Pharmafile

Therapeutic areas in focus

Volume 73 Summer 2022

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COVID-19 has accelerated innovation and growth in the respiratory field, but in what ways?

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Obstacles in oncology

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A technological revolution that works for all

Paul O'Donohoe, Senior Director, eCOA Product and Science, Medidata

The healthcare industry has not been immune to the digital transformation of the modern world over the last few decades. It has, however, tended to transform at a much slower pace compared to other industries, due in no small part to a more conservative regulatory environment. This gradual digital transformation has undoubtedly accelerated over recent years as a result of COVID-19.

A newfound willingness to adopt digital tools – from wearable technologies, to leveraging data analytics tools like AI and ML – and accept that these tools can offer huge benefits beyond the necessity caused by the pandemic, marks an important turning point for the sector. It also proves just how nimble the industry can be when it sets its mind to it, quickly adapting to new challenges and developing solutions that solve problems and make patients' experiences in clinical research more positive.

Flexibility in adopting new solutions

During the height of the pandemic, support and guidance from regulators was vital, and signalled commendable flexibility and openness to new, problem-solving ideas, giving the industry the confidence it sometimes lacks to change their approaches.

This instilled more certainty and courage to try new things, leverage newer solutions, and even challenge fundamental assumptions about what a clinical trial might look like. Over the past two years, the industry has begun to unlock the benefits of many digital tools that may have been around for years, but that perhaps hadn't been widely or synergistically adopted yet.

The regulators responded quickly to the pandemic, working with the industry to reduce disruption, while maintaining the integrity of the thousands of studies running worldwide. There was a conscious move from traditional clinical trial processes, where activities which usually revolved around central clinical research site, to a decentralised model, using one or more digital or virtual elements. This allowed for a more flexible approach which also put patient centricity at the centre of the study design. Decentralisation is not an 'all-or-nothing' approach, but rather attempting to be more mindful about when and what patients are coming in for.

Keeping patients at the core

Patient burden remains one of the biggest challenges facing the industry. About 30% of patients are said to drop out before a study ends, resulting in study delays or studies being cancelled.[1] Considering the costs associated with running a study, having them cancelled due to a lack of participation is not only a huge loss in terms of the drug development process, but also does a massive disservice to patients who would benefit from those new treatments.

There's been demand across the industry for more patient-centric approaches. In clinical research, this involves truly putting the patient at the centre of a trial, which has historically been difficult for companies to meaningfully implement, given the complexity of clinical trials. However, the increased use of technology, accelerated by the pandemic, has given the industry an opportunity to revisit and question all aspects of trial design and ensure that patients are at the heart of the clinical trial process.

Patients are more engaged with clinical research than ever before – they are often deeply knowledgeable on their disease and the current state of the research landscape, and they have expectations about how they should be included in the research process. Having patients engaged in the design of the trial itself is key in conceptualising how to build technologies and solutions to support their individual journey throughout.

To cater to those at the heart of clinical trials, we must understand that there is no typical patient, and we must continue to harness the use of technology. However, technology alone cannot improve the patient experience – we need to adopt a holistic approach and ensure that we are maintaining an open dialogue with patients and utilising their expert insights throughout. It is only with this open collaboration can we benefit from the hard lessons of the pandemic.

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Paul O'Donohoe is Senior Director, eCOA Product and Science at Medidata, a clinical software platform provider. He is responsible for developing the company's scientific expertise for electronic clinical outcome assessments and mobile health in clinical trials and supports internal teams and sponsors around the implementation of industry and regulatory best practices in studies using eCOA. He also provides strategic oversight to the development of Medidata's eCOA solutions. He is passionate about developing the field of eCOA and mobile health through research and active involvement in industry consortia, and is currently the Industry Vice Director of the C-Path ePRO Consortium.

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Tricia Lucas-Clarke, Early Talent Recruitment Inclusion and Diversity Manager, **GSK**

Noor Shaker, Senior Vice President and General Manager, **X-Chem**

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PHARMAFILE SPEAKS TO

Enara Bio

Q&A: Novel targets are the future of solid tumour immunotherapy

Kevin Pojasek, CEO and President of biotechnology company Enara Bio, sheds light on the importance of novel therapies, unconventional targets, and how the future of immunotherapy can tackle significant areas of unmet patient need

Pharmafile: **What is the importance of exploring approaches to immunotherapy outside conventional areas of discovery?**

Kevin Pojasek: When you look at the field holistically, especially with cell therapy, there has been a massive revolution over the last 10 years that's only accelerating. The challenge that we found today though, is that the majority of programmes are all exploring the same sets of targets. If you look at CAR T, for example, and I did this analysis recently, upwards of 80% of the programmes are going after the same five targets. And for TCR-T, roughly 50-60% of programmes are pursuing the same targets.

There's a reason for that: a lot of these are novel technologies, novel cells, novel edits, and novel approaches. In order to test that novelty with managable risk, it needs to be used with an existing target. That's all great, and we're cheering everybody on, but ultimately, we're aiming to get to a place where novel targets are part of the future of cancer immunotherapy. To invest in those novel targets, and to have them ready as these different platforms play out, we need to start working towards them today. Novel immunotherapy targets aren't easy to find and validate, but once developed, are differentiated and core to the future of cancer therapy.

The reason we're doing this is as a push to get the tremendous response rates we're seeing in haematological malignancies with things like the CD-19 CARs, or the BCMA CARs. For example, there's J&J and Legend's product, CARVYKTI, which was just approved in late February, with 80% objective response rates.[1] We want to try to get that level of response in solid tumours.

What we've seen up to date is that the best way to achieve responses in solid tumours with cell therapy is using TCR-directed approaches. This is our focus at Enara. We've got some interesting and novel targets that will drive broader, deeper, and more durable responses. It's a really exciting field, and it's evolving quickly. We think, unquestionably, novel targets are going to be part of the future solution, and now is the time to go after them.

I'll be perfectly honest with you: it's also fun science. It's really interesting to be at the forefront of a new area of science, and our company and our collaborators are leading the way in the work that we do, which, although it's hard, also makes it fun.

What work can be done in exploring these approaches?

We've taken two primary approaches so far. The idea is focused on solid tumours, and on getting deeper and more durable responses for more patients with TCR-based therapy. Our lead programme is targeting a molecule called MR1, which is an unconventional T cell target.

It presents metabolites from inside the cell to the immune system, and, through sets of data published more recently, has been linked to cancer. MR1 is an interesting lever for the immune system in cancer. For us, it's about better understanding that biology and what's driving it, and then being able to identify TCRs from a variety of sources that recognise MR1 in a cancer-specific fashion, that don't see normal cells. Then the aim is to turn those TCRs into products we can take into the clinic.

There's a massive effort underway, across the board, to do that – ranging from bioinformatics to metabolomics, immunology, and around cell therapy, manufacturing, and clinical development. With a focus on product development, because it's novel biology, there's always a new fringe of science that's waiting around the corner.

Another area of science to pursue is something we've called 'Dark Antigens™'. These are peptide antigens presented by HLA molecules, in a more traditional T cell presentation mechanism. But what's different about these antigens is they come from what was previously described as the 'dark matter of the genome', or the region of the genome that was thought to be not transcribed.

What we've subsequently learned, and what many others have observed as well, is that these Dark Antigens emerge from a variety of genetic dysregulations that occur in cancer. We map this biology across a whole range of tumours, and have identified a whole set of these antigens. They have a different fingerprint – there's been a big wave of folks focused on checkpoint inhibitors and neo-antigens, looking at tumour mutation burden as a function of immunogenicity and where those new antigens appear, and where checkpoint inhibitors respond.

