHS Foundation Trust, The Christie NHS Foundation Trust, and Salford Royal NHS Foundation Trust) and The University of Manchester.

Our aim is to drive health improvements and lasting change for all through creative, inclusive and pro-active research that identifies and bridges gaps between new discoveries and individualised care.

We target our research where it will have the biggest impact on improving the lives and addressing health inequalities of our 2.9m population. Our cancer research themes cover Advanced Radiotherapy, Precision Medicine, and Prevention and Early Detection, as well as cross-cutting themes in Biomarkers, and Informatics and Data Sciences.

The NIHR Manchester Clinical Research Facility (CRF) provides dedicated and purpose built clinical research facilities, bringing world-class research and experimental medicines across all types of cancer to our patients.

Benefits of our infrastructure:

- offers a single, joined-up "One Manchester" approach to research and innovation
- connects internationally-recognised cancer clinicians and researchers across multiple disciplines for shared research in co-morbidities, including respiratory, hearing health, dermatology
- links national centres of excellence, including UoM Cancer Research Beacon, Cancer Research UK Manchester Institute, the North West Lung Centre and the Manchester Breast Centre (at Wythenshawe Hospital), and the Manchester Centre for Genomic Medicine (at Saint Mary's Hospital)
- research within leading cancer treatment centres, including the Proton Beam Centre and MR Linac at The Christie

- helps support pioneering cancer screening programmes, including Lung Health Checks
- greater autonomy through a devolved health and care system for Greater Manchester
- supports researchers to design and test early-stage projects, leverage additional funding and develop innovative programmes of work
- utilises cutting-edge innovations and links with leading industry partners, through connections with the Clinical Research Network Greater Manchester and Health Innovation Manchester

**Find out more:**

**[www.manchesterbrc.nihr.ac.uk](http://www.manchesterbrc.nihr.ac.uk)**

**@ManchesterBRC**

**@ManchesterCRF**



Professor Emma Crosbie outlines some of the ground breaking gynaecological cancer research she has undertaken and outlines why she thinks a Prevention and Early Detection (PED) approach is needed in cancer research.

# DRIVING CHANGES IN CERVICAL SCREENING

"As the lead for early detection in the NIHR Manchester Biomedical Research Centre Cancer Prevention and Early Detection theme and Gynaecological Cancer Surgeon, I'm essentially trying to detect gynaecological cancers at their earliest treatable stage, when it's a lot more likely that treatment will be curative.

"One project I've been involved in recently is using urine as an alternative to routine cervical screening for the detection of human papillomavirus (HPV)."

## A game-changer

"We know that cervical cancer is caused by high risk HPV. In the past, we identified pre-cancerous changes in cervical cells by examining them under the microscope via a smear test. However, pioneering work at The University of Manchester by Professor Henry Kitchener found that testing for the virus that causes these cellular changes - HPV - is a much more sensitive way of picking up cervical cancer precursors.

"As a result, HPV testing has now been introduced as an integral part of the screening programme across the UK, and this in turn has given us the opportunity to look at other biofluids to see if we can pick up HPV in less invasive samples than those taken directly from the cervix.

"Our group undertook a research study involving women with abnormal cervical screening test results and retested them for HPV using three different samples - a vaginal swab, a urine test and a routine cervical smear.

"We found that we were able to detect HPV in urine, which of course has huge implications for women. It could mean that instead of having to undergo a speculum test, involving an appointment with a healthcare practitioner, women could simply collect a urine sample in the privacy of their own home.

"At the moment women are not going for cervical screening. In the UK alone, almost 5 million women are overdue cervical screening, with just 71% turning up for their appointments. Providing a urine self-sample is less intrusive and would undoubtedly encourage more women to be screened.

"Our early work looked at whether the HPV detection rate was similar between urine and cervical samples, and whether a urine sample can detect pre-cancerous changes as effectively as samples taken from the cervix. I'm pleased to report that the research found this to be the case. As a result we now hope to trial the urine test in a much larger population, drawn from routine, primary cervical screening populations in the community. We would offer the urine test to women who haven't attended for cervical screening - either when they go to their GP for an unrelated reason or by sending out a urine self-sampling kit to their home.

"There is a lot of interest in urine as an alternative to routine cervical screening, particularly since urine appears to be just as effective as cervical samples for HPV detection."

## New biomarker to detect pre-cancerous cells

"One potential drawback of the urine self-test is that, unlike the conventional smear test, there are no cervical cells collected that can be examined under the microscope to look for pre-cancerous changes. So we're also studying a new process, whereby if the initial HPV urine test is positive, we go on to do a methylation test to see whether or not there's evidence of pre-cancer. This would mean that only those women who have a very high chance of developing cancer would ever need to be referred for further investigation via a colposcopy.

"This is an entirely new approach which hasn't yet been tried and tested, and we've teamed with scientists based at Queen Mary University of London to trial the urine test using the methylation biomarker."

## Why Prevention and Early Detection?

"While most of the funding for cancer research goes into developing new treatments, to my mind the obvious place to make a real difference is to prevent the cancer from happening in the first place or to detect it at such an early stage that it's easy to treat effectively. So for me it's a no-brainer. PED is where we have the greatest opportunity to make a difference and have a positive impact on patients' lives.



### **The Manchester advantage**

"Manchester has an enviable reputation for cervical screening research – in part because it is home to one of only 12 national cervical screening laboratories. Via the legacy of Professor Kitchener, we have the expertise to do the HPV testing here in-house; and we have adopted a 'Team Science' approach by bringing together primary care, clinical trials expertise and laboratory science, specifically virology and cytology researchers, from across the city.

"We're still in the early days, but the overall aim of our research is to change how cervical screening is undertaken to ensure the highest possible number of women are screened. And early detection is what Manchester is really good at. For example, via Health Innovation Manchester (HiM), we are able to work extremely closely with our NHS partners, enabling us to test our ideas in large populations.

"What we've uniquely managed to do is team up biomarker discovery, that fantastic clever science, with testing new innovations in real people to demonstrate that new approaches can work. And that is where I see my role - testing ideas in large populations of women.

"That said, there are undoubtedly many challenges - it's certainly not going to be a case of 'one size fits all' when it comes to cancer PED.

"In the same way that drug treatment trials are targeting a very specific aberration in a cancer signalling pathway, I think it's going to be similar for PED - one biomarker is not going to work for all cancers. We're going to have to find specific biomarkers for particular types of cancer; and for gynaecological cancers, a lot of it is about trying to find new, non-invasive ways of picking up cancer early.

"My main research interest is endometrial (or womb) cancer, the fourth most common cancer affecting women in the UK, yet poorly studied and understood."

"At the moment, women with suspected womb cancer have to undergo a series of sequential, painful, invasive tests. But for every 100 women that get tested, maybe only five of them will actually have cancer - so that's a lot of women exposed to unnecessary and expensive tests.

"My idea is to develop new ways of triaging women into those who genuinely are at high risk of womb cancer, and those who are not, so as to quickly reassure the vast majority of healthy women while concentrating clinical care and resources on those with cancer."

### Lynch syndrome

Almost 3% of womb cancers are linked to an inherited cancer pre-disposition condition called Lynch syndrome, which affects about 1 in 300 people globally.

A similar proportion of bowel cancers are caused by Lynch Syndrome, which has led to guidance from the National Institute for Health and Care Excellence (NICE) that anyone diagnosed with bowel cancer should be tested for the condition. This is because knowing that a person has Lynch syndrome can help determine which cancer treatments are likely to be successful. It also means that patients' family members can be screened for Lynch syndrome, and those that test positive can be offered bowel cancer screening, to detect and remove pre-cancerous polyps in the bowel. This has been shown to save lives from bowel cancer.

While the link between Lynch Syndrome and bowel cancer is well established, the link with womb cancers is less well studied. So in partnership with Professor Gareth Evans, Emma led the first prospective UK

study to determine the prevalence of Lynch syndrome in 500 women newly diagnosed with womb cancer.

Lynch syndrome is caused by a fault in one of the four so-called mismatch repair (MMR) genes. These genes allow our cells to repair mistakes to our genetic code (our DNA), that occur randomly when our cells divide and produce new cells. The gene fault responsible for Lynch syndrome can be found by testing a person's DNA via a blood test.

This blood test is very expensive and takes a long time to complete, so it is important to sift out women who are very unlikely to have Lynch syndrome from those who are at risk, by performing simple tests on their tumours first. This includes testing tumours for mismatch repair deficiency by immunohistochemistry, and genetic testing for microsatellite instability, both of which are hallmarks of Lynch. Patients scoring positive on either of these measures may then be tested for MLH1 hypermethylation. Together, these tumour tests reduce the number of women identified as being 'at risk' by around 90%, leaving just 50 or so of the original 500 women to undergo the more expensive and time-consuming germline testing for Lynch syndrome.

The initial findings of Emma's research indicate that Lynch syndrome is found in around 3% of women with womb cancer

"To date we've treated 110 women from all over the country, as few clinics are offering this 'conservative' approach to treatment"

- exactly the same proportion as in bowel cancer. Her research also showed how womb cancer should be screened for Lynch syndrome, that women want to be tested to protect their family members, and that Lynch syndrome testing is cost effective for the NHS. As a result, NICE has now extended their guidance on Lynch

syndrome testing to include women diagnosed with womb cancer as well as bowel cancer. This means that more people will be enrolled in cancer prevention and screening programmes, as clinicians will be in a better position to encourage the relatives of patients with Lynch syndrome to be tested for the disease. In addition - and crucially - because womb cancer usually comes first, it is likely be the first indication of a patient having Lynch

syndrome and therefore being at risk of developing bowel cancer later in life. Emma says: "The link between Lynch syndrome and womb cancer presents a real opportunity to improve outcomes for patients. We are delighted that NICE have developed new guidance that recommends that everyone diagnosed with womb cancer is automatically screened for Lynch syndrome. Another great example of how research undertaken in Manchester is changing national policy."

"Despite being the most common gynaecological cancer affecting women in the UK, there is less overall public



awareness and in turn less research funding, when compared with other types of cancer.

"So one of my key ambitions is to champion womb cancer. There are so many opportunities to make things better by raising public awareness about the disease, encouraging women with symptoms to see their doctor straight away and speeding up the pathway to diagnosis.

#### Obesity and womb cancer

"I've also been researching the link between obesity and womb cancer - specifically the impact of weight loss on early pre-cancerous changes in the lining of the womb; and this has demonstrated that if very obese women lose weight then cancer precursors can simply disappear.

"We're already getting extremely good outcomes for obese patients who lose weight and receive hormone therapy to treat their womb cancer rather than the standard hysterectomy. And of course this has the huge advantage that it is possible

for these women to achieve pregnancy once the treatment is completed.

"In Manchester we have the UK's only clinic for this type of management of womb cancer. To date we've treated 110 women from all over the country, as few clinics are routinely offering this 'conservative' approach to treatment - most can only offer a hysterectomy. We're fairly unique in being able to bring together gynaecologists, dieticians, bariatric surgeons, anaesthetists and fertility experts in a multidisciplinary approach to deliver the best possible care for patients.

#### A PED centre of excellence

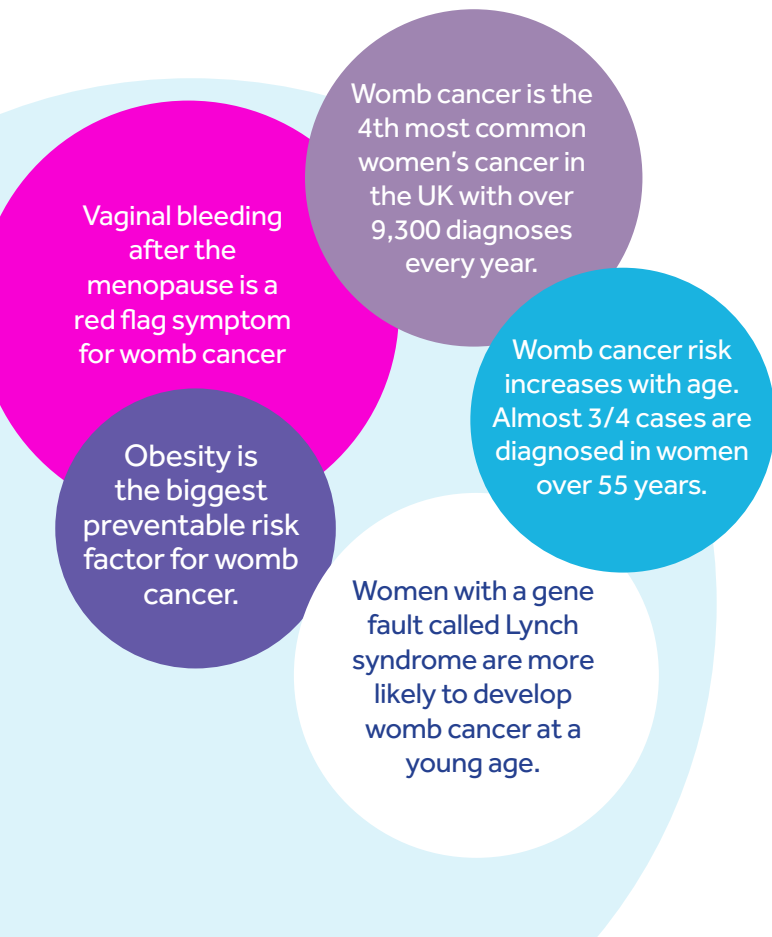
"The city already has an international reputation for cancer research excellence. It receives a phenomenal amount of funding from Cancer Research UK (CRUK) and also the NIHR via the Manchester BRC. In fact Manchester is the only BRC in the country that has a Cancer PED theme; and the city is home to one of the only three CRUK Early Detection centres in the entire country.

