

CANCER FUTURES

TOMORROW'S
WORLD
**PREPARING FOR
FIRST PROTON
BEAM PATIENTS**

UNIQUE
COLLABORATIONS
**THE ONE
MANCHESTER
APPROACH**

ROB BRISTOW TALKS
TEAM SCIENCE

February 2019

BREAK THROUGH

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



Research beacons

Research beacons

GLOBAL CHALLENGES
MANCHESTER SOLUTIONS

Advanced materials
Cancer
Energy
Global inequalities
Industrial biotechnology

Cancer

GLOBAL CHALLENGES
MANCHESTER SOLUTIONS

February 2019

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INTRODUCTION

“Cancer is the second leading cause of death worldwide. Overall the risk of getting cancer is one in two over a lifetime. The economic cost of cancer is increasing. Cancer is therefore a significant focus for the researchers and clinicians in Manchester who dedicate their careers to prevention, the treatment and care of patients, and the quest for breakthroughs that will benefit wider society.

In Cancer Futures, I'd like to share with you a snapshot of the incredible research stories, and the people behind them, that reflect the breadth and depth of expertise from the laboratory to the bedside.

Cancer is one of The University of Manchester's research beacons – examples of pioneering discoveries, interdisciplinary collaboration and cross-sector partnerships that are tackling some of the biggest questions facing society today.

Many of my colleagues featured here refer to a One Manchester partnership approach involving scientists, health professionals and policy-makers that enables us to carry out transformative and life-changing research. This fusion of expertise and experience ensures that research can have positive impact for patients as quickly as possible.

Manchester's powerful research programmes are tackling the treatment of cancer diseases, as well as prevention and early detection, and how we can improve the lives of patients living with cancer, for instance, by understanding side-effects and trying to prevent them. There are many examples in this magazine of transformative science, none more so than being able to offer the first proton beam treatment at The Christie hospital this winter and our innovative lung cancer study which has led to recent NHS policy change.

The City that gave birth to the industrial revolution and its academic cornerstone, The University of Manchester, whose discoveries have include splitting the atom and developing the wonder-material Graphene, will continue its march to improve cancer research outcomes, helped by the opportunities afforded by the Government's devolution of the £6 billion health and social care budget, the first place in the country to realise such an opportunity.

Here in Manchester we are helping to create a world in which more people can survive cancer.”

Professor Peter Clayton, Vice-President and Dean (interim)
Faculty of Biology, Medicine and Health, The University of Manchester.



Strength in partnership

Research in Manchester takes place within a unique landscape where world leading institutions work hand in hand.

This environment and the strengths of each organisation are enabling rapid transformations and developments in cancer detection and treatment.

Cancer research in Manchester is coordinated through the Manchester Cancer Research Centre (MCRC) under the leadership of Professor Rob Bristow, which brings together three organisations with reputations for excellence in cancer research: Cancer Research UK, The Christie, and The University of Manchester.

The MCRC oversees new initiatives and builds strength through consensus, ensuring that the overall research strategy in Manchester is compatible with, and influences, the ambitions and strategies of the individual organisations.

You can hear more about the different strengths of each organisation on pages 14-24.

Rob Bristow is the Cancer Domain Lead and Professor of Cancer Studies at The University of Manchester and Director of the Manchester Cancer Research Centre (MCRC). He explains what it was about Manchester that lured him from Toronto, Canada, and why he believes getting cancer team research aligned here will lead to better patient outcomes globally.

Why did you want to pursue a career in cancer research?

My initial training in Toronto was heavily weighted around mentorship by translational researchers that closely linked basic science and the clinic. The questions being posed to me and fellow doctoral students in the early 1990's centred around the tumour biology and genetics relating to resistance to chemotherapy and radiotherapy. I had started to think about oncogenes such as ras, and tumour suppressor genes such as TP53, and focused on trying to understand how these abnormalities led to cancer by placing these abnormal genes into model normal cell systems. This was hugely exciting to me during my PhD and concurrent medical specialty training. Now we're in a whole other realm, the era of the genome, which is also terribly exciting given the possibilities to link specific genetic changes to a patient's outcome. Across the planet, teams of scientists have utilised incredible technology to sequence many, if not all, of the major genes involved in the major cancers. I was lucky enough to be involved in the International Cancer Genome Consortium.

The idea now is to put these findings into a clinical context so that we can understand who has an aggressive versus less aggressive disease to place patients into individual treatment pathways: a more precise way of cancer treatment with potentially less side effects overall. The same information can be used to understand how we can prevent cancer based on their bloodline (germline) DNA that gives signal as to whether an individual will be at risk for a specific cancer during their lifetime. Knowing this, we can prevent cancers earlier on. Harnessing correctly all the information that genomics can bring to bear on a patient's cancer and co-existing diseases (comorbidities) will drive forward a new approach to patient care in Greater Manchester and indeed, the world.

PROFILE



Why did you choose to come to Manchester?

The University of Manchester is home to world-leading research led by experts spanning the full cancer spectrum from work on cancer prevention and early detection through to molecular classification of patients into innovative clinical trials using radiotherapy, drug therapy or immunotherapy. There is also important research on the 'living with cancer' theme with links to survivorship and preventing long-term complications of therapy. Of great appeal to me was the University's strong links with local NHS trusts which means our researchers work side-by-side with clinicians, quite literally taking our research from the laboratory bench to the bedside and back.

The MCRC with its partners the University of Manchester, Cancer Research UK and the Christie and other Manchester-based NHS trusts, together allows for collaborative programmatic approaches to genomics. We have a Genomics England hub that will in time link novel genetic tests to each patient when they come to clinic anywhere in the Greater Manchester Cancer Plan (GMCP) encompassing more than three million people. Also at The Christie, there is a new collaboration with SAP, the applied business solutions company, to create a 'live' clinical database where every patients genomics is linked to how they are doing with treatment and their side effects uploaded using their mobile-all being connected in time to the NHS clinical record. This will be a first 'real world' outcome protocol for the UK and a global lead in electronic data married to a patient's genetic make-up.

When you are thinking about your own personal research strategy and having maximal impact, you ask yourself 'where are the best environments to achieve what you want with your research?' Manchester also leads numerous early phase trials at The Christie which tests the latest targeted therapies and increasingly uses molecular profiling to maximise patient benefit. As a prostate and bladder cancer specialist, my personal ambition is to try and use a patient's bloodline and tumour genomic secrets to provide information to access these novel trials for a bespoke treatment that fits them best. There are very few places globally that have married the genomics using both solid tumour and liquid (blood) biopsies before and during treatment to track success of a treatment.

The liquid biopsies can also be used within the GMCP to detect cancers quite early. This is a game changer, and we have a real ambition to build this into a world-renowned program and collaborate world-wide to prevent cancer. And so, the groundwork to realising my ambitions has already been laid out by the high ambitions of the fantastic basic and discovery scientists and clinical researchers in the city. Therefore, for my personal research programme, Manchester provided an opportunity to activate all concepts of genetic sequencing that we were doing in Toronto and bring it into the clinical realm of 'real world outcome' in the NHS to directly impact patient care.

What were your first impressions of Manchester?

It's a smaller city than Toronto, but a really exciting city to live in with the Northern Quarter and music scene and the surrounding Lake District, Cheshire, Peak District and Wales within one to two hours drive. I can honestly say that I made many visits before I decided to take the role of MCRC Director, as the health care and research culture was different from what I was used to in North America. What I wanted to understand was whether there was a willingness and ambition among colleagues here to embrace new models of research and new models of change in clinical practice. You can't just simply put in place what you want to enact based on your previous jurisdictions. Instead, what happens over time with continual questioning in the new environment is that you find novel ways to leverage your new role to achieve even more than was attainable in your previous

environment. What sold me on Manchester was the concept of building effective cancer research teams with a line of sight to the clinic and a shared set of goals and roadmaps to get there. Best research is best clinical care and the best research can come from any jurisdiction. In my final visits prior to joining Manchester, I realised that many people in different disciplines and from varied training backgrounds were open to creating dynamic research teams, which was fantastic.

What differentiates Manchester from other cancer centres?


Undoubtedly, Manchester is a global powerhouse of basic, discovery and applied research. Within the University's cancer beacon, the MCRC is branding itself as the virtual space in which the collaborative research is added value to current strategies. I think we are collectively changing the way we think about cancer biology to either prevent, diagnose, treat, or minimise the side-effects of treatment. To my knowledge, there's nowhere else in the world where cancer research is elevated and activated to such a high level based on the tripartite commitment of the University of Manchester, Cancer Research UK and The Christie. It is also the basis of joint fundraising around the Paterson rebuild project which will align basic and clinical researchers in collaborations in a building that celebrates teams. The senior leadership have aligned their goals to allow us to create something quite novel here and together embrace an ambition that breakthroughs will happen because Manchester wants to be the place to do it first. A little bit of positive competition never hurt anyone.

Can you explain your concept of 'team science'?

My background is in developing strong scientific teams with an equally strong focus on answering an outstanding clinical question, like we did in prostate cancer genomics in Toronto. Together with colleagues from multiple disciplines, I built a team that within five years became a global lead in genetic sequencing of localised prostate cancer by leveraging support from people in different research institutes of the university and teaching hospitals. We married biology and bioinformatics within a clear line of sight to answer a simple but practical question in the clinic: why do some prostate cancer patients fail surgery or radiotherapy and is this due to hidden spread, or metastatic disease, at the time they are diagnosed? We therefore had a very crisp clinical question which was just as important to specialists in medical oncology, surgical oncology, radiation oncology, pathology and imaging as it was to our own basic science and discovery team. In order to answer the question as rapidly as possible for patients, you focus all of your efforts together to answering the question. You reverse engineer the science to get to the answer as quick as possible by aligning skill-sets and smaller parts of the overall goal. It becomes team science, a team comprising a wide range of professionals with deep knowledge in their own areas who are best placed to answer smaller questions that together leads to answering the big question more efficiently.

What are the advantages of team science working?

Senior and junior investigators work together across different disciplines towards a high-ambition, high-risk common goal. At the same time, it can create opportunities for all investigators to take parts of the project's discovery as it unfolds to develop their own novel research areas. So if you create the right team, and if you set up the rules of engagement right at the outset in stating your specific global study endpoint, people can go and cherry-pick discovery research as added value so it becomes an exciting effort for everyone involved. It actually broadens the scope of what is achieved beyond the question that initially brought the group together. It also prevents a solely top-down approach to the scientific team; an antiquated approach in my personal view.



“The key is that the research is so simple that everyone gets it, even though the way you all work together to achieve it may be complicated.”

Do you think Manchester will be a good centre for Cancer Team Science?

This is a good time to establish multi-disciplinary teams that are looking at cancer problems in both a mechanistic and holistic manner. I have observed a real sense of comradery amongst researchers being supportive of this cancer team science model with shared visions to transform health care through new treatments and approaches that are Mancunian by design. It provides a true conduit to drive forward extraordinary basic and discovery science and hand that over to the clinicians who are awaiting it as ‘research acceptors’ to enact the research, when actually treating patients. I personally think this is a great approach when dealing with complex patients that have multiple co-morbidities in addition to cancer; this complexity can be handled by placing the research into the clinical ‘real world’ context.

What are the challenges for creating team science culture?

Whilst I personally speak the language of both the scientist and clinician, with a Canadian accent of course, in reality, the nature of individual career aspirations, work environments and the pressures of research funding can be very different in these two areas, and so the challenge is to find true synergies within the teams. Growth and maximising the ambition and productivity of

the synergies requires mutual respect, defined common goals and frequent meetings to identify and agree to the best scientific approaches that could be changing rapidly, to keep pace with rapid scientific discoveries. Creating the environment and opportunities that will facilitate this is key. That’s one of the reasons that I’ve spent several months holding ‘One Manchester Collaborative Town Hall’ sessions enabling the research and clinical researchers to interact directly with patients. Together they come up with the ‘headline’ that they want to see in three years that summarises their innovation and aspiration for a new way to think about and treat cancer in the clinic. These meetings are truly defining the research breakthroughs that we want to see here in Manchester. I’m agnostic as to whether the breakthroughs are at basic science discovery level or in the clinic, or whether it’s about preventing cancer or living with it, or any other research areas. What I want to see, in a rapid timeframe, are real changes in our patient outcomes driven by our research.

What are the Mancunian ambitions that you’ve spoken about?

These are our ambitions to tackle important problems using all the resources that we have in Manchester and which tell a simple story about what we’re doing, that matters just as much to researchers, as it does to Manchester patients. The key is to state the research project in a simple

sentence so everyone gets it, a sentence you could tell someone in an elevator ride. The town hall sessions might not have worked and could have become complicated, but I’ve been very excited about the new research stories coming out of them that will lead to new multi-million pound grants. The MCRC will initially pump-prime these ideas so that in the space of three years, we will see our science in action. I think that’s the exciting part of this. And given that all the new projects have been peer-reviewed by non-UK experts and reviewed as outstanding, we are headed in the right direction.

What are the immediate opportunities for cancer research in Manchester?

The replacement of the Paterson building next to The Christie, which was home to a number of cancer researchers until destroyed in a fire in April 2017, affords us the opportunity to create one of the world’s top five translational cancer research centres.

All the research teams and synergies will have a new home, an exciting home for new ideas and new ways for patients to be involved in research. It will be the place to be for cancer team science in the UK and we know it will attract outstanding cancer research trainees to Manchester. This multi-million pound development is being led by The Christie on behalf of the partners within the MCRC. The new building will be a magnet for

attracting international researchers and building partnerships with other academic institutions and the pharmaceutical and biotechnology industries. We know that having doctors, nurses, researchers and scientists, all working together in one building, will accelerate the development of cancer research through to patient care on the ward.

Which developing areas of cancer research excite you?