Here there's a different genetic regulation mechanism: they're epigenetically defined, and so the spectrum of distribution is very different, and provides different opportunities. Quite frankly, in potential opportunities where those other checkpoint inhibitors and neo-antigens are less fruitful, we see a potential path for Dark Antigens, based on the work we've done so far.

It really is interesting science: these are shared across patients with a given tumour type at a fairly high rate. With a single product you can look at treating a broader range of patients, which ties back to the mission of going after these novel targets. This also brings about a broad approach: we're focused on cell therapy and TCR-based therapy internally, but we are also believers in cancer vaccines. We have a partnership with Boehringer Ingelheim, to develop some of these antigens for cancer vaccines for various cancer indications.

One of the silver linings of COVID-19 is that there's a much better understanding of vaccine platforms, and how they can influence human disease. There has been a slightly chequered past of cancer vaccines, but hopefully with better platforms and better

targets, we can achieve better outcomes. That's the approach that we've taken on our unconventional antigen front.

How do you hope that cancer immunotherapy will address areas of unmet clinical need?

Today, despite the advances we've seen, the benefits are still only for a really small subset of patients. Even looking at the PD1 or CTLA4 checkpoint inhibitors, they can be curative in settings where there had been no cure before, especially in things like metastatic melanoma, and other diseases, which is wonderful. But there's probably only about 20% of patients that are going to get that benefit.

Now, there are other approaches people are exploring, and therapies that are directly targeting specific mutations. There's a lot going on. But what we really want to do as a field is try to shift that 20%, to 50% or higher, to even more patients, in a given indication. This is a whole set of convergent areas of science trying to be brought to bear on solving this problem. We have much better datasets, better access to patient material, a better ability to interrogate that patient material through single cell sequencing and RNA TCR sequencing, and a better ability look at that data through bioinformatics for a clearer sense of what's going on in the patient, which can all be used for an informed approach.

We also have much better platforms. We spoke about cancer vaccines, but there's also work in cell therapy, and off-the-shelf cell therapy coming with gene therapy and other editing technologies.

Finally, and again, this is what gets us out of bed in the morning, there's novel target biology – trying to think about targets that matter in the areas of unmet need, especially solid tumours that will allow you to treat a broader range of patients than the existing targets and the existing approaches. The goal would be to get that 80% objective response rate seen with the BCMA-targeted CAR-Ts and myeloma. Being able to do that in a solid tumour would be a miracle today in all honesty, but hopefully one that's in sight, given the advances we're seeing across the board. Another aim is increasing the threshold of checkpoint responses, from 25-30%, to 50%, to 80% of patients benefitting. That's where we hope this is going, and we hope we can play a small part in helping bring this benefit to a broader set of patients and their families, and society as a whole.

What do you think some of the unmet clinical needs are in oncology?

Unmet need really centres on solid tumours, I think. Simply getting more efficacy in treating a broader range of solid tumours, and especially ones that have low tumour mutation burden, or 'cold tumours' as they've been called. It would be great to see cancer immunotherapies, including targeted cell therapies, start to make a difference in pancreatic cancer, where, by the time you're diagnosed, it's often too late for these advanced therapies. One of the greatest unmet needs is probably a combination of better diagnosis, and better therapies. But I think solid tumours are the next frontier, and where we need to tackle a lot of unmet need.

What are your hopes for the future of cancer cell therapies?

There was a paper published recently by Carl June's group at the University of Pennsylvania. June has been at the forefront of cell therapy for cancer, and the paper describes a few patients from some of their early CD19 work, where these patients have been cancer-free for 10 years – an unbelievable achievement and mark for the field, and it receives all the appropriate accolades for it.[2]

But what's interesting is they're starting to explain why. They're able to find the edited cells they put into these patients, they're able to see what they look like, and how they were different to the cells perhaps that they administered in the first place. From there, these learnings can be taken, from those responding patients, and integrated back into the cell therapy editing and manufacturing process. The process is about connecting that patient response with the cell phenotype driving that response, to then help create a virtuous cycle of ensuring that the cell products we put forward in the future can incorporate that learning. There are caveats to that, and different tumours are going to vary, but I think that connectivity of the clinical lessons learned, back to the product development, is really going to help try to solve the solid tumour problem with cell therapy.

What do you find most exciting about the therapeutic space of T cell therapy?

In all honesty, the most exciting thing is this: we're just getting started. We've seen that in the settings where it works, the most powerful therapy available is a T cell; it's a fundamental driver of human immunity, it keeps us alive, and when unleashed in the proper way in cancer, it has a tremendous effect. That's the reason to believe, and I think the excitement is in thinking: "That's a great foundation to build on. How do we do it better? How do we take it to more places? How do we conquer novel and unconventional targets, and novel biology?" I think it helps knowing that there's a great tool in the arsenal to tackle a daunting problem. That only increases my enthusiasm and excitement for going after novel biology, trying to map that onto the unmet need in the clinic.

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Kevin Pojasek is a passionate, people-focused biotech executive who has built and led companies in both the US and UK. Kevin is currently the President and CEO of **Enara Bio,** where he brings 18 years of leadership and strategic investment experience in the biopharma industry. He is also a Venture Partner at SV Health Investors and Director at Catamaran Bio, a company he co-founded in 2020.

Kevin was formerly Chief Strategy and Business Officer at Immunocore, where he helped shape the company's corporate, R&D and growth strategies, as well as overseeing business development. Prior to joining Immunocore, Kevin was President and CEO of Quartet Medicine, a company he co-founded in 2013 while at Atlas Ventures and held senior executive R&D and corporate development roles at several other venture-backed companies. Kevin has a PhD from the Biological Engineering Department at Massachusetts Institute of Technology.

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New treatments and new challenges: The oncology constant is change

Jack Harris at GSK discusses the UK's effectiveness at introducing innovations to healthcare, specifically the world of oncology, and his vision for making impactful improvements in an ever-evolving field

As I took on my new oncology role with GSK in November 2021, and started to review and shape our business plans for the coming years, it struck me how much of a personal, as well as professional, interest I have in accelerating patient access to innovation. And from this I asked myself – where can I make the most positive difference day-to-day? Where can I work with others, to identify and solve some of the biggest challenges that currently result in UK patients often missing out on the widespread use of new treatments that we see elsewhere?

Not only do I work for a large UK-based global healthcare company, but I'm also a UK citizen with a UK-based family, with many of my closest friends and family here. We will all be impacted by medical advances in this country in our lifetimes. These advances rely on previous advances, and those on developments that came before, and so on. The faster we move today, the faster we will all see the benefits tomorrow. And from this, the widest possible health improvements will be felt by the widest possible number of people in the UK.

