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# NCRI Daily News

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## Opening session welcomes all to Glasgow

Delegates at the 2019 NCRI Cancer Conference gathered in the Lomond Auditorium yesterday afternoon for the official welcome speeches at this year's meeting. NCRI CEO Iain Frame stepped up to the podium to first thank Joint Chairs Clare Isacke and Ruth Plummer for their leadership, as well as all members of the Scientific Committee, and the conference events and organising team. Dr Frame then welcomed Gregor Smith (Deputy Chief Medical Officer of the Scottish Government Health and Social Care Directorates) to the stage, who began by welcoming the NCRI audience. "Welcome to Scotland, welcome to the city of Glasgow; I wish you all a wonderful conference over the next three days."



### PLENARY SESSION

Deconstructing K-RAS signalling in cancer... **Lomond Auditorium** Sunday 1:45-2:25 pm

## New hope in therapeutic strategies for K-Ras mutant cancers

**M**ariano Barbacid (Spanish National Cancer Research Center - CNIO, Madrid, Spain) presented lessons learned from preclinical models of KRas mutant tumours during his plenary lecture yesterday afternoon.

KRas is the most frequently mutated oncogene in cancer, found in about one third of all human tumours including lung, pancreatic and colorectal cancers, Dr Barbacid explained to *NCRI Daily News*: "I never heard any campaigns about KRas cancers – you see a lot for breast and

many other cancers – but this represents a major public health problem." In the US, around 330,000 cases of KRas-driven tumours emerge each year, accompanied by around 120,000 annual deaths. Current therapies consist of well-established cytotoxic drugs, while thera-

"This represents a major public health problem."

Mariano Barbacid

pies that directly target KRas remain elusive. Addressing the progress of pharmacological investigations to date, Dr Barbacid said: "There is a big interest, but it just so happens that we don't know how to block KRas itself. However, KRas

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# New hope in therapeutic strategies for K-Ras mutant cancers

Continued from page 1

signals through two independent pathways: the MAP kinase (MAPK) and PI3 kinase (PI3K) cascades.

“These signalling cascades are made of kinases which are relatively easily druggable. Industry has made inhibitors against all of them. Unfortunately, none of them have been approved by the Food and Drug Administration [USA]. The reason is these drugs are too toxic; by the time they reach the therapeutic effective dose, the patient cannot take it. Some of them have failed in phase I, others have failed in phase II, and others have failed in phase III. The fact of the matter is that in the last 10 years, or even longer, no selective drug has been approved for treating KRas-driven cancer.”

One exception to this, Dr Barbacid noted, is the recently emerged AMG 510 inhibitor (Amgen, USA) which is selective for a KRas mutation that occurs in about 4% of lung cancers. Phase I trials of AMG 510 are ongoing.<sup>1</sup>

Despite this recent promise, the overarching theme in the KRas story has been the difficulty in influencing its pathways while otherwise maintaining homeostasis. Indeed, in work that Dr Barbacid and colleagues have carried out over the past 10 years, mouse models of KRas mutant lung and pancreatic cancer have demonstrated that the elimination of all MEK and ERK kinases of the MAPK pathway, as well as RAS-mediated PI3K activation, confers antitumour effects but is also highly toxic<sup>2</sup>.

Having eliminated the viability of these approaches, the group then turned to another family of kinases of the MAPK pathway, RAF, which consists of A-RAF, B-RAF and C-RAF (the latter also known as RAF-1). “We found out that one of these kinases, RAF-1, in addition to their activity in the MAPK pathway, has another activity. We are not sure exactly what this pathway is, but it



somehow relates to apoptosis.”

He added that B-RAF – which is mutated in melanoma – is very famous. “There are very good, selective inhibitors of B-RAF, such as vemurafenib, dabrafenib, etc. In this case, because it is a kinase, people have succeeded in making good drugs. But this is for cancers that are driven by mutations in B-RAF, not in KRas – and as such they have no effect in KRas mutant tumours.”

The group has recently shown that ablation of RAF-1 in KRas mutant mice induces significant lung tumour regression without inhibiting MAPK signalling<sup>3</sup>. In the pancreas, similar results with absence of overt toxicity were achieved upon combined inhibition of EGFR and RAF-1 in a subset of mutant KRas / Trp53-induced pancreatic ductal adenocarcinomas<sup>4</sup>.

“This is the first time that a pancreatic tumour has been shown to do this,” commented Dr Barbacid. “We understand that this is only in mice, and we don’t expect to be as successful in humans.”

A key question, he went on, centres upon the feasibility of efforts to develop inhibitors of RAF-1 for use in clinical patients. “The most obvious way to block RAF-1 (since RAF-1 is a kinase) is with a kinase inhibitor. This

may sound simple, but there are two problems here. First of all, it is not so simple because there are three members in the family, and if you block all three of them it is very toxic. A chemist would have to make an inhibitor that is selective against RAF-1, and does not touch B-RAF or A-RAF.

“However, we have recent, unpublished data indicating that expressing RAF-1 kinase dead isoforms do not result in the same therapeutic benefit observed upon RAF-1 ablation, thereby suggesting that inhibiting the RAF-1 kinase activity is not a suitable therapeutic strategy to block KRas mutant tumours.”

“We are now starting to collaborate with industry to try to develop protacs that work in the real world.”

Mariano Barbacid

The group is currently working on alternative methods of achieving RAF-1 depletion that may be applicable to patients. This includes the use of proteolysis-targeting chimeras – protacs – which contain a specific ligand for a target protein of interest that is connected via a linker to a ligand for an E3 ubiquitin ligase, thus representing a chemical knockdown strategy that has been shown to be rapid, robust, and reversible<sup>4</sup>.

“Using an artificial system, designated dTAG<sup>5</sup>, we have already shown that RAF-1 can be very effectively degraded,” said Dr Barbacid, concluding: “We are now starting to collaborate with industry to try to develop protacs that work in the real world.”

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## NCRI SESSION

CTRad 10 years on – celebrating collaborative radiotherapy research in the UK Carron Monday 11:00 am–12:30 pm

## CTRad: 10 years on

**T**he Clinical and Translational Radiotherapy Research Group (CTRad) is NCRI's flagship initiative. To mark CTRad's 10th anniversary, a session will be held today that celebrates the changing and positive landscape regarding radiotherapy research.

NCRI Daily News spoke to CTRad Deputy Chair Mererid Evans (Velindre Cancer Centre, Cardiff, UK), who will be leading today's CTRad session, to find out more ...

### Can you please introduce CTRad for our readers?

CTRad was established 10 years ago in response to reviews of the radiotherapy research landscape that highlighted radiation biology and oncology as significant areas of unmet need in the UK cancer research landscape. Ten years on, CTRad is regarded as the NCRI's 'flagship radiotherapy initiative' and the progress made in transforming the UK's radiotherapy research landscape will be highlighted during the session.

In addition, we will hear about new investment in UK radiotherapy research infrastructure and future opportunities for the UK's radiation research community, which will underpin the next 10 years of progress in UK radiation research.

### What talks and topics will be highlighted?

Professor David Sebag-Montefiore, current Chair of CTRad, will present his personal highlights from CTRad's 'Top 10' achievements, giving examples of where CTRad has played a crucial role, e.g. by placing patients right at the heart of the UK radiotherapy research agenda, driving the development of novel drug-radiotherapy combinations and benchmarking the UK radiotherapy research infrastructure, thereby enabling significant new investment.