Our new centre for cancer biomarkers will be globally unique and linked to a new academic pathology unit in the new Paterson rebuild to drive our academic biomarkers further into the NHS testbeds. We host the biggest and best collection of academic researchers assessing blood-based biomarkers in the world, having pioneered this area. This ‘liquid biopsy’ is the future of cancer diagnosis and monitoring. Through this, we will find cancer earlier and treat it better. Additionally, Manchester is among a small group of leading centres pioneering a ‘precision medicine’ method of treatment but we are taking a completely unique approach, which I’m sure will become a standard of care worldwide looking for clues about the cancer in the bloodstream, not in the tumour itself. Manchester is also scientific leader in the molecular targeting of cancer and early phase clinical trials, and cutting edge radiotherapy that will see the opening of the first NHS high-energy

proton beam therapy centre in the UK later this year.

What do you want the impact of cancer research at Manchester to be?

We need to remain focused on specific strengths to be at the international forefront of cancer research. Our patients can be complex and understanding and tackling this diversity of patient diseases, in addition to cancer and the complexity of cancer itself based on both tumour genetics and the microenvironment, will lead to better outcomes for complex patients who may not normally have a chance to enter a new clinical trial. I know our research can have a huge global impact. If we can get it right for the NHS and for NICE, and if the magnitude of the difference we achieve with our science is large, then we can change cancer treatment worldwide. It’s not ‘what is good for Manchester is good for the UK’, but ‘what is good for Manchester, is good for the world’. We want to say this is the ‘Manchester way’ of treating patients, based on rapid and effective discoveries using Team Science with a One Manchester approach. The idea that we can change things, by adding value to programmes in a creative and multi-disciplinary way is why it’s so exciting to be here every day.

“Manchester is renowned for its ‘team science’ approach and has extensive infrastructure support with access to state-of-the-art technologies and expertise. It’s a pleasure to be part of this extraordinary team.”

The cost of cancer to society, including costs for the loss of productivity is £18.3 billion per year and these figures are set to increase. Professor Sir Salvador Moncada at The University of Manchester outlines why the prevention and early detection of cancer is the only way forward.

THE INDISPUTABLE CASE

for the prevention and early detection of cancer

“It is possible that if we prioritise the prevention and early detection (PED) of cancer, over 60% of all cancers could be prevented or cured. This would reduce the number of people we need to treat as chronic patients down to a manageable figure and would be a huge success from a medical, societal and economic point of view. In my opinion, the reduction of the long-term burden of disease has to be the main objective in the fight against cancer.

One in three people currently get cancer and the latest research indicates that this figure will increase to one in two of us developing it at some point in our lives. These numbers are stark. There is, however, increasing evidence indicating that many cancers could be prevented, with most recent research suggesting a 42% reduction could be possible through lifestyle changes and

other actions such as vaccinations, as in the case of cervical cancer. Furthermore, if cancer is detected early it can be cured with interventions that cost a fraction of the price of later stage treatment.

Studies suggest that early stage treatment of cancers of the colon, rectum, lung and ovary costs the NHS between £3,000 and £5,000 per patient; while treatment of advanced disease will cost between £12,000 and £15,000. The difference in survival between the two groups is enormous; in the case of colon cancer for example, nine out of ten patients will be alive 10 years after treatment if their disease is caught early, while less than one in ten will survive that time if diagnosed late.



The cost of cancer

Cancer is an important and costly health problem. Historically, we've diagnosed it late and then treated it with procedures or drugs that until recently, produced dismal results from both a treatment and side effect perspective. However, the treatment for many cancers has improved to the point that a diagnosis is no longer a death sentence. Increased survival in some cancers is very impressive, such that in 1971, half of patients lived for less than a year after diagnosis, while in 2010 the same proportion survived for 10 years or more. This increase is even more significant when you consider that for some cancers, such as pancreatic, survival remains low.

The problem with cancer is that the return to health is uncertain, especially when diagnosed late. This leads to expensive follow up, which relentlessly increases with the development of newer, more sophisticated treatment and monitoring methods, and with the development of medicines that do not cure, but only extend life.

The additional costs resulting from the long term follow up of cancer also need to be factored into the equation. For example, in 2012-2013 cancer treatment cost the NHS, depending on estimates, between £5 billion and £6 billion, but the cost to society as a whole, including costs for the loss of productivity, was £18.3 billion. The cost of dealing with cancer is set to increase by about 9% per year, meaning the cost to society therefore is likely to reach over £40 billion by 2021.

Treatment

Cancer, however, cannot be eliminated and some people will require long-term treatment and follow up. We should therefore do everything we can to reduce the number of incidences, since looking after half of the population as chronic cancer patients is not affordable.

Obviously, more basic research to better understand the more advanced stages disease is needed to improve treatment but here, again, we should be investing more in research focused on the discovering the origins of cancer and its connection with genetics and different risk factors.

This research, as well as helping with our knowledge in prevention, will enable more accurate risk stratification and identify the best way of dealing with a cancer once detected early, therefore informing on the appropriate medical approach on a patient-by-patient basis.

Understanding risk factors

There are also some cancers, such as prostate, where historically, we've over-diagnosed or over-treated. Many patients have small, slow-growing tumours that don't require treatment, just observational follow-up. Improved understanding of the genetics and the risk factors associated with these cancers will allow a more accurate, and personalised, therapeutic

approach following early diagnosis. The same applies to a number of other situations. For example, young people with colon cancer, in contrast to older patients, may be given chemotherapy following surgery without apparent benefit. The reasons for this difference are not yet clear but they will be clarified by genetic and risk factor studies. It's also important to consider that in the absence of this background work, there is the danger that very powerful new tests and medicines may lead to over treatment and over diagnosis.

In Greater Manchester we've made great strides in our PED research portfolio. For example our innovative lung cancer screening project which resulted in 46 diagnoses of lung cancer, of which 80% of were stage 1 or 2 and therefore highly curable. This contrasts with historical data from Manchester in which approximately 50% of lung cancers detected were at stage 4 with a survival close to zero 10 years after being diagnosed.

Budget

We have the ideal situation in Manchester now thanks to the devolved health and social care budget. If we do it right then we can tilt the balance of all our activity to early stage disease for all the population. In other words not just managing the disease but either preventing or treating with the intention of curing it.

I believe that the PED strategy should also be applied to people who have been treated and are surviving cancer treatment. As with the healthy population, the objective in these patients is to either prevent recurrence or, if it happens, to detect it as early as possible. This suggests that many of the activities deployed for PED in the general population will be also applicable, to those patients too. Looking to the future, a key research project will be monitoring the health of the long term survivors and the impact of the side effects in the quality of their life."

Sir Salvador Moncada is a Professor of Cancer Sciences at The University of Manchester.

NHS cancer treatment costs
£5-6 billion

Cost to society as a whole
£18.3 billion
for loss of productivity

Increase of 9% per year means
£40 billion
likely cost to society by 2021



Director of Research at The Christie, Professor John Radford, tells us how team science is transforming patient outcomes and how personalised medicine can provide the solutions to the next decade's cancer challenges.

THE CHRISTIE PERSPECTIVE



Serving a population of **3.2 million**

2,500 staff
300 volunteers

Treats more than **44,000** patients every year

Largest single site cancer centre in Europe

“Manchester is an ideal location for undertaking cancer research. A key part of this strength is The Christie, Europe’s largest single site cancer hospital, where 14,000 new patients are seen every year in addition to those seen in previous years requiring ongoing treatment or follow-up.

This large patient population means that we have built up a critical mass of expertise in how best to manage different types of cancer and in undertaking research across a whole range of cancers, both common and rare. We work closely with a whole range of pharmaceutical and biotechnology companies who are developing new therapies for cancer. We are able to advise them on where these molecules might best be employed and undertake clinical trials in our clinics and the NIHR funded clinical research facility based on The Christie site. The involvement and support of our patients in this work is crucial, with many travelling from far afield to access the novel treatments available at The Christie.

Size and scale

Because we are a very large centre working with a range of experts in many different fields, we have the opportunity to access and evaluate new technologies. A good example of this is the new proton beam therapy centre, one of just two centres planned in the UK. We were successful in this bid to NHS England because we could provide evidence that we had the required level of expertise in our medical professionals and professions allied to medicine, such as physics, nursing, physiotherapy, pharmacy, pathology and radiography.

Looking forward, there are going to be a number of different challenges, one of which will be the affordability of new treatments. However, this is where personalised medicine linking specific treatment with individual molecular characteristics of the cancer will be helpful. Using a personalised medicine approach, targeted therapies, which are often expensive, are only used in patients where a relevant molecular feature is present. This provides a high level of confidence that the treatment will work and avoids patients being exposed to ineffective medicines and any associated toxicity.

The need for personalisation

It would of course be helpful if we could shift away from treating advanced cancer to prevention and early detection. Manchester as a research community is sharply focused on this and has recently submitted a bid to Cancer Research UK to become one of three UK centres working with colleagues in the United States to improve the way in which cancers can be prevented altogether or detected at an early and potentially more easily curable stage. This approach is highly attractive to patients and the population as a whole and likely to be much more cost effective than treating advanced disease.

A very important focus for researchers at The Christie is developing new therapies by evaluating new molecules and seeing how they fit into the current standard of care and taking older, existing treatments and using them more effectively. We do this by using imaging and other biomarkers to guide treatment, with the intention of stopping this as soon as the disease has been eradicated and so reducing the duration of treatment and toxicity. To help in this effort, we need to continue identifying biomarkers that can tell us what is happening with any particular treatment and what the outcome is likely to be.

Advances in treatments and detection are resulting in increasing numbers of patients cured of cancer. This is clearly very good news but these individuals are at risk of second cancers, cardiovascular disease, osteoporosis and fractures, infertility and psychological issues and so we need to decide how we can best manage this survivor population. A team of researchers at The Christie is currently working on this important area.

Team science agenda

Obtaining useful endpoints from research results from pursuing a team science agenda, which sees professionals from different disciplines working together to realise a shared aim relevant to the cancer patient. At the outset, we define what the problem is that needs solving before then agreeing on the composition of team best able to solve it. These teams will comprise of scientists, physicians, surgeons, nurses, pharmacists, in fact anyone with an expertise relevant to the issue under consideration.

Manchester is becoming increasingly recognised both nationally and internationally as a major player in practice changing cancer research. In the past year we’ve been awarded CRUK major centre status and a NIHR Manchester Biomedical Research Centre (BRC) with three cancer themes. Over the coming years I have no doubt that our influence will continue to grow with Manchester becoming synonymous with innovative developments in cancer treatment focused on improving outcomes for patients. It’s an exciting prospect and one that I very much look forward to.”

John Radford is Teenage Cancer Trust Professor of Teenage and Young Adult Cancer at The University of Manchester and Director of Research at The Christie.

As the basic science component of the MCRC partnership, Cancer Research UK Manchester Institute (CRUK MI) Director, Professor Richard Marais, outlines the challenges and opportunities that are generated by the research community's ever increasing knowledge about this complex disease.

OUTLINING THE

CHALLENGES

"We're now beginning to comprehend just exactly how complex cancer really is."

“As a basic science institute within a clinical cancer environment, our focus is on translational and clinical research. Our scientists are working on understanding the biology of cancer and how we can use this knowledge to improve cancer care. We bring the ability to work right across the board, from the discovery of cancer biology, the identification of targets, and biomarkers, all the way through to the production of new drugs in our drug discovery unit. We implement biomarkers via our biomarker centre and all the way through to clinical trials, and use the information from these trials to refine our understanding and improve patient care.

Access to patient samples and clinical data is incredibly important in modern research and this is a major benefit of the partnership to us. It means that we can have an improved understanding of how patients are responding to new treatments, drugs and strategies, and modify our research accordingly.

Equally important is being aware of the questions which are being asked within the clinical community. It's the ability to bring the clinical and the basic scientists together and interact so that we can start to find out what basic research questions the clinicians need answering, making sure that we're in the discussions about this and making sure that any new discoveries feed through to the clinic, as early as possible.

Learning more

Our increased understanding of cancer biology means there are more opportunities globally than ever before to apply this knowledge. Of course you're always going to be in a position where your understanding today is greater than it was yesterday but we're now beginning to comprehend just exactly how complex cancer really is.

We're starting to see the magnitude of the diseases' complexity; comprehending the depth of knowledge that is needed to properly understand it. While our collective global research community's understanding of the disease is still quite rudimentary, we are continually making huge advances in knowledge. The opportunity for us all lies in the advancements made in one disease area, feeding into other areas, and for us to identify how we can cross fertilise knowledge across different disease areas. For example, amongst the big four cancers (breast, lung, prostate and bowel) breast cancer incidence has reduced by 10% in the past five years whereas prostate cancer has only seen a 5-6% reduction. Can lessons in breast be applied to prostate?

Whilst increased scientific understanding is leading to improvements in patient care, and surgical techniques are resulting in better patient outcomes, at the same time we need to maintain our level of questioning; how we can improve our knowledge use of drugs in order to combine different modalities that will achieve better patient outcomes? how do you combine surgery with chemotherapy? how do you improve the new targeted therapy with immunotherapy? how do you get the best out of that? These are the learning opportunities we have.

- Basic science is concerned with figuring out how the world works. It is also called discovery science
- In biology, it involves looking at cells to understand how they grow, function and die.
- In cancer (and many diseases) scientists study how genetic mutations affect the way the cell or organ (or body) behaves.
- Basic/discovery scientists look at what causes cancer and translational scientists look at how to treat it.



Understanding our data

Our access to new drugs and increased understanding of cancer is beginning to impact on patient outcomes, with us slowly seeing more people surviving cancer than ever before. But the increased knowledge, treatment options and methodologies bring increased associated challenges, how can we best harness all this complexity? Because we're generating new data so quickly we barely have time to understand it before we have to move to the next stage.

