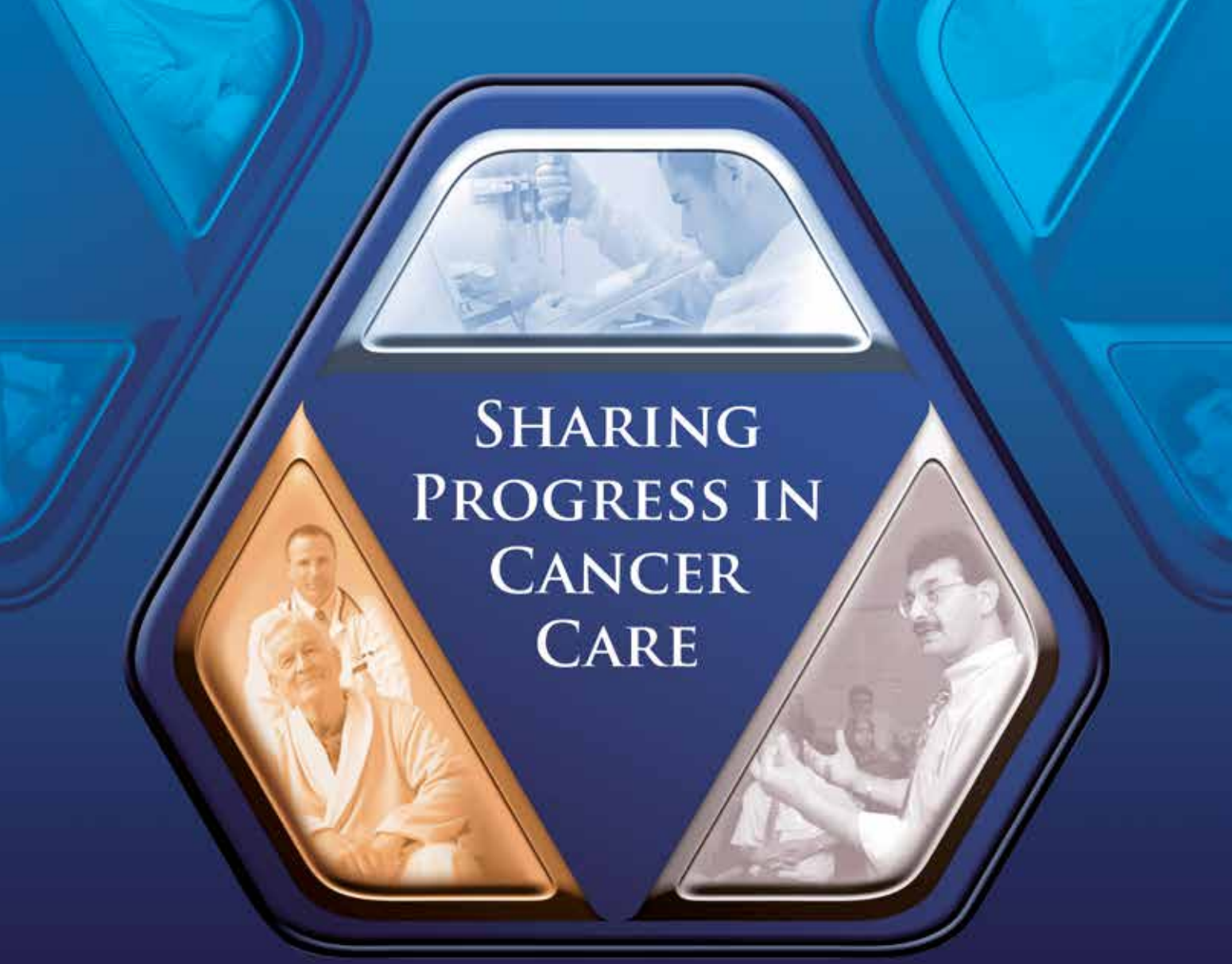
Cancerworld

www.cancerworld.net

Issue 90 Summer 2021



Sharing Progress in Cancer Care

Sharing Progress in Cancer Care (SPCC) is an independent, non-profit association, based in Switzerland. It works in the field of cancer education, care improvement and innovation in collaboration with various stakeholders, including industry and academia, in order to raise awareness and disseminate knowledge about innovative approaches, scientific progress as well as state-of-the-art treatments and methodologies in Cancer Care Continuum.

PLATIUM SPONSORS

AstraZeneca ONCOLOGY · Bristol Myers Squibb · FRESENIUS KABI caring for life · Pfizer Oncology

GOLD SPONSORS

Lilly · Roche

SILVER SPONSORS

EXACT SCIENCES · HELSINN · mundipharma · NOVARTIS ONCOLOGY

Cancerworld
Shaping the future of cancer care

Scan to access our website

'Covid did not stop cancer research'
*by **Vito Manolo Roma***

Readership of over 20,000

Contents

All enquiries to:
SPCC Sharing Progress in Cancer Care
Piazza Indipendenza 2
6500 Bellinzona - Switzerland
info@cancerworld.net
editor@cancerworld.net

Published by
Scuola Europea di Oncologia
Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004
Direttore Responsabile
Alberto Costa

Cancer World is an online-first magazine that publishes weekly news reports and features. The print edition is distributed at major conferences and mailed to subscribers and European opinion leaders.

Subscribe at: http://bit.ly/CW_Subscribe

Europe's Beating Cancer Plan, and returning to 'normal' after the Covid-19 outbreak

Adriana Albini – *Editor-in-chief*

An ageing population, environmental factors, infectious agents, and lifestyle changes all add to the rising impact of cancer on our lives.

If nothing is done, cancer will soon become the leading cause of death in Europe. A comprehensive collaboration across all sectors could reverse this rapidly rising trend. Up to four in ten cases of cancer are preventable, by immunisation, better diet, physical exercise, and greater awareness of cancer risks. Yet, at the moment, only a tiny sliver of health budgets is spent on prevention.

In 2020, 2.7 million people in the EU were diagnosed with cancer, and 1.3 million people lost their lives to the disease. On the positive side, 12.5 million people who were diagnosed with cancer are now considered cured. This points to the effectiveness of improved early detection and diagnosis, better and more tailored therapies, and a well-orchestrated support. It also raises new challenges, with many survivors struggling with quality of life, rehabilitation or family issues, and often finding it hard to keep working, or to find a job, or access insurance or a mortgage. All of these can be tackled by increased support in research and innovation.

On February 3rd 2021, the Europe's Beating Cancer Plan was presented ahead of World Cancer Day, as a political commitment to beat cancer by addressing the entire disease pathway, from prevention and early detection, to diagnosis and treatment and quality of survivorship. With several billion euros in funding, the Plan identifies aims and initiatives to tackle every stage (see Table).

On prevention, the Plan looks to achieve a tobacco-free Europe, reduce alcohol consumption, and promote sustainable and affordable diet and physical activity. On early detection, the Plan will put forward a scheme to ensure access to breast, cervical and colorectal cancer screening for the great majority of the respective target populations. Screening for other cancers will also be considered. The Plan also looks to secure equal access to high quality, curative healthcare; to improve the quality of life for cancer patients, survivors, and carers; to reduce cancer inequalities; and to put childhood cancer under the spotlight.

Dramatically, while Europe's Beating Cancer Plan was being designed and published, the Covid-19 pandemic was wreaking havoc on our lives, uprooting our sense of normality, and propelling us into a new and uncertain landscape. Early detection and timely treatment of all forms of cancer took a hit from the combination of lockdowns, self-isolation, overstretched health systems, and restrictions on family support.

We know that a backlog of cases at higher grades will need to be tackled once we have contained the

virus and returned to 'normal'. But what will 'normal' be? We can anticipate a period of economic, physical, and psychological repercussions that will need to be dealt with (Dell'Osso L et al. *J Psychopathol*, 2020). Will Europe's response favour or undermine efforts to implement the Beating Cancer Plan? If we could harness some of the knowledge and experience we have accumulated over the past year, this could help us progress towards a healthier society.

At a policy level, the EU is investing billions in its 'NextGenerationEU' recovery plan for Europe, which is presented as "… a once in a lifetime chance to emerge stronger from the pandemic, transform our economies, create opportunities and jobs for the Europe where we want to live" (bit.ly/NextGenEurope).

At a societal level, we humans see ourselves as independent thinkers, acting with free will, yet as social animals, we adopt behaviours and habits that make us fit in with our community (see, for instance, 'Why we are all creatures of habit' *New Scientist* 2007). Such ingrained patterns of behaviour can be useful to maintain continuity within the herd, which may be why it can be so hard to use free will to change our habits. And yet lifestyles can change quickly when faced with a crisis, and can become the 'new normal' – that is, become as ingrained as our previous behaviour (see, for instance, *J Biomed Informat* 79:129–142).

Some of the changes we have adopted during the pandemic we might well want to keep. People are showing much higher interest in health, and a desire to search more solid sources of information, such as reputable journalism and medical literature. We have rediscovered home cooking, with the added advantage of looking more carefully at ingredients and quantities. Although outdoor activities and gyms have been closed or less available, video fitness classes and home workouts have increased (*Front Psychol* 12:664568), which also draws the attention to inner balance and personal journeys. New technology, working remotely, travelling less, rediscovering the joys of family, can all have a positive impact. And last, but not least, the race to research Covid-19 has shown the world the outstanding results that are possible from collaboration and funding science.

Much has changed in the world of science, technology, communication, and social awareness since the Europe Against Cancer action plans of 1987–1994. All of these advances have an important role. Big data, artificial intelligence, and genomics will contribute to a better understanding of this multi-faceted disease and fill some of the gaps in our knowledge, ultimately allowing us to save costs as well as lives. Technologies and machines may shape new ways of preventing, detecting, and treating cancer. Emerging challenges must also be tackled, such as privacy concerns and cross-border data exchange, speeding the process of new technology uptake, and interpretation and sharing of data. Innovation could also worsen inequality, at least in the short term. The Plan together with the Cancer Mission and Horizon Europe will facilitate and encourage scientific research, leading to new discoveries, therapies, and affordable medicines. The success of Europe's Beating Cancer Plan will rely on intercommunication, sharing and collaborating. To quote Manfred Weber, chair of the largest political group in the European Parliament, (see In the Hot Seat p 62): "The development of the Covid vaccine is one great example of how much Europeans can achieve when they work together. What this experience shows is that promoting collaboration and supporting research and innovation across Europe can make a tangible difference in people's lives."

12 Points for a high-impact Beating Cancer Plan

1. Set Ambitious Goals to Inspire & Galvanise
2. Ensure ALL Stakeholders are Involved
3. Focus on the Quality of Cancer Care
4. Take Action to Improve Survivorship and Quality of Life
5. Achieve Better Integration of Primary Care into the Cancer Care Pathway
6. Address Inequalities
7. Support Healthcare Professional Education & Mobility
8. Improve Data Use and the Evidence Environment in European Cancer Care
9. Be Courageous on Primary Prevention
10. Increase Health Literacy
11. Assist Early Detection Including by Updating EU Screening Recommendations
12. Improve Access to Outcome-Improving Innovation

Source: Adapted from the European Cancer Organisation 'A checklist for an ambitious, unifying and change-making Plan', developed in discussion and agreement with members of the European Cancer Organisation and its Patient Advisory Committee, www.europeancancer.org/policy/1:the-europe-s-beating-cancer-plan.html

Beating cancer is complex – our messaging must be clear

With the launch of Europe's Beating Cancer Plan, the Cancer Mission, and the EU4Health programme, the European Commission has offered an ambitious vision, a road map and momentum. **Anna Wagstaff** looks at how Europe's cancer community can work together to translate that into lasting change in every member state.

A window of opportunity is opening up across Europe to reverse the ever-rising trend of new cancers and improve outcomes for patients everywhere.

It's been brought about in part by a major shift in favour of Europe taking on a stronger policy making role in health and healthcare. The traditional argument that healthcare policy must be a purely national competence has lost ground in the face of insistent demands, not least from cancer patient advocates, to end gross disparities in health outcomes, together with evidence of the advantages of collaborating to improve access to quality care. The Covid-19 pandemic has also played a part in transforming attitudes: viruses don't respect borders, and the argument that Europe's economic success can be separated from the health of its citizens is no longer credible.

EU President Ursula von der Leyen, who took office after the 2019 European elections, is a champion of expanding the EU's health remit. Under her leadership, and with strong backing from across the

European Parliament, the EU4Health programme has hugely expanded its budget, to more than €5 billion over seven years. Expanding areas of action include strengthening health systems, digital transformation of health systems, access to healthcare, and making medicines and medical devices available and affordable. Cancer is a priority.

First we have the Cancer Mission, one of only five mission areas funded within the Horizon Europe research framework, and the only one focused directly on health. With budgets yet to be finalised, this is the first time the EU has framed research funding in terms of defined goals relating to social impacts – lives saved, lives improved, cancers prevented, inequalities reduced.

Then more recently, on 3 February 2021, came the launch of Europe's Beating Cancer Plan. Led by EU Health Commissioner Stella Kyriakides, it sets out a wide range of "ambitious but achievable goals" with specific targets and timelines and backed by €4 billion of funding. These include actions in traditional EU policy areas such as public and environmental health and research, but there is also a focus on actions to level up access to high quality diagnostics, screening and care that show the new assertiveness in getting involved in issues of healthcare structures and delivery.

On top of the longstanding EU role of developing quality guidelines for screening programmes comes a new emphasis on implementation, with a target of 90% uptake of screening for breast, cervical and colorectal cancer. The goal of equal access to high quality diagnostics and care is supported by actions to concentrate cancer care within comprehensive cancer networks, which balance the need to pool specialist knowledge and experience with the need to extend access to that specialist care to people, regardless of their socio-economic means, and in whatever corner of the country or the region they may live.

While this is all music to the ears of Europe's cancer community – and indeed the result of many years lobbying to push cancer up the political agenda – it has also put on their shoulders a big responsibility. Europe's politicians have lined up behind policies that are worth fighting for – can the cancer community work together to deliver the pressure that will be required to ensure those policies lead to action?

So many different voices

One of the big challenges to working together is the extraordinary diversity of roles that play their part in beating cancer – from the public health, environmental health, and lifestyle prevention roles to the GPs, imagers, pathologists and molecular biologists involved in early diagnosis and diagnostics, to all the disciplines and specialists involved in planning and delivering treatment and care and support for survivors, and of course the patient advocates who have expert knowledge about what matters along the entire patient pathway. Each of these contributing roles will have their own priorities regarding what has to happen to improve the service they are able to provide.

Speaking at the press launch of the Beating Cancer Plan, Stella Kyriakides – herself a cancer survivor and former president of the European Breast Cancer Coalition Europa Donna – said she and her team had spent the past year "listening, consulting… and learning", and that they had received more than 2,500 contributions that helped shape the plan. She signalled that she wants to maintain this high level of interaction with interested parties as the focus moves on to getting the plan implemented across Europe: "I will be asking them… to join me on this journey, to walk this path, and to help turn this concrete ambition into concrete action."

"I will be asking them… to join me on this journey, to walk this path, and to help turn this concrete ambition into concrete action"

The European Parliament, meanwhile, has set up its own Beating Cancer Plan (BECA) committee. Chaired by Bartosz Arłukowicz, a Polish MEP and paediatrician, the committee has been holding its own public panel hearings on topics including: 'Empowering Patients and their Caregivers' (patients' rights, survivorship, quality of life), as well as 'Equal Access to Cancer Medicines and Treatments'.

Like Kyriakides, Arłukowicz also stresses the need for those involved in the fight against cancer to actively engage with the EU policy process. His message to those attending the 2020 European Cancer Summit was unequivocal: "I would like to ask you all to treat the BECA special committee as a means of achieving our common goals. To use the

opportunity to create, to put forward concrete proposals, for improving our systems of oncological care. BECA is a scene for politicians, but mostly it should be a scene for us. Doctors and patients."

It's a welcome invitation, but some doctors and patients may find it easier than others to respond.

Getting heard

A leading figure in the European Oncology Nursing Society, Andreas Charalambous has represented EONS in discussions with many policy makers on a range of issues, and has encountered many challenges. "It is not an easy task to transfer the message from the disciplines and the professions directly to the European Parliament, or any policy maker. The difficulty may lie in the fact that we don't speak the same language in the sense that we tend to be more technical when we speak to issues involved in cancer. Our issue is that it is not always receptive on the policy makers' side on the same issues that are of concern to us."

But the consultations over the Beating Cancer Plan were different, he says. "The consultation was open and policy makers were seeking extensive and detailed input… We analysed to [Health Commissioner Stella Kyriakides] the vision of the European Oncology Nursing Society as a whole, and also what the society is expecting from the EU Beating Cancer Plan, in order for the plan to be relevant and realistic in terms of the realities of the clinical context in relation to cancer nurses."

The consultations around the Plan also helped open a direct pathway to areas of the Commission dealing with related policy areas, says Charalambous: "For example research and employment, where we directly got in touch with them to raise issues of concern to us."

Europe's cancer surgeons, by contrast, say they are struggling to get their voice heard because, while they have a lot to say about how to raise survival rates and quality of life for patients across Europe, they currently lack the public relations capacity to make that case at the right time and in the right places.

Isabel Rubio is President Elect of the European Society of Surgical Oncology, and heads up the breast surgical oncology unit at the Navarra University hospital in Madrid. The majority of cancer patients will need surgery at some point in their treatment, and for most of them it offers the best hope of a cure, she says, "but when you talk about innovation in cancer or treatment, most of stakeholders, policy makers, think about medication," she says. "They forget about the other parts of the treatment."

"Imagine in surgery how things have changed in the last 10 years. We are continuously trying to preserve the organ. We are now doing surgery for hereditary syndromes to reduce the risk of getting cancer. We are doing surgery in early stage cancer, in locally advanced cancer, and in some metastatic cancers where surgery often benefits. We think that those specialists doing cancer surgery don't need to be trained in surgical oncology?"

Europe's cancer surgeons have a simple and clear message she says: "To improve outcomes, cancer patients should be operated in cancer units by surgeons who have been trained as surgical oncologists, as they have the requisite knowledge about cancer and cancer surgery." Patient advocates strongly support such a measure, she says, but she worries that the surgical oncology community is finding it hard to compete with other disciplines and specialisms to get that message across.

"There have been so many groups trying to get their voice heard in the European Commission. So unless you have an expert in public affairs…"

"With the Europe's Beating Cancer plan, there have been so many consultations, there have been so many societies, institutions, groups trying to get their voice heard in the European Commission. So unless you have someone who is an expert in public affairs… you are doing surgery, you are seeing patients you are doing clinics – you need someone who is on the policy level. That can send the message that we want to get through."

ESSO is now working with a consultancy to upgrade the society's public affairs capacity. "Unless we have professional skills we are not going to get anything changed. We can be advocates, but our time is limited, our knowledge is limited, and if you want policy changes by lawmakers done in Europe, by the European Commission, you need to be there, you need to know how everything moves around, and for us as surgeons this is way out of our area of action."

European Cancer Organisation Focused Topic Networks

Nine networks bring together different coalitions of interest groups around specific topics to develop collective policy positions, which are published on their respective webpages (europeancancer.org/topic-networks).

Health Systems and Treatment Optimisation – Over 30 participating organisations, with EORTC (clinical researchers) and ESTRO (radiation oncologists) in the chair

Quality Cancer Care – Over 30 organisations, with ESTRO and the Organisation of European Cancer Institutes in the chair

Inequalities – Over 30 organisations, with the European Association of Urology and SIOG, the geriatric oncologists, in the chair

Survivorship and Quality of Life – Over 25 organisations, with MASCC, the supportive care in cancer specialists, and IPOS, the psycho-oncologists, in the chair

Workforce – Over 20 organisations, with EONS, the cancer nurses, ESOP the oncology pharmacists, and ESSO, the cancer surgeons, in the chair

Digital Health – Over 25 organisations, with the European Association of Nuclear Medicine and the European Society of Radiology in the chair

Prevention – Over 30 organisations, with the European Society of Breast Cancer Specialists and European Respiratory Society in the chair

HPV Action – Over 35 organisations, with the Association of European Cancer Leagues and EONS in the chair

Impact of Covid-19 on Cancer – Over 40 organisations, with European Cancer Organisation board members in the chair

Joining forces

Rubio argues that every profession that plays a role in cancer care has something to say about how to improve the unique services they provide and needs their own voice to be heard. She recognises, however, that the value of super-specialisation applies across the field of cancer care, and that there are advantages in collaborating to get that message heard. "At the end, many of our problems, or many of our solutions, are mainly the same. We just need special training and we need our specialty, or sub-specialty, officially recognised by member states. This is also the case for other professions involved in the multidisciplinary care, such as oncology nurses and so on. Because cancer management has become so complex."

ESSO is now collaborating with other professional oncology societies in a network set up by the European Cancer Organisation dedicated to policy issues around the cancer workforce.

The network – one of nine such 'Focused Topic Networks – is chaired by representatives from European societies of cancer nursing, surgical oncology and oncology pharmacy, with radiotherapists, radiologists, molecular imaging specialists, geriatric oncologists, psycho-oncologists, urologists, breast cancer specialists among the participating groups.

Developing recognised education and qualification is an issue common to many of these groups, not least the cancer nurses, who have been campaigning on this issue for decades. "The argument is much the same everywhere," says Charalambous, who was recently elected as President Elect of the European Cancer Organisation. "How is it possible for somebody who has absolutely no specialisation to treat a cancer patient?"