We are delighted that Dr Iain Foulkes, Executive Director of Research and Innovation at Cancer Research UK (CRUK) will be

joining us to share some exciting news regarding radiotherapy research funding. His presentation will provide an opportunity for the whole cancer research community to discover more about plans that have the potential to help drive a step-change in future UK radiation research.

Professor Charlotte Coles will close the session by giving an insight into her own experience of how UK-led radiotherapy clinical trials have changed (and continue to change) clinical practice worldwide. She will consider the potential challenges and exciting opportunities presented by new technologies, novel drug-radiation combinations and biomarker-driven personalisation of care.

The importance of continued collaboration across the whole UK radiotherapy research community, facilitated and led by CTRad, will be a theme across the whole session.

### What can attendees expect to take away from the session?

The session will feature three world-class speakers and give people the opportunity to learn more about the radiotherapy research landscape across the UK. The presentation by Dr Iain Foulkes will coincide with a CRUK announcement at the conference and therefore his talk provides an extremely timely opportunity for all attendees to find out more about a highly significant investment in UK radiotherapy research.

The session will be of broad relevance to NHS and academic cancer researchers, laboratory and clinical researchers from across the radiotherapy spectrum, as well as medical oncologists and industry representatives, in view of the increasing importance of drug-radiotherapy combination strategies. The critical importance of multi-disciplinary team working for successful trial delivery means that every Multi-Disciplinary Team (MDT) member will find resonance in the topics and trials discussed.



"This session will highlight CTRad's achievements to date and the significant progress made by the UK radiotherapy research community over the last decade."

Mererid Evans

What's more, the importance of patient and public involvement (PPI) – which is integral to the CTRad ethos – will be highlighted, therefore PPI representatives are encouraged to attend the session.

The session will highlight CTRad's achievements to date and the significant progress made by the UK radiotherapy research community over the last decade. Importantly, we will also look to the future and consider the opportunities afforded by new investment and new technologies, as well as some of the challenges that lie ahead for the radiotherapy research community and the broader cancer research community in the UK.



## PLENARY SESSION

Thinking outside the box for the early detection of cancer **Lomond Auditorium** Sunday 4:20–5:00 pm

# Innovation and funding in early detection of cancer

**S**unday's plenary lecture by Rebecca Fitzgerald described "thinking outside the box" for the early detection of cancer. Professor Fitzgerald, who is an MRC Programme Leader (tenure) at the MRC Cancer Unit, and an Honorary Consultant in Gastroenterology and General Medicine at Addenbrooke's Hospital, Cambridge, UK, talked of her work in early detection, as well as some of the key initiatives that are now driving this important area of research.

Funding into early detection research has somewhat fallen behind other parts of cancer research, Professor Fitzgerald told *NCRI Daily News* ahead of her lecture. As she detailed, much more focus has been centred on new therapies – an important and very exciting area, for sure – but one that might not always provide a blanket benefit for all patients, as she explained: "Even if you've got a fantastic new therapy, if the disease is very advanced, it can be very difficult to really make an impact."

She added: "People have shied away from early detection research, not because people haven't thought it important, but just because actually it's quite difficult to do ... how do you use a technique that's going to be sensitive enough to find the proverbial needle in the haystack?"

Another layer of difficulty exists in how to avoid overdiagnosis from detection of incidental things during screening that would have never led to anything serious. "To do this kind of research you need to study big numbers of people because you're looking at healthy populations and most of them will stay healthy," added Professor Fitzgerald.

But despite these challenges, the potential to detect and effectively intervene in the early stage of cancer



warrants significant and reformed interest and resources. And indeed it seems to be the case. As Professor Fitzgerald stressed, researchers are interested in moving into it, funders are putting more money in, and there is even talk about building big cohorts from which to sample information over time and in whom new blood tests or other early detection paradigms could be explored.

Cancer Research UK (CRUK) now invested heavily in the International Alliance for Cancer Early Detection (ACED), a £55-million investment tasked with revolutionising research in the early detection of cancers via some of the best science across the UK and the US.<sup>1</sup> It partners CRUK with the Canary Center at Stanford University, the University of Cambridge, the Knight Cancer Institute at OHSU, University College London and the University of Manchester.<sup>1</sup>

Professor Fitzgerald is Co-Lead of CRUK's Early Detection Programme at the University of Cambridge.<sup>2</sup> This flagship initiative of the CRUK Cambridge Centre brings together basic, translational and clinical scientists,

spanning a broad spectrum of disciplinary approaches and expertise in multiple cancer types.

The Early Detection Programme actively searches for new modes of detection, and has already had success in establishing a number of novel products. One great example is the Cytosponge, an innovative test for Barrett's oesophagus – a condition which can develop in people who have regular symptoms of heartburn, acid reflux or indigestion, and whom are at risk of developing oesophageal cancer.<sup>3</sup>

The device consists of a "sponge on a string" pill which is swallowed then retrieved, allowing for molecular testing of TFF3 – a protein only found in pre-cancerous cells, and a likely indicator for Barrett's.<sup>3</sup>

Crucially, use of the Cytosponge is a simple test which can be done in a GP surgery. "If you're thinking about early diagnosis, you have to be practical," said Professor Fitzgerald. "You wouldn't endoscope everyone with heartburn."

Professor Fitzgerald is also Chief Investigator of the PAN Cancer trial which is aimed

at developing breath biopsy tests for the early detection of bladder, breast, head and neck, kidney, oesophageal, pancreatic and prostate cancers and brain tumours, with the ultimate aim of detecting cancer much earlier, when better treatment options are available and more lives can be saved.<sup>4</sup>

The technology relies on detecting volatile organic compound biomarkers on the breath, analysing them with high sensitivity and specificity.<sup>4</sup> "The company who are developing the technology [have] some exciting signals for liver cancer and cirrhosis," said Professor Fitzgerald, adding that there are high hopes for other types of cancers.

In her closing remarks to *NCRI Daily News*, she also spoke on blood tests and liquid biopsies for early detection of cancer (a field that is gathering momentum, particularly in the US), as well as risk stratification: "Should we be testing everyone or should we be thinking more carefully about who we test?"

Specifically, she said, there is new thinking around whether to use algorithms in which you can plug in data about an individual's age, sex, family history, risk factors (e.g. smoking) etc. to determine whether a certain early detection test would be warranted.

"People have shied away from early detection research, not because people haven't thought it important, but just because actually it's quite difficult to do."

Rebecca Fitzgerald

"How do you use a technique that's going to be sensitive enough to find the proverbial needle in the haystack?"

Rebecca Fitzgerald

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## PARALLEL SESSION

Treatable but not curable: Cancer as a chronic disease **Hall 1 Monday 2:00–3:30 pm**

# Fear of cancer progression: a better approach

Leading healthcare psychologist Phyllis Butow, a psycho-oncology researcher at the University of Sydney, Australia will discuss managing uncertainty during this afternoon's session on living with cancer as a chronic condition, chaired by Richard Simcock (Brighton and Sussex University Hospitals NHS Trust, UK) alongside patient advocate Jo Taylor from After Breast Cancer Diagnosis. All in attendance will play witness to important psychological theories that underpin the management approach to fear and uncertainty.