"Manchester is also fairly unique in being able to bring together brilliant discovery scientists and clinical academics who can then work with patients to test new discoveries - and for my research that's a perfect marriage between innovation and testing new diagnostics and treatments in the right people.

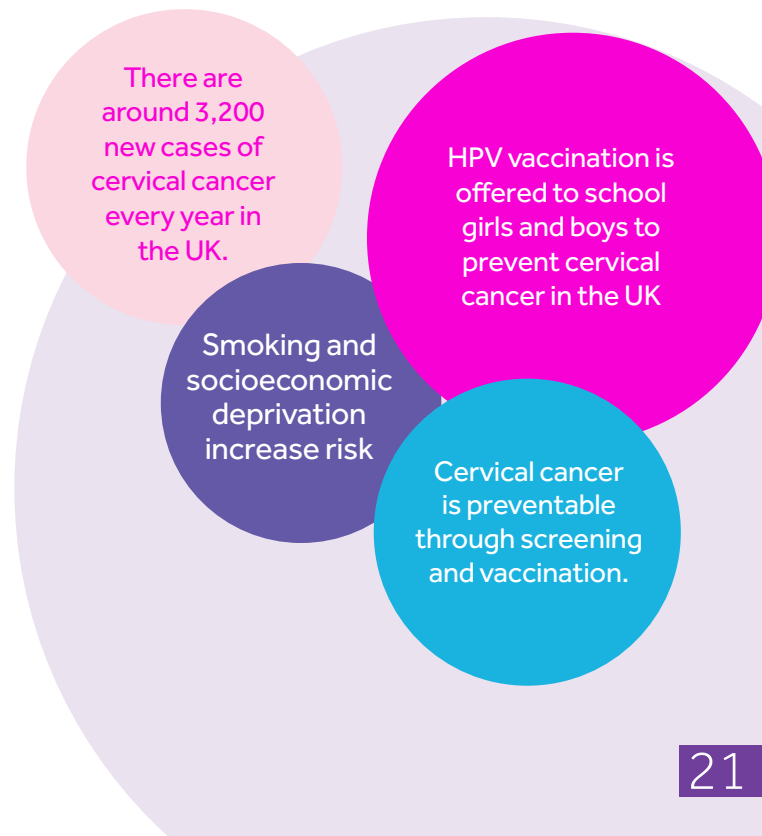
"As lead for the PED theme at the Manchester BRC, my personal ambition is to see Manchester develop as an internationally recognised centre of excellence for cancer PED. We've got all of the elements in place, but to take things to the next level we need to have new biomarkers to test sequentially in high risk groups and then more general populations."

**Emma Crosbie is Professor of Gynaecological Oncology at The University of Manchester and Manchester University NHS Foundation Trust.**

## Womb cancer



## Cervical cancer



# RISK STRATIFI

Professor Gareth Evans is an international leader in cancer genetics, particularly in neurofibromatosis and breast cancer. His research into developing and improving models for risk stratification and the early detection of breast cancer, has led him to conclude that risk stratification offers the best way of targeting prevention and early detection (PED) approaches and also provides the best approach for patient outcomes. Here he outlines why Manchester is perfectly placed to lead on this.

"I've become more involved with prevention and early detection of cancer because it's all very well identifying people's risks, but if you can't do anything about them then it's almost pointless, so my research is focussed on optimising our PED approach to cancer by calculating an individual's total cancer risk regardless of family history.

"My main focus has been risk identification for breast cancer, moving away from using family history as a risk tool and really looking at all women in the general population to enable more targeted early detection/prevention strategies that will better balance risks and benefits of population screening programmes.

"Although my main focus was initially breast cancer through higher risk and moderate risk genes, I am now more involved in looking at common genetic variants called SNPs, (single-nucleotide polymorphisms), to produce something called a polygenic risk score."

"We feel that this work is ready to be used to more accurately identify those at increased risk of other cancers, so that PED can be better targeted at those at the higher levels of risk. Potentially, those with low levels of risk can be reassured that they actually don't need screening, as screening might actually be more harmful than good for them.



# CATION

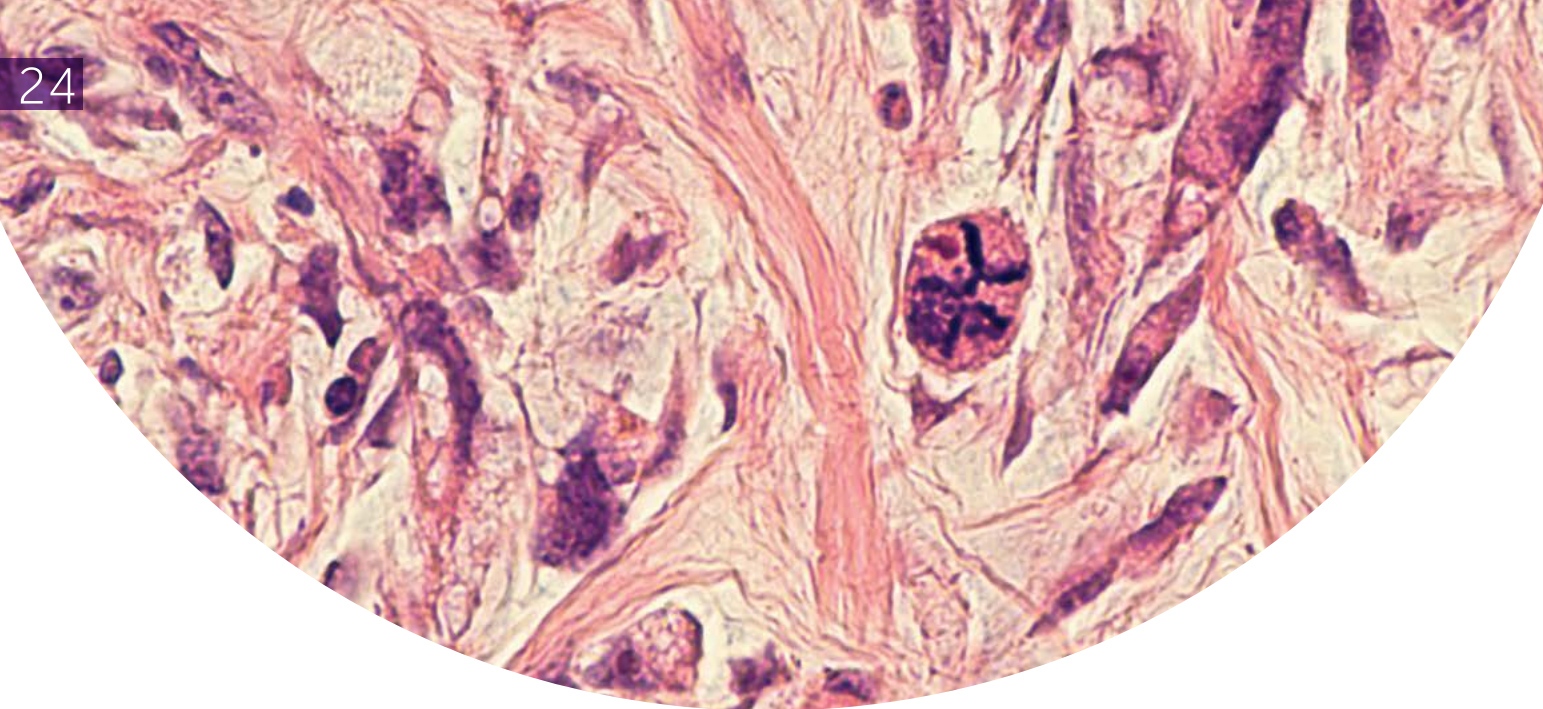
A photograph of two men in a laboratory or clinical setting. On the left, an older man with a balding head, wearing a white lab coat over a light blue shirt and a dark tie with a small pattern, is looking towards the right. On the right, a younger man with dark hair and a beard, also in a white lab coat, is seen from the side, looking back at the older man. They appear to be in a conversation. The background consists of large windows with vertical blinds, letting in bright light.

## Savings to the NHS

"For me, the reasons why risk stratification is the way forward are multiple, not least because of the potential cost savings to the NHS. If you use risk stratification properly, you can increase screening in those at higher levels of risk and reduce screening of those at lower levels, making the actual cost neutral. Better targeting means you're hopefully picking up the cancers earlier which means a cost saving in those women as they require less treatment.

"Similarly, identifying higher risk people helps identify those who would be eligible for medication prevention treatments such as the three NICE approved drugs for chemo prevention in breast cancer, Tamoxifen, Raloxifene and Anastrozole. Anastrozole went through a health economic assessment in breast cancer and was shown to be cost saving to the NHS. It only costs 4p a day to treat someone with Anastrozole, but you halve the number of breast cancers - literally cutting in half how many women will get breast cancer. This is a potentially massive benefit to the NHS.

Additionally, the risk stratification, including the genetic element which is the most expensive part of the process, only needs ever to be done once. You may need to do an assessment of the other risk factors including mammographic density, on two or maybe three occasions."



### Big change

"The NHS moves very slowly however and there is much to be done. We need to persuade the national screening committee that this is the way forward because it will be a big change for risk assessment to be brought into the screening programme. Currently, every woman is treated the same, in terms of screening.

"Essentially though, it's already being done for cervical cancer because it is now going to be different screening for those with Human Papilloma Virus (HPV), than those without the virus. Screening is going to be relaxed for those that aren't HPV positive, after the age of 50. So risk stratification is coming in, using the tools available.

"There are some high risk screening programmes taking place. In bowel cancer, there's high risk screening with colonoscopy used for those that have a high risk of bowel cancer through genes such as Lynch Syndrome. It just needs to be fully taken on board which is really the correct, most intelligent way forward rather than the one size fits all approach."

### Multi-disciplinary research

"Our researchers have identified hundreds of genetic variations and gene mutations which can switch protective tumour suppression genes off, as well as moderate- and high-risk genes for many cancers, but we need to go further and have refined this approach by analysing DNA samples collected through the Predicting the Risk Of Cancer At Screening (PROCAS and PROCAS-2) studies using exome sequencing, to identify all known

and suspected breast cancer genes and assess known breast cancer gene mutation risk.

"We recruited 58,000 women from Greater Manchester into PROCAS and now over 1,700 breast cancers have occurred in those 58,000 women."

"We created an algorithm that pulls the different elements of the risk together. We used a risk programme where you have to collect a number of risk factors from each woman. We are now in the process in PROCAS 2, of giving back risk information within six weeks of a woman attending for her mammogram, including all of her risk factors and mammographic density.

### Genetics

"In a subset of women we're going to be adding in the genetics by collecting saliva DNA when they come for their mammogram. We'll extract DNA from the saliva and run a SNP array and then generate from 143 of these common variants, a polygenic risk score. That might give them a risk anywhere between 0.25, so a quarter of the average risk, or it might give them a four-fold relative risk. So essentially, a very, very big risk range, that's also a very accurate risk range.

"So when it predicts a higher risk, it is a higher risk. When it predicts a low risk, it is a low risk - and it's accurate.

"This work brings together geneticists, oncologists, epidemiologists, and radiologists who have come together to make this happen along with image scientists and IT specialists.