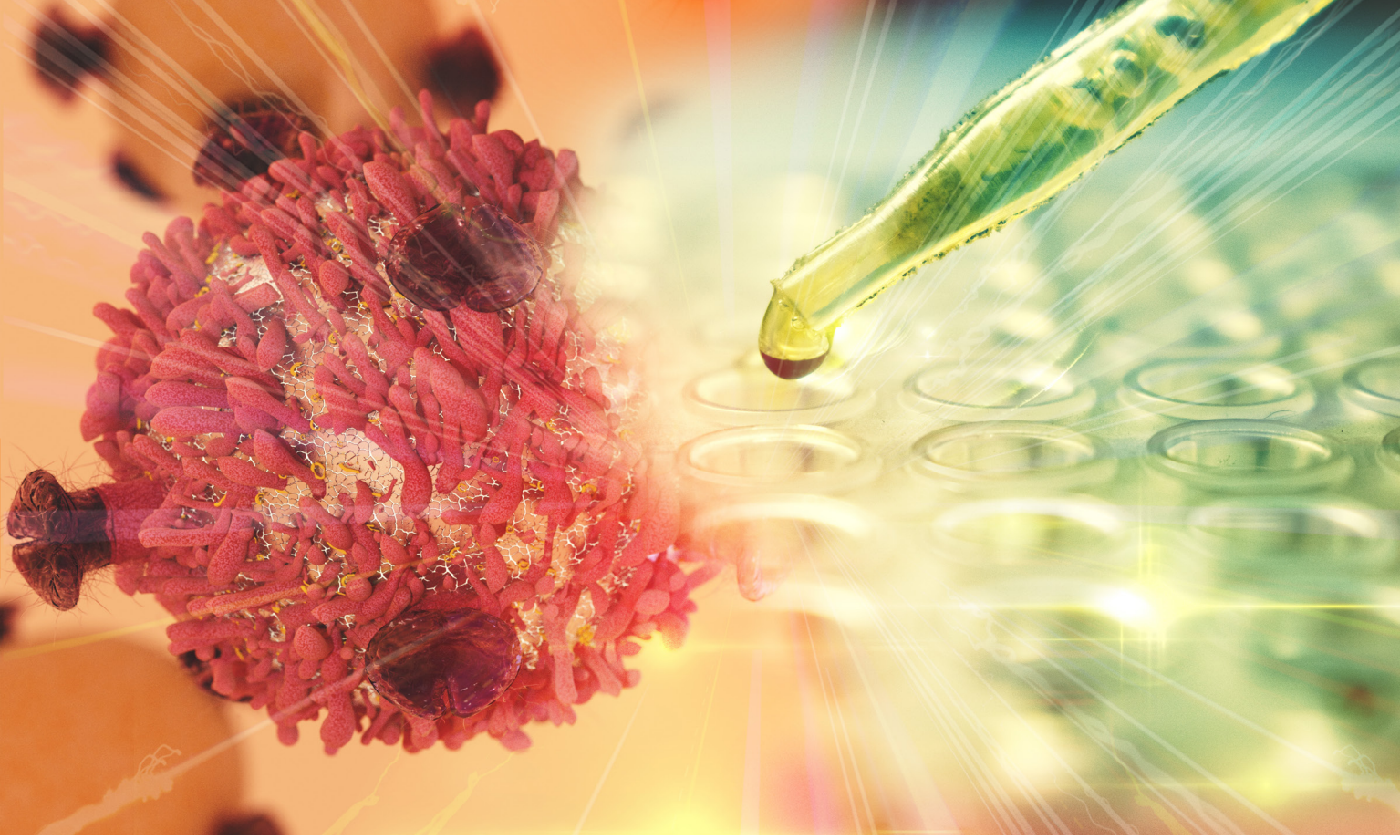
Of course, the UK is in a strong position to create fast access in the initial development and deployment phases of new treatments. The opportunities afforded by accelerated marketing authorisation initiatives, such as Project Orbis for oncology and the Innovative Licensing and Access Pathway (ILAP), are underpinned by strong commitments in the UK Government's Life Sciences Vision. We have internationally renowned institutions, such as the MHRA, and in the NHS we have world-leading specialist centres and pioneering ambitious trials. The UK remains a key market for new approaches to the very concept of how we treat patients in the future, such as in immunology, or in potentially curative cell and gene therapies. In the early development phases of innovation, the UK is well-positioned to compete with investment against comparator economies. If the most positive difference for patients is in trialling and proving concepts here, then we can be confident that GSK and the wider industry are well-equipped to continue to play our part.

However, when bringing approved innovative medicines to NHS patients early, companies are increasingly working in a system driving towards 'budget-neutrality'. There will always be the case for bespoke agreements in early access – be that due to unmet need or to improve clinical practice, where commercial return is minimal. The question is, will seeing this model become the norm create the biggest positive long-term difference for patients?

As a potential beneficiary of innovations in my personal life, I also look to the mechanisms that are set up to 'bridge' from concept to the patient, such as the Cancer Drugs Fund (CDF), the proposed Innovative Medicines Fund, and early access schemes that are in partnership with the NHS. The purpose of these is to try to make the most impactful, earliest, positive difference, in order to create a gateway from accelerated licensing routes, through managed or conditional access, and eventually into the NHS, and to provide hope for all patients; not just those in a trial or in the early access scheme itself. In this area, the biggest difference we can make to accelerated routine patient use is to do everything we can to 'de-risk' or share risk – risk that the treatment may not prove cost-effective, or risk that it may simply be unclear after a defined period of time (high-cost lifetime-benefit treatments, such as in cell therapy, could be cited here). Sharing risk could mean looking at new outcomes-based models, new funding vehicles, or expanding value assessment measures to encompass a wider range of data.

The CDF has been a success in terms of facilitating early access where evidence is not immediately clear, or data is incomplete. This relies on the Health Technology Appraisal (HTA) model accepting a level of uncertainty, but has perversely led to an increasing reliance on the CDF as a default access route for oncology innovation. Is the biggest positive difference we can make expanding the budget pot for CDF? I am sure that would be welcomed by many. Or could the biggest positive difference be creating the right environment to bring routine access through standard HTA processes, so that eventually we will not need a CDF?

Which leads me to think, are we actually missing the main goal? So much focus across the various strategies and system levers is on that initial early access, yet the real success measure here, and the biggest difference I feel we can make for patients, is in gearing every system lever towards the fastest and broadest eventual uptake. Whether a fast-track or more standard route to patient access is chosen, if all eligible patients are not benefitting from a technology as quickly as possible, then we have collectively failed.



I am acutely aware this is not a new insight. The 2019 Voluntary Scheme for Branded Medicines Pricing and Access makes improved patient uptake a key success measure. But three years on, we remain faced with the same challenge. We need to stress-test each and every system mechanism against how it is contributing towards rapid routine use and, if not delivering on that, then it needs to be reformed or replaced.

We must together support reforms to make the UK as good as, or better than, comparable global economies in uptake. We must learn from other markets, and not be too protective over our own approach. Indeed, the UK's global leadership in so many areas of healthcare exists because we learn and grow from collaboration, and not because we feel our system and approach is always best. When we look at the better rates of innovation uptake in markets such as Germany or France, what are they doing differently that we can apply in the UK? In our access system, how can we improve the existing successful concept and early access models so that broad patient use is better prioritised? How can we move beyond default conditional access, whether that is fast-track appraisals, or reimbursement models that reward those that widen access and prove value in a real-world setting?

Faster use of innovation can deliver obvious population health benefits with all the knock-on positives in quality of life, and a reduced NHS burden – so there is a strong economic incentive. Faster use by patients also generates incredibly helpful data in the UK, which can subsequently be used to deliver more innovations, ahead of other markets. Real-world data will also help us see whether innovation is appropriately valued. In this, the industry has to accept that an initial assessment could be revised up or down. If trial data does not apply to the real-world setting, then that treatment is not making the difference that we believed it could.

But what else can I do? I will ensure that when relevant data is available, or when a treatment is reimbursed, our teams are out there on day one, ensuring that every possible clinician has the information they need to assess whether it is suitable for their patients. We need to ensure that our education and support materials are as clear and relevant as possible. We need to understand from colleagues in the NHS the system barriers that are preventing patients using approved treatments where they are suitable – and where possible, help to remove them by partnering on solutions.

