Sunday afternoon saw Mark Ratain (University of Chicago, USA) present a plenary lecture on interventional pharmacoeconomics, an emerging discipline aiming to reduce prescribing costs through the development of off-label treatment regimens while maintaining equivalent efficacy.

Such approaches acknowledge both the issue of rising drug costs and the difficulties involved in regulating their prices. The strategy recently outlined in Ratain et al. (2019) represents a series of economic nudges within the realm of abundant drug targets on the free market.

Citing an analysis of the oncology care model carried out in the US, Dr Ratain noted that 60% of the total cost of care is on drugs. Furthermore, Evaluate Pharma’s World Preview of projected global prescription drug sales for 2017–2022 describes a projected 13% compound annual growth rate for oncology therapies. “This creates a tremendous cost...
Interventional pharmacoeconomics: A new discipline for a cost-constrained environment

Continued from page 1

issue,” he said.

“I am not an economist, but I work on a campus that has some of the best economists in the world. At the University of Chicago, economists are known for devising free market solutions to the world’s problems.”

Describing what free market solutions might look like, he summarised: “The goal is to reduce prescribing costs through the development of new therapeutic regimens – applying clinical pharmacology to enhance drug value.”

He outlined four basic strategies to reduce costs, and potentially toxicity, without negatively impacting efficacy: the substitution of a therapeutic alternative (e.g., sirolimus for everolimus); lowering dosages; less frequent dosing; and shorter duration of dosing.

Proof of concept of these strategies comes from a number of recent cases where the clinical community has challenged labelling dosing regimens or drug choices, as well as challenging established licensing with a view to reducing cost. One example comes from ophthalmology, where a study by the NIH National Eye Institute found anti-vascular endothelial growth factor bevacizumab – costing $40 per dose – to be comparable in efficacy to the on-label ranibizumab – costing $2,000 per dose. This led to significant change in practice, such that by 2017 off-label bevacizumab was the most prescribed drug for advanced macular degeneration in the US.

Dr Ratain also cited the case of abiraterone, explaining that many oral oncology drugs with poor bioavailability have been developed and labelled to be taken under fasting conditions. A prospective trial demonstrated the comparable efficacy of 1000 mg fasting abiraterone with 250 mg taken with food. Cost savings were deemed by the National Comprehensive Cancer Network to not only reduce toxicity but also had the potential benefit of improving compliance.

He presented a number of further examples, with the central message that several stakeholders should have an interest in funding interventional pharmacoeconomic studies, including governments, closed health care systems, and self-insured corporations.

“How do we fund these studies?” He asked. “We are wondering this. We have a paper coming out on some funding models. There is direct government support, which would be nice, except that in the US the NIH is not allowed to fund studies to reduce cost. Pharma ‘owns’ Congress in the US.

“There are still philanthropic contributions. Then there is repurposing of drug costs within a single closed health care system, such as the NHS. The NHS love this idea; they say they just need to investigators to come to us and we will figure out how to get these studies funded. “There are also consortia studies – maybe the NHS could be the lead in a global consortium.”

Looking to the financial feasibility of a system such as the NHS conducting interventional pharmacoeconomic studies, he outlined a cost benefit analysis suggesting that such studies are self-funding. He used the case example of ibrutinib and its prices according to standard care practices (£102 per day or £3,067 per month) and an experimental one-third dosage regimen (£51 per day or £1,533 per month). Within the timeframe of a 1:1 trial of standard versus experimental dosing, the saving of £1,533 per patient per month yielded by the experimental arm would be sufficient to fund the cost of carrying out the research, regardless of its outcome.

“There is a big opportunity here, because you have a single payer system. Take advantage of it.”

He concluded: “Interventional pharmacoeconomics can reduce prescribing costs for dozens of anticancer agents without price regulation. There are numerous strategies to fund and conduct interventional pharmacoeconomic studies, particularly in the context of single payer systems such as the NHS.”

Dr Ratain and Daniel Goldstein have organised the 1st International Summit on Interventional Pharmacoeconomics, which takes place on 25–27 March 2020 in Tel Aviv, Israel. Further details can be obtained by emailing dstoit@medicinebsd.uchicago.edu.

References


The goal is to reduce prescribing costs through the development of new therapeutic regimens.

Mark Ratain
Radiotherapy and immunotherapy: Looking for opportunities amongst the cast of immune players

The past, present and future of combining radiotherapy and immune therapy

Most of the immune combination trials with radiotherapy involve T cells, but little attention has been paid to NK cells.

Amato Giaccia

The ability to harness the pro-immune responsive aspect of radiation has to be taken into consideration with the immune-suppressive aspects.

Amato Giaccia

They are looking to see clinical benefit, in terms of local control, partial or complete response, and survival. “Hopefully some good things will come out of that. And there are derivatives of those types of trials. But all of them really are interrogating the combination of radiation with T-cell checkpoint therapeutics.”