New scientific and clinical techniques and drugs mean we're able to understand cancer better than ever before, but all this learning generates enormous amounts of data and we need to become smarter in learning how to solve and simplify this.

Personalisation is key

To really make an impact for patients we're going to have to learn how to get the best out of the drugs we've got, how to most effectively combine them and how to do this in individual patients so that we're personalising their treatment to ensure that we're treating their specific tumour and nobody else's.

When I first arrived in Manchester, clinicians in my field, melanoma, were frustrated because they didn't know which drugs they could put their patients on as the small number available weren't working. Now those same

clinicians have so many options that they don't know which of the multitude of drugs to give to which patient. They're overwhelmed by choice. We need to concentrate on the idea of precision medicine, which sees us giving every patient the individual treatment they need and don't just treat everybody the same. This is a technical and clinical challenge but something that Manchester is perfectly suited to tackle.

There's a huge, untapped expert community here that the cancer community could engage more routinely with and whom would bring immense value to the research. For example, we're starting to bring in the material scientists, physicists, engineers and mathematicians but alongside this, we need to build the basic biology and infrastructure that will allow this to become more routine and allow us to have more people feeding into different areas. There's potentially an enormous amount of space to fill and I think there are genuine opportunities to be broader and wider in what we do.

Whilst we are still a relatively small community, it's worth remembering that Manchester forms the core of the Cancer Research UK investment outside of the south west of England, so, in addition to the science, the research and the discovery that we have here, we've also got the political clout. This is where we make things happen".

Richard Marais, Director, Cancer Research UK Manchester Institute and Professor of Molecular Oncology at The University of Manchester.



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- Apply to our fellowship programme for funding and personal support to develop your independent research group
- Generous start-up packages to support your tenure-track career progression at our research institutes

Learn more at cruk.org/leaders-of-tomorrow

Together we will beat cancer





Cancer research at The University of Manchester takes place within the Division of Cancer Sciences and its Head, Professor Tim Illidge, is clear that it is multidisciplinary working between the clinical and scientific research which is driving innovations in personalised cancer medicine.

BETTER
TOGETHER

“For me, the strengths of cancer research in Manchester are secondary to the strength of the unique partnership that we have within the Manchester Cancer Research Centre (MCRC). At the centre of this are three very large and effective partners working together in a way that no other cancer centres do. With The Christie as Europe’s largest cancer hospital and the UK’s largest single site university and the largest cancer research charity in Cancer Research UK, exciting possibilities come to fruition. This is what sets us apart, makes us world-leading and the envy of other cancer centres.

All the partners bring something different and unique to this partnership. For the University, it’s the incredible breath of our cancer research. All of the clinical academics and many of the discovery scientists within this research community are working within the Division of Cancer Sciences. For the clinical academics these include medical oncologists, radiation oncologists, surgeons, pathologists and radiologists. Other unique groups include the growing talent of academic physicists who are now working at the interface with the clinical team and include world renowned experts in imaging, mathematical modelling experts and big data analysis within the radiotherapy-related research group.

Access to expertise

Amongst our medical oncologists we have leaders in delivering experimental cancer medicine who are pioneers in early and later phase trial design and development. The radiotherapy related research group has been transformed beyond recognition in the last few years, from just a few individuals, to a team of over 100 thanks to a recent and large scale infrastructure investment. This has led to us becoming the National Centre for Protons, receiving additional Department of Health funding.

Similarly huge investments in research have allowed us to recruit a number of world leading researchers, including Marcel van Herk, Karen Kirkby, Neil Burnet and Peter Hoskin, who work alongside a rich pool of Manchester-grown talent that these investments have helped us to retain.

We have clinical specialty in haematologists, pathologists and radiologists. We’re incredibly diverse and our uniqueness in cancer sciences is in the breadth of the research that we undertake. This is based in discovery science that allows us to move into the clinic and perform clinical translational research, which in turn enables early phase and late phase clinical trial design. The most important part is getting the discovery scientists integrated and working alongside the clinical teams.

Whole spectrum approach

We work collaboratively across the whole spectrum of research from discovery to clinical implementation, but this won’t happen if you have siloed working and the research and clinical teams don’t communicate effectively. Modern cancer research is cyclical. If you are working in the clinic and see a clinical problem or need, you then try and address that with the scientists in a dialogue. This could result in a different approach to treatment stemming from your idea or the development of a new drug which you take back to the clinic and learn from; it’s a constantly evolving cycle. What’s important to making rapid progress is the dialogue. It’s no longer just bench to bedside but bedside to bench. The cycle never stops. The challenge for us is how to make this dialogue and this team science approach happen as often as possible across Manchester.

As a clinical scientist I start with a clinical problem that I want to try and address within my laboratory research. For me, success is taking what I learn in my laboratory back to the clinic and being able to test novel drugs and approaches in a timely fashion that allows us to know if we’re making progress or not. This is currently one of the biggest challenges for the research community and something we’re able to progress our knowledge of, through multidisciplinary working.

Understanding personalisation

Today we have so many targets, drugs and so many drugable targets that the combinations and opportunities are limitless. Knowing how to approach the problem can be the biggest challenge. In the past, we’ve taken a pragmatic approach and treated all cancers in same way but now we’re in an era of personalised medicine. We know far more about the genetics and the tumour immunology of particular tumours, and through the development of biomarkers, we’re beginning to understand more about which patients are more likely to respond well to certain drugs or treatments. So the challenge now is to ensure that we offer the right treatment approach to the right patient, rather than the more generic approach that we’ve offered previously.

For a long time we’ve tried to modify treatment based on the patients age and comorbidities, and whilst that is in itself a personalised approach, we need to go beyond that and address a much wider range of the tumour biology and how it interacts with each host patient. This however is a challenge because the tumour is always evolving and so we need to revisit and re-biopsy the tumour and modify treatment according to what’s happening in real-time. This is something we’re getting better at with imaging, pathology, genomics, proteomics and immunology; because of this multi team approach, our collective efficiency is increased.



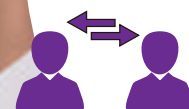
The University of Manchester is the UK's largest single site University.



It is home to the UK's largest student community.



It has an annual income of more than £1 billion.



Cancer is one of the University's five research beacons, exemplars of interdisciplinary collaboration and cross-sector partnership that are distinctive to the University.

In cancer drug therapy we're also routinely questioning the appropriateness and relevance of the right drug, for right patient, at the right time. In radiotherapy we're asking which patients need fewer treatments and which require a boost of dose. Rather than asking: do we need to treat the cancer and the regional node? Consider: can we give a smaller dose to some patients so that a personalised approach is developed? Surgery is another example of this increasing personalisation of care and here we're reviewing which patients actually require treatment for prostate, as whilst many men develop the disease, many of these don't actually require treatment, its knowing who to treat and when.

Analysing and understanding the theranostics, outcomes or big data analysis on the huge amounts of data on the patients we look after, will be crucial in informing how we can better treat future patients, identifying groups who will benefit from treatments and improving

patient treatment strategies. Mining this patient outcome data will become crucially important to us moving forward and becoming world leading.

My ambitions for our research community are simply to build on the unique partnership that we have and to encourage research teams work together, continuing to perform 'team science'. Teams that communicate, collaborate and integrate will enable us to tackle the big problems in cancer much quicker. A more unified and multidisciplinary research approach will facilitate free communication, helping us to progress our research and knowledge through mutual understanding. The future is exciting."

Tim Illidge is the Head of the Division of Cancer Sciences and Professor of Targeted Therapy and Oncology at The University of Manchester and Honorary Consultant in Clinical Oncology at The Christie.



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 Rachel Chown.

tel +44 (0)7976 277 311
rachel.chown@manchester.ac.uk
www.mcrc.manchester.ac.uk



Discovery
of the proton

1917

Ernest Rutherford, Hans Geiger and Ernest Marsden develop the modern understanding of the atomic structure, with the discovery that every atom contains a nucleus

First clinical
trial of
diethylstilbestrol

1944

Dr Edith Paterson conducts the world's first clinical trial of diethylstilbestrol (Stilboestrol) for the treatment of breast cancer

First stored-
program
computer

1948

Frederic Williams, Tom Kilburn and Geoff Tootill develop the world's first stored-program computer, nicknamed 'Baby'

First use of
cultured bone
marrow

1986

The world's first use of cultured bone marrow for leukaemia treatment

First single
harvest
stem-cell
ransplant

1991

First clinical use
of image guided
radiotherapy on
a radiotherapy
machine

2002

Discovery of
new great cancer
genes

2007

Professor Gareth Evans identifies novel breast cancer susceptibility genes from 2007 onwards

First clinical trials
of osimertinib

2013

Manchester researchers lead on the first trials of osimertinib (Tagrisso) to treat metastatic non-small-cell lung cancer

First high energy
proton therapy
centre in
the NHS

2018

The first NHS high energy proton therapy centre opens in The Christie

MANCHESTER MILESTONES

IN CANCER RESEARCH

Development of
The Manchester
Method

1932

The first international standard for radium treatment is developed and named 'The Manchester Method'

First randomised
trial in cancer

1948

Professor Ralston Paterson (husband of Edith Paterson) conducts the world's first randomised trial in cancer: adjuvant ovarian irradiation

First use
of tamoxifen

1970

Dr Moya Cole and Dr Ian Todd conduct the first clinical use of tamoxifen (Nolvadex) for breast cancer

First pre-surgical
use of tamoxifen

1987

Professor Andrew Baildam and Professor Tony Howell carry out the world's first pre-surgical use of tamoxifen

First patient
enrolled in EGFR-
TKI Gefetnib trial

1998

Manchester leads on the first Phase of EGFR inhibitor gefetnib (Iressa, a treatment for non small cell lung cancer (NSCLC) that has spread into the surrounding tissues (locally advanced) or to other parts of the body) and enrolls the first patient globally

First clinical
trials of
anastrozole
compared to
tamoxifen

2005

Professor Tony Howell shows that anastrozole (Arimidex) outperforms tamoxifen in preventing the relapse of breast cancer; anastrozole is now the major endocrine therapy for breast cancer

First clinical
trials of
radioioimmuno-
therapy

2009

First trials in Europe undertaken for pioneering radioimmunotherapy cancer treatment at Manchester

Development
of childhood
acute lymphatic
leukaemia relapse
strategies

2010

Professor Vaskar Saha designs the ALL R3 study, which now forms the basis of relapse strategies for children with ALL across the world

First UK trial of
mobile cancer
screening units

2017

A trial scheme of 'scans in vans' screens 2,500 people and detects 75 cases of lung cancer; the scheme will be rolled out nationally

First patient
treated at proton
therapy centre

2018

Whilst much of Manchester's innovative cancer research is directly responding to the needs of its local and regional populations, it is also resulting in policy changes and cancer detection improvements in global populations. Professor Andrew Renehan talks about his home-focused cancer research programmes, which are resulting in global benefits.

TACKLING REDUCTION AT HOME

“Globally, if populations had the same weight now as they did in 1982, we could avoid half a million new cancers annually. Obesity is the second most common cause of cancer in western populations and, in some countries, it is the most common cause of cancer in women ahead of smoking. In the UK, it's the biggest cause of cancer after smoking.

In the past decade, we have led internationally rated research that has contributed substantially to our understanding about the link between obesity and cancer incidence. This includes establishing obesity as the second most common cause of cancer in western populations and establishing a variety of biological mechanisms underpinning this. We have also demonstrated that the effect of obesity on cancer takes place over many decades and, in many examples, may start in childhood.

We've also looked at the impact of a significant weight gain on 20 types of cancer. Here we found that a 15kg (2st 5lb) weight rise in women triggered up to a 50% increase in the risk of cancer in the oesophagus and a 30% increase in thyroid cancer risk. A 13kg (2st) weight gain in women would increase the risk of gall bladder and womb cancers by more than half. We also saw smaller but significant links between increases in weight and kidney, bowel and skin cancers in men and kidney, pancreatic, thyroid, colon and some breast cancers in women.

Health inequalities and cancer

There are multiple factors which are contributing towards increasing obesity rates nationally and globally, including what is known as the ‘social gradient’ where obesity prevalence is higher in more socially deprived populations. But the key challenges facing the cancer research community over the next decade are the same. We need to increase public awareness of the proven link between obesity and cancer. We need to optimise the effectiveness of public health strategies and individual-level decision making around diet and exercise to minimise excess weight gain over adulthood. We need to identify high risk groups whom we need to target this activity towards in order enhance the efficiency of these interventions.

Our research has also shown that increases in body weight during early adulthood increases risk of incident (or newly diagnosed) colorectal cancer in a gender-specific pattern, that increased waist circumference is associated with increased risk of incident colorectal cancer in a gender-specific pattern and that changes in Body Mass Index over time (trends) in a population can be described in terms of ‘latent classes’ which differ by gender. All these observations point to the need for gender-specific and age-specific strategies to prevent obesity-related cancers.