Specifically, Professor Butow will discuss the fear of cancer progression (FoP). "I'll talk about how common it is, how it develops, what makes it worse, how people cope with it, and what we know about how to best help people minimise the impact that fear of cancer progression has on their quality of life," she said in conversation with *NCRI Daily News*.

Although Professor Butow has worked specifically on FoP, she has participated in several research teams evaluating novel interventions and basic mechanisms that drive a condition that has been more heavily researched: fear of cancer recurrence (FCR). Recently, she led a large randomised controlled trial of a new psychological intervention, ConquerFear<sup>1</sup>, to help cancer survivors better manage their fear of cancer recurrence. "It was very effective and has been taken up around the world."

Returning to progression, Professor Butow noted that FoP can be measured to understand how patients react once diagnosed with cancer. "Of course, most people worry about the cancer coming back or progressing," she said. "This is true, regardless of the actual chances, or probability, that the cancer will get worse."

But Professor Butow is concerned with patients that exhibit higher levels of FoP: "About half of people with cancer experience moderately high FoP, and about 7–10% experience really high FoP, with which they struggle to cope." Patients with high levels often worry that if the cancer comes back or progresses, it might take their lives, she added: "They worry they won't be around for their family, they won't achieve what they want to achieve, and they wonder whether their lives have had meaning, i.e. 'Did I matter? Did I make a difference?'"

Others become concerned as to whether they will be able cope with difficult cancer treatments again, worry about suffering and, ultimately, what death will be like. "And they worry about being a burden on their family, and how their family will cope when they are gone," added Professor Butow.



"Fear of cancer recurrence and of progression are very common, and very distressing to cancer survivors."

Phyllis Butow

"Meta-cognitive therapy helps people to accept worry but not to engage with it, shifting focus to other things that they value in life."

Phyllis Butow

People with high FoP describe these worries as being regular intruders on their thinking, said Professor Butow, causing a great of anxiety and distress that is hard to control. In addition, such patients find it difficult to plan for the future in case the cancer comes back or progresses.

"They may find themselves constantly checking their body for signs of cancer, going to see their doctor or oncologist between scheduled appointments, and asking for scans and other reassurance that they are OK," she explained. "Others avoid going in for scheduled tests and follow-up, because they get so anxious at these times."

"This can have a profound impact on their own quality of life, the lives of their family, and can cause increased health costs," she added.

As Professor Butow relayed, today there is strong evidence that theoretically-based interventions can reduce FCR and assist patients to better manage and live with uncertainty. "A theoretically based intervention is one that is based on a clear theoretical model of FoP, which explains how it develops and is maintained," she explained. "It is very important that we develop interventions based on good theory, as well as empirical evidence, so we know what is working and why."

Today, a number of reviews of theo-

ries relevant to FCR and FoP have been published<sup>2,3</sup>. In her presentation, Professor Butow will talk about meta-cognitive theory and the self-regulatory and executive function model (S-REF) on which ConquerFear therapy was based.

"Meta-cognitive theory suggests that it is not the content of worries, but beliefs about worry itself that are the problem," she said, noting that many patients have beliefs that worry is helpful, for example, and that it will help them detect a cancer early. In contrast, other patients believe that worry is dangerous because it may increase stress and make them more at risk of a cancer recurrence. "These worries, which we call metacognition, push people to worry more or to try desperately to suppress worry (which only increases the focus on worry)," Professor Butow explained.

That's why newer approaches challenge these beliefs about worry. "Meta-cognitive therapy helps people to accept worry but not to engage with it, shifting focus to other things that they value in life," she said.

One recent systematic review<sup>4</sup>, for example, identified 23 controlled trials (21 randomised) and 9 open trials of interventions to help cancer survivors manage FCR and FoP. The findings of the review were particularly interesting, Professor Butow went on. "The review concluded that there was moderate-strength evidence that interventions are effective, and that interventions using contemporary cognitive behavioural approaches such as meta-cognitive therapy are more effective than those based on traditional cognitive behavioural therapy," she explained.

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## PARALLEL SESSION

Treatable but not curable: Cancer as a chronic disease **Hall 1 Monday 2:00-3:30 pm**

# Fear of cancer progression: a better approach

Continued from page 5

Meta-cognitive therapy approaches differ from existing behavioural strategies used by oncologists or existing FoP resources, said Professor Butow. "In fact, oncologists are often at a loss regarding how to help with FoP," she said. One survey<sup>5</sup> of doctors and nurses even found that many struggled and wanted more training.

Most oncologist and nurse interventions actually use reassurance, the normalising of FoP, and education about symptoms and signs of recurrence. But according to another recent systematic review<sup>6</sup> conducted by Professor Butow's group, this approach is not as effective as meta-cognition. That's why she advocates approaches that target the worry, rather than the content of the worry, and those which focus on more nuanced facets of the condition. "In particular, there should be focus on FoP since most of the research to date has focused on fear of cancer recurrence," she said.

Yet, at the moment, it's somewhat lacking. "I am going to argue that most research on FCR interventions has focused on people with curative disease, and does not address the real existential fears that people with advanced cancer face," said Professor Butow. "I am going to suggest that we need to help people to face death and make more meaning from their current situation in interventions moving into the future."

Professor Butow plans to explain more about techniques used within the meta-

"Research on fear of cancer recurrence interventions has focused on people with curative disease, and does not address the real existential fears that people with advanced cancer face."

Phyllis Butow

cognitive approach used in ConquerFear. For example, they used the so-called 'green elephant' metaphor to demonstrate how trying to suppress thoughts doesn't work. "This is when you ask someone not to think of a green elephant for the next five minutes. They usually find that green elephants keep intruding on their thoughts," she explained. "Then you ask them to write down 10 things they can see and hear. While focused on that task, they don't think of a green elephant."

In other words, engaging with other thoughts is a much better way of dealing with FoP than trying not to think about cancer all the time, said Professor Butow.

The problem with high FoP is that it is so widespread, while access to meta-cognitive approaches is limited. "Most interventions to date have been face to face, either individually, or in a group. This is expensive, and not everyone can access such care," she explained. "Currently there are attempts to provide therapy completely online, or

in a blended model where patients see a therapist a few times, and then complete exercises online."

But even with the growth of these alternative methods, Professor Butow stresses the importance of researching which of the methods is most effective. "In the future we need to compare online approaches with face-to-face approaches. I suspect that online will not work for people with high FoP, but will be useful in a blended model perhaps," she said.

"Fear of cancer recurrence and of progression are very common, and very distressing to cancer survivors," said Professor Butow. "We need to continue exploring ways to prevent, minimise and treat these fears."

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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:

- **8:15–8:45** Mindfulness session
- **10:30–10:40** Personalised follow-up pathways: history, benefits and how they can be delivered – Macmillan Cancer Support
- **10:45–10:55** claraT - Almac's innovative gene expression report: Helping cancer researchers maximise the understanding of their data
- **13:30–13:50** Addressing the known unknowns in cancer immunotherapy and patient care – an introduction to the BSI-NCRI Partnership
- **15:35–15:45** Bionano Saphyr® whole genome imaging for the automatic detection of structural variants in cancer genomes
- **15:50–16:00** The Breast Cancer Now Tissue Bank – a vault of rich resource for breast cancer researchers

## DON'T MISS!

### The NCRI Excellence Awards

**TODAY at 17:20 in the Lomond Auditorium**



Join us to celebrate the winners of the NCRI Excellence Awards!