Despite this enthusiasm, radiation presents a two-sided coin, with some evidence of immunosuppressive as well as immune stimulatory effects that may be mediated by diverse biologic mechanisms. Indeed, as Professor Giaccia explained, immune cells within the tumour microenvironment, including stromal cells, endothelial cells, innate, immune cells and adaptive immune cells, can influence radiation response.

In preclinical models, radiation has been observed to stimulate the attraction of M2 macrophages, myeloid-derived suppressor cells and T regulatory lymphocytes (Tregs), and dendritic cells and the secretion of tumour antigens, interferon-gamma, and activation of the cGAS-STING pathway. Inflammatory signalling stimulates the activation of dendritic cell maturation, as well as activating NK, M1 macrophages and CD8+ cells.

“The ability to harness the pro-immune responsive aspect of radiation has to be taken into consideration with the immune-suppressive aspects. But most trials are focused on the immune-responsive aspects of putting the two together.”

“There is benefit of course – getting T cells into the tumour and getting them active – is a good thing. Radiation induces PD-L1 expression in a cancer cell. So the combination of radiation plus a T cell checkpoint therapeutic – either anti-PD-L1 or anti-PD-1 – is going to be effective to a degree.”

“But it is not going to affect the M2 macrophages, the myeloid-derived suppressor cells, the Tregs or the neutrophils. Having said that, we currently don’t have therapeutics to take out M2 macrophages or myeloid derived suppressor cells, or Tregs. So in one sense we are utilising what is available to the best of our abilities.”

Future research directions, Professor Giaccia continued, point towards the activation and recruitment of other elements of antitumour immunity. “Most of the immune combination trials with radiotherapy involve T cells, but little attention has been paid to NK cells,” he explained. “That is significant. ‘T cells revolve around a neoantigen that is being presented at the cell surface by MHC that a T-cell receptor can recognise. But the NK cell doesn’t really care about that. You can imagine that another means of escape is that the neo-antigen is suppressed, or the formation of neoantigen or the presentation of MHC at the cell surface is suppressed. So NK cells could represent a different approach or even a complimentary approach combined with radiotherapy. The issue with NK cells is that, much like with T cells, many solid tumours exclude them. It is not completely clear what the major mechanisms are behind NK cell exclusion.”

He said in closing: “For NK cells, we think we’ve identified one major mechanism; I am going to present that during my talk, and how this could then be combined with radiotherapy and the potential benefits of this going forward.”

References


Creating better cancer awareness campaigns requires better research. That's the message today from Kate Brain, a health psychologist at the Division of Population Medicine at Cardiff University, UK. She leads the Screening, Prevention & Early Diagnosis work stream and has been researching behavioural aspects of cancer screening, prevention and early diagnosis for over 20 years.

In this morning's session on optimising recognition and referral across the patient pathway in primary care, Professor Brain will talk about her work with the International Cancer Benchmarking Partnership (ICBP). Started in 2009, the alliance of clinicians, academics and policymakers marked the first of its kind seeking to understand how and why cancer survival varies between participating countries. "In 2010 I was invited to join the ICBP as academic lead for Wales in the public awareness workstream," she told NCRI Daily News. "The ICBP research generated considerable insights into the influences on cancer awareness and symptom presentation behaviour, and led to further research to design and test complex interventions based on these insights."

Professor Brain plans to talk about these complex influences on behaviour and how they might be changed, presenting some examples of cancer awareness interventions designed to encourage timely symptom presentation, with a particular focus on reducing socioeconomic inequalities.

"I want to give a flavour of the evidence that has accrued over the past 10 years, highlighting some of the challenges of conducting research in this area, and the contribution that behavioural and social science can make to addressing these challenges," she said.

Many cancer awareness drives – usually involving mass media campaigns designed to deliver symptom awareness messages on a large scale – have taken place in the UK in recent years. To a certain extent, they have produced positive results, said Professor Brain. "These are challenging to evaluate, but large-scale studies on the English Be Clear on Cancer lung campaign and the more targeted Leeds lung campaign have shown improved awareness of cough symptoms, with evidence of a significant shift towards earlier-stage lung cancer diagnosis," she said.

The Leeds lung campaign was a mass-media awareness campaign combined with primary care education, where community health educators delivered symptom messages to local target populations (from 2011). It was targeted initially at deprived areas of Leeds, UK, and then rolled out across the city during a five-year period. Rates of community referral for chest X-ray and lung cancer stage at presentation were collected from 2008 to 2015. "There was a significant shift towards earlier-stage diagnosis regardless of level of deprivation, which probably reflects the targeted and sustained nature of the campaign," said Professor Brain.

Campaigns are not always successful, however, if the target symptoms are still being ignored, she stressed. The ICBP studies showed that people in the UK were much better at recognising so-called red flag symptoms such as lumps and bleeding than vague symptoms such as a persistent cough, noted Professor Brain: "This is because vague symptoms can be put down to other things such as minor illnesses or co-existing health conditions, and therefore more easily dismissed than alarm symptoms."

Therefore, targeted cancer awareness interventions can be particularly powerful under these circumstances. "Those targeted at social and community networks can signal to people that seeking help quickly for possible cancer symptoms is welcomed and legitimised," said Professor Brain.