Coordinating work in this area is quite a challenge, he says, because of the wide diversity in the type of work done by the participating societies, but he agrees that teaming up on this topic with the cancer surgeons and professional groups makes good sense. The bare bones of a policy position developed by the network – on access to multiprofessional care and the need to proactively deploy the Professional Qualifications Directive "to support specialisms in cancer care in harmonising education and training requirements" – was one of a number of policy resolutions presented to the European Cancer Summit, last November, and endorsed by a vote of all participants. The intention is to use this evidence of broad backing from across the cancer community as ammunition in discussions with policy makers at EU and national levels.

A magnifying voice

"We do our best to be a magnifying voice," says Matti Aapro, President of the European Cancer Organ-

isation. "We are not seeking to speak on specific areas where our members have the expertise, but to pull it all together." Organising coalitions of interest to work on developing policy within the Focused Topic Networks, he says, is a completely new way of working. "It's not meeting every now and then to say 'hello' for one hour. It is hours and hours of collaborative work."

The first networks was launched in October 2019, as part of a transition away from the federal model used by the European Cancer Organisation in its previous incarnations as the Federation of European Cancer Societies, and later ECCO. The topics focus on different parts of the patient pathway, from prevention through to survivorship. Policy development for each topic is done with explicit reference to the list of 10 'patients' rights' defined in the European Code of Cancer Practice – a 'citizen and patient-centred manifesto' of the core requirements for good clinical cancer practice.

The initial plan was to develop the networks one at a time, says Aapro, "But there was so much enthusiasm right from the beginning from all the members, we were able to get all the networks started by the following Spring… Member organisations suddenly realised that if you have a specific area of interest in that specific area of interest you have also many other organisations that also have an interest."

The model seems to be working, judging by the number of organisations who are now contributing to the various networks. The European Hematology Association is the most recent new member, joining forces with other cancer organisations in developing an urgent response to the challenge of the Covid-19 pandemic. The flexible format also makes it easier for groups that are not primarily cancer societies to get involved, such as professional societies for sexual medicine, and study and management of pain, and of obesity.

"The advantage is to find common ground and come to a common resolution. By doing that we create an authority at the policy level"

Patient advocacy groups covering a full range of cancers played a central role in developing the European Code of Cancer Practice, and now spread their efforts across all the networks – with a particular interest in topics of quality care, quality of life and treatment optimisation. Stefan Gijssels, a patient advocate with Digestive Cancers Europe, who co-chaired the European Cancer Organisation's Patient Advisory Committee for the past two years, echoes what Aapro says about the value of collaboration in lobbying policy makers to take a broad range of actions to improve cancer outcomes. "The advantage, for all the identified topics, is to find common ground among all these associations, bringing different perspectives, different evidence and facts and stories, and to come to a common resolution. By doing that we create an authority at the policy level that very few organisations might have."

It is easier for institutions working on cancer policy to have a counterpart, he says. "Otherwise they have to have a dialogue with the individual members and of course they all have their vested interests and you have divergence and it makes it politically much more difficult to find the right way forward, because then they have to give preference to one over the other. It is much better that we create consensus among ourselves." It's a strategy that Aapro believes paid off when it came to the consultations around the Cancer Mission and the Beating Cancer Plan – indeed some European Commission DGs explicitly asked them for "clear messages on what are the priorities," he says.

Seize the moment

With the Cancer Mission and the Beating Cancer Plan now launched, Europe's cancer community now faces the much bigger challenge of turning paper policies into reality in every country, every region, every health service. Nine in every ten eligible cancer patients being cared for within the proposed networks of National Comprehensive Cancer Centres; nine in ten of those eligible for cancer screening receiving invitations to participate in programmes that comply with EU quality guidelines; improved care for survivors and an end to unfair discrimination – these and other goals on prevention, early detection and more are hugely ambitious, but all the more worth fighting for. The cancer community has shown it can collaborate to magnify its voice at a European level. Applying a similar strategy at a national level may now be crucial to convincing governments in each and every member state to do what it takes to deliver on the ambitious goals of Europe's Beating Cancer Plan.

"Best practices/state-of-the-art in precision testing in breast cancer"

on demand - available at
https://www.oncocorner.net/webinars/27

Co-chairs: **G. Pruneri, IT** - **M. Zambon, IT**

Experts: **A. Batistatou, GR - G. Curigliano, IT - J. Gligorov, FR - N. Harbeck, DE - F. Penault-Llorca, FR**

"Best practices/state-of-the-art in precision testing in lung cancer"

on demand - available at
https://www.oncocorner.net/webinars/180

Co-chairs: **A. M. Baird, IE - S. Novello, IT**

Experts: **K. Kerr, UK - N. Normanno, IT - U. Pastorino, IT - J. Remon-Masip, ES - G. Scagliotti, IT**

"Best practices/state-of-the-art in precision testing in colorectal cancer"

on demand - available at
https://www.oncocorner.net/webinars/189

Co-chairs: **S. Gijssels, BE - E. Van Cutsem, BE**

Experts: **K. Dahan, BE - J. Galon, FR - P. Laurent-Puig, FR - J. Taieb, FR**

NEXT WEBINARS - COMING SOON

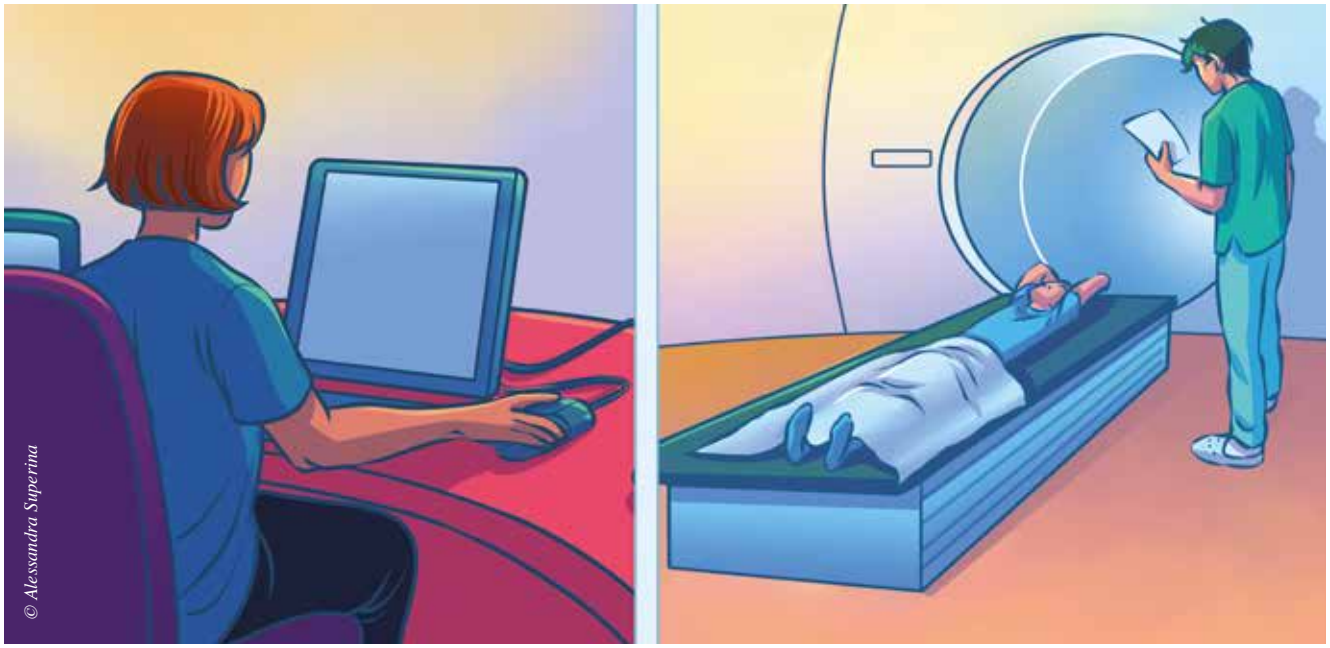
"New precision testing methodologies (NGS, CGP, circulating tumor cells)"

"Improving accessibility to precision testing"

"Best practices/state-of-the-art in precision testing in other cancers"

The webinars are made possible thanks to unrestricted educational grants and/or unrestricted sponsorships from

Supporting companies have no control over the webinars content or speakers



Their fingers on the button

Why neglecting radiation therapists is no longer an option

Can you be sure that the person who positions you on the radiotherapy table and delivers your prescribed dose has received the necessary training and education? Europe's radiation therapist profession are working hard to ensure you can, but they need support from policy makers and the wider cancer community. **Sophie Fessl** reports.

The job of a radiation therapist may sound straightforward: deliver the right dose of radiation to the right location. But it's not. These are complex tasks that involve working with data, high-tech equipment and patients. Moreover, by doing each task correctly, the risks to patients can be minimised so they derive the greatest benefit from treatment (Box). At every step of the way, an error may occur, with potentially disastrous consequences for the patient. Given this responsibility, it might seem reasonable to assume that radiation therapists receive extensive training. But across the world, including in Europe, the education and further training of radiation therapists

Delivering radiation therapy: what's involved

The job of a radiation therapist involves many tasks, each of which have to be done right to ensure the patient gets the greatest benefit with the least risk.

Data transfer
Transferring beam arrangement and dose data from treatment plan to treatment machine:
- Wrong information concerning treatment/dose/location/field size/beam energy
- Wrong monitor units

Checking treatment plans

Simulation, imaging and volume determination
Determining region of the body to be treated using typically a dedicated CT scanner for virtual simulation.

Positioning and immobilisation
Setting up the patient in a reproducible position for accurate daily treatment:
- Incorrect patient positioning
- Incorrect immobilisation position
- Wrongly applied immobilisation device

Patient setup
Placing patient in treatment position for each treatment
- Incorrect patient identification
- Inappropriate alignment with external reference system (e.g. lasers)
- Incorrect application of shifts from reference points to isocentre

Treatment delivery
Physical delivery of radiation dose
- Incorrect radiation dose (overdose or underdose)
- Incorrect beam energy
- Incorrect field size and orientation
- Undetected equipment failure

Treatment verification
Confirmation of treatment delivery using image guided radiation therapy (IGRT); monitoring of the daily setup; monitoring of side effects by regular patient review and support.

(RTTs) are on shaky ground, says Mary Coffey, Adjunct Associate Professor in Radiation Therapy at Trinity College Dublin. "The public, and even people within the discipline itself, have no idea that the people who are actually giving the treatment in many instances have no or very little knowledge of what they do."

The core problem lies in variations in the quality and extent of education covering specific radiotherapy content, says Coffey – coupled with a certain indifference towards the profession. "There is a feeling that the medics are very well qualified, so that treatment prescriptions are very well done. And medical physicists make sure the equipment is functioning really well. So nothing can go wrong! But they forget that it's actually the RTT who has to put the patient on the bed, in the right position, and turn on the machine and deliver the radiation dose that's prescribed." Added to that, radiation therapists are involved in treatment preparation and patient care. "This is a key point in the treatment chain that people don't appreciate."

No title, no recognition

Currently, across Europe, no unified educational programme exists to prepare radiation therapy

professionals. Indeed, the problem starts at an even more basic level: a lack of a unified title.

"Radiation therapists, first of all, are not recognised as a profession," says Michelle Leech, Associate Professor and Head of Radiation Therapy at Trinity College Dublin. "Even in Europe, we have 28 different titles for the profession, which makes it hard to compare curricula, training and competences across the continent. This lack of a unifying title is the first step. Radiation therapists not being a recognised profession is really the main stumbling block for any education."

Europe's radiology and oncology society (ESTRO) and the International Atomic Energy Agency (IAEA) are working on defining an internationally comparable, recognised title for the profession. The acronym RTT is recognised by both bodies, standing for Radiation TherapisTs. This title could then be used on the international stage, in addition to national titles for the profession.

"They forget that it's the radiation therapists who put the patient on the bed, in the right position, and deliver the prescribed radiation dose"

The current problems may arise, in part, from the history of radiation therapy. Historically, radiation therapy was delivered through large radiology fields with less potential for missing the tumour, but greater risk to normal tissue. No specialist education was required, because radiation therapists were drawn from a range of backgrounds and minimal radiotherapy content was included in educational programmes, explains Coffey. In the past decades, however, radiation therapy has developed into a highly complex discipline. With current approaches, small precise areas conforming more to the tumour are targeted. This limits the dose delivered to normal tissue, improving outcome and quality of life for patients. In this setting, however, the need for accuracy is critical and the risk of errors can be greater if positioning is incorrect.

In 2011, ESTRO carried out a survey on how educational programmes prepare RTTs for this complex role. With responses from 28 European countries – though possibly somewhat dated now – this showed that frequently RTT education is a component of a broader programme, in nursing, diagnostic imaging or a technical discipline. Although the education programme is, in some cases, at degree level, the academic content relating to radiotherapy is often limited, and relevant clinical education may be confined to just a few weeks of learning.

As Coffey points out, without recognition as a profession, it is difficult to insist on a standard of competences and a standard of education that achieves these competences. "Historically, radiation therapists have not been recognised as a profession within its own right. You find it lumped with something else, as part of radiography, for instance. But actually treating a patient on a linear accelerator is a very different process than taking an X-ray. Being competent to take X-rays doesn't make you competent to treat a patient," explains Coffey. "By the same token, if the background is nursing, which is a requirement in some countries, that is very positive from the patient care perspective. But a nurse has no education and technical understanding of what happens when you turn on a treatment unit and the potential for harm to your patient."

"Being competent to take X-rays doesn't make you competent to treat a patient"

Currently, the therapeutic relationship acknowledged in the term 'radiation therapists' is also rarely emphasised in educational programmes. Radiation therapists usually see a patient for the entire period of treatment, often over several weeks, during which they monitor side effects, discuss psychosocial conditions and provide support, explains Leech. "We very much see ourselves as therapists. We are here to support and educate the patients about their treatments, make sure they're involved, listen to them, support them in managing their side effects. It's a profession that, when the person is educated, contributes to the holistic way of providing cancer treatments."

The therapeutic aspect also affects the education required to carry out the job, adds Coffey.

"That's why we want to move away from radiography. Radiation therapy is a therapy discipline, in the same way as a physiotherapist or an occupational therapist, because you treat a patient. This is key, because you need to incorporate psychology, communication and patient care in the teaching environment."

How the limitations in education and training of radiation therapists affects patient care is known only anecdotally. A 2008 review of radiotherapy incidents by the WHO showed that, although a significant proportion of incidents could be traced to incorrect equipment use or setup, contributing factors included "incorrect treatment decisions, mistaken treatment delivery and inadequate verification of treatment, due to inexperience and insufficient knowledge of the staff involved."

"There is currently no equality of care in radiation therapy across Europe, and it's not just about access, it's in the actual delivery of treatment, which is nowhere near equitable," explains Leech. Velimir Karadža, Head of the Radiotherapy/Technology Unit at the Clinic of Oncology, University Hospital Center Zagreb, in Croatia, echoes this feeling. "I'm sure there have been more mistakes happening than we actually detect. But people need to have the awareness. If people are not educated well enough, they will not care, they will not see, and they will not detect the error."

Unlike many other disparities in cancer care, this is not a divide between the 'old West' and the 'old East'. "It's not specific to eastern Europe at all," says Coffey. "Countries like Australia and New Zealand, the UK, and Ireland have strong, dedicated programmes. But for example in Portugal, an excellent course in radiotherapy was closed down and replaced with a joint radiography programme."

"Unlike many other disparities in cancer care, this is not a divide between the 'old West' and the 'old East"

What is added in eastern Europe is that many countries are quickly catching up in their radiotherapy standards, says Siret Kivistik, radiation therapist at Tartu University Hospital and radiotherapy lecturer at Tartu Healthcare College, in Estonia. "The development in our country has been huge… in the 12 years that I have been actively working in this environment. So the need for trained people really grows day by day."

Train the Trainers

Efforts have been made to improve RTT education across Europe. "Radiation therapists on the ground are dissatisfied," says Leech. "They know that their standard of care could be better… and want to change it from the ground up."

Helping drive this change is ESTRO's RTT Committee, which was established in 1993 to represent radiation therapists at the European level. ESTRO supported the development of a core curriculum for radiation therapists, which was first published in 1995, with the third and latest revision published in 2011. This core curriculum sets standards for education of radiation therapists and links these to core competencies. Courses designed to fit this core curriculum should equip graduates with the defined competencies.

Additionally, ESTRO and IAEA have collaborated in a Train the Trainers programme, which started in 2008. This seeks to empower radiation therapists to address educational needs within their own countries. After a week-long training, given to three participants from each participating country, the participants organise three courses on RTT-specific topics for other radiation therapists in their own countries. Five rounds of this 'Train the Trainers' programme have been completed so far.

One consequence of this project has been increased networking among RTTs. In the Balkans, this has led to the establishment of an international platform for cooperation to exchange knowledge, experiences and solutions. Four meetings have been held so far in the Balkan region, under the title South East Europe Technology in Radiation Oncology (SEETRO) congress. The project is also helping radiation therapists to push for increased recognition of their profession. "A lot of countries have actually set up their own RTT society, and in several countries they're working in that direction," says Coffey.

One aim of the Train the Trainers project was to influence national education, so that the

radiotherapy component of programmes is increased. Karadža is one of the driving forces behind the SEETRO Congress and RTT training programmes in Croatia. "Our workshops and symposia raised awareness about the problems. But to make this something permanent, the only way is to change the official educational programme," he says. That is not always easy to achieve, says Leech. "There must be an internal recognition in various countries that there's actually a problem. And there must be a recognition by the educational institutes themselves that the programmes they are running are not fit for purpose, that they do not teach the fundamental science, that is necessary to understand your actions on a radiation therapy unit."

New models for education in Croatia and Estonia

In trying to change education in Croatia, Karadža and colleagues started out by drawing up the competences that RTTs would need. "Even the educational bodies participated in that, but when we tried to make the actual changes to education itself, we encountered problems." Nevertheless, in 2019, radiation therapists were, for the first time, appointed as lecturers at the University of Applied Health Sciences in Zagreb, Croatia. "We think this is absolutely mandatory, that people from the profession are teaching students about professional issues."

Now, Karadža seeks to change the curriculum further. "But it takes time to convince the Dean of the Faculty and everyone that they need to just cut off some subjects and bring in new learning."

Coffey, set up a degree programme for radiation therapists at Trinity College Dublin, which has been further expanded by Michelle Leech. In countries with limited resources, Coffey argues that is important to use a 'pick and mix' approach to design a course containing the most relevant existing educational content, tailored to future radiation therapists, rather than trying to establish a more costly full degree programme. "If constrained by time and resources, education should be tailored and focus on teaching key areas of radiotherapy," she says.

In Estonia, Siret Kivistik has been instrumental in setting up a two-year MSc course for radiation therapists, for which she is now the course coordinator. Estonia faces an additional problem: as the country is small, only two clinical departments in Estonia offer radiotherapy services, with a total of only six linear accelerators available in the country. "We'd need to have 15 students per year to set up a dedicated programme at BSc level. But with just two clinical departments, we do not have enough positions to offer to 15 graduates each year." A joint programme by the Baltic States to provide radiotherapy education was envisaged and developed, but failed for political reasons. An international MSc programme focusing on radiotherapy is now in its second year at Tartu Healthcare College in Estonia. The course is intended both for already practising radiotherapists, as well as for graduates of related disciplines without prior experience. "This programme, however, teaches a lot of the skills and knowledge that graduates should know already, entering a Master's level programme. But we get great backing from the clinical departments, and we are in a good situation, having such a programme established." In a next step, Kivistik wants to safeguard proper education for everyone in the radiotherapy departments as part of Estonia's next cancer strategy.

"They work really hard and care deeply for their patients, but it's difficult without proper understanding of what happens when they treat a patient"

Lack of traction at a policy level is one hurdle radiation therapists are facing. "We did try to have events inviting the ministry of health and education from various countries to attend, but we had to abandon this because there was no interest in us. It's very difficult, we never reach the top level of government," says Leech. There are also challenges at the level of professional societies, because radiation therapists are frequently members of organisations where other professions, such as nursing or radiography, are in the majority. This can make it hard to ensure attention is paid to their specific interests and needs. "One head of a national radiography society told me that

radiographers might get bored with diagnostics and want to do a bit of therapy. So therapy is still being seen as an add-on to diagnostics," says Coffey, who also encounters the fear of RTTs taking away the responsibilities from other professions. "We are not about educating people to take over someone else's job, which is another big fear… it's not about that, it's about educating radiation therapists to do their own job."

Coffey insists that, currently, radiation therapists in all settings are doing as good a job as they can do, given the circumstances. "I'm not taking away from the people on the ground, they work really hard and care deeply for their patients, but it's difficult without proper understanding of what happens when they treat a patient." She points to her own graduate students participating in discussions in multidisciplinary teams on an equal footing. "It's terrific to listen to the students actually discussing with the rest of the team from a point of absolute understanding, and it becomes an equal discussion. It just enables everybody to do a better job."

Leech points out what is at stake. "Who would you like to be treating your child? The person who is specialised in this area or someone who maybe sees this case once or twice? I think citizens know the answer to that question."

The sunshine hormone
The many wonders of vitamin D

Vitamin D has drawn much scientific interest and media coverage in recent years, and increasingly so in 2020, when a link was found between vitamin D deficiency and Covid-19, writes **Adriana Albini**. This is a very unusual vitamin, in that it behaves both as a hormone and a vitamin – our skin produces it through exposure to sunlight – but it is also supplemented by diet, one of its primary sources being oily fish. In cancer, vitamin D levels are inversely correlated to risk; it has neoplasia-suppressive effects, as recent trials confirm.