Every day I see the amazing progress the UK makes in life sciences, and across the health system, for each and every patient. If we made the biggest difference tomorrow, then there would be another big difference to make the following day. It is not easy to meet the challenge when new obstacles will inevitably follow, but progress simply has to be made. There needs to be a willingness to disrupt our systems and processes, even if that means making hard decisions. There needs to be system investment, and a shared focus across all stakeholders that can help realise this positive difference for patients. To deliver this, we must centre all pathways towards a success measure of the highest possible patient uptake, and this is a challenge worth our time.

Jack Harris is Vice President, Head of Oncology for **GSK** in the UK, responsible for GSK's Oncology portfolio in the UK, with a particular passion for accelerating access and uptake of oncology medicines. Jack has worked in the pharmaceutical industry for almost 20 years in various marketing, sales and market access roles, both in the UK and across Europe, the Middle East & Africa.

Embrace disruption: the changing landscape of clinical research

Georg Pirmin Meyer, Senior Vice President, International, at Blueprint Medicines, explores how precision medicine and personalised treatments can improve healthcare in Europe, and around the globe

Delivering on the promise of precision medicine in 'one-size fits all' health systems

Every day, new technologies are unlocking deeper insights into the molecular and cellular alterations underlying numerous diseases, and transforming our ability to diagnose and treat them. When these insights are paired with precision medicine, we can also pave the way for more precise, predictable, and powerful treatment approaches that underpin truly patient-centric care.

Researchers are now much more hopeful to treat diseases that have previously seemed untreatable, due to the lack of understanding around the underlying causes. Even some patients with certain common cancers, such as lung or breast, don't respond to standard-of-care treatments in the same manner as other patients. Researchers and clinicians have made significant strides in the last decade to understand why changes at the genetic level may trigger an illness, and how better understanding these changes may lead to treatment options that hadn't been there in the past. Recent progress from tools, such as genomics or big data, makes a direct contribution to care for patients living with cancer, or with rare diseases such as advanced systemic mastocytosis (advSM), which can become cancerous, or spinal muscular atrophy (SMA).

Within lung cancer, the introduction of precision therapies for patients with mutations such as Kirsten Rat Sarcoma virus (KRAS), Epidermal Growth Factor Receptor (EGFR), and Rearranged during Transfection (RET), have led to better clinical activity, supporting increased adoption of precision medicines. Historically, these patients may not have responded to standard treatments, and would have seen their disease progress with no further options. As more of these tools and technologies become available and enter into routine practice, researchers and physicians will be able to deliver the right health intervention, at the right time, and across more disease states.

Re-imagining treatment pathways

Realising the full value of these advancements requires a paradigm shift in the way medicine has been practiced for decades. Physicians have been taught that treatment approaches should be universally applied to every presenting patient. Until recently, a one-size-fits-all approach – aimed at the "average" patient, possibly with only minor, little understood variations – was the only option.

Precision medicine effectively turns this approach on its head. It recognises that complex diseases should no longer be considered as a single entity. One disease may have many different forms, or 'subtypes', resulting from the complex interaction of our biological make-up, and the diverse pathological and physiological processes in our bodies. This means that two patients who have the same clinical diagnosis, such as breast cancer, may really have two very different diseases,

based on their genetic make-up and any mutations they have. This may impact not only the underlying disease, but also how the disease travels through their body. This also demonstrates why biomarker testing at diagnosis is essential to ensure each and every patient understands what is driving their disease, and has the potential to receive the best possible care right from the beginning of their treatment journey.

As we integrate and analyse genomics and other data, we can find common factors and causes of variation. This means we are constantly discovering new pathways and presentation of disease, and with those discoveries, changing how diseases are thought of and treated. It enables us to recognise that the same underlying change in our DNA or genome can lead to problems in very different parts of the body, which would not have been previously identified with a more traditional care approach.

An example of this is AdvSM, which, in 95% of cases, is driven by a D816V mutation to the KIT gene. The mutation leads to uncontrolled mast cell production across multiple organ systems, and is associated with poor overall survival. Symptoms are varied across the body and may include skin lesions, chronic anaphylaxis, hypotension, migraine, and bone and muscle pain. Individually, these symptoms would be treated by different physician specialties, and the connection may not be made to the underlying cause, which impacts time to diagnosis for the patient.

The emerging precision medicine ecosystem

While precision medicine represents incredible potential for physicians and their patients, we must also recognise the co-ordination needed to operate in a myriad stakeholder ecosystem. Joining the dots between patients, clinicians, laboratories, clinical information systems, and government or other industry research sponsors, is an incredibly complex and delicate balance of information systems, personal data, and best supportive care. As we continue to grow in our ability to execute on precision medicine, we will need further collaboration among the developers and regulators of precision medicine, professional societies who will train the next generation of researchers, providers, and the regional and national health technology bodies who provide recommendations on medicines, and the other health technologies that can be financed or reimbursed by the healthcare system.

Translating the science into value

As healthcare systems aim to reset and accommodate precision medicine into daily practice, they have also needed to rethink access and reimbursement processes. Innovation uptake rarely coincides at pace, and bringing precision medicines into clinical practice in Europe has been gradual, given barriers to adoption among Health Technology Assessment systems in many European countries.

What might not be immediately recognisable is the value precision medicines can bring to the overall health system. When the right treatment is identified and deployed at the earliest possible stage of disease, it will naturally decrease the use of ineffective or inappropriate treatments, reduce hospitalisations and other costs associated with chronic conditions, and more efficiently deploy the use of healthcare resources. However, there are also a number of environmental and organisational challenges that currently prevent the effective uptake of personalised medicines, and potentially hinder their development.

Collaboration by a range of stakeholders including leading payers, policymakers, and healthcare professionals, is needed to drive patient access and reimbursement for new therapies, as well as to maximise their positive impact on health systems in Europe.

Embracing the disruption

Advances in our understanding of the genome and disease pathogenesis, combined with collaboration of families and carers of patients living with cancer, are changing the landscape for clinical research and drug development. However, to fully realise the disruptive potential of precision medicine will require a multipronged scientific, clinical, and policy agenda.

The speed at which breakthroughs in precision therapies translate into advances in European healthcare, and improve patient outcomes for debilitating diseases, will ultimately depend on how stakeholders collaborate to tackle some uniquely European challenges. Only a continuously evolving and connected healthcare system will be able to accelerate the advancement of precision medicine technologies.

Georg P Meyer, MD, SVP & General Manager International at **Blueprint Medicines**, brings nearly 20 years of industry and clinical experience in a broad variety of diseases from inline and launch products (cardiovascular, bone, cystic fibrosis), to rare diseases in early pipeline and peri-launch settings (inflammation, oncology). From 2018 to 2019, he served as Blueprint Medicines' Vice-President & General Manager, taking strategic and tactical ownership of the region, including access strategies to prepare Blueprint Medicines' long-term success in DACH region, with accountability for six indication launches and two launch products.

Prior to joining Blueprint Medicines, Georg served as General Manager Germany, Vertex Pharmaceuticals 2018 to 2019, with a business focus on cystic fibrosis stakeholders, including payer HTA and price negotiations. Georg was also tasked to drive strategic innovation for Vertex International, with a focus on digital and multi-channel customer engagements, as well as driving value-based healthcare projects.