While there are different kinds of targeted interventions, examples include the trained peer supporter model, continued Professor Brain: "Building on personal connections and trust, using a model such as this, could be a powerful way of spreading positive cancer awareness messages through the community."

Any targeted intervention must take into account the complex factors that influence people's awareness of symptoms and whether or not they act on that awareness. "Cancer fear and fatalism are important barriers to early diagnosis, especially among people living in socioeconomically deprived communities where long-term health may not be a priority due to low resources," explained Professor Brain. "Qualitative research with people living in the most deprived areas of the UK revealed that there is a fear of cancer diagnosis, a fear of cancer treatment and a persistent belief that cancer is a death sentence."

But there are also complex socioeconomic factors, she added. For instance, people may lose income in order to take time off work to visit the GP. "Some also described a lack of confidence in talking to the GP, with social relationships being an important motivator for help-seeking," said Professor Brain.

"We need to find ways of tackling system barriers relating to access to services, as well as emotional barriers reflecting deep-seated beliefs about cancer."

Currently, Professor Brain is leading the Awareness and Beliefs About Cancer.
New digital tech requires new research methodologies

Reality check in how the efficacy of digital interventions is tested will be delivered today by Eric Hekler, an associate professor at the University of California San Diego, USA. “I have a strong track record in advancing evaluation methods for digital health technologies which span a wide range of evaluation study designs including factorial trials, micro-randomisation trials, randomised clinical trials (RCTs) and system identification experiments,” Dr Hekler – who will outline robust research methods for testing these technologies – told NCRI Daily News.

Looking at the digital applications for cancer prevention and control today, Dr Hekler feels there is a gap between promise compared to reality, otherwise known as the ‘hype-evidence gap’. “I will be discussing the hype-evidence gap in relation to digital health interventions for meaningful health behavioural change.”

Digital health interventions, or therapeutics as they are increasingly labelled, encompass a range of tools from telehealth platforms, patient portals/electronic health records, wearable devices to mobile apps. “Digital therapeutics aren’t producing the desired effects consistently,” said Dr Hekler. “Some technologies do, of course, but they are often the exception rather than the rule.”

Dr Hekler will discuss the four main hype-evidence gaps. One of them, he said, is the hope that mobile health (mHealth) will effect lasting behavioural change. But that contrasts with the results of studies to date. “While plenty of studies illustrate the potential value of mHealth technologies, findings largely drawn from pilot studies and subsequent larger trials suggest a limited value for these technologies,” said Dr Hekler.

“That underscores the need for more efficient scientific approaches aligned with the pace of technology,” he said. “Secondly, there’s a hope that technology will solve problems easily and efficiently. For example, there has been a great deal of hype over wearables, said Dr Hekler. “In early mHealth research, there was an assumption that building technologies alone would produce desired results, without the need for robust science of behavioural change,” he said. “But results highlight that, to get mHealth right, evidence is needed to guide how technologies can effectively support change in behaviour.”

Different types of evidence explicitly focused on advancing and understanding the behavioural change process itself are required, continued Dr Hekler, but in reality, the predominantly funded trials and methods often force researchers to study the more distal health outcomes, which often compromises the rigor of the science related to behavioural change.

The third hype gap, ac-
Digital interventions for cancer prevention and control Dobchart Tuesday 2:00–3:00 pm

New digital tech requires new research methodologies

“...to get beyond the hype-evidence gaps with digital health, we’ll need to start using more robust methods that enable us to study these tools with sufficient rigour.”

Eric B Hekler

To get beyond the hype-evidence gaps with digital health, we’ll need to start using more robust methods that enable us to study these tools with sufficient rigour.

Dr Hekler will also be discussing another UK study which he described as a good benchmark to guide other studies. It assessed whether a version of the Smokefree app with a supportive chatbot powered by artificial intelligence (versus a version without the chatbot) led to smokers’ increased engagement and short-term quitting success. The group found that adding the supportive chatbot to what was already a popular smoking cessation app more than doubled user engagement. “It’s a great early example of how to build a robust, meaningful win/win collaboration between academia and industry,” said Dr Hekler.

He will also be drawing on his team’s own Agile Science concept, a process for creating useful and usable behaviour change interventions and corresponding evidence. “Agile Science moves scientific inquiry from asking ‘what works on average?’ to ‘what works for whom and in what context?’,” he said.

In other words, there are some fundamental methodological challenges that must be addressed when conducting research in this area. “In brief, the epistemological foundations inherited by medicine are, in my view, inappropriate, for the majority of questions that need to be asked and explored to actually enable evidence to be used to build robust digital therapeutics for behaviour change,” he explained.

“To get beyond the hype-evidence gaps with digital health, we’ll need to start using more robust methods that enable us to study these tools with sufficient rigour.”

References

Dr Hekler went on to note that there has also been an explosion in new types of research methods, for example methods used in the multi-phase optimisation strategy (MOST), micro-randomized trials, increased use of N-of-1 cross-over designs, or hybrid implementation trials, with each having unique value for advancing the science of behaviour change.