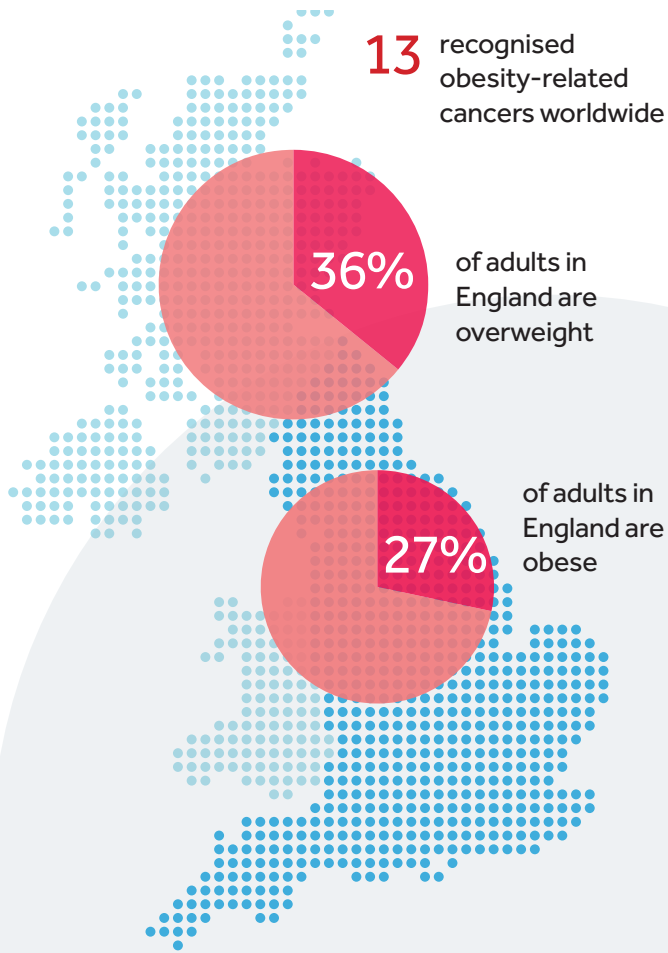
As a clinician researcher, my work is divided 50:50 between research and clinical service. In my clinic I see the very real impact of obesity, and as a researcher, I know the most powerful research response that we can provide to tackle the obesity epidemic is to build a critical mass of researchers. This research mass multiplies our efforts and accelerates progress meaning that we can tackle this global problem at a much quicker pace, saving lives. This is why one of our immediate three year challenges is to work out whether or not obesity after cancer diagnosis has an adverse effect on survival. If true, this would be the fundamental rationale for intervention to ensure that cancer patients avoid excess weight gain or for us to encourage weight loss where there is excess body mass.

The research, we have undertaken in Manchester showing that a healthy weight can substantially reduce your risk of certain types of cancer, indeed of showing a clear link between obesity and cancer, has a global benefit. But we need to ensure that the knowledge developed in this city is used to help the growing number of obese children on our doorstep. While this is a global lesson, we can’t forget the need to apply our own lessons closer to home. My hopes for the Manchester cancer research community over the next 12 months are that we continue building on increasing local public awareness of the link between obesity and cancer, something we’re now specifically targeting towards university students.

Global Impact

The time spent at university is a really intense learning period in a person’s life and a great opportunity to ‘soak up’ information. With the largest number of university students in the UK, and the largest international student population, there are immense opportunities here for us to develop a network of lifestyle ambassadors that can help in awareness raising. They can take the lessons we’ve learned in Manchester with them across the globe. They can ensure that Manchester helps not only its local communities but its wider global communities.”

Andrew Renehan is Professor of Cancer Studies and Surgery at The University of Manchester and Honorary Consultant Colorectal Surgeon at The Christie.



Our ambition

...is to be a world-leading comprehensive centre for translational cancer research – transforming the clinical care of cancer patients by developing and implementing an integrated personalised medicine strategy.

Christie Research has more than 650 research studies ongoing at any one time and is the largest centre in the UK for commercial cancer trials. We are proud to be able to give patients so much opportunity to access new therapies.

Exciting new developments demonstrate that our ambition is already being realised. A dedicated proton beam therapy research room and research programme will ensure that patient at The Christie will be the first to benefit from new advances in proton beam therapy.

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:

0161 446 8281

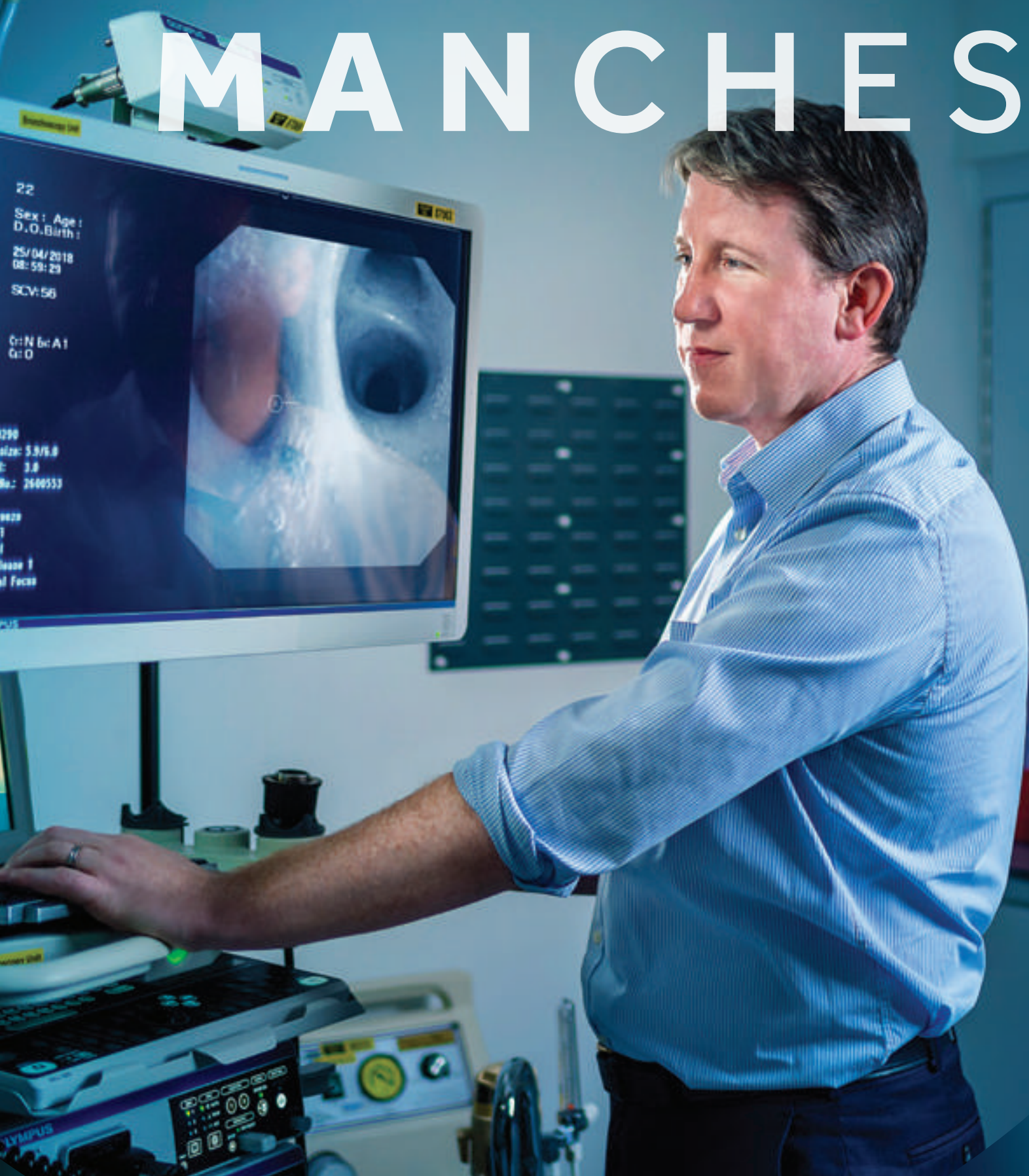
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MANCHESTER



NHS policy change on lung cancer screening to aid earlier detection has been announced following the results of an unusual mobile screening scheme which found one case of cancer for every 33 people screened – a threefold increase in detection compared to conventional approaches.

Dr Philip Crosbie, Principal Investigator of the study, outlines why Manchester was the perfect place to trial this and how they're already responding to lung cancers next research challenges.

“What we're dealing with today is the legacy of smoking and socio-economic deprivation over a number of decades. That's why Manchester has the highest rate of lung cancer deaths in the country. It kills more people under 75 than any other disease and more than all other cancers combined. Mortality rates are so high because most people are diagnosed with advanced disease, when it's too late, and survival is generally measured in a few months. Early lung cancer is eminently curable, but notoriously difficult to detect because it often causes no or only very mild symptoms. So our challenge is to detect lung cancer earlier. If we can, patients will stand a much greater chance of surviving.

Manchester has a reputation for excellence in lung cancer diagnostics, treatment and research; we are home to Cancer Research UK's Lung Cancer Centre of Excellence. It was this reputation for clinical and research excellence that led the Macmillan Cancer Improvement Partnership, funded by Macmillan Cancer Support, to task us with transforming outcomes for patients with lung cancer. When asked what needed to be done to achieve this, with no hesitation we said screening. It was instant. Waiting for patients to present to us with symptomatic disease leaves things just too late. So it wasn't a case of what should we be doing; could we try this or that? It was, what does the most effective screening model to increase early detection look like? How do we achieve good uptake in those most at risk? The paradox for lung cancer screening is that those most at risk, smokers in areas of high deprivation, are also those historically who are least likely to attend.

We considered these factors and said, why not just make it easy for people? Why should people have to factor in finding a parking spot or paying for hospital parking and what if a lack of reliable public transport was also a concern for people? We simply wanted to make the whole process as easy as possible and to take screening out to the community and that's what we did. We wanted it to be a 'one stop shop' so people didn't have to keep coming back for more appointments. We also thought about the psychology of healthcare and rebranded it. We didn't call it a lung cancer test because that's frightening, we called it a lung health check. These small but important changes worked. People came to see us and demand was very high. Indeed, the success of the screening programme resulted in NHS England announcing that our Manchester screening model will be rolled out to other sites across the country. We've achieved a national policy change by designing and delivering an innovative screening approach.

Novel approach

Our pilot scheme sited mobile, low-dose CT scanners in supermarket car parks, community hubs and shopping centres in three deprived areas of Manchester. We arranged for GPs to send letters to smokers, and those with a history of smoking between 55 and 74, inviting them to attend the van for a check whilst they were out and about meaning they didn't have to go to their GP or to hospital. The resulting demand was huge, Macmillan gave us extra money to allow us to see additional patients who had requested appointments but who we couldn't see during the study period.

More than 2,500 people underwent spirometry tests and answered health questionnaires, of which about half were offered an immediate CT scan based on our assessment of their need. The scans led to 46 cases of cancer being discovered, 80% of which were at stages 1 and 2. Fewer than 30% of cases are diagnosed at these stages through the usual care pathways after symptoms are reported. The proportion discovered at stage 4 was just over 10%, which compares with nearly 50% normally. The scheme also resulted in diagnoses of chronic obstructive pulmonary disease in 20% of those attending. The outcomes highlighted the critical clinical need for this intervention, and by targeting those at greatest risk in deprived areas, we detected a three fold incidence of lung cancers as compared to the international average.

“initiatives such as this make it easier for high-risk people to get their health checked.”

Lung cancer at a glance

16,300

deaths – most patients who get the disease are smokers or former smokers

The percentage of adults smoking cigarettes in this LA (21.7%) is higher than the England average (15.5%)

46,000

cases of lung cancer in Britain each year

Manchester is the UK's largest recruiter to lung cancer studies

Manchester is home to the lung cancer centre of excellence

Manchester has the worst premature death rate (in under-75s) in the country; the leading causes include lung cancer

There are around 46,700 new lung cancer cases in the UK every year, nearly 130 every day (2013-2015)

From palliative to surgical

Generally 75% of patients have stage 3 or 4 lung cancer when diagnosed. This is sadly, rarely curable. But earlier screening shifts the balance in terms of who can survive, with 80% of incidence being detected at stage 1 or 2 which is far more curable.

Increased survivorship however creates new and different challenges for us as we move from an end of care, palliative response to treating the disease, to surgery and treatment. This new focus on surgery brings an immediate and associated capacity issue. Increased surgery requires more surgeons, anaesthetists, nurses, radiologists and theatres as a start. But in response to these new and not inconsiderable challenges that arise from such a shift, we're already looking at how we can address them as a research community. We're looking to technologies and the role they can play. We're collaborating with industry to develop software to help us, be more precise and faster looking at the radiographs. Better precision means better detection, and if we can speed up the process, then we can increase the numbers detected.

Only Manchester

Manchester is without doubt the best place in the UK to lead lung cancer research. We have the unique mix of a population requiring help, a world-leading lung cancer centre, the university's world leading multi disciplinary expertise, the UK's leading lung cancer team and largest thoracic surgery site within the Manchester University NHS Foundation Trust and Europe's largest cancer hospital. This combined with the scientific infrastructure makes things happen. All the parts of the jigsaw are here.

It's simple in Manchester, you can make changes and we're empowered to do that. We've created an environment where people can excel and where we're all working together because we have a shared vision. We're multidisciplinary and that coordination increases effectiveness. Gradually people are seeing the value of prevention and detection for lung cancer. We're getting there."

Dr Philip Crosbie is a Clinical Senior Lecturer at The University of Manchester and Consultant in Respiratory Medicine at the University Hospital of South Manchester.

University of Manchester IMAGING FACILITIES

- **Researchers and clinicians access to leading edge clinical PET, MR and PET-MR scanners**

- **We have scanners at:**

Salford Royal NHS Foundation Trust – 3T MR

Manchester University NHS Foundation Trust – the North West's first 3T PET-MR

Manchester Clinical Research Facility – 3T MR

Wolfson Molecular Imaging Centre (WMIC) – 1.5T MR, PET-CT and the UK's only HRRT

Our Wolfson Molecular Imaging Centre houses a GMP radiochemistry facility which manufactures an extensive range of radioactive tracers for use in PET and PET-MR studies.

We have preclinical PET and MR facilities on the University of Manchester campus and WMIC sites.

Contact Sarah Wood (sarah.wood@manchester.ac.uk) or **Denise Ogden** (denise.ogden@manchester.ac.uk) for more information

<http://man.ac.uk/M7O2hE>

MAKING A DIFFERENCE

Changing lives & meeting need

Professor Vaskar Saha's research is helping to significantly reduce mortality rates in children being treated for cancer in India. Having led research which helped increase survival rates among children with acute lymphoblastic leukaemia (ALL) by 10% in the UK, he splits his time between the University of Manchester and the Tata Medical Centre in Kolkata, India.