Prior to that, he held roles of increasing responsibility related to clinical development in bone, inflammation, cardiovascular, oncology, diabetes and urology within Amgen, Sanofi-Aventis and Sanofi-Synthélabo. Georg holds an MD from Albert-Ludwigs-Universität Freiburg.

A targeted approach to developing targeted blood cancer therapies

Edmond Chan, Senior Director, Therapeutic Area Lead, Haemato-Oncology for Europe, Middle East & Africa (EMEA) at Janssen, explores how precision medicine and targeted solutions can be utilised in the fight against cancer

Over the last decade, it has become increasingly clear just how heterogenous cancer is. Different cancers – whether they be multiple myeloma, chronic lymphocytic leukaemia, or beyond – have different unmet medical and patient needs, not just from each other, but also within their cancer type.

This has reinforced the critical need for a tailored, targeted approach to treatment and management, which have the potential to deliver individualised approaches to care – or, in other words, to target the right patient with the right treatment at the right time. These therapies hold the potential to change the standard of care trajectory.

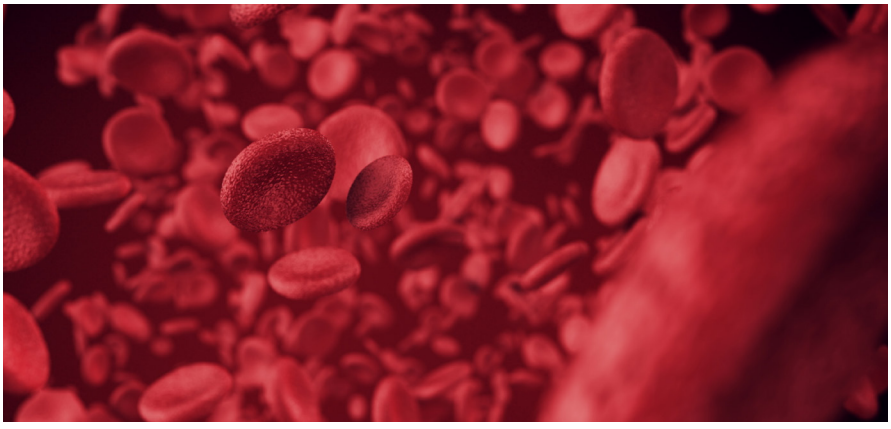
On the other hand, the targeted nature of these new therapies brings with it an increase in the possible avenues for research and development, as we explore the many different genetic factors that could influence treatment. In the last five to ten years, we have already witnessed a significant growth in cancer research, particularly in the field of haematology. Ultimately, though, every organisation working within our industry has limits to its time and resources. We cannot simultaneously innovate in every treatment route for every cancer type.

There is, therefore, a need for us to take a focused approach to innovating in targeted treatments, directing our efforts to those areas where the challenges are and that we know best, to give us the greatest chance of success. By focusing on areas that harness our expertise and experience, we can deliver meaningful improvements to the lives of those living with cancer.

The power of precision medicine

Precision medicine has been one of the areas that is becoming more and more prominent in our work in haematology. By taking into consideration cytogenetics, disease type, health status, and disease characteristics, it equips clinicians with bespoke treatment options and combinations that are tailored to the individual, allowing for a highly targeted approach.

This is already beginning to deliver successful treatments for those living with blood cancers, but the power of precision medicine is by no means exhausted. There remains significant potential to push the boundaries of current innovation, and we are seeing exciting new technologies in the field emerge all the time.



Of course, by providing a more nuanced approach, precision medicine is accordingly more complex to develop and deliver compared with traditional approaches, as it can involve many stages and stakeholders. Despite this added complexity, my view is that the potential advantages of precision medicine are worth it – and that we can give ourselves the best chance of success by taking a precise focus on developing treatments in certain disease areas where we already possess years of experience, and then apply the learnings in other disease areas in the future.

So where is precision medicine making a meaningful impact for people living with cancer? Chimeric antigen receptor T (CAR-T) cell therapy is one example – a therapy option that holds significant potential for people living with multiple myeloma who have few available treatment options, and are often faced with poor outcomes.[1]

Despite the advances that have been made in care, relapse is still considered inevitable for those diagnosed with multiple myeloma, and, almost 40% of patients do not reach five-year survival.[2] Working by harnessing the power of a person's own immune system to target cancer cells expressing a specific antigen treatment, CAR T cell therapy is a novel and highly personalised treatment.[1] Unsurprisingly, it is a complex process, requiring close collaboration between stakeholders across the industry to deliver it in the most effective way possible. But the need to harness this kind of innovation is clear – so we must

keep advancing to provide patients with this additional treatment option, as well as other 'off-the-shelf' targeted therapy alternatives such as bispecifics.[3]

Delivering targeted solutions for patients

We recognise the importance of giving patients an active role and voice in the research and development process, and precision medicine is no different.

Receiving a cancer diagnosis can be overwhelming and frightening, often leaving patients with limited time – time that is impacted by the physical and emotional burden of living with cancer. Moving away from a one-size-fits-all treatment model offers an opportunity to start to try and alleviate this burden.

As well as having the potential to deliver better outcomes for extending life, such targeted therapies may also give people living with cancer time to do the things they enjoy doing. For instance, providing treatments that can be administered more rapidly and increasing the availability of oral treatments or subcutaneous injections versus intravenous formulations, means more flexibility for patients, less time spent in the hospital, and more time to spend doing the things that matter to them.

Realising the potential of targeted therapies to transform quality of life requires putting the patient voice and experience at the heart of treatment development. This can be achieved by working closely with patient organisations at each stage of the clinical trials process, including patient perspectives in health technology assessment decision-making, or providing the forums for people living with cancer to discuss their experiences of the diseases and treatments more broadly.

Change through collaboration

As treatments become more targeted, and lead to a corresponding growth of options based on different mechanisms of action, therapeutic indications, and influencing factors, the amount of information being provided to clinicians grows ever larger as well. The knowledge and expertise required of them, and of researchers working in the field, can also become increasingly specialised. To maximise the benefit to patients of such a targeted approach, we must work in collaboration with these experts from across the world – working towards our common goal of having new, efficacious treatments for cancers with high unmet need.

In other words, precision medicine can only have the impact that we hope it can have if we're collectively able to translate scientific discovery into clinical practice. Thankfully, we are already seeing examples of this. For instance, the machine learning ledger orchestration for drug discovery (MELLODDY) project brings together academic and industry partners, to collaborate on an machine learning tool that pools insights from data generated during drug discovery programmes across the world.[4]

This is particularly important for rare diseases, where individual clinical trials have a fixed number of patients involved, and often limited access to a larger patient pool. Projects that use increasingly sophisticated technologies to collate data more broadly, allowing healthcare professionals and researchers to identify trends within a greater population size that can have a direct impact on day-to-day clinical practice, are therefore incredibly useful. Other similar examples of this are the Haematology Outcomes Network in Europe (HONEUR), which is a secure, collaborative platform allowing the combined analysis of datasets in haematological malignancies, and the European Health Data and Evidence Network (EHDEN), another data-sharing system powered by data from more than 100 million records.[5, 6]

Progress is already being made, but there is of course more we can do. Change can only come through collaboration and, with research and development only growing more ambitious and complex, working with the wider oncology and haematology community and utilising exciting new technologies, such as AI and ML, are critical for success.