In a recent paper, Dr Hekler and colleagues discussed the limits of traditional research methods, including the RCT. They stated that, while RCTs are important for evaluation of effectiveness and cost effectiveness, they are best undertaken only under very specific circumstances. That’s likely to be a rather controversial assertion, conceded Dr Hekler. “A central point for me is challenging the assumption and the dominance of the RCT for determining if something is evidence-based,” he said. “The RCT is an amazing tool but we are asking too much of it.”

In his presentation, Dr Hekler will discuss emerging work looking at how to close the hype-evidence gap with better methodology and industry-academic partnerships. For example, his team used a system identification experiment to develop an individualized intervention, JustWalk, which encourages regular walking via activity suggestions tailored to an individual’s current circumstances, to optimise intervention. “Today, Dr Hekler will present the latest results from this interesting study.

Eric B Hekler

“I will be discussing the hype-evidence gap in relation to digital health interventions for meaningful health behavioural change.”

Eric B Hekler

To get beyond the hype-evidence gaps with digital health, we’ll need to start using more robust methods that enable us to study these tools with sufficient rigour.
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Count Your Steps!

Get fit at the 2019 NCRI Cancer Conference and take part in our Daily Step Challenge. The person with the highest number of steps accumulated by the end of the day will be in with the chance to win a prize. The winner will be contacted via Twitter tomorrow morning. Here’s how to take part:

- Download a pedometer or health app on your smartphone, or use your own pedometer such as a Fitbit or iPhone Health
- Follow the official NCRI Twitter account: @NCRI_partners
- Take a screen shot or photo of the total number of steps you’ve accumulated TODAY and tweet it to @NCRI_partners by 12:30
- Tag @SECglasgow including the hashtags #NCRIsteps #NCRI2019 & #healthyvenue

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Don’t miss!

Today in Hall 4 – Silent theatre presentations

Oral presentations will take place in the Silent theatres during the coffee and lunch breaks, and are a chance for abstract submitters to present their research. A full schedule can be found below:

Silent theatre 1

10:30        Evaluation of older patients in early phase clinical trials
Jessica Lowe

10:36        Next generation Cytogenetics: Comprehensive Structural Analysis of Cancer Genomes by Optical Genome Mapping
Yannick Delpu

10:42        Genetically raised serum bilirubin levels and respiratory cancer: a cohort study using UK Biobank
Laura Horsfall

10:48        Inhibition of prostate cancer cell growth, motility and ability to alter monocyte/macrophage lineage commitment by a novel TRAF6 inhibitor
Denise Giovana Carrasco Gonzalez

12:40        Survival and Cure of Acute Myeloid Leukaemia (AML) in Children, Adolescents and Young Adults in England
Mae-Yen Tan

12:46        Exposure to ionizing radiation elicits significant lung tissue perturbations and creates a tumour-supportive microenvironment
Emma Nolan

12:52        Best supportive care (BSC) with or without low-dose chemotherapy (chemo) in frail elderly patients with advanced gastroesophageal cancer (aGOAC): The uncertain randomization of the GO2 phase III trial
Daniel Swinson

12:58        CD99 regulation of cancer cell dynamics and tumour formation
Adam Odell

13:04        Mapping Cellular Subpopulations within Triple Negative Breast Tumours Provides a Tool for Cancer Sensitization to Radiotherapy
Ariel M. Rubinstein

13:10        Addressing the variation in adjuvant chemotherapy treatment for colorectal cancer (CRC): can a regional intervention promote national change?
Daniel Swinson

13:16        High-content Profiling in Oesophageal Adenocarcinoma Identified Selectively Active Compounds for Repurposing and Novel Drug Discovery
Rebecca Hughes

13:22        Targeting melanomas MCL1 bias unleashes the apoptotic potential of BRAF and ERK1/2 pathway inhibitors
Emma Minihane

13:28        Avoidable harm: making decisions about chemotherapy with advanced lung cancer patients
Annamarie Nelson

13:34        Socio-demographic variation in routes to diagnosis in head and neck cancer: a population-based analysis
Jennifer Deane
Discounted travel
Thank you for joining us at the 2019 NCRI Cancer Conference. If you’re heading to the airport this afternoon don’t forget that discounted travel is available for journeys between Glasgow Airport and the City Centre with Glasgow Taxis.
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Don’t miss!

Today in Hall 4 – Igloo presentations
Head to the Igloo to hear from NCRI Partners, sponsors and exhibitors:

- 10:30–10:55 NIHR session
- 10:45–10:55 NIHR session
- 13:30–13:50 Q&A with Dr Susie Cooke and Lesley Stephen – Glasgow Cancer Assays