Here he talks about his mission to transfer global standards of care to a low resource country.

“For a child to die in 2018 of a disease that is curable is unpalatable. ALL is curable. Survival rates of children with ALL in the west have risen from 60% to 90%. 80% of children globally live in countries with limited resources and here, ALL continues to be a fatal disease. Globally, the survival rate for children with ALL is therefore only around 40%. We need to develop strategies, using the lessons learnt from the west to improve outcomes in children with ALL globally.

450 children in UK are diagnosed with ALL each year and of these, 400 will survive. In India this is more challenging. A number of dedicated paediatric cancer centres are well established with a reasonable infrastructure but these only treat 10% of the patients. Furthermore, survival rates of children with ALL treated at these centres has remained static at 65% over the last three decades, whereas in the west, survival rates for children have risen to 90% in that same time. In India, the number of children diagnosed annually is 15,000. Currently, 9,000 children are dying every year from a potentially curable disease. If we can improve outcomes in India by 10%, then an additional 2,500 children a year will grow up to lead normal lives.



Meeting need

India is a huge and diverse country. Pockets of wealth exist with pockets of dire poverty, such as in Kolkata, where my Indian work is based. But what happens then if you are poor, live in the Kolkata region and your child gets cancer, what are your choices? You could uproot your family, perhaps three generations living together, in order to travel to the other side of India to seek treatment for your poorly child as you've heard there is a good cancer hospital there. Or you could stay and hope for the best. That was the reality. Modern cancer centres in this region, particularly those that catered specifically for children, were few and far in between. For a child from Kolkata then to receive treatment and hopefully survive, families were forced to leave their jobs and homes and travel to find a cure. While many centres subsidise treatment for children with cancer, it is the non-treatment costs that can be crippling. Many families incur heavy debts and are reduced to poverty. In many cases, it takes the resources of a whole village to treat a family dealing with cancer.

The need for a cancer hospital in Kolkata was critical. Fortunately, the Tata family recognised this and set up a hospital, Tata Medical Center (TMC) to save families having to endure separation and months or years of poverty and distress caused by a loss of income and relocation. I was approached and asked to work with them in looking at improving cancer survival rates in children, I obviously said yes. With support from The University of Manchester agreeing to let me to split my time between my university research, clinical practice and research in India, and a successful DBT-Wellcome Trust in India Alliance grant application for initial funding, this was the start of my Indo-Mancunian commute.

There are many good hospitals across India but they often exist and work in isolation, without the exposure to the international research community which we in the UK take for granted. To address this we started by bringing everyone together, shared our knowledge and started discussions. With the help of the international community we also made it possible for people to participate in focused meetings abroad. Small things in research can make a big difference, how you give the medicine, when you give it, how you care for children and I wanted us to document this and share it amongst ourselves. That's what we do in the NHS and that's how we know we can find things out, we share our knowledge. Most importantly, we knew that, whilst in the west, treatment for children with ALL is highly successful, it does not readily translate to countries with fewer resources. We wanted to change this and to help families whose children have cancer.

Size and scale

Kolkata has a hinterland the size of Western Europe. Before TMC, patients from this region would have to travel two or three days to get to Mumbai which has a good cancer hospital. We didn't have one here, but thanks to Mr Tata and the Tata Trusts, we do now.

TMC subsidises treatment through the help of a number of charities. In partnership with St Jude's India, it provides safe, secure and free accommodation for families whose child is being treated. Before this, mum and perhaps a child and grandparents would have to go back home eventually as they couldn't afford to stay together. The dire state of our fragmented cancer care was pulling families apart. We may have cured the child but ultimately we were driving families apart and deeper into poverty by forcing them to travel and spend whatever money they had on accommodation to stay together. But now they can be treated in Kolkata, they don't need to travel.

We began by working with the five best paediatric oncology centres. We worked together to agree standards of care and formed the Indian Childhood Collaborative Leukaemia (ICiCLE) group. We have achieved multi centre standardisation for the very first time, based on the principles of the NHS. We have implemented agreed, uniform standards of care and treatment across all our cancer treatment centres.

Need for standardisation

It used to be that one fifth of Indian children used to die due to poor treatment and a one fifth would die through relapse. Poor treatment was due mainly to the absence of standardisation in testing and treatment. With help from colleagues in the UK and across the world, we've successfully integrated modern diagnostics and monitoring into routine cancer care. This not only saves lives, it is also saves money. Children who don't require intensive treatment are identified early and we are using IT tools to monitor and manage patients so they can return home early. Over the past four years, the ICiCLE group has treated over 2,500 ALL patients. During this time, deaths from treatment have halved and our survival rates have increased from 60% to 75%. More importantly, we have made the hard journey taken by families to protect their most precious possessions a little bit easier.

Not all cancer centres in India are in our hub so the challenge is how we can provide and develop support systems for these other centres. We need to bring them together. To talk and share experiences. We also need more sophisticated testing in all centres, to further improve survival rates. We need to ask ourselves how we take most advantage of the current and emergent technologies that could help us to make processes and treatments cheaper, therefore increasing the likelihood that these will be taken up by the other hospitals. We have developed a patient database which allows for real time information sharing. This is has greatly improved our ability to share data and learn from each other.

Research takes time but already I can see the difference that these small changes are making; it's tangible and our patients don't take this care and treatment for granted, they cherish it. At the end of the day, whether I am in Manchester or Kolkata, I'm a paediatrician and I do this because it's my vocation and passion to look after sick children and their families."

Vaskar Saha is Professor of Paediatric Oncology at The University of Manchester and Senior Paediatric Consultant and Director of Translational Cancer Research at the Tata Medical Center in Kolkata, India.

Professor Saha's ALL childhood leukaemia trial is featured in The University of Manchester's Breakthrough campaign.

<https://www.manchester.ac.uk/research/beacons/breakthroughs/>



450 children in UK are diagnosed with ALL each year. 400 will survive

Survival rates of children with ALL in the west have risen from **60% to 90%**

Survival rates of children with ALL in limited resource countries have remained static at **65%**

80% of children globally live in countries with limited resources

Globally, the survival rate for children with ALL is therefore only around **40%**

MANCHESTER'S
PLACE IN

TOMORROW'S WORLD

The UK's first proton beam and research centre is directed by Professor Karen Kirkby, who outlines how Manchester is pioneering ground-breaking proton beam research that will provide solutions for the next generation of cancer challenges, thanks in part to the creation of an NHS-funded clinical proton beam treatment and research facility at The Christie which will treat its first patients in late 2018.

PROTON THERAPY EXPLAINED

- Proton therapy is a type of external beam radiation therapy that uses beams of protons (sub-atomic particles) to treat cancer.
- It painlessly delivers radiation through the skin from a machine outside the body.
- A proton is a positively charged particle. At high energy, protons can destroy cancer cells. Proton therapy can be

used alone or combined with other treatments, such as radiation therapy, surgery, chemotherapy, and/or immunotherapy.

- A particle accelerator is used to speed up the protons. Accelerated protons are then beamed into cancerous cells, killing them.

- Unlike conventional radiotherapy, in proton beam therapy the beam of protons stops once it 'hits' the cancerous cells. This means that it results in much less damage to surrounding tissue.

“We’ve already had requests from international research groups wanting to collaborate with us as we’re seen as international leaders in proton beam therapy and because of our links with The Christie and The University, both of which have world leading reputations.”

“With more people surviving cancer than ever before, a new challenge for the research community has emerged, the need to find out how we can minimise the side effects of treatments to ensure survivors live long and healthy lives without fear of reoccurrence and tissue damage caused by the treatment. Put simply, we need to provide safe, effective, treatment.

Whilst, traditional radiotherapy treatment is effective it’s also damaging because of the impact it can have on healthy tissue, especially in children who, being smaller and younger, are more susceptible to tissue damage from ionising radiation.

For example, take a child treated at age six who, once treatment is over, has their whole lifetime ahead of them. They should be able to be free from the worry of developing a second cancer.

If we want to ensure that these survivors enjoy a quality of life and don’t require future interventions and ongoing care, we need to identify how to minimise tissue damage by better targeting our treatment, hitting the diseased area and not touching healthy tissue. This is where proton beam therapy can provide a solution.

Proton beam therapy allows us to specify the exit point for the beam, meaning that the beam stops where we tell it to and it doesn’t continue onwards, penetrating other sensitive neighbouring organs.

Rising to the challenges

Manchester’s forward thinking approach to cancer research has seen us become the only place in the UK to build a dedicated proton beam research and treatment facility in one centre. Our collective ability to recognise this global challenge led to us identifying the need for more research and being awarded the funding to carry this out on a single site.

This state of the art facility will pioneer new methods and technologies that will ultimately allow us to be more precise in using the beam in treatment, ensuring less tissue damage and driving our ambition to become world-leading in both treatment and research. Our first patients will be treated in late 2018, with the research facility opening shortly afterwards

Research and treatment together

Our purpose built research room will be alongside three clinical gantries, each in their own treatment room. These gantries will enable the beam to move at different angles so that they miss key healthy organs. Protons travel at the speed of light, so huge gantries are needed (ours weigh 90 tonnes). Most other systems don’t have this degree of motion so this is genuinely state of the art.

We aim to make this a world leading proton treatment and research centre and we’re already well on the way. We are installing the newest technology available including the fastest spot scanning system in existence.

Leaders

The Manchester tradition of making things happen and being given the space to try new things out has led to amazing discoveries, including the first programmable computer and more recently graphene and we’re hopeful great things will happen in proton therapy too. We’re lucky to have this facility, which has equipment and tools which we can use to experiment and innovate.

We’ll have dedicated research beam time each night when patients aren’t being treated to look at how the beam behaves. When the treatment has stopped, our research teams will come in and work through the night, trying, testing out and practising new ways of looking at the beam and how to use it. We can watch how the beam behaves in different ways, depending on how it interacts with different cells and tumours.

Collaborators

I haven’t been in Manchester that long compared to some of my peers but what has struck me in this relatively short period of time is that people here really do work together, and because of this, we can undertake truly multidisciplinary research. There are unique partnerships between the University of Manchester, The Christie and the Cancer Research UK Manchester Institute. You can move seamlessly between all these institutions and access brilliance in different disciplines, whether its clinical expertise, clinical medical physics, translational radiobiology, maths, physics, economics or basic science.

We can ask colleagues different questions and we get the answers because our expert colleagues want to help and we’re not limited to any small number of areas we can explore. For example, we’re engaging with social and health

scientists to explore how patients respond before and after treatment. We also engage with patient groups to understand how we can help to improve their experience of treatment, as it is really important that we get this right.

Protons are coming home

Manchester’s research community never stands still, it’s always seeking out the next challenges and I like to consider myself part of this, as we don’t stand still either. My research teams and I are looking at how we can optimise personalisation in order to see how and where we can help. Along with Dr Martin McCabe we’re currently looking at medulloblastoma, a brain tumour in children to see how we can optimise the treatments to the different sub-types of this disease. Traditionally, some types of medulloblastoma are immensely difficult to treat and have a poor prognosis, but by understanding the different genetic sub-types, we can better personalise the treatment which could lead to better outcomes and fewer neurocognitive side effects. I know that we don’t have all the answers yet to this, or the other research questions we’re looking at, but I do know that by enabling our research and treatment to take place side by side, we stand the best chance of getting them.”

Karen Kirkby is Professor of Proton Therapy Physics at The University of Manchester and The Christie.

The Proton Beam Therapy Centre at The Christie will host a £125 million NHS-funded research portfolio.

Thanks to the generosity of donors, The Christie Charity has given £5.6 million for the creation of a research laboratory next to the clinical facility.

Manchester will be the first treatment centre in the U.K. to combine these two facilities for the benefit of patients.

Professor Catharine West, one of only 35 scientists to have been awarded the prestigious Weiss medal and one of only 22 to be awarded the Bacq and Alexander medal for radiation research, explains how a decision to come to Manchester enabled her to pioneer developments in personalised radiotherapy.

PERSONALISATION

GENETIC SIGNATURES
FOR RADIOTHERAPY



“As a ‘Londoner’, I came to Manchester in 1986 planning to stay a couple of years before moving back south to develop my research career. Thirty-two years later, I’m still here!”

Importance of radiotherapy

Shortly after arriving in Manchester it became clear that this was the best place where I could do the research which interested me. Radiotherapy is one of the most important treatments for cancer. Around 50% of cancer patients have radiotherapy, and half of patients who are cured, received radiotherapy as part of their treatment. Because of its importance in curing cancer, it’s vital to carry out research which increases our understanding of radiotherapy to optimise treatment for patients. There is a need for biomarkers that can help predict the effectiveness of different types of radiation and drug-radiation combinations, and whether patients are likely to suffer with long-term side effects.

My specific research focuses on trying to predict how cancer patients respond to radiotherapy and measuring hypoxia, a lack of oxygen, in patients. Hypoxia reduces the ability of radiotherapy to kill cancer cells, so I’m undertaking research to help increase our understanding of how hypoxia impacts on a patient’s outcome following radiotherapy and how it can be measured routinely.

Clinical campus

This involves working extensively on samples taken from patients who are having or who have recently undergone radiotherapy for their cancer. The proximity to The Christie, which I soon found out was the largest radiotherapy centre in Europe, means that essentially no-one in the UK or Europe, could compete with me in terms of recruiting large numbers of patient samples I can run multiple, large scale projects precisely because of this access to large patient numbers.