Among the most interesting findings from the huge volume of research relating to the Covid-19 outbreak is the emergence of Vitamin D as a possible biomarker.

There is a discussion about whether, along with obesity, diabetes and high blood pressure, vitamin D deficiency is associated with vulnerability to coronavirus infection and with the severity of the disease. (*Lancet Diabetes Endocrinol* 2020, 8:570; *JAMA Netw Open* 2020, 3(9): e2019722-e2019722).

As oncologists and cancer researchers, we know that low

levels of vitamin D increasingly appear to be correlated with cancer risk and worse prognosis, as well as with response to chemotherapy. In trials, vitamin D supplementation appears promising for cancer control, as recent news has also suggested.

It is one of many potential biomarkers of sars-2-cov susceptibility and infection that are being studied by disciplines other than virology, mostly oncology and rheumatology. Interleukin 6 and interleukin 1 are other examples.

What it is and how it works

Vitamin D is a steroid hormone; the major molecular moieties in this group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Various modified forms exist, including calcifediol (25-hydroxyvitamin D or 25(OH) D), an indicator of vitamin D levels in the blood, and calcitriol (1,25-dihydroxyvitamin D or 1,25(OH)2D), an active hormonal form.

Cholecalciferol is synthesised in skin epidermis, and the reaction is catalysed by sun exposure (mostly UVB). With less efficiency, cholecalciferol and ergocalciferol can also be absorbed from the diet, and vitamin D can be provided as a supplement.

The hormone exerts its actions through the vitamin D receptor, which is part of the nuclear receptor family (as is, for example, the oestrogen receptor, NdA). The vitamin D receptor mediates vitamin-D-stimulated calcium metabolism, but it also exerts other cellular effects by translocating to the nucleus, binding to DNA-responsive elements and modulating gene expression.

The link with cancer

Vitamin D levels are inversely correlated to cancer risk. The vitamin has suppressive effects on neoplasia, and various mechanisms of action mediating cancer cell inhibition have been described. One of the major investigators into the vitamin D and cancer liaison is Edward Giovannucci, Professor of Nutrition and Epidemiology at Harvard Medical School, Boston, who received the 2019 AACR-ACS Award for Research Excellence in Cancer Epidemiology and Prevention, and in 2020 co-authored a *JAMA* paper on the 'Effect of Vitamin D3 Supplements on Development of Advanced Cancer' (*JAMA Netw Open* 2020, 3(11):e2025850).

To follow up on the hypothesis of reductions in cancer deaths, the team evaluated whether vitamin D reduces the incidence of advanced (metastatic or incurable) cancer and examined possible effect modification by body mass index, in the VITAL trial (VItamin D and omega-3 TriAL). VITAL is a randomised, double-blind, placebo-controlled, 2×2-factorial clinical trial of vitamin D3 (cholecalciferol, 2000 IU/d) and marine omega-3 fatty acids (1 g/d). The trial was designed to test the independent effects of vitamin D and omega-2 supplements, and test for synergy between the two. It concluded that supplementation with vitamin D reduced the incidence of advanced (metastatic or incurable) cancer in the overall cohort, with the strongest risk reduction seen in individuals with normal weight (i.e. not obese) (*JAMA Netw Open* 2020, 3(11):e2025850). A Giovannucci paper in a monograph dedicated to vitamin D and cancer 'Sunlight, Vitamin D and Skin Cancer' summarised that "the results from meta-analyses support that achieving circulating levels of 25(OH)D around 54–135 nmol/l may contribute to reducing cancer mortality. Although the optimal 25 (OH)D level for prevention is not established, it is likely to be higher than 50 nmol/l, and currently, a substantial portion of the world's population is below even this threshold." (*Adv Exp Med Biol* 2020, 1268:39-52).

To have the right levels in our system, without the intake of man-made supplements, is no easy task. To synthesise enough vitamin D through sunlight exposure we should ideally live in sunny countries, but also lead a lifestyle that involves a lot of time outdoors, wearing skimpy clothes (short sleeves, no gloves), and no sunscreen products filtering UVB.

As for diet, the only way to compensate for lack of sun exposure would be to follow the traditional diets of populations in cold climates, which are heavily based on fatty fish. Both hypotheses are non-viable for obvious reasons, from health risks related to high-fat diets and prolonged exposure to UV rays, to economic, religious, ethnic, and social factors that influence our diets, our lifestyles, and also our constitutions.

The Endocrine Society recommends at least 1500–2000 IU/day intake of vitamin D to maintain the levels of 25(OH)D above 75 nmol/l.

A historical perspective

Vitamin D was discovered in the first half of the twentieth century, but, from time immemorial, people have empirically understood the benefits of both sun exposure and intake of oily fish to prevent or cure a number of ailments, mainly affecting bones and lungs.

In the third book of his *Histories*, the Ancient Greek historian Herodotus (c. 484 – c. 425 BC) recounts his visit to the site at Pelusium, where, almost a century earlier, an important battle had taken place between Persians and Egyptians. The bones of the dead were still scattered on the battlefield, Egyptians on one side, Persians on the other.

Herodotus noted that the skulls of the Persians were so brittle they would be pierced by simply throwing a pebble at them, while those of the Egyptians were so strong that they would not even crack upon receiving a much stronger blow. Puzzled, he was told by the locals that the Egyptians shaved their heads from childhood and their skull thickened by exposure to the sun.

This was also the reason why there was no known case of baldness among them. On the other hand, Herodotus continues in his aetiology, Persians always covered their heads with felt hats. He therefore deduced it must be lack of exposure to the sun that made their skulls brittle.

Jumping forward from antiquity to the beginning of the last century, one in four children in Britain were affected by the bone disease known as rickets. So common was it in that part of the world that it was nicknamed 'the English disease', although other countries, particularly the United States, were also ravaged by it.

The need to find a solution prompted research for a chemical factor that would make the empirical remedies of exposure to sunlight and ingestion of cod liver oil, successful in alleviating or curing the condition. Leading researchers, such as McCollum, Mellanby, Windaus, and others, identified this factor with a vitamin that, as the fourth discovered, was named D.

The introduction of vitamin D-fortified milk and margarine, alongside sun exposure and cod liver oil, brought about an almost complete eradication of rickets – after which, chemical research on this vitamin, its components and action, stagnated. There were a few interesting discoveries relating to the mobilisation of calcium in the 1950s and again in the 1970s, but it is only in the past couple of decades that interest in the sunshine vitamin has been rekindled.

Aside from the need to tackle a global resurgence of rickets, it was the identification of the vitamin D receptor that excited the curiosity of the scientific community, as it is also found in tissues with no involvement in calcium homeostasis, such as skin, breast, pancreas, T cells, and so on.

In other words, it appears that vitamin D plays a role that goes well beyond the skeletal muscle, into many areas of immune function and disease prevention. It affects heart, lungs, cancer development and progression, obesity, Covid-19, and even depression. It has become almost a panacea in the eyes of doctors and consumers alike, with clinics carrying out vitamin D tests for a wide variety of conditions. Needless to say, the sale of vitamin D supplements has skyrocketed during the pandemic of 2020.

The cure of sunlight and cod liver oil for conditions other than skeletal is also well rooted in history. People with tuberculosis were usually treated with both. In Victorian times, those patients who could afford it went to the Italian or French Riviera in winter to benefit from sunlight and clean air. Menton, on the French Italian border, became one of the most popular health destinations thanks to the publicity given it by James Henry Bennett, a London physician, who, having contracted tuberculosis, "…departed southward in the autumn of the year 1859 to die in a quiet corner…" But die he did not. Instead, staying in Menton, he made a full recovery… His book *Winter and Spring on the Shores of the Mediterranean* became a sought-after read.

The same Bennett is also author of the treatise *On the treatment of pulmonary consumption: by hygiene, climate, and medicine*. In the chapter entitled 'The medicinal treatment of phthisis', he acknowledges the benefits of cod liver oil, but only in conjunction with other remedies such as exercise and sunlight. He is also puzzled as to what substance contained in the fishy oil produces the curative effect.

Interestingly, in the 1800s there was already an awareness

of the possible co-morbidity of pulmonary and bone conditions. Charles Dickens' Tiny Tim, the very sick child in A Christmas Carol, probably had both rickets and tuberculosis. Earlier in the century, in 1813, the British naturalist William Turton published a book with a most intriguing title: *Some observations on consumption, scrofula or King's evil, gout, asthma, softness and distortion of the bones, rickets, cancer, insanity, and other chronical diseases, with reasoning on their remote origin, probable affinity, and means of prevention and cure*. Unfortunately, the underlying common factor, vitamin D, had not yet been discovered.

Conclusions

Almost 10 million cancer deaths occur yearly worldwide. With increasing population size and aging, cancer incidence and mortality are likely to rise over time.

The most abundant data on the protective role of vitamin D relate to colorectal cancer. The evidence is increasing for several more cancers, including prostate and breast.

For some cancers there are too few studies, done in individual cohorts, to draw conclusions. The current literature is now providing more data relating to vitamin D and Covid-19. Obviously, we must not forget how this hormone is bound up with our bone health.

How many more miracles the sunshine vitamin has in store will be revealed in the not so distant future. This is undoubtedly a vitamin that keeps on giving.

With the contribution of Francesca Albini, PhD.

Mike Morrissey: At your service

Does this help cancer societies achieve their aims? Does it offer solutions to the health and economic challenges posed by cancer? **Marc Beishon** hears from the chief executive of the European Cancer Organisation about his approach to working with Europe's professional and patient advocacy groups to help develop effective ways to collaborate to get their voices heard.

The European cancer community has long had its ups and downs in its efforts to act in concert to promote policy and standards throughout its constituent countries, which differ widely in their healthcare systems and resources. There have been numerous cancer declarations and plans, promoted by politicians, policymakers, professional cancer and organ-based societies, and patient groups, but there has been much fragmentation and lack of sustainability as actions come and go, funding starts and stops, and the 'deliverables' that do take shape often take many years to complete.

At the centre of shaping policy is the European Cancer Organisation, now relaunched under new leadership, having previously navigated the often turbulent political waters with some difficulty under its old names of ECCO (as it was commonly known) and, before that, the Federation of European Cancer Societies (FECS).

The core of the organisation is still a federation of cancer societies such as ESTRO (radiation oncology) and ESSO (surgical oncology), EONS (cancer nurses) and, more recently, the EHA (haematologists), as well as patient groups, which have grown in strength and number in recent years. The determination to act together and influence politicians and policymakers at national and EU level – its consistent mission since the idea of a federation was floated in the 1980s – remains strong.

What it seems to have lacked is a leadership capable of uniting the many voices in the cancer community in the most relevant way. This seems to have been put right with the appointment in 2019 of Mike Morrissey, a Briton brought up near London.

Morrissey was headhunted for the role from the European Society of Cardiology (ESC), and before that held senior positions at member associations outside the health sector, earning a reputation as a 'troubleshooter' able to quickly address sometimes existential problems and the competing demands of members and staff. His formative working years were spent dealing with some of the most fragile egos on the planet – professional tennis players – when he was at the International Tennis Federation.

"I'm not a business-as-usual sort of guy – I look to inject new energy into an organisation, and I want a challenge and not just to make a business model a bit more comfortable. But it wasn't a straightforward decision to join the European Cancer Organisation," says Morrissey. There was no doubt that ECCO was in big trouble both financially and in lack of direction, but it was a challenge he was looking for in a second move into the health field, having learned and achieved much at the ESC and with its cardiology community.

Mike Morrissey (right) with Matti Aapro, current President of the European Cancer Organisation (2020-2021), at the European Cancer Summit 2019

"I was struck by the great enthusiasm from most of the people I met for us to be successful in a new guise. My experience with member organisations is that the main issue is being relevant – if you are, then other issues such as finance, visibility and membership tend to solve themselves."

It's a good time to be relevant in European cancer policy, which was one factor that swayed Morrissey's decision. The European Union has embarked on one of its most ambitious cancer programmes yet, in the Beating Cancer Plan, complemented by the Mission on Cancer, and there is a good deal of potential new investment. "Funding of the plan will be game changing," Morrissey says, noting that there is more than €5 billion allocated for the umbrella health initiative, EU4Health, which runs from this year to 2027.

Orchestrating European Cancer Organisation members, under their guidance, into networks that map into European priorities, and helping to build consensus with policymakers are key aims now, and Morrissey has moved quickly to produce workstreams and an overall strategy that are creating that magic word – relevance.

Finding solutions

The field that Morrissey was previously very relevant in was sport, and tennis in particular. "I was a terrible sportsman but my father was keen for me to good at it. I did the next best thing and got involved in officiating at tennis tournaments, and at 17 I became the youngest ever linesman at Wimbledon." Tragedy struck that year as his father was killed in a motoring accident. It spurred him to be passionate about the tennis world, and he went onto be an international umpire at a time when there was a need for younger and more diverse people to take over from the amateur incumbents – the 'retired colonels' as he puts it.

"Umpiring is about finding solutions and not just making decisions, and I was dealing with big egos who were under huge pressure," he says, "and we were all on TV in front of millions." It was a job that he became more nervous about as he got older – "You are fearless when young" – and no doubt, with the likes of John McEnroe on court, dealing with personalities in the cancer world, strong as they can be, is put into perspective.

(For a roundup of his tennis umpiring exploits – which include five Wimbledon men's finals and a streaker – see bit.ly/MorrisseyStepsDown.)

Morrissey went into managerial positions in international tennis, before making a switch to leadership roles in a diverse series of other member bodies – Institution of Engineering and Technology, International Council of Shopping Centres, International Federation of Air Lines Pilots' Associations, and then the health move to the cardiologists.

A common denominator with his roles is the presence of volunteers and their interaction with the organisation. As he says, they are mostly busy experts and not getting paid for working with an association. "They want to know that things that have been agreed will get done," he adds. "And you can't underestimate how much more volunteers give if we make it easy and enjoyable for them."

"They know I don't know that much about oncology but I need to demonstrate I know how to run an association"

Gaining quick respect from volunteers – which in the cancer community are representatives from currently 34 societies and 20 patient groups federated to the European Cancer Organisation – is crucial, says Morrissey. "They know I don't know that much about oncology but I need to demonstrate I know how to run an association."

That also includes staff members and their relationship with volunteers, and in his three years at ESC as chief operating officer he dealt with a formidable number of issues in this long-standing organisation that was in need of new energy, by re-organising the staff structure, fostering collaborative working and removing barriers between staff and volunteer leaders – creating a more 'family' atmosphere rather than one where staff were sometimes perceived as obstacles.

Certainly, anyone reading Morrissey's CV will be struck that he pulls no punches and has tackled such issues head on and quickly. It's a truism that all organisations say they are a 'people business' but, as he notes, member federations are different because of the need to involve an often changing base of volunteer members, some at very senior professional levels, and craft their relationships with the organisation's staff. "People cannot be overestimated in the association world," he says.

With no background in health, moving to the ESC and then the European Cancer Organisation were successive shocks to his system in terms of a learning curve. But he says he was surprised how open doctors have been about their experiences. "A case in point was a cardiologist who told me about their first patient death as a heart surgeon – it had a big impact on him, and others have told me about the difficult conversations with families and loved ones. I've also learned about the cultural differences in attitudes to health between say the Nordics and southern Europe. You are only exposed to conversations with doctors in personal situations usually. What I've learnt about is the environments they work in – not so much the intricacies of the heart or cancer."

Collaboration not competition

Two important facets he has brought to the European Cancer Organisation are extensive international experience and, from the ESC, the ability to keep a number of semi-autonomous subspeciality groups on board. The cardiology and cancer communities are probably equivalent in societal importance in Europe, and Morrissey was also involved with the annual ESC Congress, which has attracted more than 30,000 attendees, and he organised a visit by Pope Francis to the congress in Rome in 2016.

Although cancer events have moved to focus on individual cancer types such as breast and lung, one of the casualties at the old ECCO was the end of its large annual conference. If anyone won the battle of the cancer conferences, it is the powerful European Society for Medical Oncology (ESMO), which is not currently a member of the European Cancer Organisation and also sees itself as 'market leader' in oncopolicy. It will be interesting to see whether a new relationship is formed between the two.

Morrissey was well aware of the politics in the European cancer community, but says that is part of the challenge for him. "What we need to do is to amplify voices both big and small within a federation and foster collaboration and not competition," he adds. As befits a new leader at any level, he used his first 100 days to listen to a wide range of stakeholders, and drew up a new strategic plan and business model that he feels has re-established relevance under, what looks from the outside, to be a new organisation with a new brand.

The strategy has one obvious quality – simplicity, as it has clarified the priorities and given the organisation a coherent mission. Too many organisations try to do too much and end up doing little, he feels, and he can't emphasise enough how important it is that the cancer society and patient group stakeholders see the results of their efforts bear fruit.

So there are just two pillars – policy and advocacy at European level, and what is termed 'Focused Topic Networks', of which there are currently nine, including a recent 'special' network on the impact of Covid-19 on cancer. Other networks include prevention, HPV action, health systems and treatment optimisation, inequalities, quality cancer care, and workforce. The idea is that the networks establish consensus that may then feed into the policy arm of the organisation.

Morrissey also emphasises the partnership he has with Matti Aapro, the prominent medical oncologist who is the current president of the European Cancer Organisation (and on the board of the European School of Oncology) – a good relationship between CEO and president is vital if member associations are to thrive, he says. "Matti has been a fantastic guide to the oncology world and we have a great working relationship."

With Aapro and other board and staff members, Morrissey says they have networked extensively not just with member societies but also at EU level and with the WHO, and they look to have made the European Cancer Organisation relevant in the committees that have developed the Mission on Cancer and Beating Cancer Plan, such as the Special Committee on Beating Cancer (BECA), and also with MEPs Against Cancer and the Challenge Cancer Intergroup – an EU parliamentary group that was launched in 2020. The secretariat for the Challenge Cancer Intergroup is provided by the European Cancer Patient Coalition, which is a member of the European Cancer Organisation's Patient Advisory Committee. No doubt he has found Stella Kyriakides, European commissioner for health and food safety, especially receptive, given her own background as a cancer patient advocate and Past Chair of the ECCO Patient Advisory Committee. The first annual report under the Aapro/Morrissey partnership is now out (bit.ly/ECO2020AnnualReport).

He sees his team's key role as 'joining the dots' for policymakers on the basis of evidence developed among the topic networks. It is no accident that some of the networks mirror elements of the Beating Cancer Plan, such as eliminating HPV and inequalities, and as he says: "We are positioning ourselves not as an organisation with a list of complaints but with a list of constructive solutions. When talking to politicians, policymakers and the media we need to present complex medical topics in 'headline' terms. There is no doubt that they are looking to be educated, but we need to engage in real conversations, rather than almost lecture them as some associations sometimes do."

There has been a noticeable uptick in the output. Last year saw a submission to the EU consultation on the Beating Cancer Plan (bit.ly/ECOreBeatingCancerPlan) and a study, Strengthening Europe in the fight against cancer, commissioned by the European Parliament (bit.ly/ECO-EU-Advisory2020). The European Cancer Organisation is now affiliated to the *Journal of Cancer Policy*, and instead of a general conference, there is now an annual policy summit. An important publication is the European Code of Cancer Practice (bit.ly/EuropeanCodeofCancerPractice), which has its origins in the European Cancer Patient's Bill of Rights from 2014, and which has also been described in a new paper (*J Cancer Policy* 2021, 28:100282).

He can't emphasise enough how important it is that the cancer society and patient group stakeholders see the results of their efforts bear fruit

Altogether, it's a much more streamlined approach to cancer policy. Morrissey agrees though that the EU now has many, often confusing, initiatives in cancer, not least in the recent flurry of activity. "We can't change the way the EU works, and we can't do everything, but we can provide access to expertise for the way plans are made and implemented and I'm confident we can help make cancer policy better in Europe by doing what makes sense for our stakeholders."

It's probably an easier task than umpiring tennis stars and it's too tempting not to quote John McEnroe: "You cannot be serious!", which he howled at a tennis umpire at Wimbledon. Anyone who doubts Morrissey's seriousness in serving the cancer world effectively will learn, after just a few minutes in his company, that he is.

european cancer ORGANISATION

Matti Aapro, President,
European Cancer Organisation

The promise of Europe's Beating Cancer Plan won't be unlocked without addressing the cancer workforce challenges

Managers of any organisation, the world over, root themselves in the understanding that "your workforce is your most valuable asset". Yet, what ought to be a self-evident truth can also sometimes get lost within new strategy formulation. Reflecting on Europe's new Beating Cancer Plan, while I give it very many stars of approval for its breadth and ambition, among the elements I might have wished received more explicit attention, are the needs of our cancer workforce. Quite simply, there is no cancer care without a cancer workforce.

For this reason, it has been an enormous pleasure to have worked with the 3 Co-Chairs of the E.C.O. Workforce Network, Professor Andreas Charalambous (E.C.O. President-Elect, Past-President of the European Oncology Nursing Society), Dr Mirjam Crul (E.C.O. Board Member, Vice-President of the European Society of Oncology Pharmacy) and Prof Geerard Beets (Board Member of the European Society of Surgical Oncology) in writing and publishing a new cancer policy paper: **'Working Against Cancer: Giving Professionals the Right Tools for the Job'**. Each of us representing a different discipline, developed via the E.C.O. Workforce Network, and in consultation with the 34 E.C.O. member organisations, 20 patient advisory groups and many others, this has been multidisciplinary, multi-professional and multi-stakeholder collaboration in action.