We are marking the 15th anniversary of the Conference by awarding the people and teams who made a great contribution to cancer research and the NCRI Partnership. During the award ceremony we will be joined by the winners who will share some words about their work.

## PARALLEL SESSION

Digital pathology/machine learning **Dochart** Monday 11:00 am-12:30 pm

## Digital pathology: the new paradigm in biomarker quantitation?

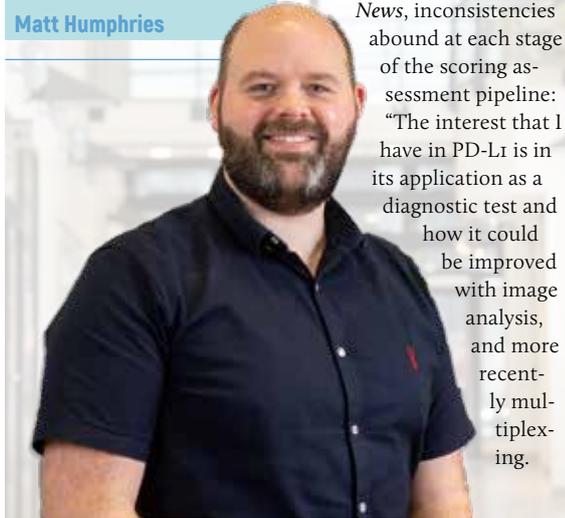
**D**uring this morning's session on digital pathology and machine learning, Matt Humphries (Queen's University Belfast, UK) presents the utility of automated tumour recognition and digital pathology scoring to overcome inconsistencies in objectivity, accuracy and reproducibility that have mired diagnostic assessment of programmed cell death ligand 1 (PD-L1) assessment to date.

The PD-1/PD-L1 axis is exploited by cancer cells, and this has enabled the development of immune checkpoint blockade and combination therapies striving to reinvigorate immune activity within the tumour microenvironment.

PD-L1 is also used as a prognostic biomarker. However, as highlighted in a

**"Digital pathology is able to accurately quantify tumour cells and biomarkers in whole slide images."**

**Matt Humphries**



2018 study by Humphries et al. in triple negative breast cancer (TNBC)<sup>1</sup>, and more recently in non-small cell lung cancer (NSCLC)<sup>2</sup>, approaches to assessing PD-L1 expression vary considerably. As Dr Humphries

explained to *NCRI Daily News*, inconsistencies abound at each stage of the scoring assessment pipeline: "The interest that I have in PD-L1 is in its application as a diagnostic test and how it could be improved with image analysis, and more recently multiplexing.

"Since being introduced diagnostically, on the back of clinical trials, the Food and Drug Administration (FDA; USA) and other global governing bodies have approved several antibody clones for use in PD-L1 assessment. These are provided by several companies, across several technical platforms in the laboratory. This has unfortunately led to huge inconsistency across labs all over the world with regard to this particular test.

"Often these platforms and antibodies provided by companies are actually tied to specific immunotherapies they provide. Therefore, there is a requirement that if you use a particular clone, you must use a particular platform, and then a particular drug.

"The inconsistencies across different labs is a

particular interest of mine. These inconsistencies stem from several factors, such as the subjective opinion of the pathologist, the samples types assessed and the clones and platform that are used.

"I believe image analysis can be a useful tool to aid the pathologist in the decision-making process and triage the more routine cases much faster, leaving more time to the specialist and time-intensive assessment of more difficult cases. More recently we have shown that multiplexing, which is the assessment of several biomarkers together, can bring a greater ability to delineate truly PD-L1 positive tumour cells in patients' samples."

Dr Humphries and colleagues demonstrated the challenges faced by pathologists in the clinical delivery

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## Introducing the Glasgow Cancer Core Panel

Where top cancer genetics expertise meets product excellence

The Glasgow Precision Oncology Laboratory has developed this affordably priced panel for comprehensive profiling of actionable cancer genetic events. Produced and commercialized by Agilent Technologies as part of the Agilent Community Design program.

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# Digital pathology: the new paradigm in biomarker quantitation?

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and interpretation of the PD-L1 diagnostic test in NSCLC<sup>2</sup>. As well as showing that high PD-L1 expression is associated with improved outcome in breast cancer as a whole, they looked to explain inconsistencies previously reported in the relevance of the biomarker, and showed that different antibodies during immunohistochemistry (IHC) can have a significant impact on the detected PD-L1 expression<sup>1</sup>.

PD-L1 is an extremely difficult biomarker to assess, Dr Humphries explained, and in part this is due to different antibody clones yielding different staining patterns. Indeed, his recent study highlighted five challenges in

**"The PD-L1 test is rapidly expanding into new cancer types."**

**Matt Humphries**

the assessment of PD-L1 diagnostically: 1) the difficulty in calculating the total number of tumour cells in the sample; 2) the presence of intra-tumoural macrophages which confound the assessment; 3) the occasional presence of PD-L1 strongly positive inflammatory cells around nests of malignant epithelium, which Dr Humphries describes as the 'hugging effect'; 4) the accuracy of calculating the percentage positivity close to clinical thresholds; and 5) the applicability of the rule requiring a minimum of 100 tumour cells.<sup>3</sup>

A central message of the paper, and the focus of Dr Humphries' talk today, is the importance of accurate re-

producible scoring of PD-L1, a facet of assessment that is highly prone to interobserver discordance<sup>2</sup>. The significant developments discussed will build on the talk given earlier in the year by Dr Humphries at this year's UK Pathological Society's annual meeting<sup>4</sup>.

"If you were to ask 10 pathologists to analyse the same slide, they would come up with different answers. If you asked the same pathologist to assess the same slide the next day, they would probably give you another different answer. There is a huge inconsistency in the reporting with this test. This may be one of the reasons why it's extremely difficult to tease out why some patients respond to immuno-

therapy and some don't. What I allude to my last paper and what my talk will focus on is the need for objectivity in the assessment of PD-L1 quantification.

"There is no greater time for this discussion. The PD-L1 test is rapidly expanding into new cancer types. Based on new trial data, the approval of PD-L1 assessment in TNBC has just been granted. The recommended clone for TNBC (SP142), which we reported on last year<sup>2</sup>, differs from that assessed in NSCLC (SP263), which we critically appraised recently<sup>4</sup>. The addition of more cancer types where PD-L1 is to be assessed will no doubt have beneficial consequences for a number

## 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** Cancer Quality of Life Metric Project: Lessons learned from an implementation pilot  
**Alice Simon**
- 10:36** Cancer Together with other Chronic Health conditions: understanding population characteristics and healthcare resource use in general practice (CATCH)  
**Michelle Collinson**
- 10:42** Phenotype dictates outcome in synchronously resected primary colorectal tumours and matched liver metastases  
**Kathryn Pennel**
- 10:48** Understanding international variation in access to PET-CT for oncology diagnostics: An International Cancer Benchmarking Partnership (ICBP) study  
**Charlotte Lynch**
- 12:40** A potent synergy between FOXG1 overexpression and Wnt signaling drives cell cycle re-entry in quiescent glioblastoma stem cells  
**Faye Robertson**