### One stop shop for risk prediction

"Ultimately the aim is that when a woman is around 40 years of age we will be able to do a full risk assessment for all the female cancers, not just one, and then work out a screening programme. Currently, the expensive part is the genetic testing which probably costs around £80 per woman but this isn't desperately expensive when you consider that if used accurately, then you're saving £80 for every mammogram you don't need to do, so you'll save money by better targeting.

I would like to see us become the go-to place for risk stratification, prevention and early detection of all the major, common cancers. My colleagues have identified new genes that haven't been identified by other groups around the world for inherited cancer syndromes and this isn't just because of our access to the diverse population. It's because we attract high quality scientists to do the innovative, new research. We need to continue to become world leaders".

**Gareth Evans is Professor of Medical Genetics and Cancer Epidemiology, The University of Manchester and Consultant in Medical Genetics and Cancer Epidemiology, Central Manchester Hospitals NHS Foundation Trust and The Christie.**



# Breast Cancer Now funds world-class research

We are currently supporting the work of around 380 breast cancer researchers across the UK and Ireland.

Find out more about funding to support your research at [breastcancernow.org/apply-for-funding](https://breastcancernow.org/apply-for-funding)

breast cancer  
**now**

Breast Cancer Now is a working name of Breast Cancer Care and Breast Cancer Now, a charity registered in England and Wales (1160558) and Scotland (SC045584), and a business name of the registered charity in the Isle of Man (1200).



TRANSFORMING  
**SURVI**  
THROUGH EARLY

Supporting its ambitions to become a world leader in Cancer Early Detection, Manchester has recently seen its application to join the International Alliance for Cancer Early Detection (ACED) succeed.

Membership of this prestigious alliance reflects Manchester's growing reputation internationally for impactful early detection research.

#### International effort

ACED represents a partnership between Cancer Research UK, the Canary Center at Stanford University, the University of Cambridge, OHSU Knight Cancer Institute, UCL and The University of Manchester. Each institution is a global heavyweight in the early detection research fields, and the Alliance's aim is to develop ideas and collaborations around some of the biggest challenges facing early detection.

Collaboration will lie at the heart of the Alliance. Scientists will be encouraged to work together on a national and international scale to identify opportunities, maximise resources and compare and cross-validate research breakthroughs to accelerate progress. The Alliance will also support researchers with training and development opportunities such as workshops and conferences, to train the next generation of early detection researchers.

This Alliance will lead the international effort and help set priorities and strategic direction in preventing and detecting cancer sooner.

Manchester with its world-class research, team science approach to cancer research and unique facilities and infrastructure was seen as perfectly placed to lead future international collaborations thanks in large part to the evidence of research early detection exemplars in lung, breast and gynaecologic cancers, led by Manchester researchers.

"Greater Manchester has been recognised via peer-reviewed processes nationally and internationally as a system lead for cancer."

#### Manchester research recognised

Greater Manchester has been recognised via peer review as a national and international system lead for cancer.

Success in research is the result of a combination of factors including the synergistic research power of the Manchester Cancer Research Centre, other Manchester NHS Foundation Trusts, the Manchester Centre for Cancer Biomarker Sciences and the Manchester NIHR Biomedical Research Centre.

This "One Manchester" approach to cancer team science, along with the research community's demonstrable impact in delivering PED cancer research projects that will benefit its 3.5 million population, will enable us to employ across a range of research projects to help achieve cancer care changes, especially in medically underserved populations.

Manchester has a track record in initiating a number of world leading unique cancer early detection programmes. Alongside ACED membership comes a £3.2M funding award from Cancer Research UK to pursue key early detection projects in Manchester. Investment in these areas will see the Paterson Building redevelopment (expected to be completed in July 2021) becoming the engine which drives the clinical translation of this collaborative research into national and international patient benefits.

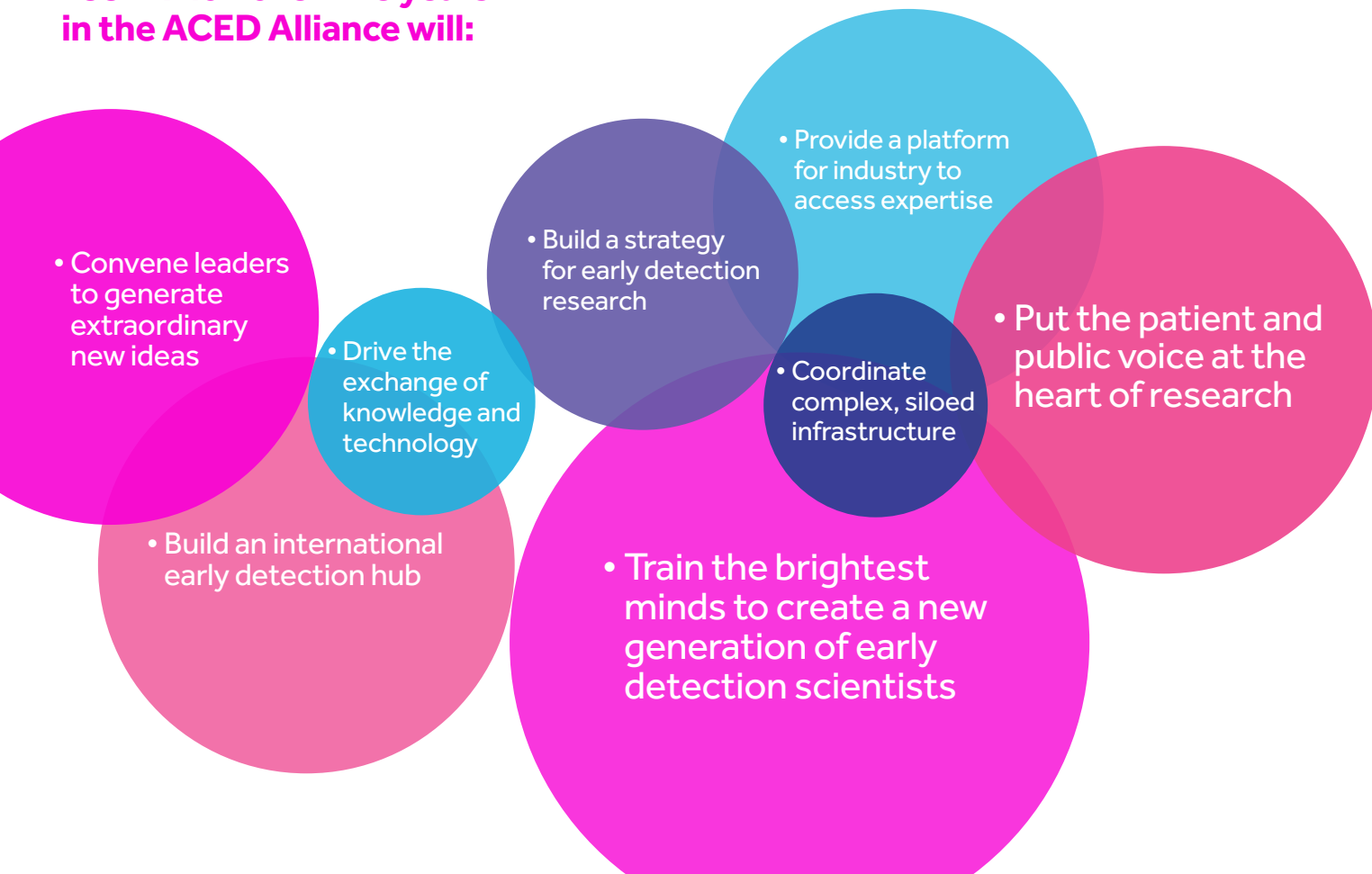
CANCER  
VAL  
DETECTION

### Cutting the cost

Cancer costs the UK economy £18.3 billion a year and the cancer burden is high in Manchester. Incidence and mortality rates are higher than the national average and late cancer detection in medically underserved populations is a specific problem in Manchester compared with the entire UK. Underserved areas in GM have significantly poorer cancer outcomes when compared to even central Manchester. This means that early detection programmes which embrace these populations are crucial and a number of world leading early detection research programmes such as the innovative mobile lung screening project, have been born out of the need to meet this need.

"Manchester is aiming to become a testbed in this area of understanding"

**The investment of up to £55 million over five years in the ACED Alliance will:**



### Research expertise

Going forward, research will use a world-first NHS early detection testbed within the Greater Manchester Cancer Plan (GM Cancer) which accesses greater than 2.9 million people, many of which are underserved. Using the GM Cancer population with improved access to health data, the research programmes will support whole population assessment of the potential impact of risk stratification allied to early detection to support hypotheses generated by national and international collaborating partners within the ICED Alliance.

In Manchester a range of professionals are leading and contributing to this research, including clinicians, bioscientists, data and machine learning specialists and engineers.

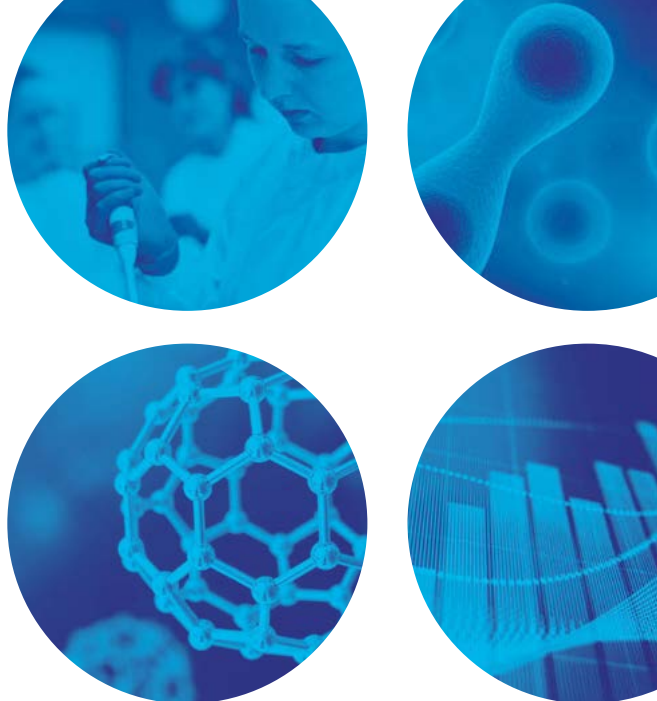
Other members of the ACED Alliance will have the opportunity to pilot and validate novel biomarker-driven early detection studies through the unique Manchester devolved health care system.

This research will help identify the right personalised early detection strategy by both reducing 'over diagnosis' in low-risk individuals and late cancer diagnoses in underserved populations. The objective is to shift the balance from late cancer diagnoses (associated with aggressive cancer treatment) with demonstrable effects on improving cancer survival.

Whilst cancer is detected earlier with this comes a challenge in being able to accurately understand how some cancers will develop. Manchester is aiming to become a testbed in this area of understanding through developing models based on samples collected from healthy and cancerous tissue.



INTERNATIONAL ALLIANCE FOR  
CANCER EARLY DETECTION



## Funding Transformational Early Detection Research

Funding your early detection research using the power of collaboration and partnerships, Manchester's membership in the International Alliance for Cancer Early Detection (ACED) provides researchers with access to regular funding calls throughout the year, including:

- **Pilot Funding:** Up to £200,000 over 12 months
- **Project Funding:** Between £200,000 and £800,000 over 36 months
- **Skills Exchange and Development Award:** Up to £40,000 for 4 months travel to a member centre

Find out more details about the latest round of funding as well as how to apply here:

[www.crukcentre.manchester.ac.uk/Research/ACED](http://www.crukcentre.manchester.ac.uk/Research/ACED)



The human body's immune system is a powerhouse that prevents, controls and eliminates threats like pathogens, bacteria and viruses on a daily basis. However, the biological properties of tumour's cells are different. Cancer tumours exhibit evasive mechanisms that make them resistant to this natural method of disease control. But what if the immune system could be engineered to target cancer cells, and use the body's defences against cancerous cells?

## IMMUNOLOGY AND TEAM

It is exactly this question that has driven years of research into cancer immunology. Over the past few years, there has been increased interest in therapies that limit tumour evasion or promote the immune response to tumour cells. However, there are still many challenges that need to be overcome. Immune response is limited by the patient and type of cancer, with some being more responsive to immunotherapies than others. This difference highlights the real need for basic, translational and clinical research to uncover mechanisms of action, identify novel targets and increase the efficacy of cancer immunotherapies.

In Manchester, it is precisely these research questions we are interested in tackling. Our researchers are interested in how tumours evade the immune system and how the immune system can be harnessed to target cancer cells. In conjunction with the Lydia Becker Institute for Immunology and Inflammation, and the Manchester Immuno-Oncology Network, our goal is to bring researchers and clinicians together to foster collaborations and solve some of the greatest challenges facing cancer immunology.