Silent Theatre 2
10:30 How representative are patients responding to the Cancer Patient Experience Survey (2010-2014) of the wider cancer population in England? Analyses for breast, prostate, lung and colorectal cancer
Saleh Alessly
10:36 Effective clinical cancer treatment, care and management for people with comorbid cancer and dementia: understanding population demographics and intervention priorities and outcomes (CanDem-Int)
Michelle Collinson
10:42 Geographical variation in access to ovarian cancer treatment in England
Ewa Zotow
10:48 A Systematic Review of the Economic Costs of Gastrointestinal Consequences of Treatment for Cancer Patients and Healthcare Providers
Mala Mann
12:40 The gut microbiome and response to neoadjuvant chemotherapy in breast cancer
Kirsty Ross
12:46 Exploring metastatic dormancy to tackle breast cancer metastasis
Stefania Di Blasio
12:52 Proteomic Profiling on apoptotic effect of keto-boswellic acid
Fahad AL Zadjali
12:58 Spreading The Word and Sharing The Load – NCRI Consumer Involvement In Cancer Research
Richard Stephens
13:04 Do Neutrophil Counts Pre-chemotherapy Treatment provide Clinical Value
Pinkie Chambers
13:10 Treatment and survival in non-metastatic muscle invasive bladder cancer: analysis of a national patient cohort
Joseph John
13:16 I thought there would have been pain A qualitative investigation of patients experiences of the route to, and diagnosis of, head and neck cancer
Jennifer Deane
13:22 PLGA-Disulfiram microparticles inhibit NF-KB and PD-L1 pathway and reverse chemoresistance induced by mesothelioma stem cells
Garima Tyagi
13:28 Waiting for a miracle or best medical practice? End-of-life medical ethical dilemmas in Bahrain
Barrak Almoosawi
13:34 Oncogenic Ras/ERK signalling alters cell shape and mechanics to facilitate cell division under confinement
Helen Matthews
13:40 Project Swallow: Living with oesophageal cancer
Henry Goodfellow
13:46 Engineered 3D-microtumours for personalized cancer therapy
Nobina Mukherjee
Gathering data on the indications for proton (particle) therapy will be the focus of a talk today by Cai Grau (Aarhus University, Denmark), Research Director of the newly opened Danish Center for Particle Therapy (DCPT). Professor Grau has great interest in the role that proton therapy plays in his centre, as well as others across Denmark, the UK, the Netherlands, Norway and other European countries – some of whom will be represented during today’s sessions.

Speaking to NCRI Daily News, Professor Grau stressed that although there are more than 20 proton centres in Europe, most have fallen outside the scope of clinical trials. “There is a possibility of generating more evidence for the role of or need for particle therapy in the future,” he said. “I think there is a potential for particle therapy in many other indications.”

Professor Grau will use the session today to lay out the importance of collaborating on new data, and gathering evidence for new indications. “We need to work together to create a critical mass of intelligence and knowledge to move this field forward,” he reasoned.

Several European countries are establishing clinical trials to determine the role of conventional radiotherapy in cancer treatment, as well as determining morbidity rates and side effects. “This is where particle therapy has some advantages, because the beam can potentially reduce side effects,” said Professor Grau. Proton therapy has been shown to lower the dose of radiation given to normal organs for example. “There have been few trials in this area so it’s very important for the future of proton therapy that we find out who needs it, and who doesn’t,” he said.

One important move in that direction is the European Particle Therapy Network, which links all particle centres in Europe. “It’s a major task to evolve the field of proton therapy and get scientists and clinicians in Europe to collaborate,” he said. “There are trials still in need of patients from many countries in order to collect enough data.”

Professor Grau will outline several projects operated by the network, encompassing both clinical trials and other projects. For example, the network will look into the health economics of proton therapy, given it is so much more expensive than conventional radiotherapy. “As such, we need to find some evidence in terms of added cost and added value compared with conventional radiotherapy,” he said.

Clinical trials are ongoing too, with considerable activity in head and neck cancer, for example. In the UK, the TOxici-ty Reduction using Proton bEam therapy for Oropharyngeal cancer (TORPeDo) randomised control trial – led by the Christie Hospital in Manchester – is looking at whether proton therapy can reduce side effects such as difficulty in swallowing and dryness of the mouth. Similar trials are ongoing elsewhere, including DAHANCA 35 in Denmark.

Importantly, the network is also collecting data from centres that may not necessarily be conducting randomised trials, in collaboration with EORTC and ESTRO. “These data are also very important,” said Professor Grau.

Interestingly, breast cancer is a very common indication for radiotherapy and the majority of cancer patients will not need particle therapy. But, as Professor Grau explained, around 4–5% of breast cancer patients may be good candidates. “In those examples, we cannot cover the lymph-node targets without exceeding the radiotherapy dose to the heart or the lungs,” he said. “This is an important group of patients who could be targeted with proton therapy.”

As a result, several trials are being established in e.g. Denmark, The Netherlands, France, Germany and the UK to look at the optimal way to undertake proton therapy in these kinds of patients. “Many people are collaborating on these trials, but it takes a long time to find patients because it’s a rare complication,” noted Professor Grau.

Professor Grau will also talk about the value of normal tissue complication probability (NTCP) modelling when carrying out clinical trials. Essentially, the planned dose using proton therapy is compared with the dose required in normal radiotherapy, and the dose distribution is calculated using computer simulations that can model the doses given to structures that are most vulnerable to side effects (such as the salivary glands and anatomy involved in swallowing).