- 12:46** Overcoming sorafenib resistance in hepatocellular carcinoma by fasting  
**Jelena Krstic**
- 12:52** Integrating Germline and Somatic Genetic Test Result Data into the English National Cancer Registration and Analysis Service  
**Steven Hardy**
- 12:58** Anti-oestrogen medication use in breast cancer patients and subsequent risk of gastrointestinal cancers: a two country pooled analysis  
**Una McMenamin**
- 13:04** The landscape of hepatocellular carcinoma in the UK in the past 20 years: the HCCUK/NCRAS partnership  
**Anya Burton**
- 13:10** A reference guide for patient and public involvement contributors. How the ECMC Network PPI group developed a resource for patients and the public  
**Nikki Hayward**
- 13:16** Total cholesterol and the risk of primary liver cancer in Chinese males: a prospective cohort study  
**Yan Wen**

- 13:22** Clinical utility of circulating microRNAs in malignant germ cell tumours  
**Matthew Murray**
- 13:28** Investigating COX isoform dependency in intestinal tumorigenesis  
**Noha-Ehssan Mohamed**
- 13:34** Improving the effectiveness of breast cancer multidisciplinary team (MDT) meetings: Implementation of a pre-MDT triage meeting  
**Hannah Winter**
- 13:40** Genome-wide CRISPR screen in 3D intestinal organoids to define novel mechanisms critical for colorectal tumorigenesis  
**Patrizia Cammareri**
- 13:46** Rapid Analysis of Disease State in Liquid Human Serum combining Infrared Spectroscopy and Digital Drying  
**Alexandra Sala**
- 15:35** Methylation Sensitive High Resolution Melting (MS-HRM) Assay for the Detection of BRCA1 and BRCA2 Promoter Hypermethylation  
**Gareth Gerrard**
- 15:41** Does augmenting the complement system improve Rituximab induced cell lysis?  
**Katy Plant**

of patients, but the pressure on already overstretched pathology departments will only increase as they required to deliver on yet more cases, using an extremely difficult and subjective test.”

Dr Humphries and colleagues have reached these observations using the digital pathology platform QuPath<sup>4</sup>, a software application designed for bio-image analysis and in particular whole slide image analysis. Originally created at Queen's University Belfast, the software is free and open source. Describing how it was employed, Dr Humphries continued: “Microscope slides were digitally scanned and presented on screen. We then apply the software's cell classification and thresholding algorithms to actually count positive tumour cells in each case.

“If you imagine being a pathologist sitting in front of a screen or microscope glass slide with tens-of-thousands of cells to count by eye, you are by definition going to make an imperfect estimate, because you could never count an entire slide accurately. In clinical practice it is an impossibility. Digital pathology is able to accurately count all the tumour cells in a sample and then quantify how positive that tumour is. Using the same algorithm, that result will be the same today, tomorrow and next year. This is the first thing: the consistency of the application of digital pathology.”

Exploring issues of biomarker expression in infiltrating and surrounding cells, Dr Humphries said: “This is a difficulty that even image analysis on IHC slides cannot

**“We are driving forward the validation of PD-L1 multiplexing.”**

**Matt Humphries**

fully overcome. Different cell types within human tissue express PD-L1, particularly macrophages, which are pervasive throughout tissues and particularly in lung cancer. When you assess NSCLC cases using the SP263 clone that PD-L1 is assessed by, it can be difficult to distinguish macrophages from tumour cells. These macrophages light

up bright with PD-L1 and can be misconstrued as tumour cells, leading to a potential overestimation of the positivity of the tumour, both by the pathologist and also by digital pathology. So not only is the method by the pathologist flawed, but there is a large hurdle for image analysis to contend with.”

Addressing this issue forms the second focus of his talk today, and Dr Humphries will discuss how multiplex immunofluorescence – which allows the tagging of multiple cells in a sample – can more accurately differentiate macrophages and hence allow for their exclusion from analysis. “This is a fairly new technique and it is something that has not really been brought to the arena of diagnostic pathology,” he commented. “We are driving forward the validation

of PD-L1 multiplexing, which will hopefully bring a further ability to accurately delineate positive tumour cells.”

.....  
Matt Humphries speaks during ‘Digital pathology/machine learning’ taking place today from 11:00 to 12:30 in Dochart.

#### References

1. Humphries MP, Hynes S, Bingham V et al. Automated Tumour Recognition and Digital Pathology Scoring Unravels New Role for PD-L1 in Predicting Good Outcome in ER-/HER2+ Breast Cancer. *J Oncol*. 2018;2018:2937012.
2. Humphries MP, McQuaid S, Craig SG et al. Critical Appraisal of Programmed Death Ligand 1 Reflex Diagnostic Testing: Current Standards and Future Opportunities. *J Thorac Oncol*. 2019;14:45-53.
3. Humphries MP, McQuaid S, Craig SG et al. Multiplex Immunohistochemistry: the next generation of molecular pathology? *J Pathol*. 2019;249(S1):S19.
4. QuPath website. <https://qupath.github.io> (accessed Oct 2019).

**15:47** The NIHR STAMINA (Supported exercise Training for Men with prostate cancer on Androgen deprivation therapy programme): data from year one  
**Sophie Reale**

**15:53** The Trigger project: Introducing electronic patient reported outcome measures into radiotherapy services  
**Amy Sharkey**

### Silent Theatre 2

**10:30** Meat intake and cancer risk: prospective analyses in UK Biobank  
**Anika Knuppel**

**10:36** Renal cell carcinoma patients under 60 should be screened for colorectal carcinoma  
**Joseph John**

**10:42** Development and validation of a risk prediction model for lung cancer with common health examination indexes  
**Zhangyan Lyu**

**10:48** Real world treatment sequencing patterns in secondary breast cancer (SBC): Pathway visualisation using national datasets  
**Ashley Horne**

**12:40** An Analysis of Prognostic Biomarkers of the Systemic Inflammatory Response in Cancers of Unknown Primary  
**Rebekah Patton**

**12:46** Digital questionnaires to help determine a face-to-face review for on treatment oncology clinics  
**Catherine Sharma**

**12:52** BEACON: A Randomised, Phase 3 Study of Encorafenib and Cetuximab +/- Binimetinib vs. Choice of Either Irinotecan or FOLFIRI plus Cetuximab in BRAF V600EMutant Metastatic Colorectal Cancer Patients  
**Harpreet Wasan**

**12:58** Dietary changes and nutritional support after a pelvic cancer diagnosis: a cross-sectional study  
**Georgios Saltaouras**

**13:04** Statin use and risk of liver cancer: evidence from two population-based studies  
**Kim Tu Tran**

**13:10** Hospital activity before and after diagnosis of monoclonal gammopathy of undetermined significance (MGUS)  
**Maxine Lamb**

**13:16** Genome-wide association study of acute toxicity and quality of life in breast cancer patients treated by surgery and radiotherapy in the REQUITE cohort study  
**Tim Rattay**

**13:22** Barriers to accessing cancer services in England and Wales by adults with physical disabilities  
**Dikaios Sakellariou**

**13:28** Coffee consumption by type and risk of digestive cancer: A large prospective cohort study  
**Kim Tu Tran**

**13:34** Secondary analysis of routinely collected data from a specialist cancer rehabilitation service in South Wales, UK  
**Judit Csontos**