Immunotherapy has already helped to extend and save the lives of many individuals across the world. In combination with other therapies such as radiotherapy and chemotherapy, immunotherapy has the potential to provide a more personalised, precise and effective method of treating patients with potentially fewer side effects.

### Manchester Based Exemplar: iMATCH

As a collaboration between 12 academic, clinical and commercial partners, Manchester-led iMATCH is one of three centres in the UK awarded funding by Innovate UK to coordinate the scale up of advanced therapies as part of the national Advanced Therapy Treatment Centre (ATTC) network.

Awarded nearly £7m million of funding, the consortium aims to maximise access, traceability, and scale of advanced therapies, including immunotherapies, with the goal of making the therapies routine treatments.

## SCIEN

## Immunotherapy explained

Types of immunotherapy that help the immune system act against the cancer include:

- Checkpoint inhibitors: drugs that help the immune system respond more strongly to a tumour. They work by releasing “brakes” that keep T cells (a white blood cell and part of the immune system) from killing cancer cells.
- Adoptive cell transfer: a treatment that attempts to boost the natural ability of your T cells to fight cancer. In this treatment, T cells are taken from your tumor. Then those that are most active against your cancer are grown in large batches in the lab before being introduced back in to the body.
- Monoclonal antibodies/therapeutic antibodies: immune system proteins produced in the lab and designed to attach to specific targets found on cancer cells. Some monoclonal antibodies mark cancer cells so that they will be better seen and destroyed by the immune system.
- Treatment vaccines: work against cancer by boosting your immune system's response to cancer cells.

Immunology research takes place across Manchester and involves all partners

Lydia Becker Institute of Immunology and Inflammation

IMMUNOLOGY  
RESEARCH

The Division of Cancer Sciences  
(The University of Manchester)

CRUK MI

Christie, and  
Experimental Cancer  
Medicine Centre

IMMUNOLOGY  
TREATMENT /  
IMMUNOTHERAPY



The image of Professor Hussell is a posed for shot and does not in any way see to imply accuracy

## Immunology is increasingly being seen as a critical component of cancer research

Recognising the importance of interdisciplinary research, the Lydia Becker Institute of Immunology and Inflammation, has been created at The University of Manchester.

Home to internationally renowned immunology and inflammation expertise, cancer has been chosen as one of the Institute's key research themes, emphasising immunology's ever increasing role in cancer research. The cancer immunology theme brings together basic researchers and medical oncologists together to expedite knowledge about the power of the immune system in fighting disease.

The Institute is directed by Professor Tracy Hussell, who is also Director of the Manchester Collaborative Centre for Inflammation Research (MCCIR), a collaboration with industry in blue sky inflammation research. She tells us about the important link between immunology and cancer and why Manchester was the perfect place to lead on this.

### Back to basics

"Immunology underpins the majority of human disease; I can't think of a single disease where it's not important, so immunologists need to be in the room. We know the immune system and it's never just one thing. It's always a combination and we need to understand that combination because if you can work out how to unleash immunity, it would be relevant to any setting where the immune system is sluggish, such as cancer, and any learnings here could be taken up by cancer researchers globally.

"We have to understand what stops and starts things in order to harness them and rather than going, 'Look at that disease in that tissue', we need to look at the healthy tissue and say 'what's missing?'.

"It's a different way of looking at it and once you start thinking differently, you can't stop and it changes everything.

There's a form of lung cancer, basal cell carcinoma, which is lots and lots of basal cells, and you think; Why are there so many of them? So you begin to ask what drives them, but equally, ask what stops them and once we've found out what stops them they stop. We have to look at disease in a different way.

"Radiotherapy for example has been great for cancer but not a lot has moved on. We've been using the same treatments for a long time, but it hasn't made us think about trying something different or made us question whether we're looking at the wrong end of the disease. So if we can change attitudes as to what disease is, that it isn't something abnormal, it's something normal that has stopped or hasn't started, we can begin to make progress.

"We have to understand what stops and starts things in order to harness them"



LYDIA BECKER

INSTITUTE



The image of Professor Hussell is a posed for shot and does not in any way see to imply accuracy

### Cancer and immunology

"Cancer and immunology haven't come together that well in the past. Before, the immune system was seen as a series of events, with cancer researchers focussing on the end events but what we need to do is draw them back to the earlier events because if you don't, you're never going to understand what's at the end, so you need immunologists for this and it's starting to happen.

"People have traditionally worked in separate silos, so lung immunologists wouldn't speak to gut immunologists and yet those sites are trying to fight the same things, so it made sense to pull these together so they could learn off each other. This way we've learned that we can share patient samples, share in vivo models and so we're doing much better joined up science.

"Good multi-disciplinary teams should be seamless. The institute has all the different people in it, it has clinicians, basic scientists, we're all part of the same mix, same grant applications, all on the same papers. The research has changed, you no longer need to do things in a sequential order, you can do everything at the same time.

### Increasing collaborations

"Our collaborations are rising expediently meaning we're now working across prostate, ovarian and lung cancers as well as radiotherapy. This means we become aware of things that we may not have considered before. I, for example, didn't know that radiation can cause an inflammatory complication in some patients and whilst it's not known what the cause is, it's likely that the cure for it is already out there because if it's excess inflammation, you can stop it happening which, allowing you to increase the therapeutic window of radiation.

"Our immunologists were part of the mobile lung screening project and we're continuing to collaborate on this project by trying to minimise the numbers of people who undergo unnecessary surgery. For example, if in a thousand screenings they find five people with lesions, those five can go on to have

curative surgery and whilst this has happened, in many cases, a non-cancerous nodule is detected but these people still go on to have surgery. So what we want to do is identify what the difference is so that only the ones most likely to require it will receive it and not those who you only realise much later didn't actually need the surgery but underwent it based on a decision made on the knowledge they had at that time.

Here we've been sampling people's airways by blotting the back of their nose for two minutes and we are getting really exciting data out of that. I'm hoping eventually that 'Miss Basic Science' will contribute to a self-test kit that people will receive at home to enable them, to self-test at home to see if they need further investigation. I'd never dreamed I could do anything like that.

### Making good science

"Someone recently asked me what I thought made a good scientist and I said, 'Ok, if there's a big red button in the middle of the room with a sign saying don't press, the good scientist will press it'. The people here are like that. How we're doing science now, drawing all these aspects together means I'm interacting with people who have access to patient health records and so if I'm

looking at chronic pulmonary disease, which precedes lung cancer, I can say, well, of the ones that go on to develop lung cancer, do they have something else as well? It may be that they are obese, have diabetes, an autoimmune disease or equally, a mental health disorder, what are the comorbidities?

We're taking our science into the patient and letting them determine what we ask. You'll never find a patient with one disease so you have to understand what diseases they have and draw in those experts to knit the patient together and understand patient complexity. It's mind-blowing."

**Tracy Hussell is Professor of Inflammatory Disease, The University of Manchester and Director, Manchester Collaborative Centre for Inflammation Research (MCCIR) and The Lydia Becker Institute.**

"Someone recently asked me what I thought made a good scientist and I said, 'Ok, if there's a big red button in the middle of the room with a sign saying don't press, the good scientist will press it'"



# HARNESSING **IMMUNE** COMPLEXITY

We are home to internationally renowned immunology and inflammation expertise in a vast array of basic and applied disciplines. We perform fundamental and translational exploratory science, applying the latest technologies to address the key new concepts in health and many areas of clinical unmet need. The great breadth and diversity of research in our institute emphasises how immunology plays an ever-increasing role in modern medicine.

## **Find out more:**

Lydia Becker Institute of Immunology and Inflammation  
The University of Manchester Core Technology Facility  
46 Grafton Street  
Manchester  
M13 9NT

**0161 275 1537**

**[www.manchester.ac.uk/lydia-becker-institute](http://www.manchester.ac.uk/lydia-becker-institute)**

Dr Santiago Zelenay is using his background in fundamental immunology to understand how the immune system can be used to design better therapies for cancer patients. A recent recipient of the CRUK Future Leaders in Cancer Research Prize, he talks to us about his work and how he came to join the cancer community.

# AN IMMUNOLOGY REVOLUTION

“Over the years I’ve become increasingly interested in the idea that the immune system not only constitutes a defence mechanism against infectious microorganisms, such as bacteria and viruses, but that it can also be a powerful barrier to cancer.

“The notion that you could treat cancer patients with therapies that harness the power of the immune system has been around for a long time but it was only over the last 10 years that undeniable evidence showed that these therapies can promote profound patient benefit across many different tumour types - to the point that it’s replacing mainstream cancer treatments, like chemotherapy, as the standard of care in some cases.”

“Immunotherapies, especially those based on the use of the so-called immune checkpoint inhibitors, have really transformed the clinical care of patients with cancer. There has been a revolution in this respect and also in thinking. All this clinical evidence has really eradicated the scepticism that was around the concept that the immune system could block cancer development and progression.”

“As someone with a background in basic immunology I got attracted to the idea of working on something that had obvious clinical implications, that could lead to direct patient benefit. I wanted to apply my knowledge in fundamental immunology to cancer biology at a time of renaissance in the cancer immunology field. This contributed to my decision to move to Manchester and join the CRUK Manchester Institute, an ideal place to continue doing basic research in cancer but also to focus on the translational aspects too, facilitated by its connection with The Christie hospital, the close interaction with oncologist, clinicians and the access to patient samples.”

“My research group is focused on understanding the principles and rules that regulate the balance between tumour-promoting and tumour-inhibitory inflammation. Inflammation can have a dual role in cancer, promoting or restricting its growth. This also happens following treatment but little is understood about what determines whether the outcome is good or bad. We study how this happens and whether we can therapeutically change the inflammatory response to make it beneficial.”

ON

"We ask open fundamental questions in the field. What kicks off the immune response against cancer in the first place, what prevents this from happening? What is the key for a strong and durable response? How can we therapeutically make an unresponsive tumour respond to immunotherapy?"

"Through the study of the inflammatory response within tumours, we aim to design new combinations to enhance the efficacy of treatments. Our ultimate goal is to contribute to the design of more efficient therapies for cancer patients."

### Research discovery

"In asking those basic questions is that we found that the use of anti-inflammatory drugs, such as aspirin, can improve the efficacy of immunotherapy in mouse models of cancer. Based on these findings and on further research in patient samples, we have designed a clinical trial to test one of our most promising combinations. This trial called ImPALA will open very soon. Led by Anne Armstrong, a Consultant Medical Oncologist at The Christie, and supported by Breast Cancer Now, and with the Christie as a sponsor, we will test the combination of high-dose aspirin, with a checkpoint inhibitor (avelumab, an anti-PD-L1 antibody), in triple negative breast cancer patients. The primary trial aim is to determine whether the addition of aspirin enhances the efficacy of avelumab treatment by shifting the inflammatory profile of the tumours towards classic anti-cancer immune pathways, one that would favour cancer control by the immune system. The general premise is that anti-inflammatory drugs like aspirin, rather than inhibiting tumour inflammation indiscriminately, they turn its 'flavour' to a good type, one that is associated with higher response rates."

"Comparisons with other places aren't easy but from experience, our interactions with oncologists are different, they're seamless."

### Manchester advantages

"We have an advantage because we're unique in that we are a community. We may all have very different expertise but we always point - like an arrow head - together in one direction of travel and that is to obtain patient benefit. Comparisons with other places aren't easy but from my experience, our interactions with oncologists are unusual in that they're seamless. This spirit of community where everyone is open to talking and working, is connected to a feeling that a new wave of immunologists, cancer biologists and other fundamental researchers are being attracted to work in Manchester."

"Besides my interactions with researchers from the CRUK Manchester Institute and clinicians from The Christie we are very fortunate to have at The University of Manchester a great number of exceptional immunologists. And as a group we interact and collaborate with them in different projects. Being the Lead of the Cancer Immunology branch of the Lydia Becker Institute of Immunology and Inflammation has helped meeting and establishing new collaborations."

"My interactions with this community have led me to redefine myself. I used to define myself as pure mouse immunologist but I feel that's now changed. They've broadened my definition of what I do."

**Dr Santiago Zelenay is lead for Cancer Inflammation and Immunity Group at the Cancer Research UK Manchester Institute and Lead of the Cancer Immunology branch at the Lydia Becker Institute of Immunology and Inflammation.**





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With our partners, we are also developing a nationally recognised centre for advanced cellular therapies. Known as iMATCH – the Innovate Manchester Advanced Therapy Centre Hub - this work will ensure patients benefit from a new generation of drugs modifying patients' own cells to act as a 'drug' to treat disease.