“Then we compare the dose distribution in the target to decide whether we can use proton therapy,” he explained. “The model predicts all the complication rates if you give a particular dose. Too high a dose – as we know from conventional radiotherapy – will be associated with a risk of side effects.”

This modelling technique allows such effective theoretical comparison that it might be able to identify the subset of patients with the highest chance of success, or the best candidates for clinical trials, said Professor Grau.

The DAHANCA trial, for example, will formally test NTCP models to demonstrate their clinical utility. In the trial, only patients expected to benefit from proton therapy (specifically, in terms of reducing risks of dysphagia and xerostomia) can participate in the study.

“Within the network we would like to look more deeply at how far we can go with this model-based approach,” continued Professor Grau. “However, although it makes a lot of sense, this approach is not generally approved and there is no direct evidence that reducing the dose with proton therapy would impact long-term outcomes and morbidity.”

To test whether proton therapy is better than conventional radiotherapy, the most preferable method might be to conduct a randomised controlled trial or direct head-to-head comparison. “But it does not make so much sense to compare in situations where conventional radiotherapy cannot be done without significant side effects,” warned Professor Grau.

Interestingly, the TORPeDo trial will not use this comparative dose planning technique. Rather, patients will be randomised to either therapy at a very specific tumour stage and diagnosis. “It’s simply a different approach,” noted Professor Grau.

Indeed, different options and ap-
approaches – i.e. randomisation or dose planning comparisons – will be discussed at NCRI 2019, as Professor Grau commented: “Maybe it’s even a strength that we are conducting trials in different ways, so we can know in a few years what is the optimum way of doing things.”

These kinds of model-based comparisons are specific to Europe for now, he went on, as American proton centres are not following suite. "So of course we will try to establish a critical mass of data in Europe so that we can show others that this is a better way to do clinical trials,” he said.

Professor Grau offered his conclusions for NCRI Congress News: "We have a fantastic chance to create evidence as to who would benefit from proton therapy and, importantly, who wouldn’t. Going forward, we need to collaborate with the rest of the radiotherapy community and get proton therapy integrated into radio-oncology. Yes, we have one of the more advanced tools, but we are just part of the equation. We are not something special.”

References

“It’s very important for the future of proton therapy that we find out who needs it, and who doesn’t.”

Cai Grau

DON’T MISS!

‘Our Cancer Journey’ – Artistic expressions of living with cancer

All days, Hall 4, Poster Boards

‘Our Cancer Journey’ is a consumer artwork display aimed to bring together people living with cancer to reflect and share on their diagnosis through the creation of two reflective mono-prints. This project is a collaboration between cancer researchers Anthony Matthews, Yuki Alencar and Camille Maringe from the London School of Hygiene and Tropical Medicine, and Jayne Dent, a Newcastle-based artist.

Throughout all three days of the Conference you will have the opportunity to see this display in one of the poster areas in Hall 4.
The 100,000 Genomes Project: Experiences, discoveries and future plans

Anna Frangou (University of Oxford, UK) will be one of the discussants of the 100,000 Genomes Project during a session dedicated to the venture this afternoon.

The project, launched in January 2018, is an international research effort to establish the most detailed catalogue of human genetic variation to date, with the aim of embedding genomic medicine into routine patient care. The project is focusing on some 17 cancers, including both common and rare forms, and around 1,200 rare diseases affecting children and adults.

The 100,000 Genomes Project has now reached its original sequencing target, and continues to collect data. During the session, results will be presented from the colorectal Clinical Interpretation Partnership (GeCIP) of Genomics England, a consortium performing analysis of >1,500 pairs of colorectal whole genome sequenced (WGS) tumour and germline samples from across England’s GMCs. This is the largest study to date of WGS colorectal tumour-samples, providing the power to detect new mutational drivers in this cancer, including at the single nucleotide, copy number, and structural level, across both coding and non-coding regions.

Dr Frangou is a computational bioinformatician working in cancer genomics within the project. Speaking to NCRI Daily News, she discussed some of the challenges of collaborating as part of a large-scale genomics project with a distinct clinical goal.

“My work is very much pan-cancer,” she began, “And I will be talking about the value of the 100,000 Genomes Project as a huge effort between researchers and clinics to gather and analyse a great mass of data, with the intention of bringing forward the era of personalised medicine.

“Often, we have collaborations between clinicians and bioinformaticians, but of course we come from different disciplines with some inevitable differences in perspectives. For example, I come from a computational bioinformatics group, so our first focus might be quite methodological, whereas research clinicians are of course focused very much on how this is going to help the patient. Bringing together these perspectives in full and extended collaborations is hugely valuable.”

Dr Frangou and colleagues have been working on quality control of data for the project’s budget, as well as arguments suggesting that whole genome sequencing remains overkill for most cancers – all amid high public expectations.