Our clinical campus, with the co-localisation of the laboratory building on the hospital site, means that I’ve always been based close to the clinical oncologists and so I have access to ask any clinical questions that arise during any point in a study. For every researcher seeking to achieve genuine patient-centric research, this multi-disciplinary approach to research is essential. This existed here in Manchester from the outset, and its value in delivering high quality patient relevant research, cannot be underestimated.

Our unique geography, with the university just a stone’s throw away from The Christie, has enabled me to conduct a number of internationally leading radiobiology studies. This required working on samples from cancer patients and being able to liaise with oncologists, pathologists and data experts to access information at different points of the research journey. I’ve been able to take a short walk along a corridor to talk to someone to discuss an idea, to sit with them face to face and discuss it before then taking another small walk to collect samples, take them to the lab and do more experiments. All the time I’m seeking and bringing in the expertise of colleagues from different disciplines in the university, such as, physicists and statisticians. This culture of multi-disciplinary working wasn’t like anything else I had experienced before and, along with access to patients, provided another reason for me to stay.

The building of expertise, of knowledge and facilities that has been gained in Manchester through collaboration at every opportunity has resulted in us being able to expand radiotherapy related research several-fold in the time that I’ve been here. This unique Manchester offering of ours, the huge numbers of patients that we can treat and who can participate in our research, the ‘kit’, the new proton research centre and the MR-linac machine and the established culture of multi-disciplinary working means that we’ve attracted some of the best people in the world to come and contribute to our research expertise. What we can offer is incredible and everyone is noticing.

The amazing technological advances that followed the human genome project, which allowed rapid and affordable genome-wide analyses, to my mind offers the cancer research community some of the best opportunities for increasing our knowledge over the next decade.

International collaborations

Similarly, the associated opportunity of being able to carry out studies involving international collaborators, where we run studies in parallel in multiple countries, is definitely the way we need to go to speed up progress. If we can do this, the opportunities for accessing more patients and increasing patient data means that we can find the patterns and upscale any learning. We’ve already made a significant contribution towards helping to respond to this need globally.

We have led the creation of an international radiogenomics consortium to help facilitate collaboration and sharing of data for research which is aimed at identifying the common genetic variants which affect the risk of toxicity following radiotherapy. We also currently lead an EU-funded study that is carried out in eight

countries that involves everyone collecting the same data and such a scaling up of data collection will massively increase our knowledge base.

It’s my hope that Manchester’s cancer research community become international leaders in biomarker-driven trials that personalise radiotherapy based on an individual patient’s biology. We’re already at the forefront of this and it’s my hope that in 15 or 20 years’ time, we’ll look back to how we used to treat everyone the same and regard it as archaic, precisely because each patient and their cancer is different. It would be fantastic to be the pioneers of achieving this shift.

We’ve already developed and validated a gene signature which characterises hypoxia status in head and neck cancer. Our research shows that cancer specific gene signatures are needed to identify hypoxic tumours. These signatures can then be used as biomarkers in personalised healthcare approaches that will improve survival. So far we have a phase 3 trial in head and neck cancer patients that is testing whether our signature can be used to select patients for treatment that targets hypoxia. The next step is to establish early phase biomarker driven trials, in other cancers, and to increase collaborations with pharmaceutical companies.

All this is possible because of where we are and how we work together. Although I never intended to stay this long, I can honestly say that I’m very glad I did!”

Catharine West is Professor of Radiation Biology at The University of Manchester.



Manchester and radiation

Manchester is home to world-leading clinical and experimental radiation facilities, including the Dalton Institute.

The radiotherapy facility is the largest in Europe with 8,500 patients treated and 120,000 radiation fractions delivered annually.

The first UK NHS High Energy Proton Therapy Centre will open in Manchester in late 2018 to treat around 750 of the most complicated cancer patients each year.

Manchester will be the only UK site with three state-of-the-art techniques: stereotactic ablative radiotherapy, a magnetic Resonance Imaging scanner combined with a radiation machine (MR-Linac; opening in 2019) and high energy Proton Therapy (opening in 2018).

Clinical oncologist, Professor Ananya Choudhury, is leading one of the world’s most innovating and pioneering radiotherapy treatment machines, one of the first seven of its kind globally. Here she tells us how the *MR-linac* will transform patient outcomes once it starts treating patients in 2019.

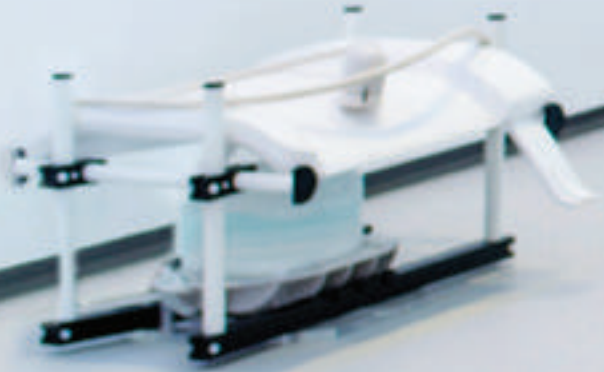
PIONEERING

TREATMENT



“I’m in what I consider to be one of the most enviable positions in the world for anyone working in radiotherapy. I’m fortunate enough to be able to work on a new and pioneering radiotherapy machine, one of only seven of its kind in Europe’s largest cancer hospital. In terms of what I do, it really doesn’t get much better than this.

The MR-linac is a tremendous piece of machinery which will transform treatment for patients undergoing radiotherapy as it will allow us to treat patients whilst, at the same time, taking magnetic resonance (MR) images. At the moment, lower quality CT images are taken of a patient’s tumour before radiotherapy is given, to help us to target the radiation to the cancer. With the addition of MR imaging within the linac itself, we should be able to make treatment delivery more precise. We can pinpoint the location of tumours, tailoring the shape of the x-ray beams in real time and locking onto the tumour outline during treatment to enable us to accurately deliver radiotherapy, even when the tumour tissue moves during treatment. For example, a tumour in the lung will move up and down as a person breathes.





- Magnetic resonance imaging is a medical imaging technique used in radiology to form anatomical pictures and physiological processes.
- Magnetic resonance imaging is a medical application of nuclear magnetic resonance (NMR).

New era for precision

This technology will usher in a new era of personalised radiotherapy as the machine can see if a tumour changes shape, position or size between treatment sessions. We can ensure that the cancer cells are targeted accurately for treatment on every visit, adapting the treatment to a patient's unique anatomical makeup in real time.

My research focuses on personalised radiotherapy treatment in bladder and prostate cancers, I'm looking at how we can combine advanced biology and physics techniques to improve patient selection and minimise side effects. It is here I believe that the MR-linac genuinely heralds a revolution in radiotherapy.

It will make a substantial difference to our patients as it allows us to see the tumours clearly and to treat them with such incredible accuracy that it will minimise some of the risks associated with standard radiotherapy treatment which, although very effective, can accidentally damage healthy tissue due to a lack of detailed precision.

With earlier diagnosis and improved treatments meaning that more people are surviving cancer than ever before, we're therefore making a significant contribution to the health and wellbeing of this increasingly large cohort. This improvement is threefold: reducing the risk of secondary cancers, achieving better clinical outcomes and reducing side effects such as nausea, lethargy and soreness. The value of this, financially, economically and emotionally, to the patients, their families and the NHS cannot be underestimated. And it is achievable all through more precise and targeted treatment.

Reflecting research strengths

For me, the MR Linac at The Christie in Manchester signifies the strength of the unique partnership that exists here; the infrastructure, facilities, the people and the collaborative culture, all of which worked together to facilitate us getting this machine. No one partner could have achieved this without the help of the others and I see the machine as a symbol of this. This genuine collaboration is currently being evidenced in an exciting new project that my research group, the Translational Radiobiology Group is looking at. We're truly multi-disciplinary, comprising of clinicians, oncologists, medical physicists, physicists, biologists, radiotherapists, software engineers, statisticians, bio-informaticians and radiographers amongst others.

As we're part of one of Europe's largest universities, it means that we're able to collaborate across different disciplines and so we're currently working on projects with academic colleagues in pharmacy, mathematics and physics.

One of these projects is where we are applying techniques which are used to map stars and constellations, learnt from colleagues in astrophysics, to see if similar methods can be used to process medical images and improve the diagnosis of cancer.

This is an innovative approach as we've never linked to astrophysics before. We also hope it is a potentially ground breaking project in that it will highlight the opportunities that exist for other cross discipline collaborations with less obvious research partners. For me, it's here in thinking outside of the traditional box where we will be able to find solutions to some of the challenges we face as a research community; one of the most pressing of these being how can we do more with less, as we face a squeeze on funding for both research and healthcare delivery.

Responsive and agile

We've got to be ready to respond to all the different challenges that will impact on us, such as Brexit for example which, whilst we don't know in what shape this will take, we can expect to be significant. We can't possibly begin to know what form these challenges will take, so we need to be in a position where we're already working together and are in the best possible position to come up with creative, innovative solutions to whatever they are; solutions that mean we can continue to develop innovative and patient focused research which delivers real patient benefit.

It will be difficult at times to know what the best response to these different challenges will be, but my approach, and that of colleagues here, is to be as united as possible. We're working in genuine partnership with colleagues in the clinical and research community and it's this team science approach which I know will bring about the advancements in knowledge that can help to address tomorrow's challenges, and which will also provide that essential critical mass of research expertise.

Manchester has a history of innovation in using advanced imaging technologies to improve radiotherapy delivery and the MR-Linac is just our latest demonstration of this.

It's incredible to be able to play a small part in the huge global effort to fully understand the transformational potential of MR-Linac, and to have it in Manchester is a bonus. I love knowing that any research will benefit this regions patients as well as global populations. The lessons learned in Manchester will be shared across the world."

Ananya Choudhury is Chair and Honorary Consultant in Clinical Oncology at The University of Manchester and The Christie.



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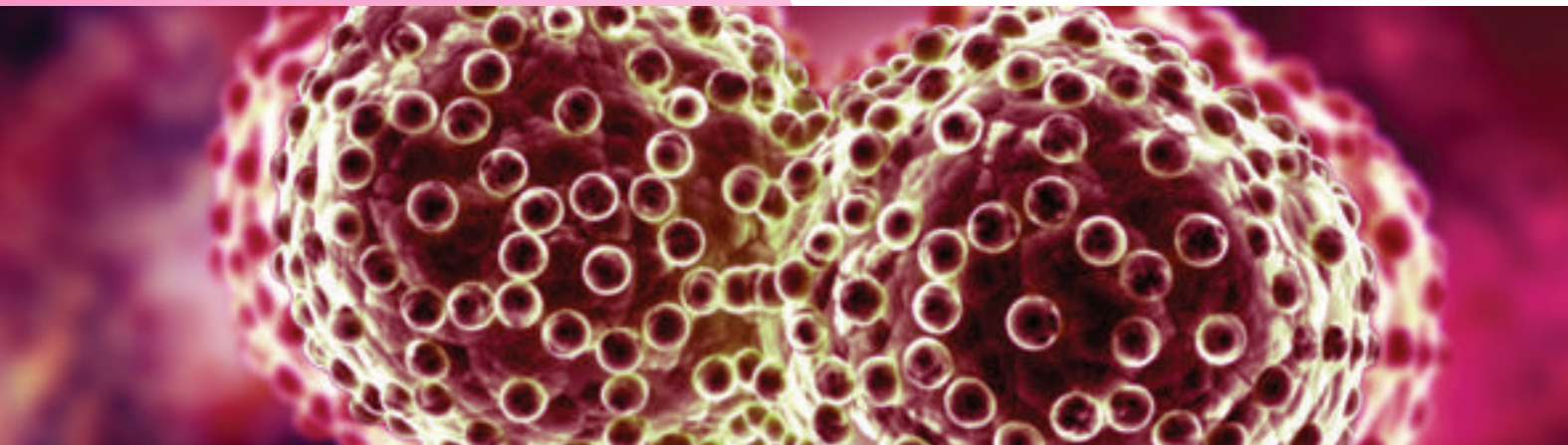
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DEVELOPING

PIONEERING TREATMENTS

Professor Caroline Dive and her team are working side by side with colleagues at The Christie, developing 'liquid biopsies' to hunt cancer cells that have broken free from tumours and are circulating in the bloodstream. Here she tells us why her anticipated three years in Manchester has turned into 19 and counting!



“Manchester and I have a very long history. I only ever planned to stay for three years, it wasn't ever meant to be forever!. I came here in 1990 and I've seen the place just go from strength to strength. As time progressed I rapidly saw that this was a place where basic and clinical research can interface; there are very few places where this could happen so effectively, so I've never left.

My research is focused on lung cancer, the world's biggest cancer killer, and I'm developing blood tests to capture cancer cells that can help researchers understand how lung cancer changes as it grows and spreads and how it can become resistant to treatment. This will open up opportunities to develop new therapies to treat this deadly disease more effectively.

There has been a revolution in the basic understanding of cancers and how we can personalise treatment. We have entered an era of personalised medicine, where information about the molecular makeup of an individual patient's cancer is used to tailor their treatment. Understanding a patient's cancer usually involves taking a tumour biopsy. This doesn't always paint a full picture of the disease though, especially if the disease has spread through the body. On top of that, taking repeated biopsies can be difficult and very invasive for patients.

A research first

My research group (within the CRUK Manchester Institute) has a strong interest in lung cancer research, particularly small cell lung cancer (SCLC), the most aggressive type that kills 220,000 people every year. Tumour biopsies are scarce in SCLC so back in 2014, we showed that circulating tumour cells (CTCs) can be taken from the blood samples of patients with small cell lung cancer and grown to form tumours, just like the patient's, in mice. This was the first time lung tumours had been grown away from the patient in this way, with only a 10ml sample of blood needed from the patient rather than an invasive lung biopsy. We call these new models, patient CTC Derived eXplant models (CDX for short) that mimic the donor patients' tumour

pathology and response to chemotherapy. Our growing panel of SCLC CDX models are enabling our investigations into the biology of SCLC and its mechanisms for dissemination. These models also facilitate testing of new therapies and biomarker development, leading to early clinical trials in patients with urgent medical need. This is helping us to understand the biology of addressing small cell lung cancer.