Our research encompasses every stage of the patient journey from prevention and early detection, to living with and beyond cancer. It covers everything from understanding the molecular and cellular basis of cancer to the development and testing of novel treatments and improving the patient experience.

## Contact us:

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Following the discovery of graphene in 2004 by Manchester scientists Professors Andre Geim and Konstantin Novoselov, interest in the use of tiny materials in healthcare has become an extremely popular research field. In particular, nanomaterials are increasingly being used for various diagnosis and treatment applications across the healthcare field.

Oncology is no exception, with the topic of nano oncology becoming more popular over the years. Functional nanomaterials are now being used in imaging, biodistribution, and drug delivery applications as an alternative to traditional chemotherapy agents. Driving this change are the intrinsic properties of a nanoparticle. Their microscopic size makes them useful as both the drug or as the delivery mechanism for a drug, able to pass the blood-brain barrier and target hypoxic cells in cancers.

One of the challenges faced in cancer research is ensuring the drug is delivered to the right site, mitigating harmful side effects from non-targeted traditional chemotherapies. Therefore, one of the aims of nanomedicines is to address this challenge of targeted drug delivery. To achieve this, drugs are packaged with nanoparticles that are primed to release within certain parts of the body, for instance tumour cells where the cellular properties are different to healthy cells. In such situations, once the nanomedicine is inside the cell, the external conditions stimulate the release of the cytotoxic agent and cell death is initiated without harming any healthy cells.

Work from Manchester's National Graphene Institute is seeking to explore the connection between nanomaterials and healthcare further. Our researchers are exploring in vitro and in vivo studies to design and engineer delivery systems that can be translated into clinically effective therapeutics and diagnostics. Alongside our other collaborations across the world, nanomedicine research in Manchester is seeking to identify novel nanomaterials including viral and non-viral gene therapy vectors, carbon nanomaterials including fullerenes, nanotubes and graphene.



# NANO ONCO

## NANO MATERIALS

- *Nano-oncology/nanomedicine is a branch of nanotechnology. Nanooncology is the application of Nanomedicine to cancer diagnosis and treatment.*

- *Nanomaterials (organic and inorganic) with dimensions below one hundred nanometers are being exploited as promising tools for cancer therapeutic and diagnostic applications due to their unique characteristics of tumor targeting.*

- *Nanotechnology is the design of small devices on the nanometer scale (nm), from 1 to 100 nm. This miniscule scale allows these devices to reach places in the body that conventional treatment methods cannot.*

- *They have the potential to alter clinical oncology for different cancer types and the ability to create novel drug delivery systems that can specifically target the tumour sites.*

# LOGY

# A MARRIAGE OF GIANTS

The marriage of two of The University of Manchester's research beacons, cancer and advanced materials, is anticipated to bring huge advances to the earlier detection of cancers.

At the heart of this union is Professor Sarah Cartmell, Head of the Department of Materials, who is helping to pioneer this fusion of advanced materials into cancer research, beginning with lung and breast cancer.

In bringing together medicine and engineering, she will act as a work package lead on the £3.2 million Manchester early detection Centre of Excellence, as part of the ACED Alliance. She will look at how to further develop three dimensional (3D) in vitro models, using the state of the art tissue engineering skills and bioreactors available in her laboratory.

Outlining the project Sarah says, "We're aiming to develop a personalised early detection strategy for breast and lung cancers. One of the keys to this is identifying people at high risk of these cancers. Then we can start to understand the key drivers of tumour initiation that contribute to increased risk and ultimately, detect these cancers much earlier and therefore improve patient outcomes.

To succeed, we need to understand the changes in signalling and gene expression at the very start of lung tumour development. This is a promising way of identifying new bio-markers, which we can then use to develop new tests to diagnose cancer. If we use this approach, then we need tumours with multiple read-out options that accurately reflect the clinical situation for these patients, in comparison to cancerous cells that have developed in the patient with no genetic predisposition.

We need to work with cancer tissues with a genetic component to their formation to facilitate the development of treatments targeting the genetic causes behind the tumours. It is here where tissue engineering technologies can offer the integration of components of the tumour microenvironment which can assist in modelling, in vitro, the disease progression.

By collaborating with industry, academic and clinical colleagues, we will establish 3D lung carcinoma models which will allow us to look at tumours at their earliest point of development. The benefit of this is that we can control the environment to see exactly what happens at the point of tumour creation, then we can develop tests to detect the very earliest signs of cancer.

## Building blocks

Explaining the process Sarah says, "When we're trying to grow 3D tissue, we need a scaffold. We need a new biomaterial that is appropriate for whatever tissue we're trying to grow. For example, with a tissue such as a tendon, we need something that's parallel and aligned and fibrous whereas for cartilage we need a scaffold such as a hydrogel that can encapsulate cells and keep them rounded. In cancer research we can essentially use the same techniques, but for a different application, for example, you might want to create a cancerous mimic and then test if your therapy is appropriate. We can use human cells, because we do that with tissue engineering rather than using animal cells. There are different models that researchers use in a mouse, but there are sometimes difficulties translating this research into a human due to our different pathologies. We bring to the mix 3D human structures that enable us to perform/ carry out multiple imaging and testing on in the laboratory, something that you wouldn't ethically be able to do in animals.

The idea is that certain people are more predisposed to lung cancer than others so if we can understand more about the underlying mechanisms we can potentially develop or identify new biomarkers before these patients they show symptoms. This insight could also support the development of new therapies as we could test them in our models and we could source cells from people who are more predisposed to developing lung cancer than others.





### Benefits of the marriage

"For me, the innovation would be controlling the environment then designing tissue mock-ups of predisposed versus healthy cancerous tissue. Then we can use some of the techniques that we have in the Faculty of Science and Engineering, some of which members of the cancer team wouldn't be aware of or have access to such as the fantastic imaging capability.

By bringing the two disciplines together, we can share the latest developments in each other's spheres and explore how they can progress knowledge on both sides. If one of our cancer colleagues updates us on their research, we are then able to discuss new analytical methods that could be used. For example, we could image at a sample in 3D with our CT imaging, but without having these discussions, it is possible that our colleagues may not be aware of our current capability. Whilst people are familiar with computed tomography, often people think that the resolution is around about 1mm but that's just not true. Our resolution capability is 50 nanometres with some samples, which is approximately 1/1000 of the width of a strand of hair, meaning that we could label up specific new biomarkers, perhaps using gold nanoparticles and track their position in cells using this technique.

### Making a contribution

"Biomaterials and tissue engineering are still relatively new chapters in cancer research's history but we're at the stage where we can build on this critical mass of understanding.

Tissue engineering uses a scaffold to grow tissue in 3D, which is ideal as cells in monolayer only gives you so much information. Potentially high throughput 3D tissue will let us test and assess, and the ability to do this with human cells gives us the kind of research power that hasn't existed before.

We can help escalate research, reduce risk and obtain information that currently isn't available. If the research is performed at higher throughput, then we are speeding the process up and making it much quicker, so we are able to test more and get the right information. Using human cells also makes the research more clinically relevant.

With human cells, greater understanding about the mechanisms means that you can develop new treatments. It's concerned with finding out new information, escalating it and developing new innovations. It's not just about the material itself, but if we had a particular assessment technique, whether spectroscopy or an imaging technique, we might be able to find out more about what's happening with the biological mechanism to give new treatments.

### The right place

"Manchester is the right place to lead this bioengineering revolution. For me, it's because of our size giving us breadth and depth, and because everything is right here on our doorstep. Smaller organisations will have niche areas but they won't have everything, whereas we do.

As the biggest single site university in the UK with its own research giants, including cancer and graphene, which we've got the potential of incorporating into our scaffolds, we've also got the MCRC and The Christie. These are all USPs in themselves but together they're incredible.

This is the first time that the MCRC has received a grant of this size uniting researchers from across advanced materials and cancer or had a leader who has brought it all together. It's a really exciting time to be in Manchester".

**Sarah Cartmell is Professor of Bioengineering and Head of the Department of Materials, The University of Manchester.**

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🔍 Discover    ⚙️ Develop    🚀 Deploy

## As Professor of Experimental Therapeutics, Kaye Williams' research involves exploiting nanotechnologies in different ways across her research programmes in the Division of Pharmacy and Optometry.

Here Kaye gives us an overview of how they are being used, whether as targeted delivery vehicles for novel cancer therapy agents, for developing novel means of tracking molecules and cells through non-invasive imaging or providing 3 dimensional substrates that mimic tumour architecture and characteristics as a better model for cellular studies.

### Patient benefit

"We've many new molecules that have potential as anti-cancer therapies, but they often don't possess all of the characteristics that are needed for success as a clinically used cancer drug. They may not accumulate sufficiently within the tumour to cause the desired effect, they may be excreted from the body too quickly or cause unwanted toxicities.

"One of the main aims of cancer-associated nanomedicine development is to generate therapies with improved drug targeting to cancer cells. Nano-carriers can provide a vehicle in which to encapsulate drugs and enable selective delivery to cancer cells. Hopefully by doing this you increase the chance of your approach having an impact on the cancer cells whilst reducing the chances of it affecting other cells in the body and causing toxicity. That's certainly the approach we've been trying.

"We're using nanomedicines to try and target the delivery of novel cancer therapeutics to specific types of cancer cells that are thought to be associated with poor treatment response. We're exploiting nano-carriers designed to bind to particular molecules that are expressed on the cell surface of cancer cells to selectively deliver novel therapies that prevent tumour growth.

"We have been able to show that we can manipulate the interaction between hyaluronic acid and the receptor CD44 that's on cancer cells to deliver specific targeted molecules. We also been involved in research to develop additional approaches whereby the nano-carriers respond to specific "cues" within the

tumour microenvironment, and only release their drug cargo when they encounter the tumour-specific cue.

### Hypoxia and the tumour microenvironment

"One key research area is hypoxia in tumours, a condition that naturally arises in all solid tumours. The problem however is that it causes resistance to therapies such as radiation treatment and can cause resistance to standard chemotherapy agents. This is problematic because it links with poor patient outcomes and with development of metastases and aggressive disease.

"It can be challenging to deliver drugs to hypoxic regions so what we want to be able to do is selectively deliver new therapies to hypoxic cells in as safe way as possible for patients. In the context of a nanomedicine approach, you can potentially exploit hypoxia as a "cue" for a targeted-drug release or use characteristics specific to hypoxic cells that enables selective delivery which forms part of the research that we're trying to do.

"In material science, we're generating specific materials to mimic the tumour micro-environment more rigorously than our standard cancer cell culture conditions, and provide an environment where the cancer cells start to behave more like they would do naturally within the body.

This helps us if we're screening new drugs, or trying to understand cancer evolution or processes such as metastasis, when cancer cells develop the ability to invade different tissues which are regulated via the interaction of cancer cells and their immediate environment.

### Challenges

"One challenge from this is being able to selectively deliver drugs to tumours, because even when we develop drugs that we think should target a biology that's specific to the tumour, you still have associated side effects. It's not enough that you're trying to target a tumour-specific characteristic, on its own that won't prevent any potential toxicity. Of course classic standard chemotherapy agents that we're using routinely have considerable side effects associated with them, but they're very good at killing tumour cells.

"Even routine chemotherapy agents could be delivered better. One important aspect from the nano-technology side is to get a much more targeted delivery of drugs where you want, over the timeframes that you want. There's huge potential in the application of nano-technology to bridge these challenges, with work in many groups pushing towards the development of systems that can release therapies over time only under specific conditions to targeted sites. It's a very complex area but significant advances are being made. For me, it's all about improved outcomes and not just improved outcome from the tumour response; it's reducing toxicity, it's having therapies going into patients that have a much improved safety profile whilst maintaining excellent anti-cancer effects.

### Imaging

"Part of my role within the Manchester Cancer Research Centre is to lead on preclinical imaging, and through this role I work with a team of talented researchers who can develop novel means of non-invasively tracking labelled molecules or cells. In cancer, and many other areas of research, we need to be able to visualise what's going on inside the body in real time and imaging allows us to do this. Two routinely used methods are positron emission tomography (PET) and magnetic resonance imaging (MRI). Our imaging team has supported nano-technology research in both areas.