The paper conveys in short form the critical challenges for the cancer workforce in the context of implementing Europe's Beating Cancer Plan. The 4 key challenges are described as:

- Resolving the difficulties caused by workforce shortages;
- Reducing unnecessary barriers to professional mobility;
- Improving occupational conditions to protect the safety and well-being of healthcare professionals working in cancer care; and
- Enhancing education and development opportunities for healthcare professionals that are now even more achievable in the digital age.

Clear, pragmatic and achievable recommendations are provided, including among many others:

- Populating Europe's Beating Cancer Plan's Inequalities Registry with a clear section dedicated to measuring patient access to cancer professions across Europe;
- Establishing a RescEU style mechanism to help alleviate cross-border oncology workforce shortages;
- Proactively deploying the EU Professional Qualifications Directive to support specialisms in cancer care in harmonising education and training requirements;
- Addressing exposure of healthcare workers to cytotoxic products through coverage of this issue within the EU Carcinogens and Mutagens Directive; and
- Legally codifying at the EU level the already widespread (but not yet universal) practice of continuous professional development as a mandatory requirement for healthcare professionals.

Europe's Beating Cancer Plan has set out the 'what' to be done. E.C.O.'s networks will this year be helping the European Commission and EU member states fill in further detail on the 'how'. It is appropriate, therefore, that our first Network publication following the Plan's publication should be on workforce needs. Healthcare professionals across Europe working in cancer care are the core delivery tool for improvement. We hope our new paper helps to remind of this and offers concrete suggestions for further action.

2021

24-26, JUNE

MASCC/ISOO Annual Meeting

SUPPORTIVE CARE IN CANCER

Reserve Today

Plenary Sessions Highlights

Models of Supportive Care

- Supportive Care - 30 years of MASCC
  Prof Dorothy Keefe (Australia)
- Models of Supportive Care - What's the Evidence?
  Dr Florian Scotté (France)
- Supportive Care - A Luxury in Low and Middle-Income Economies?
  Dr Enrique Soto Perez de Celis (Mexico)

Cardio-oncology

- Cardio-Oncology: Beyond Left Ventricular Dysfunction
  Dr Thomas Suter (Switzerland)
- Looking at Cardio-Toxicity in the Clinical and Research Setting
  Dr Michael Ewer (USA)

Bioethics

- Ethical Principles – One Size Fits All?
  Dr Richard Huxtable (UK)
- New Treatments, New Ethical Challenges
  Dr Ian Olver (Australia)
- Evidence Based Medicine – The Answer to Ethical Dilemmas?
  Prof Andrew Davies (Ireland)

The MASCC/ISOO Annual Meeting is the foremost international and multidisciplinary conference focused on themes of critical importance in supportive cancer care including the impact of COVID-19 and the pandemic. At the 2021 Annual Meeting, you'll discover what's new and what's on the horizon in the diverse and exciting field of supportive care. We believe that *"supportive care makes excellent cancer care possible."*

2021 MEETING THEMES

COVID-19 PANDEMIC

BIOETHICS

CARDIO-ONCOLOGY

MODELS OF SUPPORTIVE CARE

SESSIONS ON VARIOUS MASCC STUDY GROUP TOPICS

For all of the program details, visit:

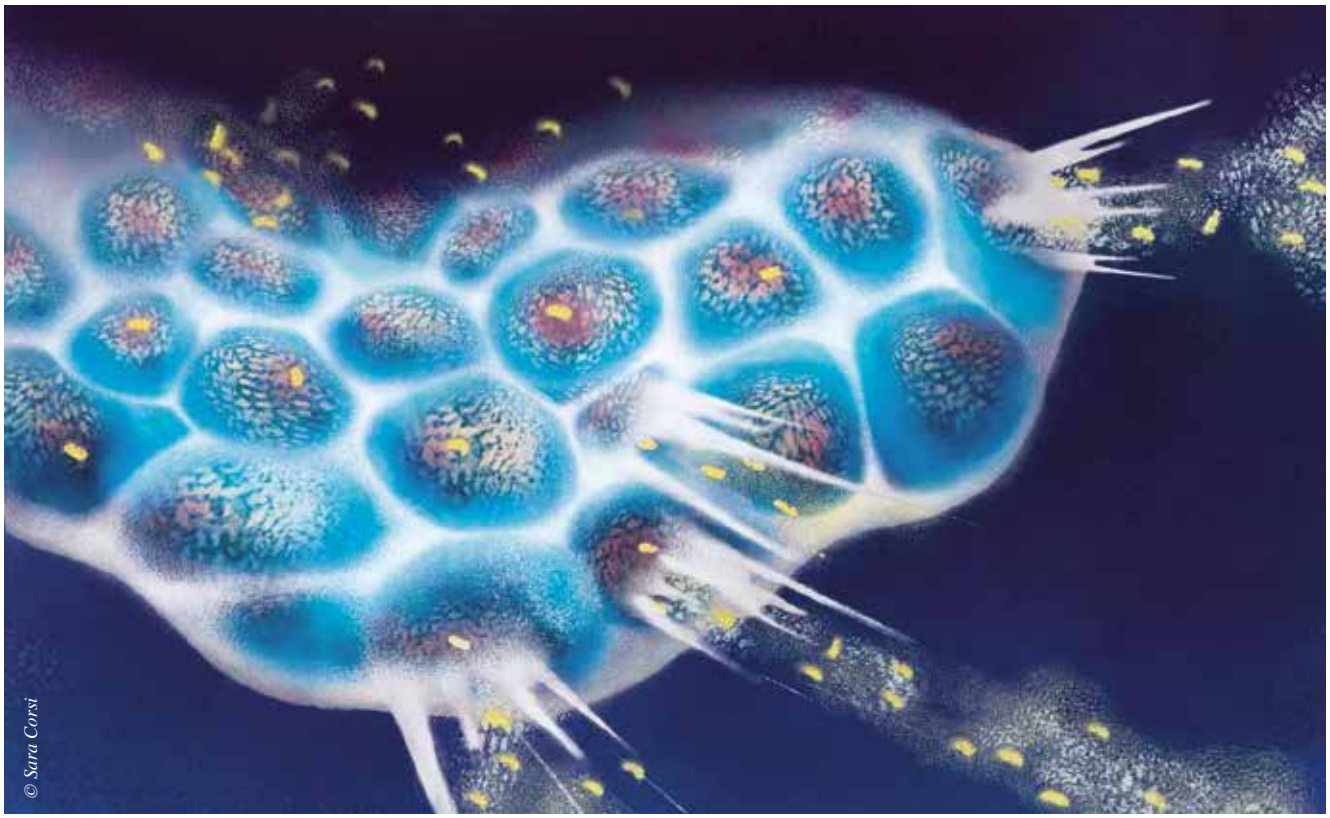
WWW.MASCC.ORG

MASCC
MULTINATIONAL ASSOCIATION OF SUPPORTIVE CARE IN CANCER

ISOO
INTERNATIONAL SOCIETY OF ORAL ONCOLOGY

Follow us on Twitter
@CancerCareMASCC

#MASCC21



Oncolytic viruses – a new wave of therapeutic possibilities

Over the past two decades, significant advances have been made with oncolytic viral therapies. The lack of long-lasting adverse effects, and synergy with immunotherapy combinations, make them an attractive therapeutic tool. **Rachel Brazil** talked to researchers and developers about what is coming down the line.

Going back to the nineteenth century there were reports that infectious diseases seemed to provide brief periods of remission for cancer patients. One case from 1896 reported that the enlarged spleen of a woman with "myelogenous leukemia" shrank to nearly normal size when she contracted influenza (Dock G, *Am J Med Sci*, 1904). "It wasn't until a little later on when viruses were actually discovered, that correlations began to be made," says Adel Samson, who leads the Translational Cancer Immunotherapy Group at the University of Leeds. From the 1950s onwards

serious attempts were made to therapeutically harness the effect of 'oncolytic viruses' – viruses that cause cancer cells to disintegrate – but only in the past two decades have significant advances been made and a wave of oncolytic viral therapies is now entering the cancer treatment landscape.

The first oncolytic virus to be approved by a national regulatory agency was RIGVIR, a non-pathogenic enterovirus, approved in Latvia in 2004 for the treatment of melanoma, but withdrawn in 2019 due to a lack of data supporting its efficacy. In 2006 the H101 oncolytic adenovirus was approved in China for the treatment of head and neck cancer. The first approval in Europe and the USA came in 2015, with talimogene laherparepvec (T-Vec or Imlygic, from Amgen), a modified herpes simplex virus (HSV) approved for subsets of patients with melanoma. When injected directly into lesions it generates an immune response against the patient's cancer. Real world data has shown response rates of up to 88.5%, with complete response rates of up to 61.5% (Franke V et al. *Int J Cancer,* 2019).

Given that the effects of viruses have been known for over a century, progress in exploiting their therapeutic value seems to have been slow. "One reason is that people came from different [disciplines]," says Angelica Loskog, from Uppsala University, Sweden, and CEO at Lokon Pharma. Research started in virology, but it has been the recognition of the importance of cancer immunology and the ability to genetically engineer viruses that has allowed the field to flourish, according to Gabriella Campadelli-Fiume, a virologist from the University of Bologna, Italy, whose lab has developed their own oncolytic HSV strain. Following approval of T-Vec by the US and European regulators, research "literally exploded," she says. There are currently almost 40 clinical trials of oncolytic viruses recruiting patients, covering a variety of cancer types.

Harnessing the immune system

Why some viruses are able to preferentially infect and kill cancer cells is only partially understood but seems to be connected to the changed metabolic status of cancer cells that makes viral replication favourable. The viral infection will then cause tumour cell lysis – the cells disintegrate. But it has become clear that the real power of oncolytic viruses is their ability to harness the immune system into further attacking cancer cells. "There's really a kind of natural synergy between the antiviral response and anti-tumour response," explains Eric Quéméneur, chief scientific officer at Transgene, a clinical stage biotechnology company developing oncolytic viruses, based near Strasbourg, France.

Once lysis occurs, cancer cells release signalling molecules that are able to utilize the body's immune system. The released signals, which include a cascade of chemokines and interferons, ultimately induce immunogenic tumour cell death and subsequently restore the ability of dendritic cells to prime antitumour T cells.

A number of viruses including adenovirus, reovirus, measles, herpes simplex, Newcastle disease virus, and vaccinia have been clinically tested as oncolytic agents. Although some, such as reovirus and the senecavirus, occur naturally, most will be genetically engineered so they cannot damage healthy cells. "You have to manipulate the genome so they will be selective, and [for our] adenoviruses we decided to remove one gene that otherwise stimulates the virus replication… so it can only replicate if it is in a tumour cell," explains Loskog. Transgene are using the vaccinia virus, which has proved safe for many years. 'The strain we're using now are double deleted in the sense that two genes have been destroyed, to improve the selectivity for replication in the tumour cells compared to normal cells," says Quéméneur.

"The approach taken by my laboratory has been quite different," says Campadelli-Fiume. "We modified the 'key' that HSV uses to enter and infect cells." By modifying a surface glycoprotein, the virus becomes 'retargeted' and infects only cancer cells with the corresponding tumour-associated antigens on their surfaces. "The retargeted oncolytic HSVs are not attenuated, hence they are very effective at killing the cancer cells, and at eliciting anti-tumour immunity." This will make these viruses specific to cancers carrying this antigen across indications – the HER2 antigen, for example, is present in a fraction of glioblastomas, breast, stomach, lung, and pancreas cancers. Campadelli-Fiume has also generated viruses

retargeted to some prostate cancers and brain tumours.

Modifying the immune response

"We were a bit naive on the type of response we could generate with the first-generation viruses," says Quéméneur. Early work indicated it was not enough to rely on the virus's innate ability to kill cancer cells, because the body's own anti-viral defences are able to shut them down.

"It's not so much about the oncolysis, but more about what kind of transgenes we put into the viruses to make the tumour microenvironment really stimulatory"

"People now realise that the immunological part of oncolytic viruses is what is important," says Loskog. "It's not so much about the oncolysis, but more about what kind of transgenes we put into the viruses to make the tumour microenvironment really stimulatory." Quéméneur says the current third generation of oncolytic viruses are engineered to improve the immune response by producing immune stimulatory agents. "We call them payloads," he says. "Those additional genes that we put in the virus would be delivered specifically in the tumour… we could add antibodies, enzymes, or whatever function would be beneficial in changing the phenotype of the tumour."

The approved oncolytic virus T-Vec has been modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF) – a cytokine that stimulates the movement of cells towards sites of inflammation or infection to mount a co-ordinated immune response. Another oncolytic virus being developed by Transgene, BT001, has included a second genetic modification, that also encodes for an anti-CTLA-4 antibody. The antibody is able to deplete the levels of regulatory T cells (also called Tregs), which are known to suppress other cells in the immune system. The BT001 virus has shown cure rates of 70% in multiple mouse models (Semmrich M et al. *J Immunother Cancer*, 2020).

Transgene has also developed an oncolytic virus, TG6002, which expresses an enzyme able to convert the molecule 5-fluorocytosine (5-FC) into the chemotherapy agent fluorouracil (5-FU). When the pro-drug is administered to the patient orally, the enzyme will be present only in cancer cells, allowing high concentrations of the drug to be produced within the tumour, whilst limiting chemotherapy-induced side-effects in other tissues (Abstracts, *Human Gene Therapy*, 2014). The company has announced positive data for its phase I clinical trial in patients with advanced colorectal cancers.

The oncolytic viruses designed by Campadelli-Fiume express GM-CSF and the cytokine interleukin-12 (IL-12), which regulates T cell responses. "The immunostimulatory antitumour molecules accumulate in large amounts in the tumour bed and are absent from other compartments, where they would cause toxicity and side effects," explains Campadelli-Fiume. In a recent study she showed a double-armed virus (R-123) was effective in tumour-bearing mice, with a 100% response rate achieved when given in combination with other immunotherapies (De Lucia M et al. *Mol Ther Oncolytics*, 2020).

So far, oncolytic viruses are largely being used in combination with other immunotherapies. "The idea is to use [oncolytic viruses] to deliver, locally, modalities that would… render the tumour sensitive to immunotherapy," says Quéméneur. Cancer cells have developed immunosuppressive mechanisms and this explains why resistance builds up to some cancer drugs. For example in HER2-positive breast cancer, drug resistance develops in about 40% of patients. Campadelli-Fiume says what they can do with oncolytic viruses is "turn an immunologically cold tumour into an immune hot spot," allowing current immunotherapies to succeed in patients where they may have previously failed. "The name of the game is combinations," she adds.

Match made in heaven

A particularly successful strategy so far has been combining oncolytic viruses with a drug that targets PD1/PD-L1 immune checkpoint proteins. Immune checkpoints are molecules on certain immune cells that control

the intensity of normal immune responses, but are harnessed by cancer cells to prevent T cells from responding and killing cancer cells. Unfortunately, as Samson points out, "We've recently discovered that viruses quite strongly stimulate the upregulation of PD1 and PD-L1, and this limits the immune response against the cancer that's stimulated by the virus." Using checkpoint inhibitor drugs could prevent this by taking the brakes off any mounting immune response. "By combining a virus with PD1 or PD-L1 antagonist, we suddenly have a synergistic combination therapy… there's a lot of ongoing work on combining viruses with PD1 and PD-L1 immune checkpoint inhibitors," he says.

"Checkpoints [and oncolytic viruses] are a match made in heaven," says Loskog, "because viruses will attract T cells and T cells are needed for checkpoint antibodies to work." Following trials combining their oncolytic adenovirus, LOAd703, with conventional chemotherapy agents for pancreatic cancer (Musher BL et al. *J Clin Oncol*, 2020), Lokon Pharma are now collaborating to use their oncolytic virus in combination with the PD-L1 inhibitor atezolizumab (Tecentriq) from Roche. They have initiated clinical trials in advanced pancreatic cancer, melanoma, and metastatic colorectal cancer. The virus is armed with two modifications – one to express the tumour-associated antigen CD40L, which Loskog says "kickstarts" immunity, and the other to express the receptor 4-1BBL, which "prolongs the response".

Oncolytics Biotech in collaboration with SOLTI, a clinical cancer research cooperative (Spain and Portugal) have embarked on a clinical trial (AWARE-1) of the oncolytic reovirus pelareorep, with atezolizumab, in addition to other appropriate therapies, after successful results in metastatic breast cancer for combinations with systemic chemotherapy agents.

"Just arriving with a needle in the tumour doesn't mean that you will administer the virus everywhere in the tumour"

The US biotech, Replimune, has also started trials with their herpes simplex oncolytic virus in combination with nivolumab (Opdivo), Bristol-Myers Squibb's PD1 inhibitor. Their phase II trial in cutaneous squamous cell carcinoma and anti-PD1 refractory melanoma has shown a clear improvement on nivolumab alone. The company is recruiting for a further study to obtain regulatory approval.

Whether oncolytic viruses can be developed as monotherapies remains to be seen. Loskog says in the future she could see such viruses being used for small early-stage tumours, "but as soon as you have a little bit of disease spread, you get immunosuppression, and I do think you [then] need either chemotherapy or a checkpoint [inhibitor] or perhaps even both." Oncolytic viruses could present an alternative for patients unable to tolerate anti-PD1 therapy. Replimune is currently running such a trial for treating cutaneous squamous cell carcinoma in people who have organ transplants.

Quéméneur says the next tranche of marketing approvals is likely to be for viruses in combination with other therapies, but this may not always be the case. Samson agrees: "There's a possibility it could be used as a monotherapy, if we can engineer those other drugs into the virus, so that the virus expresses them adequately. And then you've got an all-encompassing combination treatment in a single virus."

Tackling delivery

One other major issue concerns how these viruses should be delivered. The first generation of oncolytic viruses and those currently approved are given intratumourally. Lokon's oncolytic virus therapy for pancreatic cancer is administered this way. "[Where] the tumour is located [inaccessibly], towards the back [of the pancreas], we do it endoscopically, [using] ultrasound guiding, and it works really well," says Loskog. The approach allows a high number of viral particles to concentrate locally, although they will still activate systematic immunity through the lymphatic system. But Quéméneur says there can be problems: "Some tumours are very fibrotic, and just arriving with a needle in the tumour doesn't mean that you [will] administer [the virus] everywhere in the tumour." Plus, this approach is less viable where a patient has multiple tumours.

Some trials are looking at ways to deliver oncolytic viruses intravenously (IV). "We believe that there is a lot of value in going IV," says Quéméneur. A potential drawback, as Samson points out, is that, "An intravenous route means that you get toxicity all over the body, whilst not delivering as much as you could to the tumour." Together with Transgene, he has started a clinical trial to evaluate a compromise option by delivering an oncolytic virus, TG6002, via the hepatic artery – a targeted intravenous approach. "This is a local-regional delivery approach… where we are concentrating the virus at the bulk of the tumour in patients with liver-dominant colorectal cancer metastasis," says Samson. The method is routinely used to deliver therapeutic agents into patients with liver tumours. Quéméneur suggests in future the delivery route is likely to depend on the type of tumour: "We know that some are poorly vascularised [and others] pretty well vascularised."

Safety is of course another important issue. To date oncolytic viruses have been found to be relatively safe, compared to other cancer treatments. In clinical trials, in addition to local inflammation at the injection site, around 30% of people treated with T-Vec experienced flu-like symptoms; 2% of people had severe reactions, mainly cellulitis (EMA Imlygic Product Information: Annex 1, retrieved 16 December 2020). "You can have cytokine release syndrome a few hours after injection," says Loskog, but "usually they are rather mild… nothing has happened that we feel is really dangerous."

Samson says that while viruses give an acute toxicity – "as you can imagine, dumping a whole bunch of virus into your bloodstream will make you feel unwell until the body deals with it," there are no long-lasting effects, "which makes them quite attractive as a combination therapy."

"There are no long-lasting effects with oncolytic viruses, which makes them quite attractive as a combination therapy"

Transgene's viruses show a similar safety profile, says Quéméneur: "In our trials we have never seen any kind of cytokine storm as strong as was reported for CAR-T or other antibodies. So I think that it's a more tolerable therapy than other existing immunotherapies."

Who benefits?

There is real excitement around the potential of oncolytic viruses, but they do not work for all patients and part of current research efforts is to discover which patients will benefit. "We really need a couple of big breakthroughs with viruses, making a big difference to patient outcomes, and once we have those, we can start to pick out who responds better, who responds less well," says Samson.

One signifier is tumour burden, says Loskog, with higher tumour loads creating more immunosuppression, "but otherwise, it's very difficult to predict who will respond. I have seen patients with higher tumour load also respond, and someone with a rather small tumour not respond. So I don't think we fully understand it." Lokon are now screening for biomarkers to try to 'fish out' what's going on. Transgene are also looking for clues: "We don't have a clear vision of the mutation profile or kind of phenotype that would be associated with a good prognosis, but we have some ideas, and [are carrying out] some sampling and genotyping studies."

It is likely to be a few years until the bulk of current research comes to fruition and many of the oncolytic viruses being developed receive marketing approval. "I think that within a five-year period we will definitely have more approved viruses, and within a 10-year period, it will be one of the options for several different tumour types… likely combined with checkpoint [inhibitors]," says Loskog.