At the start of my career, most clinical trials were run without informative biomarkers, but today we are seeing tumour biology being better understood and the biomarkers that come from this understanding are driving the design of clinical trials. Our new Manchester Centre for Cancer Biomarker Sciences is at the heart of this.

Biomarker research doesn't happen overnight, it takes time and thanks to long term Cancer Research UK funding, I've been able to build something, an infrastructure and critical mass of motivated staff, that will allow us to undertake long term biomarker research, within our biomarker centre.

Meeting need

Aligned to these incredible facilities and the basic and clinical science is the huge unmet need within Manchester's population, and a culture which says let's get together and do this, let's bring together our lab and clinic at the interface. These multidisciplinary teams respect each other.

Manchester's reputation for cancer research just wasn't here when I arrived. It's been such a pleasure to be part of the journey to where we are now, becoming acknowledged as international leaders in cancer research.

Manchester is hugely ambitious but with that comes the risk of trying to do too much, of spreading ourselves too thinly. We're getting so many requests for collaborations that it's not a matter of what to do next, but what not to do. Personally there aren't enough hours in the day but we're developing an amazing team and with that capacity, anything is possible.

We're in an exciting expansion phase and in the future, I hope that personalised medicine will become more and more commonplace in the clinic and that we will be using liquid biopsies (blood tests) routinely to inform a patient's treatment. For me, the biggest challenge that I think we're facing in lung cancer research is the lack of early detection biomarkers and we are trying to develop tests to pick up early cancer associated molecules shed into the bloodstream at low levels. Ultimately I'd like to see the development of very sensitive tests and people giving blood samples within their communities, so that cancers could be diagnosed earlier with better chance of effective treatment, especially those who are hard to reach but are at high risk.

Global ambition

Long term, I hope that we'll become the best biomarker centre in the world. There are of course things we need to do make this happen: we need to expand and diversify, but it's all possible.

Manchester has the potential to make the difference on a grand scale. It is a jigsaw puzzle which has all the pieces and we're rapidly putting them together.

Manchester has enabled me to have a fantastically enjoyable and challenging career and our future research plans are ambitious and exciting, bringing the science and the clinic ever closer together.

I've got wonderful colleagues who share a passion for clinical and translational research. We can express ourselves scientifically here because the culture is conducive to answering all those scientific questions that we have."

Professor Caroline Dive CBE is Senior Group Leader and Deputy Director at the CRUK Manchester Institute and Professor of Pharmacology at The University of Manchester.

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BRINGING TOMORROW'S MEDICINES TO PATIENTS TODAY

Working together to scale up activity and develop best practice is what Dr Fiona Thistlethwaite, Experimental Cancer Medicine Team lead, considers is the answer to increasing our ability to deliver cell therapy clinical trials in Manchester. She outlines the complexities involved and tells us how links across the city are being strengthened in order to help advance activity in these cutting-edge treatments.

“Delivery of clinical trials of advanced cell therapy is always going to be complicated but my ambition is to make delivery as routine as other clinical trials and treatments. By working together to develop the systems and infrastructure to do this, more patients in Manchester will have opportunities to participate in these trials and ultimately bring tomorrow's treatments to patients earlier.

Advanced cell therapy, uses the patient's own cells to fight disease. My particular focus is on the use of a patient's own T-lymphocyte cells (T-cells) to attack their cancer. These cells can be gene modified or selected to increase their activity against the cancer making this a personalised form of immunotherapy. For example I am working on trials of CAR (chimeric antibody receptor) T-cells and TIL (tumour infiltrating lymphocytes).

Trial complexities

These are challenging trials to run because they involve many different steps and processes. At the clinical site there will be an initial assessment period to see if a patient is suitable for the trial and whether they wish to participate. We then need to acquire the appropriate cells, manipulate them in the laboratory and eventually return the cells to the patient, usually done by infusion, so that they can fight the patient's cancer. In this context the cells are referred to as advanced therapy medicinal products (ATMPs). Before we give the cells back, a patient may need chemotherapy as a conditioning treatment and we also need to frequently give other drugs to support the cells such as cytokines. Unfortunately these additional interventions can add to the side effects and often mean that the patients have to stay in hospital for a significant length of time. These multiple steps, from obtaining the cells to giving them back, makes developing this into standardised processes very challenging.

Collection and manufacture of the ATMP (cell treatment) is no less complex. It is very variable and depends largely on which type of cells are required for the treatment. For example, in CAR-T trials, to ensure that we have enough lymphocytes as starting material, the cells are usually collected by a process called leukapheresis. This involves the patient being connected to a machine for several hours to extract sufficient lymphocytes from their blood. These cells then have to be transported at the correct temperature to the manufacturing laboratory. Next the cells are manipulated, for example in CAR-T therapy they are genetically modified using a virus so that they express an antibody fragment specific for the patient's tumour. Once they have been genetically modified, the cells need to be expanded to very

high numbers under sterile conditions before they can be returned to the patient.

In other types of therapy, such as TIL therapy, the patient's cells are not taken from their blood but taken from a piece of the tumour itself. Here the patients must undergo surgery to remove a piece of their cancer which is transferred to the lab, dissected and manipulated so that the T-cells can be grown out and activated. Once they have been expanded to billions of cells they can be given back to the patient.

Cells

At the moment these trials involve relatively small numbers of patients, however they still require a very high level of co-ordination across many different teams to ensure the ATMPs are safely delivered to patients. For example at the clinical site, for every cell therapy trial, in addition to doctors like myself, there are the nursing teams who will administer the cells to the patient when they are ready and look after the patient as an in-patient. We need to link into laboratory teams, not just where they are manufacturing the cells, but where we may be doing some immune monitoring to check the levels of cells in a patient. There are the pathology teams who store the cells and who coordinate release of the cells in collaboration with pharmacists who ensure that the products are safely dispensed.

At The Christie, to ensure the high level of co-ordination that is required, we have set up a specialist Cell Therapy Team which is focusing on getting more of these trials up and running. This team has a number of initiatives in progress including the development of an education programme to equip more staff with the skills and knowledge required to manage patients on cell therapy trials.



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"I don't know where else you can say, 'I want to try and do this' and where you're then empowered to do it."

Upscale activity to improve outputs

Up until now, cell therapy studies have often been run as small, academic investigator led trials with just a small team working hard to deliver them. To take these trials and therapies to the next level I believe we need to work together to reach a critical mass of activity across Manchester which will make trials more efficient to deliver. By doing this we can increase the number of patients and look to run larger scale trials in both the investigator-led and commercial setting. It's here where the unique aspects of Manchester come to the forefront because of our existing clinical centres of excellence, our close geographical co-location, our existing links to commercial partners and our ability to successfully operate in a progressive landscape of innovation.

Meeting future challenges

Although my focus is on using cells to treat cancer, there are many other applications of cell therapy to other diseases such as childhood genetic diseases and degenerative diseases. Working with colleagues at The Christie, The University of Manchester, Manchester University NHS Foundation Trust and nine commercial partners, we have formed a new consortium,

iMATCH (Innovate Manchester Advanced Therapy Centre Hub). We believe that by working together we can scale up our activity in these complex therapies across Manchester in both the adult and paediatric, cancer and non-cancer settings. iMATCH has recently been successful in its bid for almost £7million in funding over three years from Innovate UK to become one of three national advanced therapy treatment centres. Alongside the other successful bids (Northern Alliance and Wales-Midlands) we will work together to form a UK network which we hope will maximise the potential for cell therapy development in the UK. All too often we see ground-breaking research originate in the UK, but then fail to capitalise on those early advances in terms of taking research beyond small early-phase clinical trials to later phase trials, and ultimately to commercialisation. We hope that by forming this national network to share best practice and optimise collaborative working we can secure the UK as a global hub for cell therapies.

As we have put together the iMATCH consortium, I have been hugely impressed by the 'can-do' attitude here that has enabled us to rapidly turn what was just an idea a few months ago into a three year programme of work that I

believe reflects the team science approach in Manchester. Without buy-in from many senior NHS, academic and industry leaders it would simply not have been possible and I doubt there are many places in the UK where it could be done.

As a busy NHS consultant it's very easy to become focused on day to day firefighting and management of patients, and while patients are quite rightly central to everything we do, it is always challenging to think of the bigger picture and develop the networks and interactions that can led to real step changes in our practices.

I believe that putting together the iMATCH consortium has galvanised Manchester's research community, alongside commercial partners, to come together and to develop a programme of activity over the next three years to enable us to take things to the next level. The opportunity is here to form those networks and work together to be able to deliver on the big projects and ultimately bring effective treatments to more patients, more quickly".

Fiona Thistlethwaite is a Medical Oncology Consultant within the Experimental Cancer Medicine Team at The Christie and Honorary Senior Lecturer at The University of Manchester.

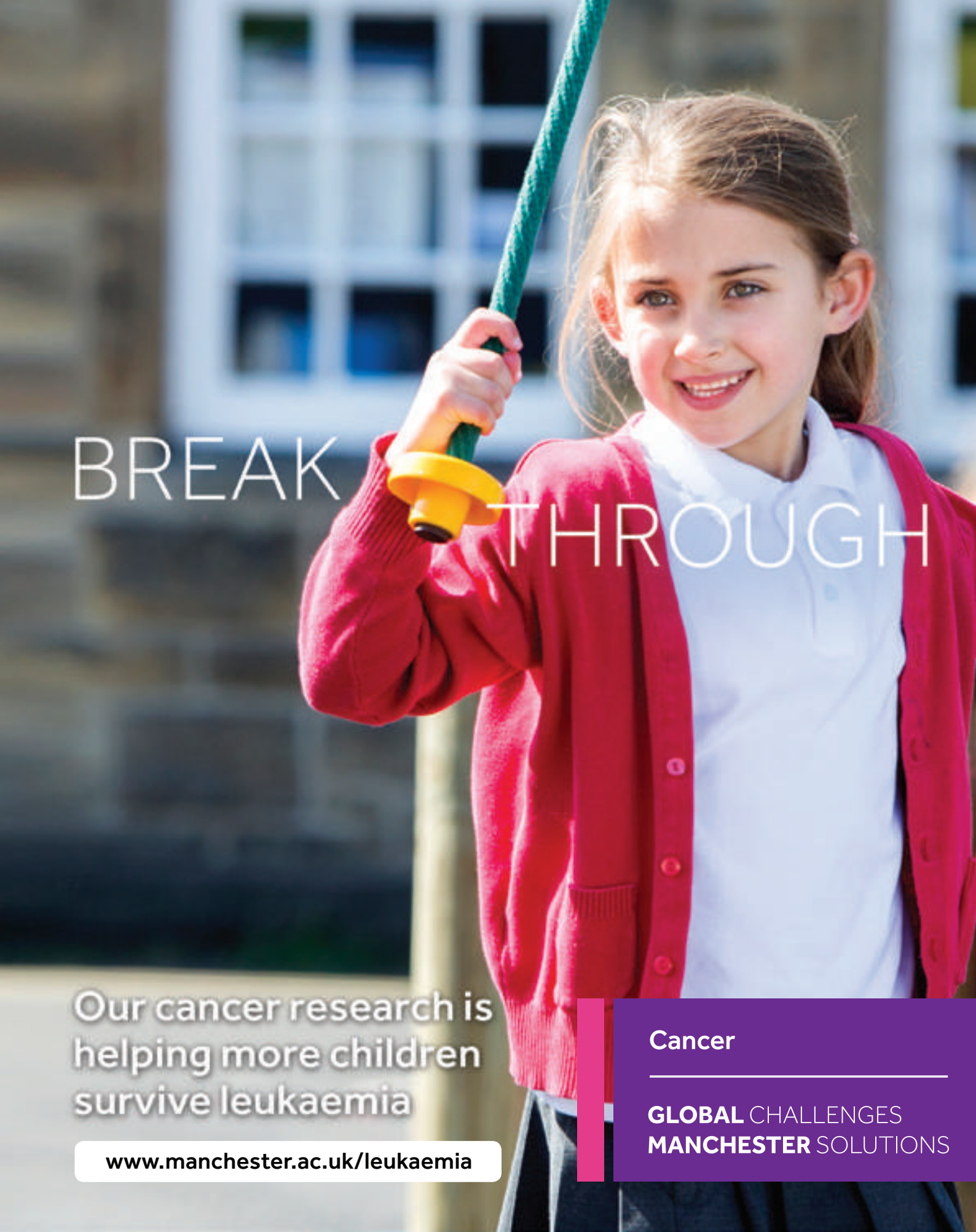
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Professor Gordon Jayson is a clinician researcher whose work offers the complete pipeline of research. Focusing on ovarian cancer and drug development. He reveals why Manchester's ability to run multiple novel clinical trials is driving international recognition for the City's cancer research community.

FROM BEDSIDE TO BENCH AND BACK AGAIN





“My career has involved developing new treatments for cancer and I’ve been able to do this in Manchester because the infrastructure and facilities naturally lend themselves to this. I work each day on a clinical campus which includes The Christie hospital, the University and the research facilities.

Anyone who works with me will testify that my day is spent crossing the road, back and forth, commuting between my patients in the hospital and the laboratory, which is just over the road. How many people can enjoy a commute so short yet so productive and rewarding? I’m literally traversing two worlds, the clinical and the basic science, many times a day. It’s amazing and something I try not to take for granted.