"PET is one of the most sensitive imaging techniques. Many patients will have a PET scan, most commonly using the PET-tracer 18F- fluorodeoxyglucose - FDG. This is glucose labelled with a positron emitting radionuclide, which indicates where a cancer is in the body because of the increased uptake of glucose by cancer cells. Similarly, you can label other types of molecule and see where they end up within the body. Dr Mike Fairclough has led our research linking non-invasive imaging approaches to nano-technologies and materials science.

"We worked with Professor Alberto Saiani to use PET-labelling of hydrogel molecules, developed as biomaterials for use in tissue engineering, to investigate how they behaved when administered in vivo.

"We've also used different types of nanotechnologies, such as nano-rods, which are visible by MRI. Again we've tagged those with PET tracers, so that enables you to develop brand new imaging agents for application in both MR and PET.

TARGETED

# DELIVERY

PHASE

Kaye Williams  
University of Manchester

"Cancer treatments are not only about using drugs, increasingly cells can be used as a potential therapy within patients. Another application bridging nano-technologies and imaging was to design a means of labelling cells to enable them to be tracked by PET. This would allow you to visualise where the cells end up when administered to a patient. Here, a nano-carrier was loaded with a positron-emitting radionuclide and used to deliver the radionuclide to cells that we know are important in cancer biology and therapy response. This technology would allow us to then track those cell populations when we introduce them into a pre-clinical animal disease model, or eventually into patients.

### Graphene and Manchester

"Obviously graphene has lots of potential applications in healthcare, but what we really need to know is where it might accumulate in a body when it's given. You might want to test whether it's accumulated in a specific place, but equally you may want to know how the body handles graphene. Does it accumulate in specific tissues that might actually cause a problem down the line and how can we track that?

To do that, working with Professor Kostas Kostarelos' group, our imaging team have labelled different types of graphene with positron-emitting radionuclides that allow us to track it in vivo via PET imaging. They were then able to track the bio distribution of the different graphene molecules within the body and monitor how formulation affected tissue accumulation and excretion of the graphene in the urine. There's obviously a lot of interest in Manchester about the applications of graphene in healthcare, and these types of studies showing how graphene distributes in the body and whether there would be any potential toxicity risk associated with this are very important".

"Manchester has expertise across a huge range of areas"

### Multidisciplinary Research

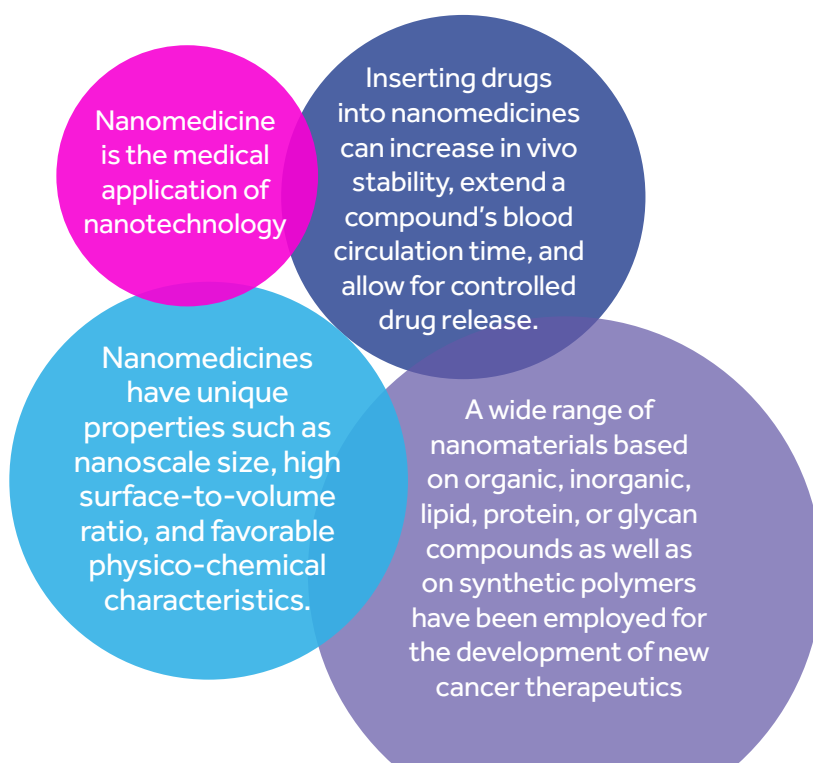
"I'm based in the Division of Pharmacy and Optometry so I spend my time surrounded by colleagues who do everything from developing new drugs and nano-technologies through to influencing policy and practice.

"Manchester has expertise across a huge range of areas and the research within my team is heavily reliant on collaborative networks that bring in expertise across many different areas. Imaging is a great example here as we are always aiming to translate our findings from bench to bedside. We want to be able to track how well the anti-cancer approaches we are developing are working as quickly as we can, not only from the perspective of our research questions, but also in terms of refining the work we do.

"That's incredibly important research, and of course the types of imaging that I've focused on here are ones that are immediately translatable into patients. If we're thinking about drug targeting, then we have a means of tracking that it has been successful through an imaging based approach that has been developed in parallel, so when we go into our clinical situation we're in a much more powerful position to be able to evaluate drug-response in patients quickly.

"That's where the multidisciplinary work is coming from, I'm not a chemist so if I think we've got a good target in cancer, I liaise with my colleagues who would develop the potential drug to hit that target. We then may need input on formulation, and targeting approaches afforded by nano-technologies. I can evaluate these approaches, and we can look for developing biomarker and imaging profiles that would help us define response and select the right patients for the approach. With the expertise in Manchester, we can cover all of these aspects in a coordinated approach - that's a really exciting environment to be in".

**Kaye Williams is Professor of Experimental Therapeutics at The University of Manchester and Pre-clinical lead for oncology imaging within the Manchester Cancer Research Centre (MCRC).**





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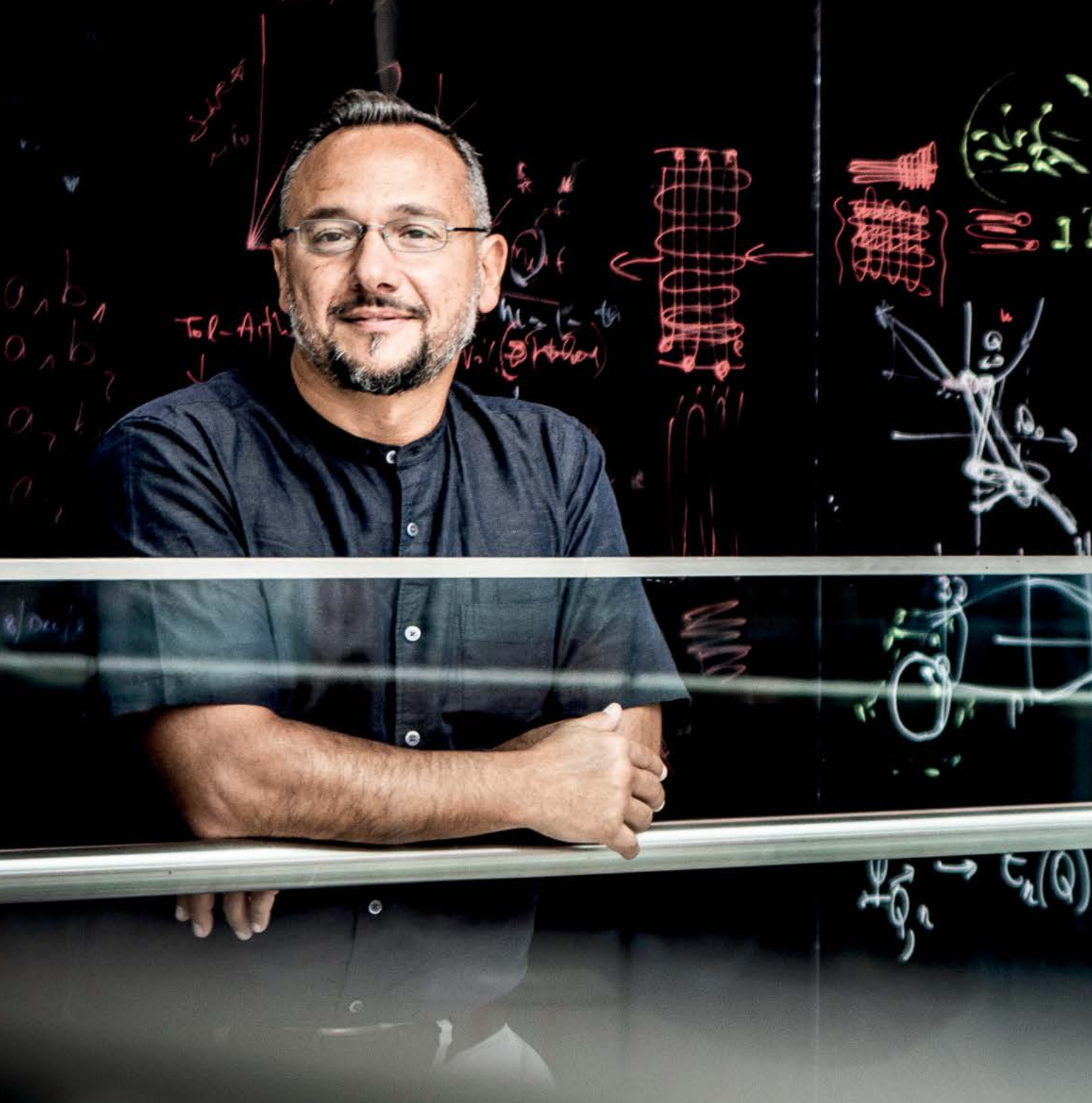
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# GRAPHENE

AND CANCER



Kostas Kostarelos is Professor and Chair of Nanomedicine in the Faculty of Biology, Medicine and Health at The University of Manchester, leader the Nanomedicine Lab that is part of the National Graphene Institute and the Manchester Cancer Research Centre. He is also the Severo Ochoa Distinguished Professor at the Catalan Institute of Nanoscience and Nanotechnology (ICN2) in Barcelona, Spain running a smaller nanomedicine research group there.

His research looks at how nanotechnology and nanomaterials, including graphene and other 2D materials, can be utilised to offer advanced tools for early diagnosis, progression and treatment of cancer.

"When you fish in a pond, you can either throw the bait in and move it around, or just leave the bait in one place and let the fish come to it. In the same way, we put the nanoparticle in the bloodstream and simply wait for the protein to adhere onto it."

#### How is nanotechnology being used in cancer research?

"In terms of existing benefits to cancer patients, nanotechnology is being used to develop safer, more accurate tools and therapies, resulting in reduced drug toxicity and better targeting.

Traditionally, nanotechnology helped oncologists to deliver very effective therapeutics specifically or preferentially to cancer cells. Put more simply, you take a potent anti-cancer drug and package it in a nanoparticle, which then takes it to the cancer site by minimising damage to healthy cells. The first nanotechnology-based products were designed to achieve this - targeting cancers and delivering the therapeutic agent with less cytotoxic effects.

A good, early example of this is a liposome, a spherical nanoparticle made of lipid, which has two separate compartments that can be used to encapsulate hydrophilic therapeutic agents, such as doxorubicin, or hydrophobic molecules, such as paclitaxel. The 'loaded' liposome can then be targeted to cancer cells in the patient. Meaning the drug reaches only the cancer cells, not surrounding healthy cells.

Another example is the use of iron oxide nanoparticles in neurosurgery, whereby these are injected into brain tumours to enhance the therapeutic effects of radiotherapy.

Nanotechnology is also being used to help improve the accuracy of MRI and CT scans. Nanoparticles that emit much more sensitive signals are able to localise deeper into the tissue and help identify tumours and lesions, improving precision of treatment.

These are just some examples of course. There is a great variety of applications being explored.