**13:40** Qualitative exploration of cancer rehabilitation in South Wales, UK from the perspectives of people affected by cancer and healthcare professionals  
**Judit Csontos**

**13:46** Detection of EGFR mutations in the plasma and urine of NSCLC EGFRm+ patients  
**Ling Li**

**15:35** Using a four-step co-design model to develop and test a peer led web-based resource (PLWR) to support informal carers of cancer patients  
**Olinda Santin**

**15:41** A single centre review of the NICE approved, standard of care, treatment cost savings for patients with metastatic castrate-resistant prostate cancer (mCRPC) enrolled in clinical trials  
**Louisa McDonald**

**15:47** Non-invasive methylation test to detect cervical pre-cancer in self-collected vaginal and urine specimens  
**Belinda Nedjai**

**15:53** Metabolic functions of astrocytes are retained by glioblastoma stem-like cells and support glioblastoma growth in vivo  
**Tobias Ackermann**

## PARALLEL SESSION

Treatable but not curable: Cancer as a chronic disease **Hall 1 Monday 2:00 -3:30 pm**

## Changing the lens on cancer

**T**his afternoon's session on cancer as a chronic disease will feature a unique patient perspective from Paul Cosford, who recently became a consumer member of the NCRI Lung Group. "I was diagnosed a couple of years ago with a stage IV lung cancer. I am a non-smoker, and my experience is someone with treatable but incurable cancer," he told *NCRI Daily News*.

But what will give an extra dimension to this experience with cancer is that Professor Cosford has worked for some years as the Medical Director of Public Health England, where he has just been appointed Emeritus Medical Director. He has been behind efforts to improve all aspects of public health in England, from cancer prevention to infection control, and leading emergency responses to Ebola and other infectious diseases.

Professor Cosford will begin by talking about his diagnosis and the treatment strategy thus far, before looking to an emerging realisation: his cancer does not fit in with the traditional view of the disease. "There's a prevailing narrative that to be diagnosed with an incurable cancer means somebody in their peak of life is struck down by a terminal illness, struggles on for a year or two and then dies," he said. "That's how we tend to understand cancer."

While the understanding that cancer can be incurable but chronic is hardly new, there are still assumptions around cancer being a short-term terminal illness entrenched within health systems and beyond. "It is inbuilt into a whole range of things across society," said Professor Cosford.

For example, he described seeing planning assumptions for services for people with incurable cancers, where the assumption is that the vast majority will die within 12 months, with principle needs centring around end-of-life care.

The same applies to other areas of life outside of the healthcare system. "There's an assumption that you are critically ill and on death's door and therefore you don't get any travel insurance, for example," he said.

But the reality is that there are increasing numbers of patients, like Professor Cosford, who defy this narrative. "Two years down the line I'm still here, still reasonably healthy apart from having this malignancy which is therapy-suppressed," he added. "In reality, some of us are experiencing a significant period of reasonably good health. We just haven't a clue how long that's going to last for. That's why I'll talk a little bit about the difference between this sort of rapid-demise narrative and what is actually happening."

Access to new treatments are particu-

larly important in the context of incurable cancer. "You are always thinking about how long the current treatment will continue to work, new treatments that might come along and research into those new treatments," continued Professor Cosford, adding that he has been rather lucky in terms of being eligible for new treatments. "From my point of view, being eligible for a targeted biological treatment in the first place was really important," he said. "It's a really crucial step because I wasn't put straight onto traditional chemotherapy."

Professor Cosford would like to see more choices going forward, but research into new treatments can be tricky for patients, especially where the research involves randomisation.

For a cancer patient, he went on, the impact of losing control of what medications one is on cannot be underestimated: "As a cancer patient, you are not in control of the disease, as well as many aspects of it, so you do try very hard to keep control where you can."

Another important issue for research is how to extend the time that a treatment continues to work, said Professor Cosford. The median response time for the first treatment Professor Cosford was prescribed was 12 months, and it was almost exactly 12 months when his disease started to progress. "Though I know people have lasted two years on that treatment," he said. "The second one was said to last for a median of 10 months – this time I am doing better having been on it for more than 13, and may be for longer."

Taking this onboard, Professor Cosford would like to see more research into what might lengthen the time on any given

**"More research on the practical things that patients can do to give them a higher chance of living longer in better health I think is really important."**

**Paul Cosford**

treatment. "What is rarely talked about with patients is the evidence for things you can do that stand a decent chance of putting you into the group that will survive for longer on a particular treatment," he said.

For example, improved survival from any kind of cancer is linked to a decent level of physical activity which, for Professor Cosford, means cycling regularly. "I managed 70 miles last weekend," he said. "It's not as much as I used to manage, but it's important. The evidence suggests it has a significant



impact, even to the extent of a 30% reduction of year-on-year specific mortality for some cancers. As a doctor I was aware of the benefits of physical activity, but I don't think most patients would be."

In fact, many people think exercise might even be harmful: "The prevailing narrative is that if you get a nasty illness you should rest. But it's exactly the wrong thing to do," he said. "So more research on the practical things that patients can do to give them a higher chance of living longer in better health I think is really important."

"It's not just about increasing your physical activity levels to give you an extra two weeks of life or so. Taking these issues together with new treatments, it actually becomes about whether you might live for five years or more with in effect a chronic disease," he added.

Professor Cosford added that there are real questions about how treatments generally considered as palliative care interventions can best be used for patients living for a reasonable length of time. "The issue is about treatments that in the past have been thought of as palliative, or when you are in end-of-life care, but now you might need on a longer-term basis" he said.

Take draining a pleural effusion, which

Professor Cosford has received roughly every three weeks for the past year. "Draining a pleural effusion has usually been a one-off palliative intervention in the last weeks of life to give a bit more symptom control," he said. "For me, this has become a treatment that must be continued over longer periods of time, since I do not want the alternative which is a permanent catheter in my chest."

However, such issues have not been encountered on a repeated basis in the past, and my treatment is off-label and not stipulated in any clinical guidelines, said

**"As a cancer patient, you are not in control of the disease, as well as many aspects of it, so you do try very hard to keep control where you can."**

**Paul Cosford**

Professor Cosford, though it is remarkably effective. It follows that exploration of new areas of care are now required when people start to live for longer with disseminated cancers.

Changing guidelines might be one way to help update understanding, said Professor Cosford, but there are other things researchers can do. "It's also about publishing patient series when time allows so that developing experience is shared to help understand what the best management strategies are," he explained. "There must be plenty of other examples beyond pleural effusion."

As such, research must begin to look at handling the realities of having cancer as an incurable, but chronic, disease, said Professor Cosford in closing.

**PARALLEL SESSION**

Could medically assisted dying be part of cancer care in Britain? **Hall 1 Monday 4:00–5:15 pm**

## Medically assisted dying in cancer care

**T**his afternoon plays host to a session that will tackle the sensitive question of whether medically assisted dying could become part of cancer care in Britain. Different forms of medically assisted dying or suicide have been legalised in many jurisdictions in Europe and North America. In Britain, Parliament has repeatedly rejected the possibility of changing the law to facilitate medically assisted dying.