Targeting better treatments for the future

Precision therapies have potential as a future mainstay of treatment for haematology. As we move away from a one-size-fits-all approach, there is such scope to continue improving cancer therapies – and it is only by taking a targeted approach to developing these therapies, and working with experts across the region, that we can give ourselves the best chance of success. As the pace of advancement in precision medicine continues to accelerate, we will continue in our focused approach, targeting the areas in haematology that we have strong heritage in, and facilitating partnerships with the scientific community and wider oncology industry. The European Haematology Association Congress in June will provide another milestone on this journey, and will also give us further insight into what precision medicine holds in the future.

The last ten years have seen us make incredible progress in understanding cancer heterogeneity. The next ten years offer an opportunity to turn this better understanding into better outcomes for patients – but only if we target this opportunity in the most effective way possible.

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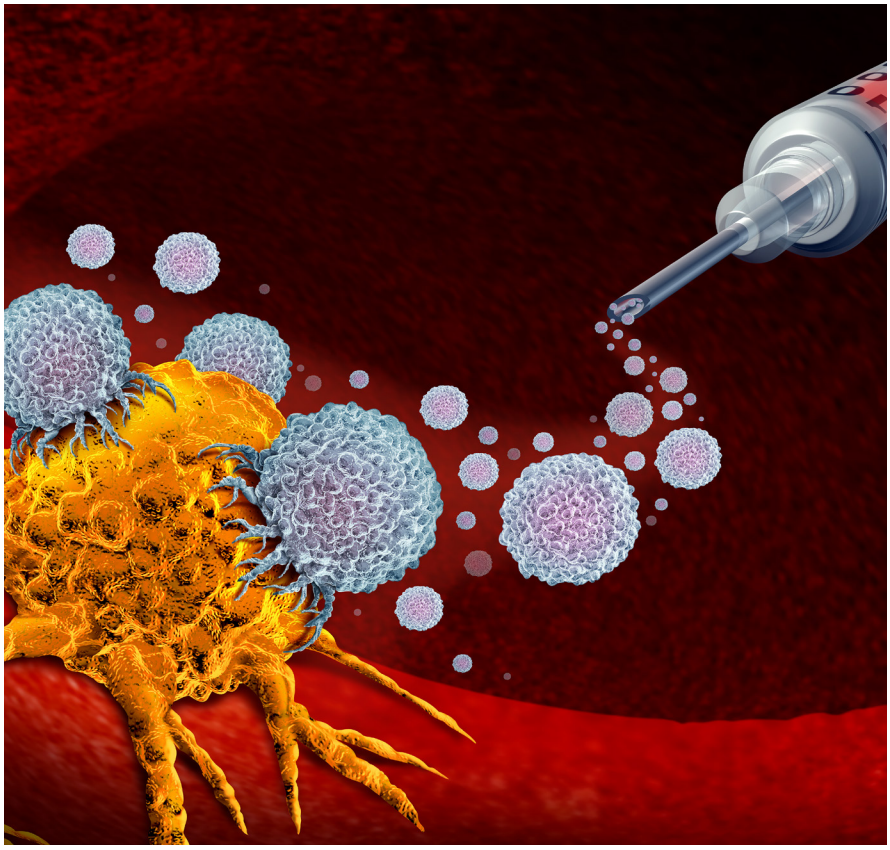
Edmond Chan joined **Janssen** in 2012 and has led multiple different functions in the organisation, including R&D, local, regional and global Medical Affairs. He currently heads the EMEA Medical Affairs Haematology team, focusing on haematological cancers such as multiple myeloma and chronic lymphocytic leukaemia, and driving patient-centered solutions and treatment in areas of unmet medical need. He is an experienced, UK-trained pharmaceutical physician, specialising in renal medicine, and holds a doctorate in clinical research in solid organ transplantation.

Supporting the challenges of innovative systemic treatments

Dr Stuart Hill, Medical Director, Merck UK & Ireland, highlights how the benefits of immunotherapy can be maximised to meet the needs of each and every patient

In recent years, we have seen significant innovation in the way that we treat cancer, as newer treatments such as immunotherapies, including CAR-T therapy and targeted therapies, have all brought with them a new set of challenges. These range from equity of access (stemming from practical issues around resources in hospitals hindering treatment delivery), to how best to manage complex immuno-related side-effects, and to the ongoing issues around biomarker testing. Many cancers have recently had new systemic treatments approved for use by the MHRA and recommended by NICE on the NHS, and brought to light these challenges faced by clinicians across the treatment pathway and throughout the healthcare system.



Service design adaptation is needed

As a result of the increasing number of patients being initiated on immunotherapies, for example, there is an increasing impact on overall clinic capacity. There aren't suddenly more chemotherapy chairs and spaces that can be used to support these new treatments. Service provision and capacity needs to be addressed to accommodate the growing patient numbers. As more cancers are being treated with immunotherapy options, the number of patients treated with them will continue to grow. There is significant variance across the country on how service design is set up to support the provision of newer therapies – with some regions/models of care faring better than others.

There are also many ways immunotherapies are used, for example, as a single agent or as part of a combination treatment. This can also create challenges with the service capacity and timing of treatment. Patient experience also needs to be considered in terms of distance travelled to receive treatment, as well as the overall amount of time that they receive treatment.

While this will not change overnight, these issues need to be addressed and reviewed to ensure the potential benefits of immunotherapies can be fully unlocked. Although the pharma industry can't necessarily offer support to improve service design, we have collaboratively worked with clinicians to bring to light the key challenges and needs, and will continue to do so. We've also raised awareness and understanding among key decision makers who can use the clinicians' personal experiences to create solutions.

Biomarker testing is on the increase

In addition to service design and provision, we have seen an increased use of biomarker testing, which brings additional challenges across the UK in terms of speed of testing, lack of consistency in testing across the UK, and how testing is funded and positioned in the treatment

pathway. These factors can impact how patients get the right treatment at the right time for their type of cancer. These challenges are not unique to any one tumour type, but are consistent across the board for immunotherapies, as well as the newer targeted therapies. Pharma has an important role to play in fully understanding the significance of testing, and in educating clinicians to ensure the best clinical outcomes.

Learning from clinical experience

We now have 10 years of follow-up data from the melanoma trials where immunotherapy was first used, and there is a clear long-term benefit of these treatments, including an increase in overall survival. All the lessons that we have learnt can be directly transferable to Genitourinary (GU) cancers, such as how to manage the side-effects, and how to best manage the treatment pathway and decision-making by the multi-disciplinary team. Whilst we've got to wait and see the long-term outcomes in other cancers, we shouldn't assume that because it's happened in one cancer type that it's going to happen elsewhere. However, the data as it stands does potentially indicate a similar trend. Whilst we wait for long-term data, pharma has an important role in collating real-world evidence to support the use of immunotherapies, and to continue to inform clinicians on the benefits of these treatments, along with how to interpret the data that is continuing to emerge.

Support required for all in managing side effects

Managing the side-effects of immunotherapy is one of the biggest clinical challenges. Successful management is critical to both patient outcomes and the patient experience. Managing side-effects appropriately can only be done if there is an understanding across the wider clinical team of who may encounter a patient during treatment, such as A&E and acute care. There are many healthcare professionals (HCPs) who need educating on understanding the toxicities associated with immunotherapies, and appreciating that they are very different from chemotherapy, where they may have more knowledge and experience. There is an opportunity for larger teaching hospitals who have more experience, to help support smaller regional/district hospitals in helping manage side-effects appropriately. This specialist knowledge is something that is only acquired through experience, and it's important to recognise that with any newer therapy, education is key to ensuring the best patient care.

How pharma can help

At Merck, we are committed to providing good quality information for HCPs. With innovation comes some form of challenge, and there is a need to ensure that information is provided to ensure the best possible clinical and patient outcome.