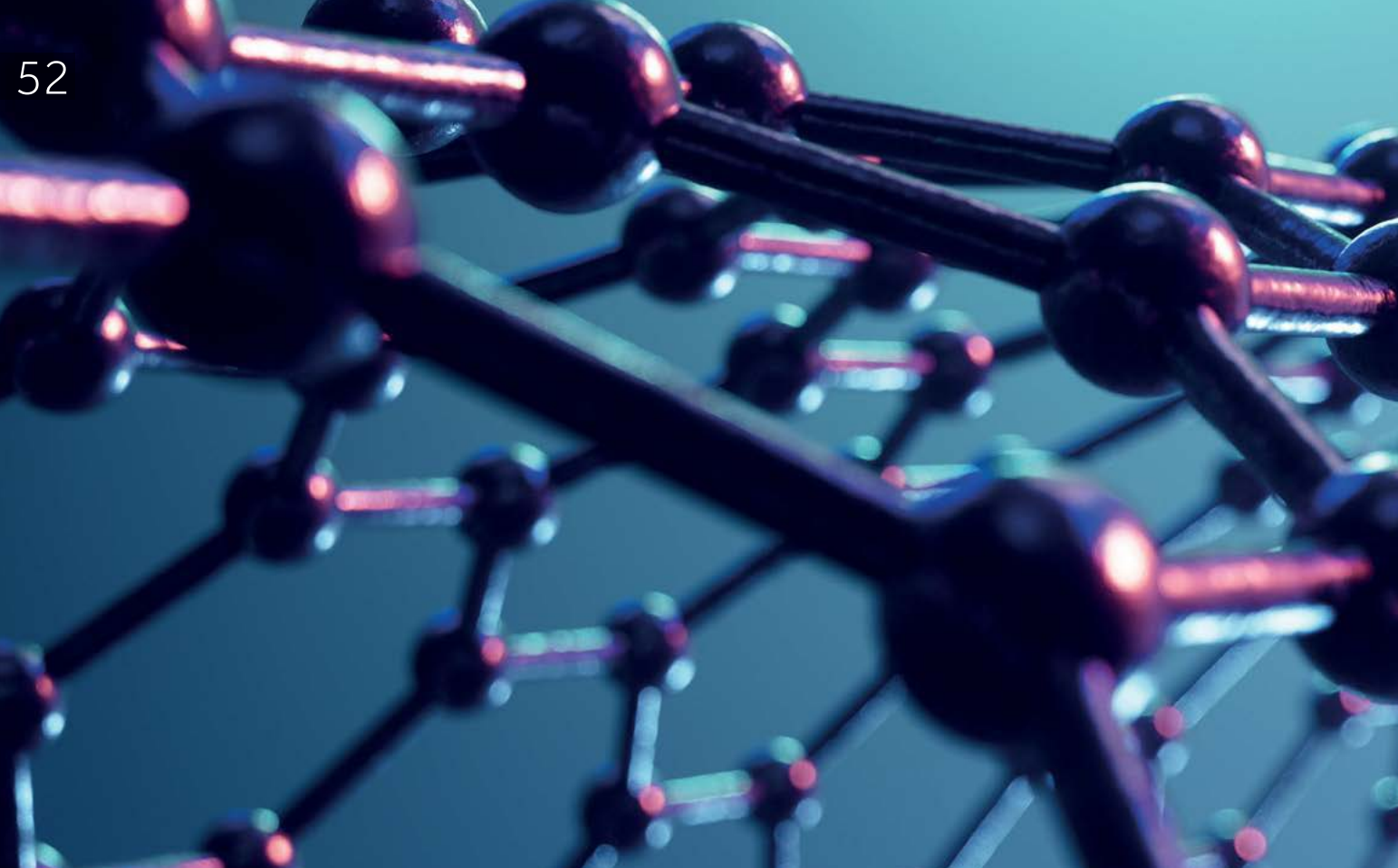
#### Can you outline a key project you're working on?

We're currently working on one which has been running for five or six years and involves the use of nanoparticles as scavengers for plasma samples that are able to provide a much cleaner and high definition blood proteomic signature. This is tremendously important in the quest for the discovery of new markers in cancer and its various stages.

One of the biggest problems in proteomics biomarker discovery is that the highly abundant proteins that are circulating in our bloodstream are 'masking' all the smaller, lower concentration proteins some of which are secreted by cancer cells or in response to cancer progression.

Due to this masking effect, the identification of smaller and rare proteins is difficult, so we cannot obtain clear and high-resolution proteomic signatures. The idea is that the nanoparticles interact with all of the proteins in the sample - large and small - some of which we know will adsorb onto their surface. In this way, we allow also some of the small molecular weight and lower abundant proteins to adhere on the surface of the nanoparticle, avoiding the masking effect, resulting in a much higher definition proteomic signature that isn't dominated by the larger, highly abundant proteins.

Sometimes we use the analogy of fishing to explain how this works. When you fish, you can either collect buckets of water hoping you catch some small, rare fish or throw a net and move it around. In the same way, we use the nanoparticles as 'nanonets' immersed directly into the bloodstream or into an extracted blood sample and simply allow as many of the proteins to adhere. Lift the 'nanonets' and analyse only the proteins that adhered onto them.



### Can nanomedicine be used to detect cancer earlier?

Nanotechnology can be used in various ways: by developing sensitive contrast agents for imaging, or to help analyse biological samples more accurately and sensitively, as discussed above. All of these technologies can also be used to identify whether a tumour has started building up, dividing, growing or receding. We think that various nanotechnology tools can contribute to the challenge of early cancer detection.

### What is the role of graphene in nanomedicine and cancer research?

Identifying biomedical applications for graphene and graphene-related 2D materials is a growing area of nanomedicine research, but clearly at early stages. There have not been any clinical studies using graphene and 2D materials in any oncology setting.

One of the key discoveries in our Lab is that macrophages - specialised cells involved in the detection and destruction of bacteria in the body - have an intrinsic affinity to internalise graphene and graphene oxide. When we present

graphene oxide flakes into a tissue in vivo, or in cell culture, macrophages are able to very efficiently capture it.

This phenomenon then begs the question: What if therapeutic agents are also attached to graphene, or what if we have some kind of antigen-presenting biomolecules onto the surface? We are therefore now trying to design such therapeutic strategies and approaches against brain cancer based around this very efficient macrophage internalisation.

### Why has a lot of your research focused on brain cancer?

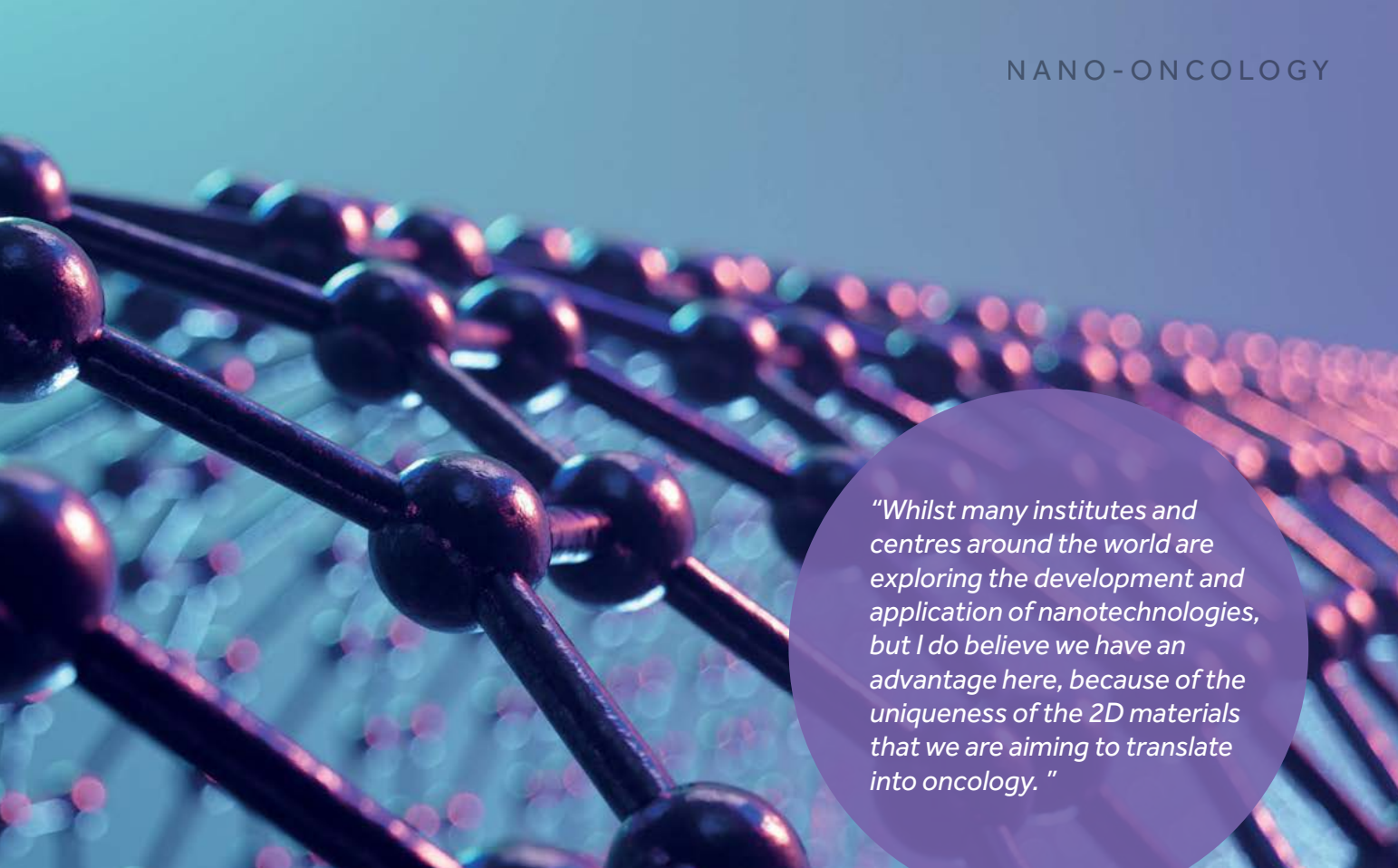
From our perspective there are two key reasons. Firstly, because traditional systemic immunotherapy is quite poor in this area - it doesn't work very well, if at all, in most cases of aggressive brain cancers, like glioblastomas, for a variety of reasons.

Secondly, from the nanoparticle transport and delivery point of view, it is because neurosurgeons offer us a very distinctive target area post-resection where we can deliver the materials directly, therefore not having to by-pass the challenges of crossing the blood-brain barrier.

Our hypothesis is that if we work with this population of macrophages within the tumour, we'll be able to trigger different types of responses, or enhance the response to radiotherapy, chemotherapy, or immunotherapy. In other words, we can use the macrophage population in brain cancer as a target or an adjuvant to enhance other therapies.

Graphene can also be used in brain surgery to fabricate a robust, ultra-flexible and highly conductive substrate that can record neural activity. Graphene has a multitude of advantages over traditional metallic materials that are used clinically today, such as platinum or iridium, able to detect very high-resolution electrophysiological signals.

So, working with neuro-oncologists at the NHS Salford Royal we are designing and clinically studying innovative neural recording probes for use in brain cancer resection surgery. These will allow surgeons to clearly differentiate between normal, electrically-active neuronal tissue and cancerous tissue to allow for high-precision surgery with minimal peripheral damage of the healthy brain structures.



*"Whilst many institutes and centres around the world are exploring the development and application of nanotechnologies, but I do believe we have an advantage here, because of the uniqueness of the 2D materials that we are aiming to translate into oncology."*

#### How can nano-oncology enhance Manchester's research ambitions?

Manchester has a unique opportunity in this field because of the breadth, width and quality of expertise between cancer research and physical sciences and engineering of novel materials. It has the capacity to take a new material or technology from a physics lab into the clinic in very short time, and in the right way.

Whilst many institutes and centres around the world are exploring the development and application of nanotechnologies, but I do believe we have an advantage here, because of the uniqueness of the 2D materials that we are aiming to translate into oncology.

Another great advantage is that the University is a single large campus institution - it's much easier to translate something here, compared to other parts of the world. You have the engineering campus next to Physics, next to Chemistry, next to the Medical School and I think there are very few places around the world that have this seamless connectivity between the different disciplines.

That is for example, what we are trying to achieve with the graphene neural interface technology I described above. With the funding of the largest-ever research consortium by the European Commission, the Graphene Flagship (<http://graphene-flagship.eu>), we are aiming to start studying clinically the graphene-based neural electrodes developed within the next year with our neurosurgeon colleagues in Manchester.

On the other hand, I am fully aware that the effort should not be uniquely on graphene - we need to look at other nanomaterials too - not everything needs to revolve around the graphene and 2D materials portfolio. So it's a balancing act.

#### What are your ambitions for nanotechnology research?

I want to see more proof-of-concept, small scale clinical studies on the use of graphene and other advanced materials in nanomedicine and nano-oncology sooner and faster. These will help create knowledge and allow all stakeholders (clinicians, patients, investors, regulators) to feel more confident with the use of such novel materials in the clinic.