This session will review the ethical, legal and societal issues that apply with respect to models of assisted dying models in the care of cancer patients. An ethicist, a patient representative, a member of the House of Lords and a palliative care physician will all discuss their perspectives.

In conversation with *NCRI Daily News*, session Co-Chair Celia Manson, an independent nurse adviser in palliative care and pain, shared her perspectives on the importance of the session, and what all in attendance can expect to hear.

**What can you tell us about the session programme, and the topics to be covered?**

I hope that Conference delegates will find this session a little bit different, thought-provoking and challenging. I

understand that this is a fairly unusual session for the NCRI Conference as it is not especially research orientated.

We are going to hear brief presentations from four speakers, all of whom have pondered the question of medically assisted dying in different ways. It is hoped that will be able to take one or two questions after each presentation, and then have some discussion and summary before the session wraps up.

The first speaker is Bobbie Farsides who is Professor of Clinical and Biomedical Ethics at Brighton and Sussex Medical School. Bobbie has published extensively on the moral and ethical dilemmas associated with assisted dying.

She will be followed by Bill Noble, a senior lecturer in palliative medicine at the University of Sheffield. Bill has many years of experience of caring for patients at the end of their lives, and he might be described as working in the frontline of palliative medicine.

Our next speaker is Lord Charles Falconer, a life peer in the House of Lords. He set up an independent commission to look at whether or not assisted dying might be legalised in England and Wales, and followed this up with a bill introducing legalisation in the House of Lords.



**"An important aspect of palliative care is the team approach addressing physical, psychological, social and spiritual needs."**

**Celia Manson**

**What take-home messages can we expect to hear?**

My Co-Chair Sam Ahmedzai (National Institute for Health Research) and I are asking each speaker for their own take-home message, and I suspect that they may be all quite different.

My personal view is that a change in the law is not required. There is much on offer for people at the end of their lives in terms of good palliative care. And, importantly, we are able to tailor this to meet individual needs and to support friends and family.

I would add that this is not an exclusively medical activity. An important aspect of palliative care is the team approach addressing physical, psychological, social and spiritual needs.

The final speaker in this session is Roger Wilson who is a member of the NCRI Consumer Forum. He describes himself as a patient who has survived sarcoma in spite of multiple recurrences.

## PARALLEL SESSION

The changing face of clinical trials and trial endpoints... **Boisdale** Monday 2:00–3:30 pm

# Reconsidering patient-reported outcomes

**T**he patient perspective in clinical trial design and drug registration strategies will be presented this afternoon by Roger Wilson, CBE, of the NCRI Consumer Forum.

Mr Wilson has been a cancer patient advocate in and around cancer research since he was diagnosed with a soft tissue sarcoma in 1999. "I have had six recurrences of my cancer, 10 operations, an amputation, open lung surgery, chemo and radiotherapy, but am currently cancer free," he said. "I have had 24 CT scans but do not glow in the dark!"

Importantly, Mr Wilson, who created what is now Sarcoma UK, is extremely active in the patient perspective of research around the disease. "I went to my first NCRI meeting in 2002," he said, noting his role as the second chair of the organisation that eventually became known as the NCRI Consumer Forum. He served on the NCRI Board, and has represented patients through many NCRI initiatives between 2003 and 2012. That means a broad view of research which he has continued internationally; he works with cancer organisations such as the European Organisation for the Research & Treatment of Cancer (EORTC) charity, where he serves as chair of its Patient Panel. He also advises on treatment intervention studies for both academic researchers and the pharma industry.

Today, quality-of-life (QoL) and the impact that treatments have on patients are Mr Wilson's primary focus. He leads the Consumer Forum's work on QoL, working with EORTC and several academic groups, and has been focussing his attention on these issues for around a decade now. "I started taking a close interest in quality of life and PROs (patient-reported outcomes) after representing the patient at the NICE

Appraisal of a new drug in 2009," he explained.

Specifically, Mr Wilson has become interested in the dichotomy between the need for scientific rigour in clinical trials and the urgency for short-term results. "The latter meets the demand for rapid access to new treatments while the growing absence of the former leads to lack of knowledge, bias, deception and bad advice. Clinical trials are historically what we have relied upon to avoid these flaws," he said.

Take olaratumab, for example. A Phase 2 trial looking at this drug in combination with doxorubicin as a first line treatment of advanced sarcoma produced a marginal progression-free survival (PFS) benefit but an exceptional overall survival (OS) benefit, said Mr Wilson. It was given an interim licence subject to results of a Phase 3 randomised controlled trial, which was already underway.

The Phase 2 study was very small, with the randomised component only including around 30 patients, noted Mr Wilson.

"When the Phase 3 study reported earlier this year the OS benefit had disappeared. The drug was withdrawn," he explained. "Ten years ago this could not have happened."

In the US, where regula-

**"A lottery for treatment is emerging in which high costs, social media hype of marginal results, and peer pressure on patients ... is leading to exploitation."**

**Roger Wilson**



tion is more relaxed, there are even more examples, said Mr Wilson. "Targeted drugs with a 'survival' benefit such as PFS in a small Phase 2 study, get hyped in patient social media," he explained. "Studies have poorly documented side-effects and patients who are already close to end of life get pressured into a less than desirable pathway".

The irony is, while some research is showing only incremental effects for certain drugs, other research clearly is demonstrating that proactive palliative care gives a better quality of life for many terminal patients. "And in some instances, they even live longer," stressed Mr Wilson.

In other words, a rather worrying trend is evident. "A lottery for treatment is emerging in which high costs, social media hype of marginal results, and peer pressure on patients ('treatment X is really good...') is leading to exploitation," he said. "It's not just in cancer – go and have a look at any crowd-funding website."

So, the challenge will be to reverse such trends, said Mr Wilson. "Current approaches are like bandages to cover the wounds – a very appropriate medical simile, I think,"

he said. "We have to be more radical."

That's why PROs must be taken into account, said Mr Wilson. A QoL assessment and, specifically, patient-reported outcome measures (PROMs) that capture the subjective patient experience are where real and lasting progress can be made, as Mr Wilson writes in his 2018 paper<sup>1</sup>. "The idea that you can have PROs without patient-provided inputs to inform the methods and processes used is irrational and probably unethical," he said.

Mr Wilson will refer to an unpublished study reported at ESMO 2019 in Barcelona last month [29 Sept – 1 Oct]. It is the first large-scale study using a PRO-CTCAE toolkit<sup>2</sup> created by a development team including Dr Ethan Basch (Memorial Sloan-Kettering Cancer Center) and Dr Deborah Schrag of Dana Farber Cancer Centre, Boston, USA and funded by the US National Institutes for Health (NIH). PRO-CTCAE is a PROM developed to evaluate symptomatic toxicity in patients involved in cancer clinical trials. "Among their findings was that patient reports which are fed back to their doctors resulted in different decisions by those doctors," he explained.

"As patients, we would like to see real-world evidence (RWE). However, there are no methodologies or standards in RWE so it is open to bias and manipulation."

Mr Wilson went on to note that he would like to see more RWE methods such as those which test a sequence of therapies, combination therapies (including new with old), and look for minimum effective doses rather than relying on maximum tolerated doses. "The introduction of PROs with co-primary endpoints is also critical," he added.