She countered: “There will inevitably be the concern raised that whole genomes won’t add more than panel data or exome data, in a clinical sense. But my view is that there is a need to perform the analysis first, fully and completely, see what we come up with, and then potentially pare back what we’ve found to what will have clinical utility. We can’t know whether this will add significant clinical benefit until this whole genome exploration has happened, but given that there is so much in cancer that we are yet to understand, and to even explore, in terms of the non-coding regions of the genome, it seems to me like an obvious step to take. And having both the academic and clinical sides involved is a huge and real benefit of this type of project.”

As one of the few clinically focussed large-scale projects of its kind, she added, criticisms may well be premature. She cited the discovery of mutations in non-coding regulatory regions of the genome – such as telomerase (TERT), a non-coding driver element – as demonstrating the importance of whole genome studies. “TERT has been shown to be important across a number of cancers. That is quite a significant regulatory mutation, meaning potentially a low hanging fruit has been found, and that there may be much more to find for individual cancers. This may be at least partially explained by the fact that the methods for detecting non-coding drivers are at this point quite heavily based on methods for detecting coding drivers. It is perhaps likely – and at least possible – that many non-coding drivers exist, but that they each have a small effect, and may work in a complicated network. So methods may need to develop further in order that we can make these discoveries.”

The dataset collected by Genomics England provides the opportunity and motivation for such things as these methods develop. “It seems logical to me that we need to dig down into the genomics of cancer, and see what comes out. For example, we know we can confidently call copy number and structural variation with whole genomes, tasks which are pretty tricky with anything less, so my view is that we should put everything into this approach, and find out what can be used in the clinic. It may show that whole genomes are crucial for personalised medicine – or it may be that we find additional sets of mutations that we can sequence in a targeted panel. Either way, we hope to add clinical utility.”

The session ‘100,000 genomes and other cancer genome sequencing projects: experiences, discoveries and future plans’ takes place this afternoon from 2:00 to 3:30 pm in Boisdale.

Reference
1. Turnbull C, Scott RH, Thomas E et al. The 100,000 Genomes Project: bringing whole genome sequencing to the NHS. BMJ. 2019 Apr 26.
Sub-type specific aberrant transcriptional programming in acute myeloid leukaemia

Constanze Bonifer is Chair of Experimental Haematology at the Institute of Cancer and Genomic Sciences (University of Birmingham, UK). Today she presents her recent work on aberrant transcriptional programming in acute myeloid leukaemia (AML) which is making steps towards the identification of druggable targets to halt disease progression and resolve aberrant cell differentiation.

Blood cell differentiation is regulated by blood lineage-specifically expressed transcription factors (TFs) that read the DNA sequence and interact with the epigenetic regulatory machinery to regulate the expression of genes specific for each lineage. AML is a highly heterogeneous cancer associated with different patterns of gene expression determined by specific DNA mutations, all of which occur in the gene regulatory machinery.

Professor Bonifer and colleagues have conducted global analysis of gene regulatory networks (GRNs) in AML using patient samples with characterised mutations in genes encoding TFs and signalling molecules that lead to blocked myeloid differentiation. GRNs consist of TFs and their target genes with which they interact and define cell type and differentiation status. The group have defined pathways within GRNs that are differentially rewired within particular mutation-specific subclasses of AML.

Drawing on a large collection of patient samples, the group focussed on specific sub-groups of patients carrying mutations in genes encoding transcription factors (RUNX1, CEBPA) and signalling molecules (FTL3-ITD, RAS, NPM1). They then demonstrated that each class of mutations establishes a specific transcriptional and signalling network different to that seen in normal cells. They hypothesised that identifying the AML subtype specific components of such GRNs would lead to those absolutely required for sustaining the expression of unique sets of genes required for AML growth and maintenance.

"Each type of leukaemia adopts a different GRN, and from there we can identify the main players in this network, which we then can target." - Constanze Bonifer

If you knock out one of these TFs that drive this process, or it’s mutated, such cell fate decisions are perturbed and cells get stuck in an immature stage. However, all differentiation processes are highly robust with multiple levels of control; cancer cells rewire these controls and differentiate ‘sideways’ in a direction that is determined by the type of original mutation. In essence, they become a different cell. All AML cells that we see (and this is true for all cancers) adopt different GRNs that are unique for each subtype. They go out on the rim and become something else which is often barely related to the original cell they come from. However, the fact that this type of differentiation is aberrant, also makes such cells vulnerable.

Novel therapies might involve perturbing this aberrant transcriptional environment, said Professor Bonifer. Turning to examples where this has been successful, she cited acute promyelocytic leukaemia, a subset of AML that is characterised by a chromosomal translocation involving the retinoic acid receptor alpha. Its treatment with all-trans retinoic acid prompts a direction that is determined by the type of original mutation. In essence, they become a different cell. All AML cells that we see (and this is true for all cancers) adopt different GRNs that are unique for each subtype. They go out on the rim and become something else which is often barely related to the original cell they come from. However, the fact that this type of differentiation is aberrant, also makes such cells vulnerable.

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Sub-type specific aberrant transcriptional programming in acute myeloid leukaemia

“All cancers have a problem with the regulation of gene expression and growth. However, we are starting to understand the rules.”