On a broader level, I would like to see Manchester researchers be respected for what we can deliver in this field. I want the University to be securely placed on the map in the niche space of nanotechnology for cancer. I wish people to associate us with excellence, exactly as they connect with the Christie Hospital in terms of excellence in oncology patient care.

I think we already have the respect amongst researchers globally, but it's just a matter of maintaining and gaining the reputation. You don't win anything without persistence and effort. Manchester United needed to be successful consistently for 50 years to build the global reputation and following they enjoy today. We can't expect to be the Manchester United of nanotechnology (apologies to City fans...) within just a few years!

**Kostas Kostarelos is Professor and Chair of Nanomedicine at The University of Manchester. He is leading the Nanomedicine Lab, part of the Centre for Tissue Injury and Repair and the National Graphene Institute.**

As our understanding and appreciation of cancer evolves over time, we need new drug molecules to identify the are needed. But before a drug even reaches the clinic, it passes through the discovery process, where targets are identified and screened with lead compounds taken through to the clinical trials and further development. It can be a lengthy and expensive process, involving the screening of thousands of potential compounds that could only lead to one drug reaching the patient.

One of the challenges with conventional chemotherapies is the unwanted side-effects they can cause. This could be anything from nausea and vomiting to hair loss and infection. But these side effects are caused by the non-targeted nature of the chemotherapy itself. Conventional drugs are often highly effective at killing cells, regardless of whether the cell is cancerous or healthy.

Complicating this process further is that cancer is unique to the patient and type; a drug that is active at treating prostate cancer won't necessarily be as active for a different patient suffering from breast cancer or melanoma for instance. It is therefore the goal of researchers to find new drug molecules that exhibit high affinity and activity for cancerous tumour cells while leaving healthy normal cells alone.

To overcome these harmful side effects and improve patient outcomes, clinicians need new drug molecules that provide a more targeted, personalised approach to cancer treatment. One of the aims for our drug discovery teams is to find new molecules within cancer cells that aren't present in normal healthy cells and then develop new drugs that are specific to these sites.

# DRUG DISC AND TEAM



# OVERY

SCIENCE

**Drug discovery and  
development pipeline**

1. *Target Identification & Validation*
2. *Compound Screening*
3. *Hit validation*
4. *Lead Identification & Optimisation*
5. *Clinical Trials & Approval*

*The process is  
estimated to take  
10-14 years and  
cost more than  
\$1 billion*

Professor Caroline Springer is Director of the Drug Discovery Unit (DDU) at the Cancer Research UK Manchester Institute that builds upon fundamental biology discoveries made within the Institute as well as the wider environment of the Manchester Cancer Research Centre.

The DDU investigates novel drug discovery targets to discover new chemical entities for the treatment of unmet clinical needs in cancer patients.

With a career in cancer therapeutics spanning over 30 years, involving all stages of the drug discovery process, Professor Springer tells us how the Unit is driving new drug innovations.

"Having started work in medical research, I knew I wouldn't want to do anything else. It's fascinating and I still get excited about all our research projects in the DDU: one of which is the Gene-Directed Enzyme-Prodrug Therapy, GDEPT. Although it at first seems quite complicated, it is actually trying to achieve something relatively simple.

"Much of what we do is to work with our CRUK Manchester colleagues to find selective new targets within cancer cells that don't appear in normal cells. Then we work out how to make inhibitors that work selectively on those targets to stop the cancer cells dividing. We have many such targets in our portfolio of projects at the moment.

"Previously, 'conventional chemotherapy' cancer treatments used targets within the cancer cell that were also present in normal cells so that whilst these conventional drugs were good at killing cancer cells, they were often good at killing the normal cells too, thus causing unwanted side-effects, such as nausea and vomiting.

So we are aiming to find new ways of directly tumour-targeting these types of cytotoxic drugs, the drugs that kill cancer cells, and thus spare normal cells.

#### Old versus new

"The original conventional chemotherapy way was to take drugs that were toxic to the cancer cells and deliver them in the highest possible dose that the patients could withstand to spare their normal cells.

"Traditional chemotherapy works because it kills cells, and the side-effects are sadly the drug working in the way it's supposed to, but in an inappropriate place. You can't divorce those two things because it's the way that those drugs have been designed to work. Many of these types of drugs were designed to inhibit the replication of cancer cells by targeting their DNA; since cancer cells need to replicate their DNA to proliferate, but unfortunately they work on the normal cells that are dividing too, like those in the bone marrow, gut and hair follicles.

#### Selective delivery

"Our Gene-Directed Enzyme Prodrug Therapy, or GDEPT project uses the design of these the sorts of cytotoxic drugs but delivers them selectively to tumours so they can't kill normal cells in the gut or bone marrow. To do this we synthesise a detoxified form of a drug called a 'prodrug' whereby we have attached a molecule to the drug that chemically deactivates the drug."



# THE DRUG DISCOVERY UNIT



"The prodrug is no use on its own however so we need something that activates the prodrug to form the cytotoxic drug only in the tumour.

"So the first step uses a non-toxic vector that can home in on tumours selectively and then the vector forces the tumour to produce a completely new enzyme that is different from all the natural enzymes in the patient.

"We have been working on a new viral vector, which is a virus with some of its critical genes removed so it's no longer active as a virus, but retains some of the properties that enable it to infect cells.

"We've removed those virus-essential genes so that the virus no longer has toxic effects but it can still act as a delivery vehicle, to take foreign enzyme genes to cancer cells. This enzyme is not a mammalian enzyme and is different from our native enzymes so it is able to catalyse a different reaction; it's not harmful but it acts in a different way from any enzymes that we have.

"So first we inject this modified viral vector, which contains the gene for the bacterial enzyme, and which is excellent at seeking tumours. We have designed the vectors to avoid seeking normal cells. When the vector arrives at the tumour it produces a lot of the foreign enzyme. We designed our prodrug so that it is cleaved only by the bacterial enzyme to release the cancer killing drug.

"The way it works is that in the first step we administer this viral vector and then we wait a few days for it to localise in the tumour. Then, in the second step, we administer the prodrug. As soon as the prodrug arrives at the tumour it is cleaved by the bacterial enzyme there to form the active drug, and now this active drug is only in the tumour."

## Challenges

Cancer is not just one disease, it is over two hundred across many different tumour types and each of them may require different kinds of treatments and drugs. Thus each cancer needs to be looked at individually to see what is driving it and identify the best therapy for it.

There may be multiple subtypes of each cancer and multiple resistance mechanisms, such that the focus needs to be on each individual's patient's disease, rather than globally on a disease type as in the past.

"The term 'personalised medicine' is key, that each patient receives the right drug for their particular tumour type.

"The challenges here are great and are expensive in terms of research. Fortunately CRUK funds our core drug discovery research.

## Ambitions

"What we're doing here using the fantastic expertise and skills of the scientists and clinicians in Manchester to deliver new inhibitors and drugs.

"We all have the desire to get the inhibitors we discover into clinical trials as quickly as possible so that cancer patients are able to benefit from them. We all hope that they will be effective and benefit those patients. I love what I do and so do my colleagues."

**Professor Caroline Springer is Director of the Drug Discovery Unit, Cancer Research UK Manchester Institute.**

*"The term 'personalised medicine' is key, that each patient receives the right drug for their particular tumour type."*



A low-angle photograph of the University of Manchester's main building, a large stone structure with Gothic architectural features like pointed arches and a central tower. The sky is clear blue.

MANCHESTER  
1824

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# BACK TO BASICS

High quality science and doing things differently in translational science in Manchester are yielding new drug discoveries that can be used to treat ovarian cancer. Professor Stephen Taylor, Head of the Division of Cancer Sciences at The University of Manchester tells us what this approach is yielding.





"For me, the key to any discovery is high quality science, processes and experimentation and interpreting the results with rigour. For any research to translate effectively into clinical practice and patient care it absolutely must be underpinned by high-quality science and that's happening here.

"One important Manchester led project which had this good science at its core is a collaboration between the University's Drug Discovery Unit, the Cancer Research UK (CRUK) Manchester Institute and the Christie NHS Foundation Trust. This involves researchers coming together to investigate the PARG (Poly ADP-Ribose Glycohydrolase) enzyme, and how this might be used in the treatment of cancer.

"Firstly, researchers developed new drugs to combat the PARG enzyme and then they began to explore the effect of the new drugs on various cancers, latterly focusing efforts on ovarian cancer. Quite quickly we discovered that while some cancer cells were resistant, some were highly sensitive. This was an exciting observation because it meant that there may be a subset of ovarian cancer cells that have an underlying vulnerability, which makes them sensitive to this inhibitor.

"We then explored the underlying mechanisms responsible for drug sensitivity and discovered that certain ovarian cancer cells that a priori have an underlying DNA replication vulnerability are sensitive to this inhibitor. We then validated this by testing the drug not only on additional cell lines, but on patient biopsies. We didn't necessarily have to be an expert in oncology. What was more important was our ability to do high-quality experiments that were relevant to the biology of that area.

### Doing things differently

"We do translational science slightly differently here and work on different model systems. In my laboratory, we work on established cell lines grown in culture and on patient biopsies.

That's a relatively unique angle - the fact that we can isolate living cells from patients, bring them into the lab, grow them and do high resolution cell biology on patient biopsies.

"This contrasts with the more traditional method of cancer pathology, which involves the analysis of cells that have been fixed. By definition these aren't 'living' cells. Our methodology allows us to observe living tumour cells that are dividing - for more effective analysis and diagnosis.

"We can also grow the living cancer cells in culture over a number of days and weeks and add chemotherapy drugs to see how they respond - so we can actually start to measure the chemotherapy response in the lab.



### The road to translation

"After almost 15 years working on pure scientific research, my team and I wanted new challenges and to explore new avenues; this led us to focus more on translational research.

"I was interested in applying our experience and high quality, rigorous research to an area in which, at the time, there seemed very little interest - the biology of chromosome instability in the context of ovarian cancer. A lot of the existing genomics research in this area was based on the analysis of dead cells; and what I wanted to bring to the table was the ability to do high-resolution, high-quality cell biology analysis on patient material and apply our mitosis expertise to that.

"Some people would describe this as reverse translational science, as opposed to traditional translational science, where you hope your experiments in the lab will have an impact on patients. Instead, what we're doing is taking the patient material - living cells - and bringing that into the lab in order to learn more about the disease.

"So, rather than studying established cell lines, which often aren't necessarily representative of the disease you are researching, we are collecting biopsies from patients. And the advantage of

establishing ex vivo cultures is several fold. First and foremost, because we work very closely with the Christie Hospital, we have the full clinical histories of the patients. We know exactly what kind of disease they've got; we know exactly what chemotherapy is being used; and we've got all of their survival outcome data. You have none of that when you use an established cell line in your research.

"Also, we're now getting more and more living cell samples - from biopsies before, during and after treatment - longitudinal samples taken from the same patient at different times in their journey through their treatment cycle. This is a key breakthrough, because if we also examine the tumours post mortem we have the potential to establish a rapid autopsy programme to help us understand the changing biology of the tumours and ultimately why they have caused the death of the patient.

"Like the collaboration with the PARG inhibitor, we took some of the samples from our living biobank and we showed that some were sensitive, others were resistant and we could show that the ones that were resistant, we could make them sensitive by treating them with this new drug in combination with an existing drug and you can develop ideas and hypotheses about new drugs, new drug combinations.

"The ideal would be to build up a living biobank of viable cultures that have been generated from biopsies isolated at presentation, surgery, during chemotherapy, at relapse and at death, so that we can see how cancer cells evolve and change and this biobank of well-characterised samples would provide an amazing test bed for new therapeutic drugs.

### Biobanks

"To have a biobank of 100-plus highly characterised well-understood samples that we can routinely screen against all the FDA-approved drugs to identify novel drug combinations that you wouldn't have explored otherwise would be incredible. It would be the dream.

"There are challenges around realising this obviously as high quality data requires high quality science carefully and rigorously and that requires investment, but we'll succeed.

I can see how Manchester is really going to take off and become one of the best places in the world to do cancer research. That's incredibly exciting, to be part of something that's on the way up, as opposed to something which is just maintaining status quo, and Manchester isn't standing still."

**Stephen Taylor is Leech Professor of Pharmacology and Head, Division of Cancer Sciences, The University of Manchester.**

## **Find out more**

For more information about the university of Manchester research beacons, please visit [www.manchester.ac.uk/beacons](http://www.manchester.ac.uk/beacons)

To learn more about cancer research activity at The University of Manchester, including our impact and key people visit [www.manchester.ac.uk/cancer-research](http://www.manchester.ac.uk/cancer-research)

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