Some agencies are moving towards RWE already, Mr Wilson continued: "Whether researchers like it or not, a new research paradigm is

**"Whether researchers like it or not, a new research paradigm is emerging under regulatory pressure for real-world evidence."**

**Roger Wilson**

emerging under regulatory pressure for RWE. Patients are very happy with that. We need this new paradigm, not the 'bandages' I mentioned earlier which the research industry is trying to use.

During his presentation, Mr Wilson will look at who the regulatory influencers are, and why patients have no problem with it. The Food and Drug Administration

(FDA) in US and the European Medicines Association (EMA) in Europe have both stated openly they want to see more PRO use and co-primary endpoints, said Mr Wilson. The UK's MHRA is open to this evolution too. "NICE and similar health technology assessment agencies want more patient-centred data to aid in their decision-making. They operate by mutual consent so

getting mandatory PROs will take time," he added.

Mr Wilson will look at other obstacles to the take-up of PROs. "The big challenges are within the PRO/QoL community," said Mr Wilson. "We need to get them to change from big QoL tools, which deliver largely meaningless numbers, to detailed individual PRO data which can be tracked over time."

The community must get to grips with other measures, he continued: "They are finding the idea of longitudinal measurement very challenging too. It requires the acceptance of tools like a smartphone, some important data protection work, analysis of lots of data and opening up new opportunities for doctors and nurses to deliver care in new ways."

Despite the difficulties, Mr Wilson said the movement towards such patient-centric measures is inevitable. "A positive change is in the air; breathe deep and enjoy it," he said. "Resist the bandages."

#### References

1. Wilson, R. Patient led PROMs must take centre stage in cancer research. *Res Involv Engagem.* 2018;4:7.
2. <https://healthcaredelivery.cancer.gov/pro-ctcae/>



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## Keep active throughout the Conference and greet speakers with a standing ovation!

As part of our Wellbeing Programme we want to get you moving throughout the day, which is why our session chairs will be encouraging you to give a standing ovation at the end of each session.



## PARALLEL SESSION

Mechanotransduction and invasion: The tumour microenvironment perspective **Dochart** Monday 2:00–3:30 pm

## ECM as gatekeeper: mechanical properties of the tumour microenvironment

**D**uring today's session on mechanotransduction and invasion in the tumour microenvironment (TME), Fran Balkwill (Barts Cancer Institute, London, UK) discusses biomechanical and cancer invasion studies in ovarian cancer.

Professor Balkwill and colleagues recently described the evolving human metastatic TME in a study of biopsies of high-grade serous ovarian cancer (HGSOC) metastases at different stages of disease.<sup>1</sup> In the study, each biopsy was interrogated for gene expression, matrisome (extracellular matrix [ECM] and ECM-associated proteins) proteomics, cytokine and chemokine levels, cellularity, ECM organisation and biomechanical properties, revealing the gene and protein profiles that predict extent of disease and tissue stiffness as well as the complexity and dynamic nature of matrisome remodelling that takes place during the development of metastases. This is the first study to associate molecular changes with higher-order TME features.<sup>1</sup>

The significance of features of the TME that can be linked with prognosis are poorly understood, Professor Balkwill explained to *NCRI Daily News*. "Thinking about prognostic features in cancer TME, we know that if you have lots of T cells in or around the malignant cell areas of a cancer, this is a good prognostic sign. We think this is related to the fact that there is some sort of immune response that may be harnessed by treatment.

"What is also known, but less explored, is that if you have a lot of ECM and fibroblasts in a TME, that is associated with a poor prognosis. What we found in ovarian cancer, by studying the development of metastases, is that this increase in tissue modulus (stiffness) and increase in the general stromal reaction to disease, was bad prognosis. We also found a very similar pattern in 12 other common solid tumours. There are other studies that have found slightly different ECM signatures or high fibroblast densities to be associated with a poor prognosis, but it all points to the conclusion that a fibroblast-rich, ECM-rich TME is a bad thing in many cancers."

What is striking, Professor Balkwill added, is that they have found similar features in their mouse ovarian cancer models and in multicellular human cell models of this disease. She will be presenting such data (as yet unpublished) during her talk today. "There is maybe something quite fundamental about this," she commented. "But we don't know, at the moment, why this stromal reaction has a bad effect. That is the big question.

"There are many theories, and there are



important experiments in the literature that suggest various hypotheses. Is the cancer ECM stopping the immune cells reaching the malignant cells? Is a very stiff environment increasing cancer cell malignancy and invasion? Does it affect the development of blood vessels? Clinicians, when they are examining patients, will often diagnose a tumour because it is stiffer than the surrounding tissue."

Professor Balkwill also discussed the importance of an integrated understanding of the different components of the metastatic microenvironment, exemplified in the multivariate approach taken in Pearce et al.<sup>1</sup> that has yielded a complex impression of interacting processes. The study also provides insights into dynamic processes of ECM remodelling during metastases development, through its sampling of tissue samples of minimal to extensive disease: "Nobody had really done this before. Because we took metastases at all stages of development, we could understand how that tumour microenvironment evolved – not in the same patient, but we can see how that environment evolves with time. This is important."

Asked whether such approaches have been extended to multiple sampling within

single patients with metastases, she replied: "Yes, that is what people are doing now more and more. But there are problems with that. If you have a patient with metastatic disease, they are going to have a lot of quite large metastases. When we are doing molecular biology, we are going to study only a few hundred microns. So it is quite difficult to know how that relates to the whole thing.

"But in general, I completely agree that what we need to do is to look in-depth at a number of tumours in a patient. But you really need to find ways of doing this non-invasively, which is still not possible. In the future it may be, using radiomics, where you can do really detailed imaging and get a lot of information from that."

The findings from the studies undertaken by Professor Balkwill and colleagues serve to inform models of TME, as well as prognostics and drug delivery, and indeed she will discuss some newly developed mouse models during her talk. She explained: "If we are studying the tumour microenvironment, we need models of that complex environment. We study the mouse models to find out what the similarities and differences are with the human TME, so that we can then come in with treatments that can modify them. We can also understand how existing treatments modify that TME, because we have this foundation of knowing what it is like in the real patient."

She and others are also building multicellular human models, which involve the concerted growth of multiple cell types mimicking the TME. "The advantage there is that we have human cells. Also, we can get quicker results than in mice. It also fits with all our ethical goal of the reduction, refinement and replacement of animal models. That is why it is very useful to have this baseline data of what happens in the real patients."

She concluded: "What I like to think is that our research is led by what happens in the patients and the problems that happen in patients. We then try and have the best models to understand treatments that modify the TME, but also in our case to understand why this stiff matrix-heavy TME is so bad."

Professor Balkwill speaks during 'Mechanotransduction and invasion: The tumour microenvironment perspective', taking place in Dochart from 2:00 to 3:30 pm today.

## Reference

1. Pearce OMT, Delaine-Smith RM, Maniati E, et al. Deconstruction of a Metastatic Tumor Microenvironment Reveals a Common Matrix Response in Human Cancers. *Cancer Discov*. 2018;8(3):304–19.

**"A fibroblast-rich, ECM-rich TME is a bad thing in many cancers."**

**Fran Balkwill**

# 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.



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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 16:00
- Tag **@SECglasgow** including the hashtags **#NCRIsteps**, **#NCRI2019** & **#healthyvenue**





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# 2020 NCRI Cancer Conference

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