Survival rates

The partnership between the University, St Mary’s Hospital and The Christie provides a unique environment in which to manage our patients. In 2016, we published a paper, showing that patients managed by us and other similarly large, research-active cancer centres resulted in international levels of survival, which were 42% better than the UK national average. It’s within this unique group of experts that we have developed The University of Manchester ovarian cancer group, which brings together experts in gynaecological cancer surgery, medical oncology and laboratory science to lead research on the disease.

My research looks at how we can develop new treatments for cancer, particularly ovarian cancer, by focusing primarily on drugs that can block blood vessels forming so that tumours are then starved of oxygen and nutrients. Angiogenesis, the formation of new blood vessels, has been validated as a target in ovarian cancer in patients with recently diagnosed ovarian cancer, as well as in patients with chemo-resistant disease. However the drugs that target angiogenesis have a range of negative side effects and they are expensive so there is an imperative to identify patients who benefit from them and those that won’t. This research is really important as it will allow us to stop treating patients who won’t benefit from the treatment, from suffering any unnecessary side effects, whilst also reducing the costs of unnecessary treatment for the NHS.

Our drive to personalise treatment has led us to delivering a number of biomarker studies, the first of which was an international translational research programme within the ovarian cancer clinical trial (MRC ICON7) which saw our data identifying the first vascular response biomarker, the concentration of plasma Tie2.

The best way of validating this finding was to conduct a similar study in another disease. Therefore, in an entirely Manchester-based biomarker study, we looked at blood and imaging biomarkers in patients with metastatic colorectal cancer to confirm that the concentration of plasma Tie2 is the first generic, tumour vascular response biomarker for vascular endothelial growth factor (VEGF) inhibitors. Having completed this work we now propose to apply the test in the NHS and if validated, this test would

be used to determine when, and for how long, patients benefit from VEGF inhibitors.

One of the most exciting findings that emerged from this research was that in ovarian and colorectal cancer, we could improve the modelling of progressive disease if biomarker data from the epithelial compartment were studied alongside the biomarker data from the vascular tissue compartment.

Tumour targeting

Taken in conjunction with numerous clinical trials, which have shown that targeting the tumour vasculature postpones recurrence of cancer, the inference of these findings is that the vasculature should be treated at each recurrence of angio-sensitive cancers (e.g. colorectal and ovarian) using Tie2 to guide therapy. Accepting this novel concept, we are now proposing trials that will treat and re-treat these tissue compartments at each recurrence; the multi-tissue compartment model of cancer treatment. Extrapolating these concepts further, if we accept that we should target tumour epithelium and vasculature, then it remains possible that other tumour compartments e.g. the immune system, should also be targeted at each recurrence.

I think it’s safe to say that this research, carried out by teams in Manchester, has made a significant contribution to how we treat ovarian cancer, in whom and when. This ability to run clinical trials and to take our learning from these into the hospital is making a huge and positive difference to thousands of women’s lives. We’re enabling them to live longer and cancer-free lives, and protecting others from unnecessary treatment.

Building a clinical trials infrastructure

My hope for Manchester’s cancer research community is that we come together to develop a truly world leading clinical trials infrastructure that makes us the envy of every other cancer centre. We have opportunities here that many other centres don’t. We have the access to patients and the willingness of the clinical, academic and basic science partners to work together. The key is to expand so that clinical researchers like myself can run more trials which result in increased knowledge about how we can better improve patient care and treatment. Not just in ovarian but in all cancers. This is how we’ll run the trials that change patient management and how we’ll become world leading.

Manchester is an incredible centre to carry out cancer research and I have seen a fantastic transformation of the Manchester Cancer Research Centre into a leading international focus of research and high quality cancer care.”

Gordon Jayson is Professor of Medical Oncology at The University of Manchester and Consultant Medical Oncologist at The Christie.

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through collaborative
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Professor Paul A. Townsend is an academic entrepreneur with a unique position at the interface of research and industry. An internationally-renowned researcher in molecular and cell biology cancer, and Associate Dean for Business Engagement at The University of Manchester, he outlines the focus for future innovation in both sectors.

“Cancer is going to become a disease that we learn to live with rather than necessarily cure.

I hope we will be able to live with cancer as a chronic disease rather than it killing us as a huge, scary acute one, which is what we've known for many years. We're going to need healthier living and healthier aging to help us control cancer. As a research community we need to ask ourselves: how can we manage cancer/how can we live with it better? what medicines do we need? how do we stratify and diagnose patients to fit into different treatment groups.

There is a massive opportunity for us but we can't do this all by ourselves, which is where working and partnering with industry comes to the fore. Business engagement and entrepreneurship play a crucial role in our research community and they will increasingly do so, if we're to realise the immense opportunities that are afforded to us over the next decade, such as the growth of artificial intelligence (AI), and the role of immuno-oncology, immunology and inflammation. These are areas in which we can make a huge difference. As one example, we could semi automate pathology screening to both cost save and help to improve accuracy.

Making sense of data

While this data generation provides information and patterns that are undoubtedly transforming our knowledge of cancer, there is so much of it that there's a collective cry of what do we do with it all? how can we make sense of the data chaos? We need to look directly in to that chaos, listen to all that noise in order to draw out the important patterns within. Industry comes to us because we have so much chaotic data in our hands and they know that we can see the patterns in it. Our expertise in reading the data is allowing us to stratify and personalise treatment, making it more accurate, more efficient and more cost effective.

Statistics for early death rates in Manchester compared to the rest of the UK are shocking. The likelihood of a male reaching 75 years old here is nearly 20% lower than some other parts of the UK. This needs to change but unfortunately, in the past, getting health messages out into some of Manchester's complex communities with been difficult. We've only found out about cancer when it's too late, generally when people present with chronic illness. However, there's an education, an undertaking, that's happening right now which we hope will result in an improvement in those statistics. The way to do that is by education and engagement and the patient working alongside us in their healthcare pathway.

We may be doing the world's best science but if communities don't know about it, then they're not going to take the learning on board and we might not get there until it's too late. So, we must develop the science, use that science and engage the patient to help improve their health outcomes

and do it all in Manchester. I think that's highly achievable, under the 'One Manchester' and Health Innovation Manchester umbrella. That's one of the reasons that I came here and one of the reasons the UK government has given Manchester a devolved health and social care budget.

Having it all

Being the biggest doesn't always equate with being the best, but for us it does. Our centres of excellence in different cancer disease areas, including prostate, melanoma, lung and breast, all attest to this.

As a collective research centre we can respond quickly and flexibly. That's the Manchester approach. It means we can become the first adopters and first to develop new treatments, taking laboratory science to the patient as quickly as possible; from bench to bedside and back again.

Working with the Christie is incredibly rewarding, it's part of the NHS and so it's patient care focused. That's a very different approach to business and industry which can be seen as cost effectiveness focused. However research has been rising rapidly up our collective care agenda, so allowing us to utilise our expertise in undertaking basic fundamental translation research, working with The Christie, looking after the patients, drawing that together and bringing external companies into that ecosystem, allows us to have a 'One Manchester cancer' approach. We can be patient focused, undertaking fundamental translation research and looking after patients but

The opportunities created by working across disciplines are multiple but bring challenges in equal measure. The worlds of mathematics, engineering, computer science and AI are going to be huge in helping to personalise treatments, stratify populations and diagnose cancer. Despite these being relatively new areas, at Manchester we are already working with world-leading health data scientists the Health eResearch Centre and the Farr Institute, to understand how we can use these technologies for patient benefit.

One of the most recent and high profile activities which we have worked on with industry is in the development of digital pathology for rapid assessment of cancer diagnosis. Funded by SBRI (Innovate UK) for more than £1.1M, we are working with the DeepMed Ltd to help develop AI algorithms and novel digital scanning approaches to help expedite and increase the accuracy of diagnosis. This has been exemplified in breast cancer but it now being rolled out to other solid and liquid tumours.

“The worlds of mathematics, engineering, computer science and AI are going to be huge in helping to personalise treatments.”

bringing external companies with cost-focused expertise into that ecosystem. Nobody can do what we do in terms of rapid recruitment to trials or experimental medicines initiatives. We've got the largest Biomedical Research Centre (BRC) outside of the south of England, of which half is cancer driven, and the excellence of our business engagement strategy and portfolio was recognised by the National Institute for Health Research. This is one of the reasons that we can work with our industrial partners to translate our cancer research into help for patients quickly and effectively.

Uniquely placed

We have Europe's biggest cancer hospital, we're home to the largest number of clinical trials annually, the largest number of spin out companies and we have input from and access to expertise and facilities at a world-leading university.

Bringing together funders, discipline experts, government, international industry and most importantly, our patients and the community, is critical. In my view, this is the unique offering of the BRC, Health Innovation Manchester and the 'Devo Manc' ecosystem. This collective environment is the future for cancer research and industry, a future we've shown we can deliver and that's what we'll continue to do as we face the next chapter of challenges.”

Paul A. Townsend is Associate Dean for Business Engagement in the Faculty of Biology, Medicine and Health and Professor of Molecular Cell Biology at The University of Manchester.

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As our understanding of cancer grows, so too do the often unseen teams of experts pulled from different disciplines working together to answer big research questions. Andy Brass, Professor of Bioinformatics, outlines the diversity of the data and expertise that is now needed in cancer research, from computer science, through to medicine and genomics.

“With The Christie and Manchester’s other hospitals as prominent landmarks, it’s sometimes easy to forget that, as well as a clinical and medical campus, we’re also a scientific campus. Here we’ve got maths, data science, computing, physics, imaging and chemistry. Our unique selling point is that we’ve got all this expertise and brilliance on a single campus because we share a common road; we’re a connected campus.

My research is focused on developing methods and tools to help us understand biological data. In its broadest terms, bioinformatics is concerned with applying statistics and computing to biological sciences. It’s an interdisciplinary field of science which combines computer science, biology, mathematics and engineering to help us analyse and interpret biological data.

“We’re all experts in different fields but working for a shared goal – to improve life chances for people with cancer.”

THINKING DIFFERENTLY

Statistics
Computer Science
Bioinformatics
Engineering
Biology
Chemistry
Biochemistry
Mathematics



Thinking outside of the box

Whilst this may seem a world away from the biological research that is usually associated with cancer research, we’re becoming more and more part of the core cancer research team. When you consider all the information that is needed to understand cancer, you can see why.

Cancer’s touch is so widespread that reducing its reach will require us to be able to develop an infrastructure that can store, analyse, integrate and visualise large amounts of biological data and this is the focus of bioinformatics.

Needing data

This big data comes in many forms and requires different levels of interpretation. We need large scale population health data: numbers of people being diagnosed, treated and surviving, as well as patient demographics. This is fundamental and we’re expertly placed to do this here as the University is home to two world leading centres, Health eResearch Centre (HeRC) and the Farr Institute, global leaders in crunching big data.

We also need to access primary care data from GPs and pharmacists. This data is key to identifying missed diagnosis opportunities, assessing patient health pre-diagnosis and identifying windows for earlier detection. If you want to identify cancer earlier, population level data is where the answers lie. We’ve already done this in early stage lung studies and we’re leading the research pack here.

The second tier in the data mix is omics, such as genomics, proteomics or metabolomics, to see what’s going on inside the cancer, what changes are taking place in the DNA. Changes are happening all the time in the cancer genome, but we need to know what these are and it’s now possible to examine the full genomic data contained within a tumour sample.

A number of projects are now collecting this data from large patient groups, including the 100,000 Genome Project that Manchester is involved in, and which has helped to develop genomic medicine services for the NHS. This data is potentially transformational in terms of improving diagnosis, prognosis and the design of ‘personalised’ drug treatment that can properly match the molecular basis of a cancer to an individual’s therapeutic requirements.

This however, is an enormous task. Cancer is an ecology of cells, representing different mutated versions of the patient’s own genome. As the patient’s immune system and the cancer drugs attack a cancer, the cancer cells themselves can evolve to respond to this threat.

Genomic data is large, complex, and noisy, and therefore difficult to analyse effectively. Nowhere is this challenge more evident than in oncology, which as one of the world’s most widespread diseases affects more people in more different ways than any other. Whilst progress is being made to make medical sense of the data, this is a complex task. A number of analytical methods have been developed in the research setting to work with this data, however much less use is being made of this data to support the treatment of individual patients.

The final component in the data mix is imaging: looking at images of the cancer itself and seeing what patterns can be identified. This involves machine learning, teaching software to distinguish between healthy and tumour tissue and complex modelling.

Whilst we’re not oncologists or clinicians, cancer research needs bioinformaticians to help analyse the increasing amount of data involved. For both clinical and academic partners, the partnership between the teams needs to be genuine. We need to appreciate each other’s strengths and expertise.

Problem solving

As a bioinformatician, cancer presents us with interesting and challenging problems to help solve and that's the way you develop computer science, by taking on new challenges. Cancer gives us that; they help us and we help them. It's a mutually beneficial virtuous learning circle.

We're all experts in different fields but working for a shared goal, to improve life chances for people with cancer.

Currently I'm working with proton therapy research teams because they need maths and data science input to help improve the evidence base for this emerging treatment. The clinical work can't be undertaken in isolation.

Our partnerships between disciplines means that we have a genuine team science approach to working. It's not just the mathematicians, the biologists, the physicists or any other discipline supporting the cancer research team, but a collective working together to progress the global knowledge base.

I always say that here we're a little bit maverick and we ignore institutional boundaries where necessary, if it means that we get to carry out the research we need to do for us to get the answers

we want. We pull together the right teams for the right science and, as we're so connected as a campus, we speak to each other. Our co-location and proximity works for us.

We're also agile and brilliant at working flexibly, we have to be. Technology moves so fast that we have to ensure we can adapt and respond. That's why getting the right teams together means nothing is impossible!"

Andy Brass is Professor of Bioinformatics and Head of the Division of Informatics, Imaging and Data Sciences in the Faculty of Biology, Medicine and Health at The University of Manchester.

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