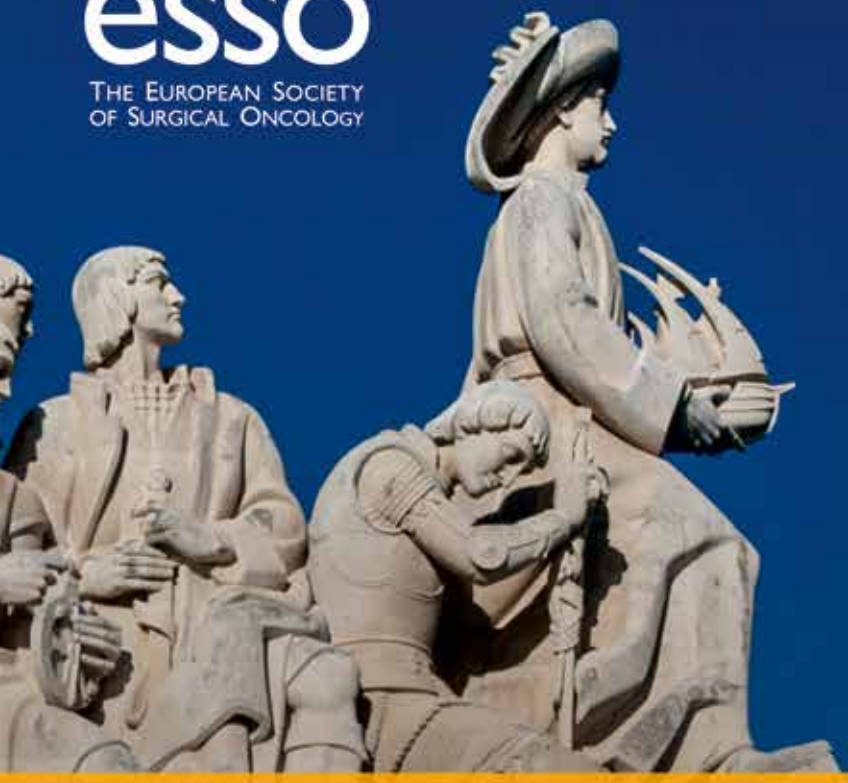
For Quéméneur, oncolytic viruses represent an important new tool in weaponising the human immune system to fight cancer. It is the ability to rationally engineer viruses that can deliver any number of immunotherapies that will ultimately provide the significant therapeutic impact. "We want to keep the oncolytic properties of the virus, [but] we really want to use them as advanced nano-machines to control immune profiles… I think we are moving from a vision where viruses would be used mostly for their oncolytic properties to an era where they will be used as drug delivery systems," he concludes.

esso
THE EUROPEAN SOCIETY OF SURGICAL ONCOLOGY

esso 40

Lisboa

Portugal



Shaping the Future of Cancer Care

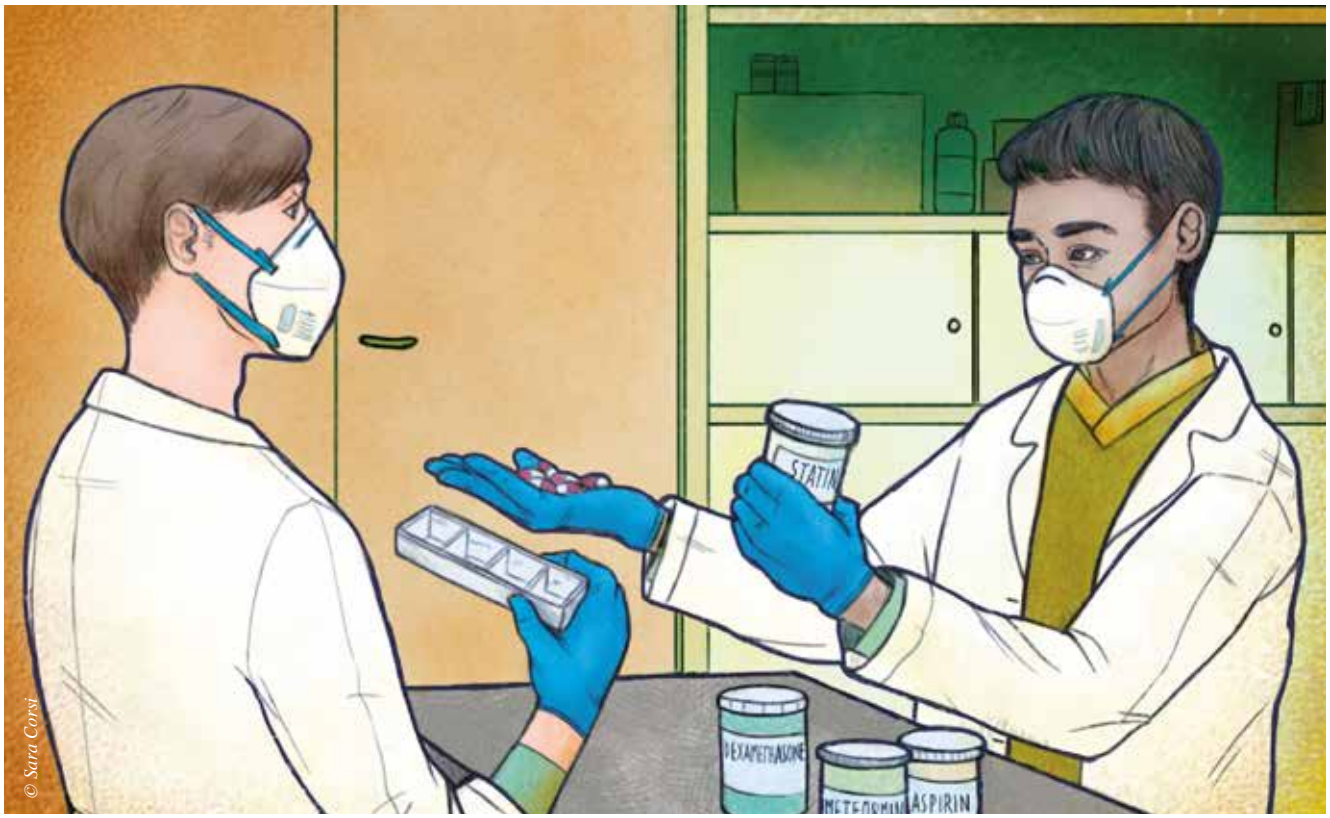
40th Congress of the European Society of Surgical Oncology

8 - 10 November 2021

TURISMO DE PORTUGAL

Turismo de Lisboa

www.esso40.org



© Sara Corsi

Could Covid-19 boost interest in drug repurposing in oncology?

During the Covid-19 pandemic, a number of approved therapies have been assessed as potential treatments against the virus and its effects. It's known as drug repurposing and has a long history in oncology research, with some successes. **Marc Beishon** looks at whether repurposing for cancer could receive a lift from Covid-19.

Could the frantic search for drugs to treat patients severely affected by the Covid-19 virus be a shot in the arm for new cancer treatments? There have been many headlines about repurposed agents, such as the highly debated antimalarial drug hydroxychloroquine or tocilizumab, an anti-rheumatic drug targeting Il-6. Along with many others, the research to find effective treatments (and vaccines) has resulted in some of the most rapid scientific collaboration of recent years, compressed into just a few months.

Drug repurposing – 'new targets for old drugs' – has been an

active research field in cancer for many years, with many thousands of papers on numerous agents for treatment and prevention. The experience in oncology has informed the hunt for Covid-19 drugs in terms of strategies and tools for treatments and vaccines, and some cancer drugs are themselves also candidates (Ciliberto G et al. *J Exp Clin Cancer Res* 2020). A new field of computational drug repurposing has opened up in response to the high cost of drug development, and this approach is being applied to Covid-19 (Park K *Transl Clin Pharmacol* 2019).

But could Covid-19 also spark more interest in speeding up new drugs for cancer, particularly in addressing regulatory and financial obstacles that stand in the way?

Those barriers are significant because the burden of establishing new uses for old, off-patent agents that have low financial value resides mainly with organisations outside of big pharma, such as institutes, academia and healthcare payers, mostly in the non-profit sector. Industry has little interest in repurposing these drugs, especially for limited markets, such as rare and paediatric cancers. Nevertheless, the maze of trials, patents, marketing authorisations and product vigilance still has to be navigated, and few shortcuts exist, although a key advantage is not starting from scratch because the drugs are already available and have been through pre-clinical testing for safety.

Covid-19 has created impetus to change the landscape of repurposing, as it has opened the door to billions of dollars of funding for treatment and vaccine research, with a major focus on repurposing drugs such as remdesivir. Given the synergies with oncology repurposing, it is a good time to assess whether there is likely to be a boost for other fields, such as cancer, and a new opportunity to make changes to pathways to drug availability. This is what the Anticancer Fund, a Brussels-based advocate of repurposing, duly did in an online meeting in June, 'Drug repurposing for cancer in the Covid-19 era'.

Anticancer Fund ReDO

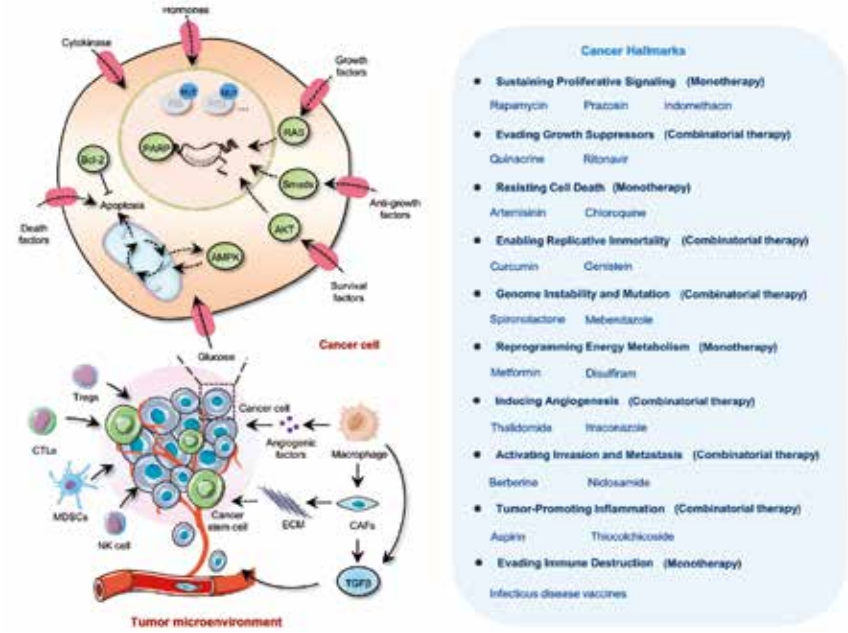
The Anticancer Fund is the home of the Repurposing Drugs in Oncology (ReDO) project, launched in 2014 with the remit to support repurposing well-known non-oncology drugs as cancer treatments. Its database, last updated in January 2021, lists 340 drugs that 'warrant scientific investigation' for their potential use in cancer, although the existing evidence for effects is 'very limited' for most agents. The database itemises existing main indications, whether a drug is on the WHO Essential Medicines list, if it is on or off patent, and what level of cancer-related research has so far been carried out (such as *in vitro, in vivo*, or human trials).

Of the two main categories for use of drugs in cancer – prevention and therapy – the majority of candidates are in the latter. Prevention drugs, which include preventing tumour recurrence, comprise aspirin, statins, the diabetic agent metformin, and selective oestrogen receptor modulators (SERMs). Two SERMS have been approved and are in clinical use for some time, namely tamoxifen and raloxifene. Most therapeutic investigations concern drugs used in cardiovascular conditions, which include beta-blockers; antipsychotics and antidepressants; antimicrobials, antibiotics and antivirals; and non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, celecoxib and ibuprofen.

Also under active research are drugs such as leflunomide, approved for rheumatoid arthritis, and thalidomide, a teratogenic compound, which has gained approval for the treatment of multiple myeloma, as well as the steroid dexamethasone, which coincidentally is one of the more promising treatment candidates in the fight against Covid-19. Two examples of repurposed agents approved for oncology are arsenic trioxide and the acne drug all-trans retinoic acid (ATRA), both for leukaemia. The addition of non-oncology drugs to existing treatments is also a feature of many investigations owing to potential synergistic effects.

Indeed, most repurposing in oncology concerns new indications for existing cancer drugs. Pan Pantziarka and others who run the ReDO project describe this as 'soft' repurposing (Pantziarka P et al. *Front Pharmacol* 2018) rather than 'hard' repurposing for non-oncology drugs.

But, while there are advantages in having extensive experience with drugs already approved in oncology, in the era of personalised medicine there has been limited progress in finding effective new indications for targeted drugs by trying to match them to patients with different tumour types and mutational profiles suggestive of benefit. Furthermore, most targeted agents and immunotherapies ben-



Identification of drug candidates targeting the hallmarks of the cancer cell using drug repurposing enabled by recapitulative signalling networks. The complex signalling interactions contributing to the hallmarks of cancer cells can be orchestrated, rationalising the complexities of neoplastic disease. Drug candidates interfering with cancer capabilities are shown

CAFs – cancer-associated fibroblasts; CTLs – cytotoxic T lymphocytes; ECM – extracellular matrix; MDSCs – myeloid-derived suppressor cells; NK cells – natural killer cells; Tregs – regulatory T cells.

Figure redrawn based on Fig.2 in the original article published by Z Zhang et al (2020). Overcoming cancer therapeutic bottleneck by drug repurposing. *Sig Transduct Target Ther* 5, 113. Republished under a Creative Commons Licence.

efit only small subsets of patients with certain cancers.

An overlooked area is cytotoxic chemotherapies – while few new cytotoxics have been introduced in recent years, they are still a mainstay of adjuvant therapy and treatment for advanced cancer (Maldonado E et al. *J Clin Oncol* 2019), and the perceived reduction in use of cytotoxics is more hype than reality (Feinberg B et al. *Am J Manag Care* 2019). There is advocacy for doing more research on combinations with all types of agents, and research is identifying potential new uses. For example, pentostatin was found to work in a form of leukaemia other than originally proposed (finding uses for failed drugs is part of the repurposing picture). In proposing candidates for a repurposing pilot, the Anticancer Fund has included a chemotherapy drug (docetaxel) and also hormone (letrozole), as well as the osteoporosis drug (zoledronic acid) alongside non-oncology drugs.

The missing link?

But the array of non-oncology agents is regarded as the 'missing link' in the current armoury of medical therapies for cancer (Pantziarka P et al. *Front Pharmacol* 2018), and some say it is even a 'treasure trove' that "should not be ignored since [the drugs] could target not only known but also hitherto unknown vulnerabilities of cancer". This and other recent papers are characterising the spectrum of non-oncology drugs as potential candidates for combating most of the hallmarks of cancer. Papers tend to fall into two camps: those that review agents or groups of agents for potential, and those that take a certain cancer and discuss potential repurposed options, such as triple-negative breast cancer (Spini A et al. *ecancer* 2020).

While few of the candidates for hard repurposing have yet been approved for new indications in cancer, the sheer volume of investigational research is seductive, and shows no sign of waning, as illustrated by studies of acne, allergy and arthritis agents, as those for depression and diabetes, and parasitic infections and Parkinson's disease.

Are the barriers mainly organisational, which was mostly the focus of the Anticancer Fund webinar, or scientific, or more likely a combination?

Numerous phase III trials of approved cancer drugs have shown limited survival benefit, and some trials of repurposed drugs have mirrored these outcomes. For example, results recently reported of a trial of adding celecoxib, a Cox-2 inhibitor used in arthritis, to an adjuvant (FOLFOX) regimen for colorectal cancer showed no disease-free survival benefit. Celecoxib has been studied preclinically and in trials of cancer prevention and treatment with promise in colorectal cancer (Toloczko-Iwaniuk N et al. *Curr Drug Targets* 2019), so this result was disappointing.

There is solid evidence that Cox inhibitors, in particular aspirin, which

is probably the exemplar drug in non-oncology agents, have anti-cancer properties. Analyses of its use in preventing heart attacks have shown preventive benefits in colorectal cancer, especially, which is well known. Despite this promise, Cox inhibitors can have side-effects, such as gastrointestinal bleeding with aspirin, and latest research indicates that aspirin may actually have an adverse effect for cancer among older people (McNeil JJ et al. *J Natl Cancer Inst* 2020). Moreover, an early prevention case-control study of Cox inhibitors proved to be cardiotoxic and lethal in a certain percentage of patients, which limited their use (Graham DJ et al. *Lancet* 2005). Indeed, it's been said that aspirin would not be approved today owing to side-effects that would have been revealed in animal studies.

The array of non-oncology agents is regarded as the 'missing link' in the current armoury of medical therapies for cancer

Nevertheless, there are many aspirin studies in both prevention and treatment, such as a basket trial, Add-Aspirin, which has resumed recruiting patients with colorectal, breast, gastro-oesophageal and prostate cancer. Evidence may establish aspirin as a standard of care, possibly through identifying people who benefit rather than treating by a population approach (Coyle C et al. *Curr Colorectal Cancer Rep* 2016), but there would appear to be little incentive for any marketing authorisation holder to seek a regulatory indication for one of the cheapest over-the-counter generic drugs. The same would apply to other agents such as high-dose vitamin C, which is the subject of renewed interest in cancer, and statins, but where such agents are shown to complement cancer drugs or radiotherapy, they may pave the way, owing to the clout of a major oncology player.

Of course, there is nothing to stop oncologists prescribing medical therapies off-label, as numerous cancer drugs are prescribed this way, especially in advanced tumours in later lines when other therapies fail or for rare or paediatric cancers. Guidelines recommend off-label use – for example the UK's NICE, in its colorectal cancer guideline, says daily aspirin can be considered as a prevention drug in people with Lynch syndrome, but notes that as of January 2020 this was an off-label use (bit.ly/NICE_CRC).

The advocates of drug repurposing are aiming their sights much higher, as other drugs that lack any scrutiny by regulators for cancer indications will probably fail to be used widely owing to perceived lack of evidence and publicity. Not least, there is the biggest incentive of all at stake: money, with 'prescription bias' towards costly, well-marketed treatments. There are echoes with the controversy over the use of the much cheaper Avastin instead of Lucentis in macular degeneration, as both agents have a similar mechanism of action, and recognise the same target.

An example in oncology is in agents used to treat nausea and vomiting caused by chemotherapy. Costly antiemetic drugs with chemotherapy indications, such as aprepitant, are often used, but there is evidence that cheaper approaches, (Gyawali B et al. *J Global Oncol* 2015), including the drug olanzapine, an antipsychotic, are also effective, and could be offered to patients less able to afford treatment. Olanzapine is now appearing in guidelines.

Where are the incentives?

At the Anticancer Fund webinar, attention turned to Hans-Georg Eichler, senior medical officer at the European Medicines Agency (EMA), who is engaged publicly and academically in regulatory policy. Eichler noted that if an academic group obtains good results for a repurposed drug they would have to approach existing holders of marketing authorisations, and there may be concerns that trials of these drugs are not good enough to meet regulatory standards. This may be because of lack of resources to obtain scientific advice on trial quality. Then, if a licence for a new indication is granted, there must be commitment to ongoing pharmacovigilance and post-authorisation studies. Notably, he confirmed a lack of incentives for a marketing authorisation holder if there is zero or close to no revenues from a new indication.

Eichler said the EMA can offer informal advice and its hefty fees can be waived for scientific advice to academic groups developing orphan drugs. But, most licensing obligations and costs cannot be avoided and he urged that they be taken into account in grants given for drug development. He suggested that one way to cover all bases is to set up small spin-off businesses from universities (the EMA does offer help with this), and also noted that a similar lack of

Drug repurposing pipeline in oncology
Figure redrawn based on Fig.2 in the original article by P Pantziarka et al. (2020). Repurposing drugs in oncology: From candidate selection to clinical adoption. *Semin Cancer Biol*. S1044-579X(20)30011-0

incentives exist in other areas, such as developing new agents to combat antimicrobial resistance.

Clinicians presenting in the webinar said it is a struggle to get colleagues to take repurposed drugs seriously – most want to work on the 'sexy' targeted or immunotherapy drugs and not on drugs that are not studied primarily in cancer, because they may have a perceived less well-defined target mechanism of action. It was mentioned that repurposed drugs seem to require a higher evidentiary standard than the expensive new agents trialled by industry, which mostly have low response rates, below 10%. Eichler countered that approvals may be given preferentially to drugs researched in small trials for life-threatening diseases where there is an unmet need and no other treatment options, but that does not indicate lower standards.

An example of a promising trial supported by the Anticancer Fund was given by Nicolas André, an oncologist at the Timone children's hospital in Marseille. This phase I study in children with a rare optic nerve glioma, tested a low-risk combination of an anti-inflammatory and a statin, instead of chemotherapy. André reported a 50% success rate in controlling disease after 6 months among participating centres in France, a standard that should be required for a new treatment strategy. But, at present, there are no partners on board to help take this work to the next phase.

Audrey Tran and Vinay Prasad have commented that repurposing efforts, while well intended, might be misguided as the agents often lack single-agent activity (Tran AA & Prasad V *Lancet Oncol* 2020). Overall, they state that alternatives exist that achieve the same goals as repurposing but are a better use of resources.

Bringing stakeholders together

The Anticancer Fund aims to bring stakeholders together to further repurposing research. Lydie Meheus, the Fund's managing director, also noted how researchers are dependent on engaging marketing authorisation holders with compelling clinical data. One promising avenue she pointed to is using the power of platforms to generate evidence for a range of agents at the same time, which is what the world-leading Recovery trial has done in the UK with Covid-19 drugs. It compared several treatments with standard hospital care and found that dexamethasone, the low-cost steroid, reduced mortality in those receiving respiratory support, and found no benefit for hospitalised patients with Covid who received hydroxychloroquine.