It is our duty as an industry to help support and provide guidance to HCPs, who are part of a treatment pathway on how to manage care with these new systemic treatments, and how to best deal with the complex needs of patients.

There is a focus on sharing best practice to support some of the themes already mentioned around service design to deliver the best care to their patients. With there being such variance across the country in the way that things are done, anything that we as an industry can do to help bring equity of delivery in the care pathway is important. At Merck, we have several initiatives working closely with HCPs to capture key learnings and best practice. These are developed into resources and content that are shared across different audiences, to help drive discussion and address some of the areas where improvements to patient outcomes can be made.

With any new treatment innovation, pharma is instrumental in ensuring that the right studies and research are conducted that inform important clinical decisions – proving that outcomes will last in the real world, as we've seen in clinical studies. It's also important that we set up trial designs that are innovative and forward-thinking – looking at how to best maximise the benefit of immunotherapy, using them as single and combination agents across different tumour types.

We must also ensure speed of access so that patients get the treatments as quickly as possible. We have a responsibility, to those patients who may potentially benefit to work closely with regulators and funding bodies, to minimise the time in those processes to speed up access.

NICE's Innovative Licensing and Access Pathway process, launched last year, is a step in the right direction. The initiative allows companies to work with NICE and the MHRA much earlier in the development process, receiving advice and input on clinical trial design, to ensure optimal data generation for both regulatory approval and health technology appraisal. This process should lead to quicker market access for companies, and faster access to innovative medicines for patients.

With companies and key stakeholders in healthcare systems coming together to align quicker in decision-making and benefit-risk, clinical outcomes for patients should ultimately be improved.

Looking to the future

Given the body of evidence that is still emerging in long-term use of immunotherapies, closely evaluating the data to make sure we are personalising treatment, and understanding the drivers of treatment efficacy, is critical. Irrespective of what the systemic treatment is, the only way we are going to be able to do the best for patients in the future is by identifying the right oncogenic drivers that are causing the cancer to grow and develop, so that we can target the right intervention to stop it.

Dr Stuart Hill is Medical Director, **Merck UK & Ireland**. In 2010, Stuart joined Merck and has worked for the last 10 years in the Oncology Business, which he has led as Business Unit Director for the last 3.5 years. The heavy focus on translating science into improved outcomes for patients has inspired Stuart to now take up the leadership of the Medical Affairs team for Merck's UK & Ireland operation.

NHS waiting lists: the second healthcare crisis?

Roland Kreissig, Oncology General Manager at Novartis UK and Ireland, sits down with Pharmafile to discuss how COVID-19 affected patient access to cancer treatments, and how pharma can support the NHS to face this challenge

Pharmafile: **What challenges have the NHS faced in providing cancer treatments to patients over the last couple of years?**

Roland Kreissig: The last couple of years have provided endless challenges to patients and NHS staff – and we have all heard about increased waiting times and pressure across the healthcare system. As we learn to live with the realities of a post-COVID-19 world, we now face a second healthcare crisis, in which millions of people are waiting for NHS treatment. When thinking specifically about cancer care, every point along a patient's journey through treatment has been affected by the pandemic – from delayed diagnoses, cancelled or postponed appointments, and concerns about coming into hospital for treatment, side effects, and follow-up. Cancer Research UK has been collecting data about what these delays really look like for patients, and they provide insight into the scale of the issue. They found that screening – crucial for early diagnoses in many cancers, like breast, bowel, and cervical – went down significantly in 2020/2021 when compared with 2018/2019, both in terms of those being invited, and those participating. In breast cancer, for example, the number of invitations was down 22%, and the number participating was down 33%, equivalent to almost 600,000 women.[1] This same trend was seen in people waiting over six weeks for a diagnostic test, where in radiology the waiting in November 2021 was 16 times higher than pre-pandemic, with almost 200,000 patients waiting for their diagnostic test.[1]

Even as we move back towards a 'normal' way of working, we all need to remember that the pressure on the NHS resulted in shifting and juggling priorities, with many patients waiting in the background for their turn. This backlog for appointments, tests, and procedures will continue to be felt across the country, with some estimating it could take until 2033 for the backlog to clear.[2]

The NHS will need to manage this backlog, while also progressing and improving care for the future. From the perspective of a pharma company, there was also a need to adapt clinical trials so we could continue to develop treatments and go through approval processes, despite the massive changes in healthcare. This challenge will require bold solutions, close collaboration, and exciting innovation, to ensure cancer patients are receiving the care they need, when they need it.

At Novartis, we believe we are strongly positioned to help the NHS recover, during a time when collaboration is more important than ever. We have been working very closely with partners across the life sciences ecosystem to identify individual issues hindering the delivery of treatments, and to offer tangible solutions to address these to support patients and the NHS.

How can pharma companies support the NHS cancer backlog and improve patient access to cancer treatments as we continue to live with COVID-19?

The NHS has been leading the charge in the UK through the pandemic, dealing with unprecedented pressures, and looking to staff to fill many roles to keep clinics and services running. But if COVID-19 has taught us anything, it's that if we are to bring about real change, we must collaborate like never before. Those in the private sector, including pharma companies, must provide the necessary tools and support to the NHS, giving frontline staff more resources to focus on their growing patient lists whilst also looking ahead to deliver for the patients of tomorrow.

These private-public collaborations are an opportunity for organisations with invaluable knowledge, technology, and resources to be used in collaboration with the NHS to support the backlog and help with innovation of care. At Novartis, our digital innovation lab, Novartis BIOME, identifies digital and data-led solutions to reimagine medicine for the better, and ensure no patient is left behind. For example, our newly-launched Evidence Lab has been set up through our Biome digital innovation programme to work within the health system and with health tech innovators, to test and validate digital health solutions, to see what the system would benefit from most, before investment in full-scale implementation.

What developments and innovations do you think will make the biggest difference to the NHS' cancer care in the coming years?

The NHS has ambitious goals for providing improved care for patients, and as it is currently developing a 10-year plan for how it will tackle the biggest challenges in cancer care, we are pleased that Novartis has been able to actively participate in this process by providing our recommendations. It's an opportunity for all players in the UK cancer space to reflect on our priorities for the future.

At Novartis, we plan to continue supporting the NHS by prioritising innovation across the patient pathway. As we move towards more personalised care, we see a real opportunity to radically reform cancer diagnosis. New diagnostics, innovative technologies, and genomics, can all support patients to reach a more accurate and faster diagnosis. This will in turn enable patients to access new treatment options, including personalised and targeted medicine.

Digital health solutions will become an important tool to not only speed up the diagnostics process, but also help track disease progression and symptom burden, empowering patients to be more engaged with their clinician and treatment decisions. For example, the myeloproliferative neoplasms (MPN) Tracker, introduced by Novartis, helps people living with MPNs to recognise symptoms, regularly track them, and start a conversation with their doctor. Additionally, by harnessing health data, we can ensure interventions can be both targeted and informed by behavioural insights, to ensure that they have the biggest impact on diagnosis. Moving forward, the health system must work to improve the accessibility and integration of health data across the treatment and care pathway, from clinical research, to cancer outcomes, and quality of life.

What lasting changes has COVID-19 had on the treatment of cancer?

With the rapid development of COVID-19 vaccines, we have seen the power of public/private partnerships in addressing public health issues. We can now take the lessons learned through this process and apply them to improving care for cancer patients, to address the lasting changes of COVID-19.