Constanze Bonifer

“Evolution has shaped this beautifully. There is very little you can do to derail this process. If you want to derail it, you really have to hit the cells hard. Most of these mutations that we see are not the only ones. The stem cell gets one mutation, and the cells then can’t differentiate properly, but then the second comes and then the third; then the body tries to attack it, and the cells evolve – some get killed and others survive. Darwinian selection is alive and well in our bodies. “These cells, which come out of this process are not only very aggressive, but they are also vulnerable, because they are cells where evolution has not had so much time to shape them. We can attack them and they stop growing, where normal cells won’t because the process is so robust. But since gene regulation and gene expression control is so complicated, we really have to dig very deep in order to find those sweet spots to tackle them.”

Professor Bonifer concluded by stressing the practical infrastructures necessary for such breakthroughs to occur. At the University of Birmingham’s Institute of Cancer and Genomic Sciences, all patients with AML are screened according to their mutation status as a prerequisite for this type of research. Samples are not easy to come by, and the group have been accumulating them over the past 10 years, supported by recurrent funding from the Bloodwise charity. Importantly, all of these data are in the public domain. “This is truly personalised medicine,” she said, “But first you need a knowledge base that underpins this type of diagnosis. Our paper is one of the first steps. “What we are discovering now is pretty much true for all cancers. The strategy and the way to go about it that the AML research has spearheaded will also be applied to any other cancer as well. All cancers have a problem with the regulation of gene expression and growth. However, we are starting to understand the rules.”

References

Parallel Session
Epigenetics – biology of non-genetic drivers of cancer (cancer and therapy)
Hall 1 Tuesday 11:00 am–12:30 pm today

Sub-type specific aberrant transcriptional programming
in acute myeloid leukaemia

Continued from page 13
differentiation of these cells, drastically improving prognosis in this patient population.
She continued: “There are now other people that are targeting TFs. For example, the group of John Buschweiler (University of Virginia School of Medicine, USA) are targeting RUNX, a TF which is often mutated in AML. There are also other people targeting chromatin components, such as BRD-4, which is part of a transcription complex, using bromodomains and extraternal (BET) inhibitors. In addition, there are a large number of people that try to target those epigenetic regulators that cooperate with TFs.

The transcription therapy is on its way towards the clinic, but we are not quite there yet. We will hopefully, using small molecules and other reagents, be able to reprogram the aberrant transcriptional complexes within those cells and inactivate them. But before you do that, you have to find out much more about how these cells have been reprogrammed.

The AML subtypes currently under study by Professor Bonifer’s group represent those with mutations in TFs, and in particular those representing high unmet clinical needs. In recent study, they showed that knockdown of GRN-specific TFs abolished AML growth in vitro. Then, in mice, they showed that blocking genes bound by these TFs halted leukema development.”

Summarising the logic of this approach, Professor Bonifer said: “We have to work out which genes are targeted by such TFs from which we know that it is absolutely required for tumorigenesis. For the subtypes we have studied, we now know all of these genes. Some of them encode products that are druggable and we are working through those lists of genes.”

Asked whether, given the complexity of the GRNs of AML illustrated by her group, it is likely that multiple TF targets will emerge with respect to particular AML subtypes, Professor Bonifer replied: “There will be multiple targets, that is very clear.

“We should be past the point of treating all cells, all AML, the same. We are still conducting chemotherapy, we are still poisoning people, we are still hoping for the best. Especially for the elderly this is not good enough, because they relapse or they can’t be treated.

“In principle, you want to understand all of these different subtypes of AML and you want to derive therapies that target the cancer from several angles that is specific for each sub-type, in the hope that if you hit it hard enough it will go away. The only way to find out what target is to do the kind of work that we do. You need a deep understanding of the global processes that shape the GRNs of these cells. How do they maintain these aberrant gene expression patterns? What is required?

“And it turns out, very interestingly, that by targeting many of these components of these aberrant networks, the cell immediately stops growing. When you do this with normal cells, they are usually nowhere near as sensitive. That tells you that the way blood cells are developing is the result of millions of years of evolution. The process is unbelievably robust. Have you never wondered why we more or less all look the same, when we have come from one little cell? The process is so wonderfully regulated that it is all encoded in our DNA – which is read by TFs. The same is true for the development of blood cells from stem cells.

“Evolution has shaped this beautifully. There is very little you can do to derail this process. If you want to derail it, you really have to hit the cells hard. Most of these mutations that we see are not the only ones. The stem cell gets one mutation, and the cells then can’t differentiate properly, but then the second comes and then the third; then the body tries to attack it, and the cells evolve – some get killed and others survive. Darwinian selection is alive and well in our bodies. “These cells, which come out of this process are not only very aggressive, but they are also vulnerable, because they are cells where evolution has not had so much time to shape them. We can attack them and they stop growing, where normal cells won’t because the process is so robust. But since gene regulation and gene expression control is so complicated, we really have to dig very deep in order to find those sweet spots to tackle them.”

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‘Epigenetics – biology of non-genetic drivers of cancer (Cancer and therapy)’ takes place in Hall 1 from 11:00 am to 12:30 pm today.
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