It's an approach that could be used more widely in oncology she said, as it can eliminate futile interventions and focus on promising ones, and can also attract industry money for some investigational arms; platform trials are costly to run. An award-winning platform trial in the UK studying prostate cancer is Stampede, where industry and non-profit organisations have put agents into comparison arms. Stampede, which has been running since 2005, and is currently testing metformin among other agents, has also included the now off-patent chemotherapy, docetaxel. Another platform trial in the UK is Focus4, which includes an arm looking at a different way of using capecitabine, an off-patent chemotherapy drug, in colorectal cancer.

Innovative trial designs are a way to increase the chances of success with repurposing, but more incentives and funding are needed for independent research, and to encourage more

collaboration among research institutions, industry and regulators. There are a number of barriers for certain agents that show promise as repurposed options, and have yet to reach regulatory approval; these include nelfinavir, which is no longer marketed in Europe; propranolol, which has been reformulated for a childhood illness and given patent protection; clarithromycin, which has more than 200 marketing authorisations authorised by national procedures, which complicates label extensions; and auranofin, which is barely used and has been withdrawn from most markets, thereby hindering repurposing adoption (Pantziarka P et al. *Semin Cancer Biol* 2020).

STAMP brings a helping hand for Safe and Timely Access

Help is at hand from the European Commission's expert group on Safe and Timely Access to Medicines for Patients (STAMP), which was set up in 2015. It has been piecing together a framework for how organisations could advance a repurposed drug over the regulatory hurdles. A draft, issued in March 2019, defines the components of repurposing projects. There should be a valid marketing authorisation holder in an EU member state or at EU level; the organisation driving the project is termed a 'champion'; and the steps it should take include seeking scientific advice, and forming partnerships with marketing authorisation holders, which then take forward a regulatory dossier.

The Anticancer Fund has proposed a pilot comprising drugs that would test a number of scenarios in the framework, including 'hard' and 'soft' candidates; early versus late stage of development; national versus centralised approval – drugs developed to treat cancer must go through the EMA, but most others have only national approvals; and drug combinations versus monotherapy.

"If an academic group obtains good results for a repurposed drug they would have to approach existing holders of marketing authorisations"

The challenge of keeping potential partners committed is exemplified by one trial, CUSP9, which has been investigating no fewer than nine repurposed drugs in combination with temozolomide for treating recurrent glioblastoma, and is a good test case for the framework of early-stage research. By contrast, docetaxel for hormone-sensitive prostate cancer, which was already used off-label and was a candidate in the Stampede trial, was discussed to test a late stage entry into the pathway. In fact, last autumn the EMA did extend the drug's approval for this indication. The pilot though is currently on hold.

The EMA's strategic reflection on regulatory science to 2025 (bit.ly/EMA_strategy2025), commits the agency to supporting a repurposing framework (the EMA is a member of the STAMP expert group). There is little indication though that such regulatory issues will be taken on board in the latest EU cancer initiatives taking shape, namely the Mission on Cancer and Europe's Beating Cancer Plan. There is reference in the interim report by the board of the Mission on Cancer to the burden of toxicity from using old off-patent, off-label drugs in treating childhood cancers, and lack of approvals of new paediatric agents.

The Covid effect

There is no doubt that the Covid-19 pandemic itself is a pilot for possible change in how new drugs are assessed and authorised at a time when a number of traditional processes, such as site visits, were not possible (Saini KS et al. *Br J Cancer* 2020). The wider agenda is also about the future of independent clinical research and strategies, such as treatment optimisation, for which reform of regulatory frameworks may be necessary (Beishon M *CancerWorld* 2020).

The EMA is currently reviewing the results of the Recovery trial and the potential use of dexamethasone, following discussion by the agency's Covid-19 task force. Dexamethasone is an inexpensive, off-patent drug that is authorised in the EU by national medicines authorities. The trial has been praised for its speed, scale and transparency.

As Martin Landray, one of the investigators in the Recovery trial, has said: (Wise J & Coombes R *BMJ* 2020) "How can we build on the involvement of patients and clinicians and the timely access to relevant data? We now need to apply the lessons from this approach to other major health challenges such as heart disease, cancer, arthritis and mental health."

European Code of Cancer Practice

YOU HAVE A RIGHT TO:

1. EQUAL ACCESS
Equal access to affordable and optimal cancer care, including the right to a second opinion.

2. INFORMATION
Information about your disease and treatment from your medical team and other reliable sources, including patient and professional organisations.

3. QUALITY, EXPERTISE & OUTCOMES
Information about the quality and safety of care, the level of expertise and the outcomes achieved for your type of cancer in the centre where you are being treated.

4. SPECIALISED MULTIDISCIPLINARY CARE
Receive care from a specialised multidisciplinary team, ideally as part of a cancer care network.

5. SHARED DECISION-MAKING
Participate in shared decision-making with your healthcare team about all aspects of your treatment and care.

6. RESEARCH & INNOVATION
Be informed about ongoing research relevant to you, and your ability and eligibility to participate in research.

7. QUALITY OF LIFE
Discuss with your healthcare team your priorities and preferences to achieve the best possible quality of life.

8. INTEGRATED SUPPORTIVE & PALLIATIVE CARE
Receive optimal supportive and palliative care, as relevant, during any part of your cancer journey.

9. SURVIVORSHIP & REHABILITATION
Receive and discuss with your care team a clear, managed and achievable plan for your survivorship and rehabilitation.

10. REINTEGRATION
Be fully reintegrated into society and protected from cancer-related stigma and discrimination, so that, in so far as is possible, you can return to a normal life.

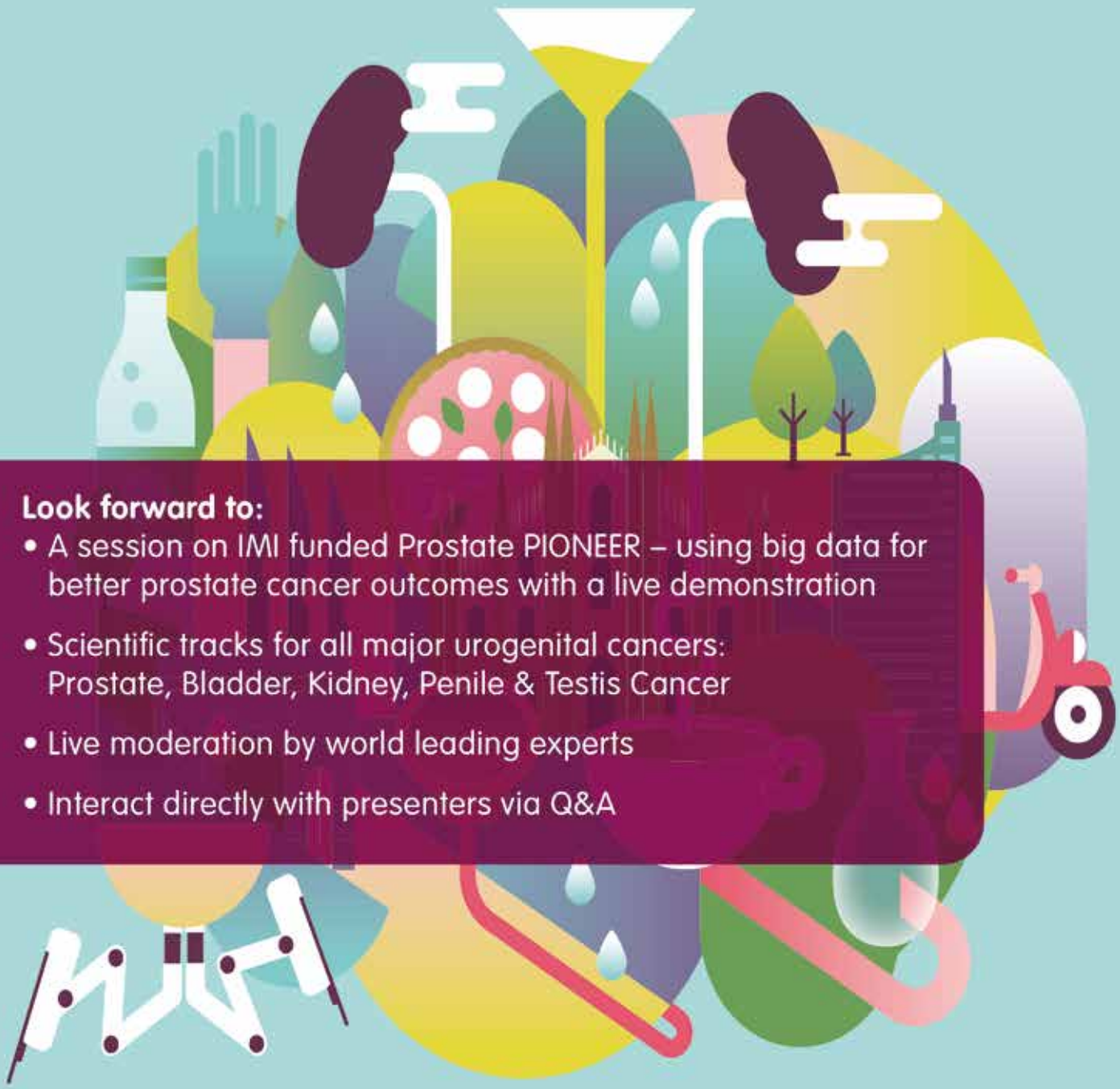
european cancer ORGANISATION

www.europeancancer.org/code

info@europeancancer.org

EAU21 | VIRTUAL 8-12 July

Cutting-edge Science at Europe's largest Urology Congress



Look forward to:

- A session on IMI funded Prostate PIONEER – using big data for better prostate cancer outcomes with a live demonstration
- Scientific tracks for all major urogenital cancers: Prostate, Bladder, Kidney, Penile & Testis Cancer
- Live moderation by world leading experts
- Interact directly with presenters via Q&A

www.eau2021.org

European Association of Urology

"Liquid biopsy can potentially revolutionise lung cancer screening"

Alberto Costa talks to Christian Rolfo, a leader in lung cancer early trials and experimental therapeutics, about the implications of a novel integrated genomic strategy to detect early-stage lung cancer, using a cell-free DNA machine-learning platform. The strategy was proposed in *Nature* (Chabon J et al., vol 580, pp 245–251). Christian Rolfo commented on it in *Nature Reviews Clinical Oncology* (Rolfo C & Russo A, vol 17, pp 523–524).

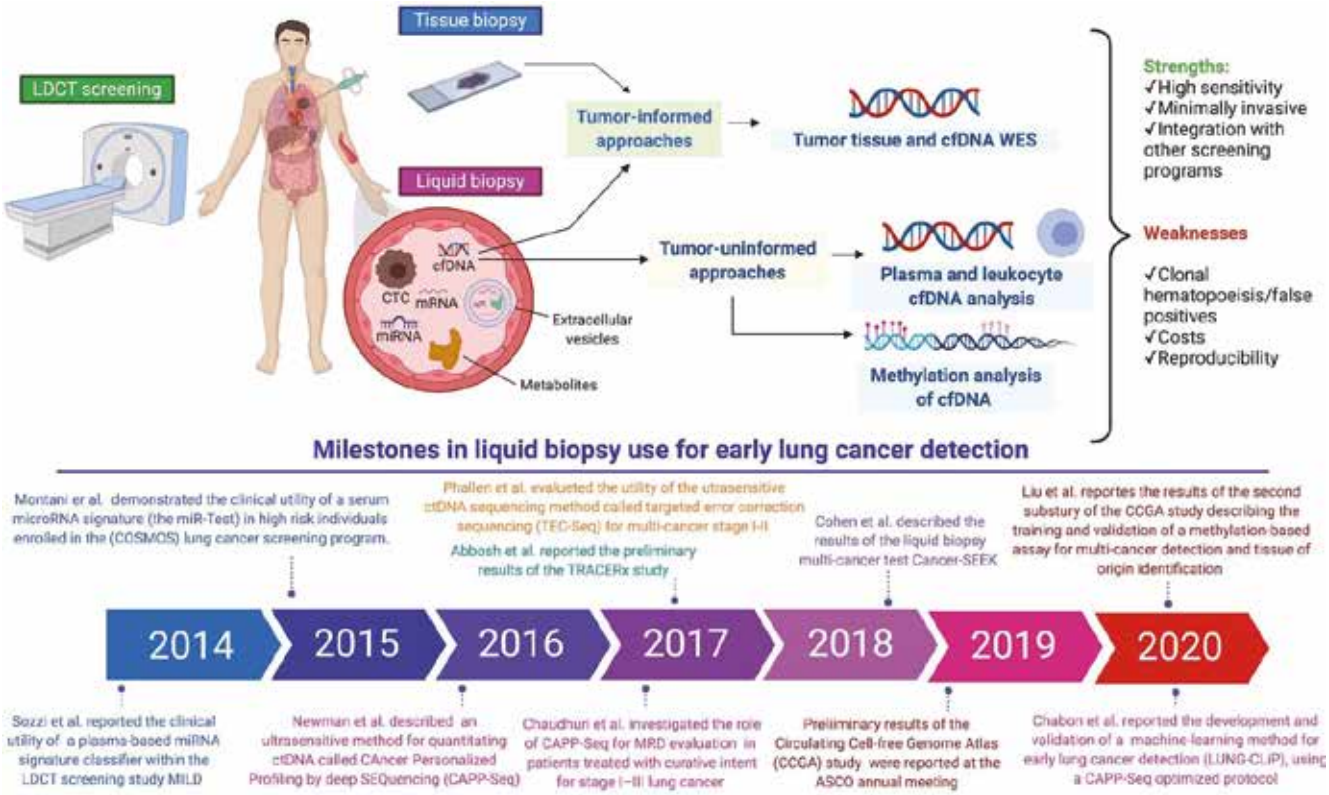
Cancer World: *What are the main limitations of the strategy proposed by Chabon and colleagues for early detection of lung cancer?*

Christian Rolfo: The results of the study of Chabon et al. are very promising and suggest that cell-free DNA (cfDNA) analysis, using the Lung-CLiP (lung cancer likelihood in plasma) algorithm, might provide, in the future, a valuable tool for early lung cancer detection. A good point of this study is the auto-validation. However, this study has some important limitations. For instance, the majority of patients included in the study were smokers and had incidentally diagnosed cancers, leaving unresolved the performance of this test in the population screened with low-dose CT (LDCT) and in never-smokers. Moreover, the sample size was too small and large-scale reproducibility of this test should be explored further.

CW: *Do you believe that liquid biopsy approaches could revolutionise lung cancer screening?*

CR: Liquid biopsy can potentially revolutionise lung cancer screening due to its minimally invasive approach and the possibility to repeat the tests over time. If the technical limitations against which we are struggling at the moment would be overcome in the future, circulating tumour DNA (ctDNA) might represent a game changer in early-stage lung cancer, saving thousands of lives.

However, it is unlikely that liquid biopsy can reach sufficient sensitivity and specificity for cancer detection without integrating data derived from these analyses with other methodologies, such as LDCT scan. The use of liquid biopsy in this setting will likely not be a substitute for currently validated screening approaches, but rather might represent a pre-screening tool for reducing the costs and socio-economic burden of LDCT programmes, and/or data from these screening methodologies could be integrated in order to reduce false positive results and minimise the risks of unnecessary invasive procedures.



Adapted from Fig.1 published in: C Rolfo and A Russo (2020) Liquid biopsy for early stage lung cancer moves ever closer. *Nat Rev Clin Oncol* 17:523–524

CW: *Do you still see a future for low-dose CT scan screening programmes?*

CR: In my opinion, at least in the near future, liquid biopsy could not replace definitively LDCT screening, but rather might represent a complementary tool either in the pre-screening setting – Which patients should be screened with LDCT scan? or post-screening setting – Which suspect nodules require further invasive procedures, such as bronchoscopy or CT-guided biopsy?

CW: *What is the essential message of your paper?*

CR: In our editorial, we expressed our interest and enthusiasm for the great advances made in the last few years with the use of circulating tumour DNA (ctDNA) for early lung cancer detection. However, it is still a long way to go before clinical implementation. Several technical and biological limitations hamper the adoption of liquid biopsy for this purpose at the moment, and further studies are required. Notwithstanding these limitations, the study of Chabon and colleagues represents a major step forward in the field, and pushes ctDNA analysis for early lung cancer detection into a novel dimension. An integrative approach with conventional LDCT screening and, likely, with other components of the large liquid biopsy family, might represent the key for success.

About the author

Christian Rolfo, MD, PhD, MBA, Dr.h.c.

Professor of Medicine
Director of Thoracic Medical Oncology Program
Director of Early Clinical Trials
Experimental Therapeutics Research Program
Marlene and Stewart Greenebaum Comprehensive Cancer Center
University of Maryland School of Medicine

OECI
Organisation of European Cancer Institutes

In collaboration with:

Fondazione IRCCS Istituto Nazionale dei Tumori

Oncology Days

OECI43

SCIENTIFIC CONFERENCES

Virtual Event

PROMOTING INNOVATION AND QUALITY FOR PATIENTS

The increasing complexity of cancer care raises the question of **the role assigned to multidisciplinary care, as opposed to the organ-based approach**. The literature clearly associates a pan-cancer approach to cancer care with better adherence to clinical practice guidelines and enhanced co-ordination of hospital services.
Whilst several national health Systems across the EU recognise multidisciplinary care as a health priority, OECI is currently the only European Cancer Organisation whose quality Programme, certified by the International Society for Quality in Health Care, is based on a multidisciplinary approach. OECI certifies centres all across Europe, approaching all the countries to attract their cancer infrastructures to the OECI membership and thus endorse quality improvement where advancement is still needed.

10.00-11.00
Building on the succesful experiences of patient involvement

11.00-12.00
Cancer Economics and Benchmarking

16 June

12.00-13.00
Biobanks and Molecular Pathobiology

14.00-18.00
Cancer Quality Session: Evaluating Quality Improvement in European Cancer Services

The participation is free - registration available at:
http://www.oeci.eu/Assembly.aspx

EAUN21

VIRTUAL

3-4 September 2021

22nd International EAUN Meeting

www.eaun21.org

Join us!

eaun European Association of Urology Nurses

A silver lining

Could changes forced by the pandemic point to better ways to conduct our clinical trials?

By **Janet Fricker**

Pragmatic adjustments to trial protocols were seen to be essential during the Covid-19 pandemic to avoid trials being abandoned or delayed. Most changes involved reducing the requirements for travelling to centralised trials centres and reducing the level of reporting requirements. These measures were agreed between trial sponsors, regulators, contract research organisations (CROs) and trial centres as acceptable compromises in the face of unforeseen and unprecedented circumstances. And many clinicians and patients found the reduced demands for travel and reporting made their lives a lot easier.

The changes were made to reduce the risk to patients of exposure to Covid-19 and minimise opportunities to spread the virus. However, the question now arises: could embracing these changes as standard practice help expand the number of cancer clinical trials and the rate of enrolment, by reducing the burden on trials centres and patients, without compromising the safety of patients or the credibility of the trial results?

In a viewpoint piece published in *JAMA Oncology* in August 2020, under the title 'Rethinking Clinical Trials Reform During the Covid-19 Pandemic', three US-based authors argue that they could, and they make the case for grabbing the opportunity offered by the pandemic to take a critical look at how clinical trials are conducted (Nabhan C, *JAMA Oncol* 2020).

They argue that, despite only one in 10 adult cancer patients being enrolled in clinical trials across the USA, steady reductions in cancer death rates since the early 1990s have saved almost 3 million people from dying early from cancer. "One can only imagine the magnitude of benefit that patients would experience if we improve and accelerate clinical trial enrolment," they say.

They propose six areas where reforms could be made. These cover: greater use of telemedicine and virtual platforms, greater use of local laboratories, reduction in the administrative burden, changes in the relative emphasis placed on progression-free survival (PFS) endpoints and patient reported outcomes (PROs), and validation in a real world setting of changes to the way clinical trials are conducted.

Cancer World asked three European cancer trialists and two leading cancer patient advocates what they thought about the changes argued for in the *JAMA Oncology* article.


Clinical triallists

The trialists perspectives were given by **Jaap Verweij**, Managing Director of the Cancer Drug Development Forum, and **Udai Banerji** and **Judith Bliss**, respectively deputy head of the Drug Development Unit and Director of the Clinical Trials and Statistics Unit at the Institute of Cancer, Research, London.


Patient advocates

The patient advocacy perspectives were given by **Jan Geissler**, co-founder of the CML Advocates network and head of Patvocates, a German patient advocacy thinktank, and **Bettina Ryl**, founder of Melanoma Patients Network Europe and member of the EU Cancer Mission board.

What they said

Point 1: Greater use of telemedicine and virtual platforms

Pre-Covid: Clinical trials were often only available at academic medical centres and frequently required face-to-face visits, which sometimes presented barriers to participation owing to patient out-of-pocket expenses, and the need to travel long distances to centres.

Proposed changes: The introduction of virtual platforms would limit in-person visits only to those that are necessary, and hopefully lead to increased participation in clinical trials. The Covid-19 pandemic has led to the widespread adoption of telemedicine and virtual visits to minimise the risk to patients of unnecessary exposure.


Clinical triallists

Udai Banerji thinks use of telemedicine and virtual platforms would be impractical for many aspects of phase 1 trials, but might work for phase 2/3 trials. "In phase 1 trials, where drugs are being used in humans for the first time, risks are very high. For dose-limiting toxicity evaluations, the patients need to come to the academic medical centre for regular clinical examinations, blood tests, ECGs and other investigations, such as CT scans," he says.

In the case of patients responding to the trial medication and who are on study for extended periods of time, telemedicine may be appropriate to reduce the number of visits if the patient is on study for longer than 4–6 months. But because only around 50 patients are enrolled in phase 1 trials (versus 400-800 in phase 2 and 3 trials), Banerji feels that only academic medical centres have the capacity to accommodate intensive monitoring.

Although online questionnaires could be used to evaluate toxicity, he has reservations. "In-face-to-face meetings, healthcare professionals get subtle cues from the patient's facial expressions," says Banerji, who conceded that such issues might be tackled by using video links.


Patient advocates

Jan Geissler agrees that direct contact with the treating physician should remain a top priority. "There's a danger less intensive interactions could lead to toxicity, side effects and quality of life issues going undetected. Such matters are often only discovered by direct observations through face-to-face discussions. At the same time, there's no value in spending hours in transit or the waiting room to have a 10-minute appointment with a clinician. So we need to take the best of both – virtual and face-to-face – whatever is most appropriate."

Adherence to virtual visits, Geissler reflects, might prove an issue. "It's much easier for patients to forget about virtual meetings than physical meetings. So we need to develop new approaches to ensure consultations take place."

Bettina Ryll welcomes telemedicine as a way to reduce the considerable burden clinical trial participation places on patients. She quotes the pre-Covid example of a friend who recorded spending 800 hours over the course of a year participating in a clinical trial. "Such commitments have all too often led to patients declining to participate in clinical trials," she says.

Point 2: Use of local laboratories

Pre-Covid: Many centres did not allow laboratory studies or procedures to be performed outside of centres where the trial was being conducted, even if patients lived far away and facilities were available locally for laboratory studies or procedures.

Proposed changes: The pandemic has resulted in some sponsors and regulatory bodies being more flexible and agreeing to tests being performed locally and less frequently. The *JAMA* Viewpoint says there is no reason why routine and basic tests should not be performed at locations convenient to patients, provided no special expertise is needed.


Clinical triallists

A limitation, says Banerji, is that many specialist tests used in cancer trials (for example, testing specific drug markers) can only be performed in tertiary centres where laboratory staff have specific accreditation and training. "But there's no reason why straightforward measures, like full blood counts and standard biochemistry, shouldn't be done locally," he says.

An issue for toxicity monitoring is the turnaround time. Banerji explains that tertiary centres turn around liver and kidney function tests in less than a day, whereas, in the UK, it can take five to seven days for GP-ordered test results to come through. "Such delays could be detrimental for patients on trial medication, but might not matter so much for long term follow-up once patients have completed treatment," he says. Jaap Verweij argues that test turn-around times may differ between European countries. "In the Netherlands, liver- and kidney-function tests ordered by GPs are usually available the same day," he says.

The option of having patient samples posted or couriered to tertiary centres is already in play, says Banerji, at least as far as Covid screening is concerned. "We're already using this approach for Covid testing before admitting patients on to our wards. We post out the testing-kit, the patient takes the sample and posts it back to us, and if negative we admit them," he says. Verweij adds, "If we focus on trying to capture only truly clinically relevant changes, we can easily make use of routine and basic tests performed at locations convenient to the patient, and at the same time decrease the number of those tests."


Patient advocates

Geissler, who is a CML patient living in Germany, says as a favour his GP takes the regular blood samples that the specialist centre, located 400 kilometres away, needs to monitor his response to treatment. "For this approach to become widespread, we would need to consider how to reimburse GPs to ensure that they're willing to cooperate," he says.

Point 3: Reduction of administrative burden

Pre-Covid: The burden of administrative tasks required by Contract Research Organisations (CROs) from investigators limited the number of patients who

could be enrolled into studies and the capacity of investigators to open additional study sites.

Proposed changes: Owing to research site restrictions during the pandemic, CROs were forced to be on site less frequently, and use remote monitoring to ensure quality of collected data. Additionally, some organisations relaxed the need for timely data entry and protocol deviations. Clinical trials exploring vaccines or anti-Covid-19 therapies started recruitment in record times. This process could be applied to cancer trials, especially those recruiting critically ill patients.

The regulatory monitoring process, where the CRO, pharma company, or academic sponsor undertakes site visits to ensure the correct information has been entered into the trial data base, can be labour intensive, agrees Banerji. "Since the medical notes are now often online, the process could easily be performed remotely; however, there are significant information governance challenges. You would need to develop a new infrastructure to ensure unauthorised people cannot gain access to patient information. Remote monitoring can substantially reduce travel costs and increase speed of data verification, all of which make clinical trial administration more effective.''

Geissler says, "We're convinced the bureaucratic burden of trials has reduced the speed and intensity of research while not increasing patient safety. We welcome the fact Covid-19 necessities are leading to assessment of which rules and regulations are really critical to ensure quality safety and outcomes of clinical trials."

But Ryll cautions about the dangers of cutting corners. "Overall, reporting and quality control are an important part of clinical trials since these experiments are conducted on human beings. A recent review found that, in the rush to get things done, some Covid-19 trials failed to capture essential information, such as age," she says.

Point 4: Reduced emphasis on PFS as an endpoint

Pre-Covid: Driven by the use of progression-free survival (PFS) as the primary endpoint, most clinical trials required frequent imaging studies for assessment of disease status.

Proposed-changes: In the era of Covid-19, even for patients receiving antineoplastic therapies, imaging studies have been delayed. Emerging guidance from the FDA suggests tumour assessments (when appropriate) may be delayed for ongoing trials. Decreasing the frequency of imaging has the advantage of exposing patients to less radiation and iodine contrast, and generating cost savings. However, PFS as an endpoint is heavily dependent on frequent imaging assessments. A way forward, suggest the authors, is to increase the time between imaging studies so that fewer studies are undertaken over the course of the trial, and to use overall survival as the primary endpoint.

Verweij comments, "For a long time clinical investigators have argued we shouldn't be looking for the statistical significance of micro-improvements, but rather for clinically relevant improvements. I believe introducing longer periods between imaging would positively contribute to this."

Judith Bliss adds, "Overall survival may not be relevant or achievable in metastatic disease, where several subsequent lines of therapy would be envisaged. Here PFS is more useful and, if imaging proves impractical, PFS could be considered more broadly in terms of time to starting next therapy or palliative care referrals. Where a radiological component is mandatory, it might be possible to consider relaxing some of the RECIST requirements, for example removing the need for confirmatory scans."

Geissler says, "PFS has always been an important endpoint for patients, as no one wants to be treated until death with a drug, which is what overall survival data requires. If assessments are the issue, we need to find a mechanism to under-

take imaging locally rather than just returning to overall survival because we can't adapt our logistics." Ryll adds, "The endpoint of PFS isn't some 'nice-to-have', but actually represents the clinically actionable time point: it's at disease progression you switch the patient to alternative treatments, and not missing this time point is critical for outcomes."

Point 5: Increased use of patient reported outcomes

Pre-Covid: Imaging studies were used to make decisions on whether to continue or discontinue individual patients on treatment regimens.

Proposed changes: In the absence of frequent imaging studies, oncologists have redefined 'clinical stability' in terms of how the patient feels. In addition to using efficacy, the *JAMA Oncology* article proposes that investigators should continue to add patient-reported outcomes (PROs) as another endpoint in future studies. This, they argue, is because these measures have inherent value to patients.

Bliss comments, "So far the focus of PROs has been on quality of life, well-being, symptoms and side effects. Patient self-reports of disease-related events represents a separate strand of work. There's still much work to be done about how patients feel about self-reporting these outcomes." Verweij adds, "While I agree PROs should be further developed, we don't know yet if there's any correspondence between them and imaging results. Also, it's unlikely they'd be acceptable endpoints for regulatory agencies approving new treatments."

Geissler says, "PROs should be an integral part of all studies, since treatments aren't just about clinical effectiveness, but how patients feel and function in their daily lives. However, pharma often uses PRO measures that are outdated, not externally validated and not specific to the disease, its symptoms and expected side effects."

He mentions a recent initiative, Setting International Standards in Analysing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) which is currently looking to determine more consistent and comparable quality of life results for cancer clinical trials. Ryll adds, "It isn't the reporting of PROs that provides value to patients, but ensuring that meaningful action is taken to help the patient. This aspect is all too often missed in clinical trials."

Point 6: Real world evidence studies to test whether Covid trial changes are beneficial

Finally, the *JAMA* Viewpoint points out that the pandemic offers a great opportunity to use real world evidence to 'pragmatically' test whether changes to clinical trials implemented during the pandemic proved detrimental or helpful to patient care. The authors cite the example of the Covid-19 and Cancer Consortium (CCC-19), which aims to collect and analyse observational data at scale (through crowd sourcing) to inform clinical practice in real time.

Verweij says, " Real world data and evidence are interesting, but there are caveats to their use. I've no doubt that in the near future their use will increase, but this will require further analysis of their potentials and limitations, and appropriate alignment of sponsors and regulators."

Geissler says, "I agree proper evidence needs to be collected to inform planning of future trials and clinical practice. Without this we won't be able to prove whether the changes worked or not and there's a real danger we'll just snap back into the way we did things pre-Covid." Ryll adds, "In combination with artificial intelligence and tight, closed feed-back loops, real world evidence offers the opportunity to considerably accelerate learning."

For people living with advanced breast cancer, time matters...

What would you do if you had more time?

#MyTimeOurTime #MTOTArtivism

www.wearehereandnow.com/my-time-our-time

NOVARTIS

Novartis Farma SpA
Lgo U. Boccioni 1 Origgio (VA)

G-AFI-1223356 October 2019

HELSINN

Building quality cancer care together

Going further to bring better todays to even more people with cancer

At Helsinn, we are delivering more treatments to lift the burden of cancer and investing in research to meet the needs of patients, for better tomorrows.

www.Helsinn.com

Who wouldn't want to cure 100% of childhood cancers?

More than eight in ten children and young adults diagnosed with cancer now survive their disease, often going on to live long and fulfilling lives. But the serious life-long damage that is inflicted by many treatments is still a bit of a taboo subject. **Sophie Fessl** hears from parents and survivors who want to see more openness and higher priority given to ensuring all survivors get the support they need.

Daily epileptic seizures, little possibility of living independently, heavy reliance on family support to get through school and receive therapy, an uncertain future on the job market: for Emma Becker's son (name has been changed for privacy), the brain tumour he was treated for when he was six years old has consequences that will last his entire life. "Our son does not need care, but we can never leave him alone. He will never gain the independence his contemporaries have," says his mother. "As parents, we had to create the support for our child. And how well you can deal with this challenge depends on the environment, your own support structure, and your finances."

With a cure rate of around 85%, childhood cancer is understandably seen as the posterchild for progress in oncology. But this success some-

times comes at a high price. A 2020 study found that, by 45 years of age, more than 55% of survivors of childhood cancers had health conditions considered severe and disabling, life-threatening, or fatal (grade 3–5) (Suh E et al. *Lancet Oncol,* 2020). Those figures relate to children diagnosed in the US and Canada between 1970 and 1999, and are likely to have improved for some cancers treated more recently. The trade-off between cure and the damage to health was highlighted in separate study, published the same year and looking at the same historical period, which compared the mortality profiles of childhood cancer survivors who were treated in the US/Canada with their counterparts treated in the UK (Fidler-Benaoudia MM et al. *JNCI*, 2021). While those diagnosed with a childhood cancer in North America were less likely to have died from recurrence or progression, at 40 years from diagnosis they were twice as likely as their surviving UK counterparts to have died from subsequent cancers, cardiac and respiratory diseases, and other health-related factors. The authors concluded that "US survivors may have received more intensive regimens to achieve sustainable remission and cure, but the cost of this approach was a higher risk of death from late effects."

In human terms, the cost is represented not just by the mortality from late effects, but the toll on survivors' quality of life arising from the chronic conditions – cardiovascular, respiratory, neurological, musculo-skeletal – that lie behind those early deaths. The cost is also borne by families who often struggle to get the help they need to enable their son or daughter to live life as fully as they can.

As Emma Becker points out, even in Austria, which has relatively high levels of health and social care, her son relies almost entirely on his family to provide the support he needs. "We had and still have support, from our family, friends and the Austrian Childhood Cancer Organisation. But what would the situation be like without support from all sides?" The family was also able to pay for additional therapies, including music therapy, ergotherapy and tutoring. And while all families would want to provide the same level of support for their children, not all have the capacity or resources to do so.

While as a society we have become increasingly open about discussing cancer and the many ways it affects our lives, the long term impact of some therapies for childhood cancers is still a taboo topic, according to some survivors. Many feel that the overwhelming pressure felt on the front line of paediatric oncology to save the life of every child can overshadow an equally important need to minimise the damage done to the quality of those lives. It is perhaps noteworthy that while children being treated for cancer frequently feature in campaigns to raise money for cancer research, the emphasis tends to be on finding new treatments that can push up the cure rate beyond the current 85%, rather than finding treatments that can do less damage to the 85% who are cured.

Balancing priorities

A Manifesto for Childhood Cancer launched in advance of the 2019 European elections has been seen as an important step towards pushing the needs of survivors up the professional and political agenda (bit.ly/ChildhoodCancerManifesto). Developed jointly by European paediatric oncologists and parents and survivors groups, under the heading 'cure more and cure better' it calls for a goal of 'zero deaths and zero late-effects'.

The document, published by the European sections of the International Society of Paediatric Oncologists (SIOPE) and Childhood Cancers International (CCI) Europe, outlines recommendations for MEPs to tackle childhood cancer, including more resources for childhood cancer research and enabling the legislative environment to develop new drugs more quickly.

Pamela Kearns, Professor of Clinical Paediatric Oncology at the University of Birmingham and President of SIOPE, says it would be wrong to aim any lower than a 100% cure rate. "When a family asks you, 'Can you cure my child?' At the moment, you have to answer, 'I'm going to try.' Wouldn't it be fantastic if we could get to a stage where the answer to that question is a simple 'Yes'? But there should be no long-term effects that impact on the child's ability to lead the life they want to lead when they grow up."

Anita Kienesberger, who chairs the European committee of the CCI – a patient support organisation that includes parents' and survivors' groups – wants to put the emphasis on long-term impacts. "The demand that no child should die from cancer is a given, all parents want their child to live. But this doesn't mean that we should aim for this at any price," she says. "Such a demand needs discourse…

As it is, this demand reminds me of competitive sports: The goal should be reached, but the prize, the quality of life, is not considered important." Wanting every child to survive is one thing, she says, but the quality of survival has to be taken into account.

A difficult discussion

Jaap den Hartogh and Carina Schneider are very concerned with quality of life. They both survived childhood cancers and are now active within CCI Europe. "We know survivors who experience days where they wish they wouldn't be here anymore," says Schneider. "It is a tricky balance that we live with in our daily lives. In many cases, it also depends on the support system around you: Do you have a family who cares? Do you have friends who care and understand? In your job, in your society – do they accept you with your late effects and your issues around quality of life?"

"It is a tricky balance that we live with in our daily lives. In many cases, it also depends on the support system around you"

Ultimately, the discussion surrounding zero deaths and zero late effects boils down to one issue, says Schneider. "Who can judge what kind of life is worth living? And what kind of life is not worth living?" And den Hartogh adds, "Every life is worth living. But sometimes, there are things that make living life difficult…" He emphasises the difference between being cured of cancer, and 'positive health'. "Health is much broader than the absence of disease. We hope that there will be more attention to the quality of life of survivors, also in terms of mental health and psychosocial wellbeing."

"Should we keep treating children for this or that price or should we not – that's not a nice discussion to have," says Schneider. "It's a taboo. But I think there should not only be a focus on childhood cancer, because children also die from other diseases. I think that we live in a society where we lost a little the connection to death and dying."

It's important be realistic

It's important to be open and honest about what is currently possible, says Agathe Schwarzinger, a psychologist at the Medical University of Vienna, who leads psychosocial after-care projects run by the Austrian Childhood Cancer Organisation. "Of course, the patient's well-being is at the core. But when we discuss a 100% cure rate, we also need to look at what this means for everyone connected with the patient," she says. "The wish to achieve a 100% cure rate is natural and understandable. But the question is, how realistic is it? Which burdens will the patient and also the family have to carry, and under what circumstances? The burdens, but also the circumstances and possibilities will vary from individual to individual, as well as from family to family."

Children and their families should receive psychological support from the start of diagnosis, she says. Once a relationship is established with the family, psychologists can also accompany them through very sensitive phases, such as when the cancer returns or progresses. "Shared decision making is the optimum. At the junction between curative and palliative treatment, we need to also consider what the individual child or adolescent can carry, what it means for the family. As healthcare professionals, we need to listen to the patient and their family to find out what they need, what they think and wish for."

Schneider and den Hartogh know as well as anyone how hard conversations about long-term effects can be. "We once made a wordplay about 'scare, share and care'. So it's scary, but you should share in order to care. Although it's a difficult topic it should be shared, it should be discussed, to get good care and to make the right decisions."

Schneider stresses the huge value of involving psychologists in these discussions, but points out that, at least in Austria, most psychosocial positions are still financed by parent organisations, rather than the healthcare system, "which indicates that when it comes to costs, psychosocial care is not seen as the high priority it should be."

Cure more, cure better

Funding much more research to push up cure rates while minimising long-term damage is something everyone agrees on. Gathering high-quality data on long term effects, and running trials to understand more about efficacy/toxicity trade-offs using different protocols will be key.

Kearns mentions a trial carried out by the SIOP Renal Tumours Study Group, which tested whether doxorubicin – a chemotherapy drug that can inflict long-term damage on heart health – could be omitted from the treatment of some children with Wilms' tumour. "Because of this trial, we can spare a whole cohort of children the risk of having heart toxicity," she says.

Progress has also been made in safeguarding fertility in children and adolescents treated for Hodgkin lymphoma. A trial randomising between the standard of care and an experimental protocol using drugs less toxic to fertility was halted early when the results showed clearly that the less toxic regimen achieved an equivalent survival rate, says Kearns.

Kearns believes that the childhood cancer survivorship passport (SurPass; survivorshippassport.org), offers important opportunities for generating evidence on long term effects. The passport is a standardised electronic record that was developed to improve the care of childhood cancer survivors as they grow up and lose the ties with their original treatment centre. It carries details about the diagnosis and clinical course of the disease, as well as details about the treatment, along with information about raised risks for different types of late effects, how and when to monitor for these and what action to take if problems arise. But it could also be an important source of information about the incidence and nature of long term effects associated with different treatment regimens, which tend to be poorly tracked.

"In this context, we should monitor and collect data about long-term effects of treatment in a systematic way, also for newer drugs coming onto the market," says Kearns. Or, as Jaap den Hartogh puts it, "make use of the late effects we have, so that the medication children receive now can be improved."

Kienesberger would love to see more systematic gathering of data on long-term effects, but she says more work is needed to develop better ways to capture what really matters to survivors. Patient-reported outcomes are essential she argues, but she says they are currently underdeveloped in paediatric oncology.

Schneider agrees that the assessments used to judge quality of life frequently focus on medical issues or ask questions that are sometimes not the most relevant in terms of the everyday life of survivors like her. "There are things more relevant that are often not taken into account, including psychosocial aspects," she says. She and den Hartogh would both like to see more attention paid to assessing and documenting the quality of life and mental health of survivors. "Currently, research in this field has a strong focus on physical late effects. But we can give feedback on what we think are important issues, such as receiving good care and assuring a good quality of life."

The best care for every child

The top priority for CCI Europe is for children and adolescents with cancer to benefit from the best possible treatment, care and support, anywhere in the world. "If we want to cure 100%, we need to cure better," says Schneider. "But the point is as long as we are not there with having zero late effects, we need to create an environment which provides the best possible support for survivors."

She points to large variations in the support available across Europe and even within each country. "In southern and eastern Europe, some clinics do not provide follow-up care. Doctors already have scarce resources to treat patients who suffer from cancer now, let alone for taking care of survivors," she says, but adds that "even in Austria, at some sites, we have only been able to firmly establish long-term follow-up care this year… So it doesn't necessarily depend on whether it's a low-income or high-income country."

She advocates for a more open approach towards late effects, in which it is accepted that they are a reality and are addressed as such. "If we start having this discussion more openly, also in our community [of parents and survivors], we have to make clear that we will still try to do everything we can to save every life we can. But having this discussion more openly might help to strengthen the support systems, also for those who have to suffer a lower quality of life as a consequence of their disease and treatments."

Emma Becker sees every day how important adequate support is to maintaining the quality of life for survivors who struggle with long term effects. She agrees on the need to focus on how society can better care for and support survivors. "The children, later adults, not only have a right to survival, but should at some point again be able to participate in all areas of life, including gainful employment, social life, and more. I would like to see more awareness and acceptance of late effects, to make life after cancer easier."

Cardiovascular and Interventional Radiological Society of Europe

CIRSE

IASIOS, the world's first accreditation programme for interventional oncology, just opened for public enrolment

The International Accreditation System for Interventional Oncology Services (IASIOS) has passed its pilot phase with flying colours, and is now open for public enrolment. Twelve pioneering hospitals from nine countries successfully participated in the IASIOS pilot phase. This robust accrediting system, tested and optimised over the past two years, now stands ready to accept applications from facilities offering interventional oncology (IO) services worldwide, regardless of the institution's size or location.

IASIOS is the world's only accreditation scheme focussed exclusively on minimally-invasive treatments for cancer. Its main goal is to establish the highest quality standards in IO care throughout the entire service line and patient pathway.

Cancer patients can benefit greatly from IO treatments whose minimally invasive nature is proven to provide numerous advantages, such as less pain, fewer complications and shorter recovery times than conventional surgery, radiation or chemotherapy. Furthermore, many IO procedures can be performed on an outpatient basis, increasing efficiency, reducing costs and waiting times, and allowing earlier resumption of normal life. This is especially important in these challenging times, as the pandemic has resulted in backlogs in cancer care which IO could help to substantially reduce.

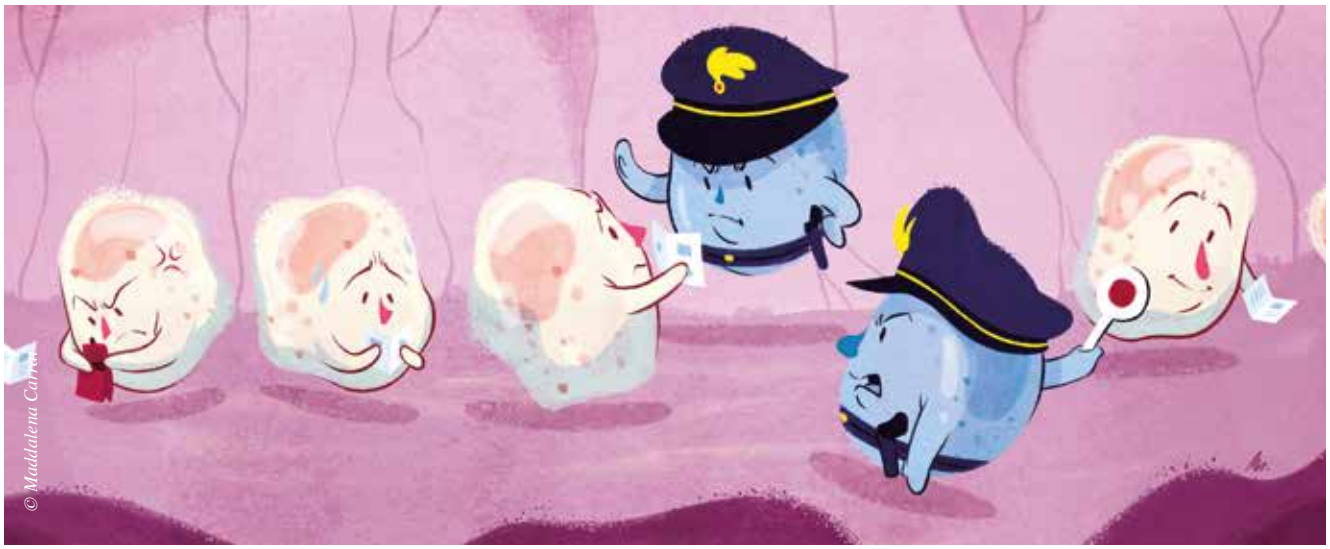
With the continued growth and recognition of IO as an important clinical discipline and the fourth pillar of cancer care, facilities providing IO therapies must follow appropriate guidelines if the relevant treatments are to be used safely and appropriately. It is likewise

essential for patient safety and satisfaction that interventional oncologists have the ability and means to officially prove their value and expertise to patients and hospital administrators, not merely as technicians, but rather as primary clinical healthcare providers. In order to achieve exactly that, the Standards of Quality Assurance in Interventional Oncology, published by the Cardiovacsular and Interventional Radiological Society of Europe (CIRSE), were used as a blueprint and set the foundation for developing an accreditation system that will be instrumental in the standardisation of IO services on a global scale.

Chairman of the IASIOS Supervisory Board, Professor Andreas Adam, provides insight into this global launch commenting: *"IASIOS is the culmination of years of dedicated work by CIRSE. It is exciting to reach this stage, as this pioneering accreditation scheme will help improve cancer care around the world."*

Centres that enrol in the IASIOS system become part of a greater worldwide community of top IO centres working together to further develop and promote the practice of IO and raise awareness of the benefits of this discipline amongst both patients and medical providers.

For more information, visit www.iasios.org



Natural killers: a new tactical unit joins the cancer immunotherapy brigade

Despite their name, their impressive cytotoxic weaponry and their role patrolling our bodies on the lookout for cells behaving badly, natural killer cells hardly feature in our current cancer immunotherapy strategies. That looks set to change, as **Adriana Albini** explains.

There was a time when all that oncologists treating solid tumours needed to know about leukocytes was how to measure the damage that cytotoxic drugs inflicted on their patients' white blood cell count and their capacity to fight off infections.

With the introduction of monoclonal antibodies, and more recent molecular discoveries, that is all changing. As immunotherapies expand their role to an ever-widening range of cancer indications, oncologists are quickly becoming familiar with the concepts and the language: cytotoxic T cells, CAR T cells, immune checkpoint blockade are now part of everyday oncology vocabulary.

A new player is now set to find a place within the cancer treatment armamentarium. Natural killer cells (NKs) have a distinct role within our astonishingly complex immune system. Trials are underway to explore the benefits of mobilising them alongside T cells, to seek out and kill elusive cancer cells.

Our body's many lines of defence

Our immune systems can deploy a range of tactical assets to defend our health in the face of constant attack by external enemies and by rogue elements within our own

bodies. The first line of defence of the organism is mainly physical: skin, mucous barriers, the gastric acid. Once the barricades are breached, other defensive weaponry is brought into play. These comprise mainly a variety of white blood cells, which share responsibility for recognising the enemy and killing it, without damaging healthy cells. Our second line of defence consists of neutrophil granulocytes and macrophages – innate immunity – which are capable of recognising general 'enemies', but do not differentiate between different types of enemy or mount attacks targeted at their specific characteristics.

The eradication of serious infections requires a third line of defence, B and T lymphocytes – our adaptive immunity. These are highly trained combat units, each of which specialises in a specific infection. T and B lymphocytes are accordingly never activated en masse; deployment is limited to the units most suitable for dealing with the pathogen in question. They are selected to never attack a healthy cell. If that command fails, autoimmunity is the consequence. The presence and identity of the specific infection is flagged up by antigen-presenting cells (dendritic, Langerhans, macrophages), which present a segment of viral or defective protein by means of a group of genes known as the major histocompatibility complex (MHC).

These lines of defence work well against many attackers. But there are forms of infection, as with herpes simplex, for instance, where the virus is able to skilfully hide any trace of its presence. It does this by blocking the infected cell from exposing on its surface any protein that could alert the immune system to its infected state. This same deception is practised by cancer cells, which elude immune detection by not presenting their hostile face.

This is where an intermediate line of defence – our NK cells – come into their own. NKs have the unique ability to recognise not the 'enemy', but 'non-friends' – namely cells that have lost their identity. They are able to specifically kill tumour cells without the priming or prior activation required by T or B cells.

The unique capabilities of NK cells

B and T lymphocytes identify the invaders by recognising proteins that the virus, or the cancer, induces to appear on the cell surface, or through antigen presenting cells, via 'presentation' in MHC. NKs, by contrast, recognise allies, and suppress – almost indiscriminately – any cells that have lost their identity (dubbed 'missing self' by Klas Kärre who identified the phenomenon). The mechanisms that mediate this action are a fascinating and elegant example of how self-control is at the basis of… control.

What the NKs are looking for are molecules of the family of MHC class I. These act as the identity card of a cell and alert the specific immune system (T and B lymphocytes) to intervene if a pathological alteration occurs. When viruses – or tumours – are able to block the production of MHC class I molecules, they succeed in hiding their enemy status from the specific immune system. The NK cells are not so easily fooled. When they see a cell that is not expressing MHC class I family molecules, they identify it as 'clandestine' – carrying no ID. And they swing into action.

Constantly patrolling our bodies, these 'armed police' check out every passing cell looking for any that are failing to express MHC. They are looking for infected cells or tumours that are carrying no ID.

The receptors in charge of verifying the MHC are called killer inhibitor receptors (KIR). If the right MHC is present, the NK cell moves on. If not, it launches an immediate and lethal attack, using perforin – a perforating enzyme that destroys the membrane of the targeted cell, and granzyme A and B, which destroy the inside of the cell.

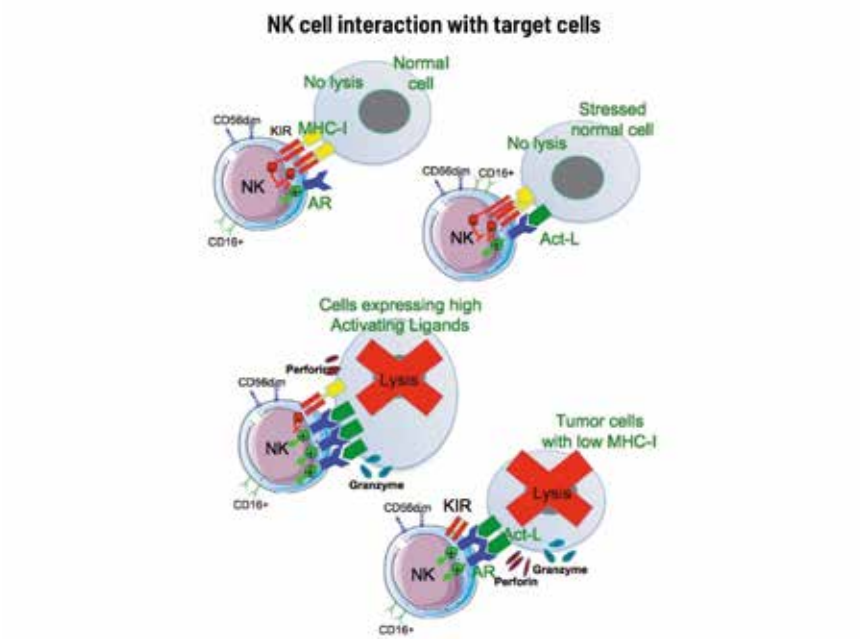
This defence system, based on an indirect recognition of danger, plays an essential role in all acute viral infections, because it can kick in immediately, giving T lymphocytes the time they need to fully activate (at least 2–3 days) and giving B lymphocytes the time they need to produce protective immunoglobulins (around 5 days).

NKs prove indispensable when enemies become too numerous and heterogeneous to be recognised individually. In the chaos of battle – as military commanders know – it can be easier to identify allies and attack the rest.

A new tool in immunotherapy?

Killing off cells that have lost their identity cards is not the only way that NKs protect us. It seems they also carry receptors that are able to pick up signals from infected or cancerous cells that the specific immune system is unable to see (which may further explain why NKs are able to kill only enemy cells and never allies).

The natural cytotoxicity receptors



MHC-1 – major histocompatibility complex class–1; KIR – killer inhibitor receptor; NK – natural killer cell; AR – antigen receptor; Act-L – activating ligand

(NCRs) on the surface of NK cells were first identified by Lorenzo and Alessandro Moretta and their groups nearly 20 years ago, in a series of lysis experiments using human NK cells. NCRs are hypothesised to bind to many cellular ligands that are implicated in NK surveillance of tumour cells. Many of these interactions (as well as adhesion molecule roles, discovered by Angela Santoni) have been shown to evoke the cytotoxic and cytokine-secreting functions of NK cells.

These capabilities have long excited interest in the potential for NK cell-based anti-tumour therapies. While the great majority of cell-mediated immunotherapies currently in use focus on T cells, NK cell-based therapies are rapidly emerging in research and in the clinic. NK-based adoptive immunotherapy has already demonstrated some success in haematological cancers including acute leukaemia and myeloid malignancies (Sivori S *J Clin Med*, 2019).

Coming down the line we can expect to see the now-familiar strategy of checkpoint blockade extended to help NK cells positively identify cancer cells and attack them using their perforin and granzyme B cytotoxic weaponry. The PD-1 checkpoint protein, which is the target of certain current immunotherapies, is expressed not only by tumour-associated T cells but also by NK cells. Recent studies have proposed that inhibition of the PD-L1/PD-1 axis could therefore activate NK cells as well, enabling them to play a crucial effector role against MHC class I-deficient tumours, which are undetectable by T cells.

Aside from PD-1 – and KIRs, LIRs and NKG2A, which have long been known about – new research is now revealing multiple inhibitory receptors on NK cells, including, TIGIT, TIM-3, LAG-3, CD96, and IL-1R8, which all present potential targets for checkpoint blockade. Novel engineering strategies are also being developed for targeting solid tumours with NK cells, such as production of chimeric-antigen-receptor-engineered natural killer cells (CAR-NK).

Overcoming challenges

As with all new therapies, however, we may still have a lot to learn before we know how to use them to best effect.

One potential challenge is that, under certain conditions, NK cells may have a tendency to 'defect' to the enemy, making them potentially unreliable assets. Instead of exerting an anti-viral and anti-tumour effect, they can change their role to one of support by both losing cytotoxic capability and promoting inflammation and tumour angiogenesis.

In the case of cancer, the circumstances that trigger such defections are closely tied to interactions with the various cellular components of the tumour microenvironment. Cell-to-cell contact, cytokines, chemokines, immunomodulatory molecules, extracellular vesicles, can all play a role in inducing NK cells to 'polarise' to exhibiting more pro-tumorigenic properties, leading to promotion of proliferation instead of elimination of tumour cells.

The conversion of NK cells from anti- to pro-tumour ones can be connected to a behaviour that in healthy bodies is associated with pregnancy, where the embryo requires a nurturing environment and also protection from being rejected by the maternal immune system as a quasi 'foreign body'. My own research group has spent many years investigating a subset of NK cell associated with

tumours that has properties similar to the 'decidual' NK cells present in the uterus lining during pregnancy, and which differ in important ways from NKs found in the peripheral blood and tissues.

Decidual NK cells accumulate at the foetal-maternal interface and represent 70% of immune cells in the decidua at first trimester pregnancy. They regulate trophoblast invasion – the development of the layer of tissue that supplies the embryo with nourishment and later on forms the major part of the placenta – and they induce vascular remodelling and spiral artery formation, by producing pro-angiogenic cytokines and chemokines (including VEGF and CXCL8).

We and other groups have described a subset of NK cells in cancer patients that have features in common with decidual NK, including expression of CD9, CD49a, and CXCR3, being poorly cytotoxic and pro-angiogenic, and mimicking the decidual nurturing role. The tumour microenvironment seems to have induced 'good' NK cells to change to be like decidual NK cells, which consequently start feeding tumour cells instead of lysing them.

One approach to countering the 'decidualisation' of NK cells could be to 'repolarise' decidualised cells via inhibition of the TGF-β axis, with e.g. galunisertib. This could be expected to remove a major obstacle to the effective use of NK cell immunotherapy against cancer. Other potential targets for repolarising NK cells include NKG2A, glycodelin and galectin-1.

There are excellent reasons to be optimistic about the prospects of harnessing the unique defensive capacities of NK cells as the next generation of immunotherapy. But understanding – and countering – how interactions with elements in the tumour microenvironment might change their behaviour from cancer killer to cancer nurturer, will be important to getting it right. This challenge is now the focus of efforts to ensure that the NK cell-based anti-cancer therapies beginning to emerge in the clinic can be used to maximum effect.

The AACR journal *Cancer Discovery* dedicated the first issue of 2021 to NK cells in cancer, including contributions by Eric Vivier – a giant in the field – on tumour-infiltrating NK cells, and by Katayoun Rezvani on the outlook for new CAR-based therapies with a focus on CAR NK cells in the race against cancer, accompanied by our In Focus article on nurturing NK cells.

Manfred Weber

Chair of the European Parliament EPP group

As chair of the European People's Party, Manfred Weber has been highly influential in securing support for effective cancer control policies, even as the Covid pandemic threatened to absorb all the energies of the EU in terms of its citizens' health. In 2019 the EPP launched an 'EU masterplan to join our forces against cancer', and the following year Weber was instrumental in establishing the European Parliament's Special Committee on Beating Cancer (BECA) to provide input into Europe's Beating Cancer Plan. **Alberto Costa** asked him about his vision for Europe's role in tackling cancer.

Alberto Costa: *How was Europe's Beating Cancer Plan conceived and designed?*

Manfred Weber: The European Union is ultimately there to make the lives of Europeans better. For European politicians, this is our end goal. We know that with less than 10% of the world population, Europe has 25% of the cancer burden, which may reach 50% in 2030 if we do not act decisively against the disease. Cancer disrupts the lives of so many Europeans and all of us have been touched by it, too often closely. Therefore, in 2019, we set out to collaborate with several leading experts in the field, to inquire into what are the obstacles health professionals, researchers, patients, survivors and caregivers face in in their daily fight against cancer and how Europe could concretely support them and make things better. For this, the European School of Oncology deserves our thanks for their expert and trusted advice.

Indeed this was a first step, but the great resonance of the "EU master plan to join our forces against can-

cer" (bit.ly/Joining_forces_Masterplan) among citizens showed we were on the right track in addressing their concern. The EPP Group is proud that the European Commission is carrying forward this great ambition in this legislative term.

AC: *What is the role of the BECA Committee?*

MW: Our Group urged for the establishment of a Special Committee on Beating Cancer to provide further input to the European cancer plan and follow up closely the elements that require further development. Most importantly, its establishment showed that the cancer fight is not a partisan initiative, but the whole Parliament has taken ownership and everyone is on board.

That is what makes us confident of its impact. Through the work of the Special Committee, we want to show the Parliament's solidarity, but also a deep responsibility towards citizens. It provides an open forum of discussion with experts, patients and all those involved in the continuum of cancer research and care, from prevention, to early detection and treatment, but also on innovation and technology, to finally provide a set of concrete recommendations to Member States and institutions.

Much work needs to be done; that is why our colleagues in the committee have pushed for an extension of its mandate until the end of 2021.

AC: *How will the Parliament interact with the Health Commissioner Stella Kyriakides?*

MW: The EPP Group is particularly proud of having two great ambassadors for the cancer fight who are carrying on this ambitious project: Commission President Ursula von Der Leyen and Health and Food Safety Commissioner Stella Kyriakides. Our cooperation is consistent, especially on this particularly sensitive issue of cancer.

At Parliament level, the BECA committee, chaired by our colleague Bartosz Arłukowicz has already had frequent exchanges with Commissioner Kyriakides. The committee is determined to elaborate further on the Commission's cancer plan presented last February, and to contribute to accomplishing its goals. With the Cancer Plan, we have set ambitious targets.

Now we must take a step forward, being even more ambitious and focusing on delivery for patients and survivors.

AC: *In a public letter signed a few months ago with MEP Antonio Tajani, you mentioned, 'en passant', the idea of a European Medical Research Institute in the name of Marie Skłodowska-Curie. Could you tell us more?*

MW: In the EPP Group, we believe Europe should drive the key tasks of our time, rediscover its great projects. Investing in innovation in medicine, such as in precision medicine, artificial intelligence and big data, and creating a true European Health Union can be the next ambitious goal of European integration.

The development of the Covid vaccine is one great example of how much Europeans can achieve when they work together. What this experience shows is that promoting collaboration and supporting research and innovation across Europe can make a tangible difference in people's lives. This is the idea behind the proposal to create a European Marie Skłodowska Curie Institute for High-Level Research. Its goals would be to bring together our best minds and to attract the best talents, so that we can step up the fight against terrible diseases like cancer, but also Alzheimer's and infectious diseases like Covid-19. To make it possible, ambitious initiatives such as this must be supported by the appropriate investments. That is why, in the negotiations for the new budgetary cycle, our Group has managed to overturn the European Council cuts and triple health funding. We also fought to bring the EU research and innovation funding back to the level of the initial Commission proposal and we have achieved that. We are laying the groundwork and are committed to accomplish this: Europe can become the new hub for innovation in health care.

Manfred Weber graduated in physical engineering from the Munich University of Applied Sciences in 1996. In 2002 he was elected as a Christian Social Union member of the Bavarian State Parliament and in 2004 as a Member of the European Parliament, where he has sat on the Committees on Constitutional Affairs, on Civil Liberties, Justice and Home Affairs, and on Regional Development. Weber has been a Member of the Bureau of the European People's Party (EPP) Group since 2006 and become Chair in 2014.

RACE FOR THE CURE®

Join the biggest run & walk for women's health in Europe

26.09 - 10.10.2021

Register your run or walk, team up with family, friends and colleagues, or plan your team-building activity to support breast cancer patients all over Europe

Participate or make a donation on

www.raceforthecure.eu

STRONGER TOGETHER

think pink europe

Over 20 years of innovation in breast cancer care

Breast cancer is not a singular disease, and neither is our approach to treating it.
Visit breastcancervision.com for breast cancer resources and support

Pfizer Oncology Breakthroughs that change patients' lives®

Onco Corner

SPCC e-learning programme

- Educational sessions on topics in oncology
- Regular webinars
- Online courses and conferences
- Completely free

Visit the new platform: www.oncocorner.net

On demand events and webinars:

- Molecular Diagnostics and Genomics in Breast Cancer
- Spotlights on Improving Efficiency in Cancer Care Series
  - What is efficiency in cancer care
  - Moving towards efficiency: examples
  - Optimisation and efficiency in cancer care
  - What is efficiency in Latin America?
  - What is efficiency in cancer care in Australia?
  - What is efficiency in Japan and Korea?
- Precision Testing Project – Webinars Series
  - Best practices/state-of-the-art in breast cancer
  - Best practices/state-of-the-art in lung cancer
  - Best practices/state-of-the-art in colorectal cancer
- St. Gallen 2021 highlights in drug treatment of breast cancer
- SABCS 2020 highlights HR+/HER2- breast cancer
- ESMO 2020 highlights HR+/HER2- breast cancer
- Cachexia is now a specific item in ICD-10 – does it help physicians to look for it?
- Patient-centered care and nutrition: surgeons and patients together
- Antiemetic usage today: risk-adapted approach
- Supportive Care of Cancer Patients during the COVID-19 Pandemic