For example, the long-term challenges in the treatment of cancer go beyond the immediate backlog of care that we are experiencing now. Not only do existing patients need to be treated, but there are new diagnoses and late presentations that need addressing simultaneously.

One way this is being addressed currently is through appointments being made digital, to provide easier and quicker access to HCPs. However, with more appointments moving online, how can we ensure communication remains at a high enough standard? This is an opportunity for private organisations to support the NHS with new and innovative solutions aimed at improving telehealth, so people have access to the same quality of care while speeding up the process.

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Roland Kreissig is Oncology General Manager for **Novartis UK and Ireland**. He joined Novartis UK in January 2022, prior to which he held the position of Oncology General Manager for Central Europe.

Q&A

PHARMAFILE SPEAKS TO

Open Orphan

Helping the world prepare for future pandemics

Yamin 'Mo' Khan, CEO of Open Orphan, guides us through the respiratory disease arena, and how the world of human challenge trials may help us to understand it better

Pharmafile: **How has the global respiratory disease market shifted in the last 10 years?**

Yamin 'Mo' Khan: Prior to COVID-19, I think it had basically mirrored most of the other therapeutic areas, as there had been growth in the field. COVID-19 has had a significant impact; at one point there were over 300 candidates in development to treat the disease. COVID-19 is such an outlier, and it changes the whole paradigm when it comes to respiratory disease, as well as the development of broader vaccines or antivirals.

On the other side, we have a lot of pressure on pricing as well. That's one of the key factors that people in pharma and biotech are looking at, especially to see how they can speed up the process of drug development, to offer a lower price for marketing authorisation. That's going to require more work. Everyone can appreciate and understand that the speed of these vaccines that came out against COVID-19 was amazing. People who are not in the industry don't fully appreciate the speed at which the work was done.

Typically, it takes eight to twelve years to come up with a new product on the market. With COVID-19, the teamwork across the different kinds of groups internationally was amazing. From the discovery of the virus in Wuhan, different academics, sites, and pharma companies like Pfizer and Oxford-AstraZeneca, came together to expedite response to COVID-19. The regulatory bodies were happy to review the data on a rolling basis, which was not very common.

I think that part has been pretty amazing, and hopefully it goes some way towards putting together a blueprint for future epidemics and pandemics. I'm hoping that we will be better prepared next time. I think there was some criticism at the start – a lot of people talked about a potential pandemic and why we weren't better prepared for this one.

What potential do human challenge studies have in helping us understand more about respiratory diseases?

When you want to run a challenge trial, you find healthy volunteers – usually young, healthy people. We will find around 160,000 unique volunteer leads this year to fill our studies. For our challenge studies, we offer a number of strains of influenza, RSV, coronavirus, malaria, and so on. There's a long process of checking volunteer eligibility to participate in trials. For example, if you were a volunteer, we would do a serology test. We need to make sure that with an influenza challenge trial, you've not been exposed to that strain before, so you wouldn't have antibodies for that. If you don't have innate antibodies, you will get infected, but if you don't get infected, you're not really that useful to the trial. We do those kinds of screening processes, which means that we lose about 85% of the volunteers because they're not suitable.

We would first give vaccines to the ones that are most suitable, and then two to four weeks later, we would challenge them with a live virus. Then we measure the signs and symptoms while they quarantine for ten days. These challenge drug trials have been done quite often in the past, but with the current pandemic, it has been brought to a higher

level. We are now seeing more and more emphasis on doing challenge trials. WHO, for example, has put forward new working guidelines on how challenge trials should be conducted. There have been discussions at the highest levels in the US, at the FDA, regarding challenge trials. We work with the MHRA here in the UK in getting every challenge trial approved. We also work with some of the key academics – for example, Imperial College London was involved in the COVID-19 trials that we ran. Remember, we know the exact point we inoculate a volunteer, and we know to the second when a patient gets infected.

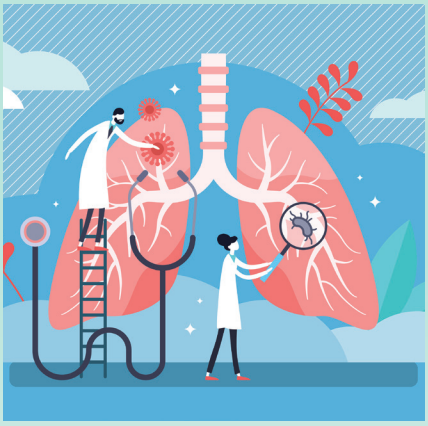
As CEO of Open Orphan, are there any particular hopes and visions you have for the company in 2022, as well as for the respiratory disease space?

There's no other company that has the breadth of challenge models we have. We have over nine challenge models and have done over 60 challenge studies, so it does put us in a unique situation. We also have a fantastic scientific team, with consultants from CMC through to clinical. With regards to respiratory, on a small scale, we started working on asthma, using HRV as an agent. We've developed a chronic obstructive pulmonary disease (COPD) model, but globally, we want to help the world to be better placed in fighting a future pandemic. We can't just be doing trials on a day-to-day basis – we need to look at the long term and see what the key risks are for all of us as a global community.

As a company, developing new challenge trials all the time is something we invest in. We ran the first SARS-CoV-2 challenge trial, and the results of that were published in *Nature Medicine* in April. We are also working with some key academic leaders as well, to develop this model to make them better and faster. We were able to grow the company with the challenge agents and the new service portfolio, and are helping prepare for any future pandemics.

What are the main obstacles that arise in human challenge studies?

Recruitment: trying to find a sufficient number of healthy volunteers is a huge challenge. We have a large dedicated recruitment arm



called FluCamp, which advertises via social media and traditional press to recruit potential volunteers. These people are compensated when they go into quarantine, but I think that's one of the key challenges.
The other challenge is that for Phase I studies in respiratory using healthy volunteers, they require nurses and physicians with specialised skill sets. That's different to the standard indication. When doing trials with respiratory disease patients, there's more sampling and specialist procedures required. Doing multi-site trials in respiratory does increase the variability of data across the site. You avoid that in a challenge trial because this tends to be conducted at a single site. You have one site, one group of nurses, and one group of physicians, who do all the patient procedures and sampling. So there is less variability of data.

What is the potential of technology in human challenge studies?

Technology has changed, and will continue to change the way clinical trials are run. Let's talk about patient-reported outcomes, when a patient is taking part in a clinical trial. With technology, you know in real time when data is being entered into the electronic diary. This increases the data integrity and the data quality. It also shortens the timelines for analysis, and gives the ability to collect more data. You have to ensure you only collect the data you really need. Technology enables you to get more data than otherwise possible in paper.

At Open Orphan, we run clinical trial challenge studies with wearables as well. We collect data on the patient 24/7. We analyse the correlation between the variable data versus the signs and symptoms the patient is showing. When a patient is at home, you can continue to collect the data. We have more kinds of clinically-targeted wearable devices to collect this.

COVID-19 illuminated the need for safe treatments that manage the inflammatory responses to respiratory infections. What else did the pandemic highlight about respiratory diseases?

I think it highlighted the potential for new treatments. The use of high quality placebo trials to test treatments has been key. Even though we expedited the clinical development programmes for the COVID-19 vaccines, they've been shown to be safe and effective. Understanding the viral disease helps with regard to what treatments to test, and also deciding to target the underlying cause of disease, in the right population, at the right time, is key. For example, it was shown that dexamethasone is beneficial in more severe patients, but not so much in the mild-to-moderate COVID-19 disease. Identifying infection early on in at-risk groups was also important, of course. It did show that in a lot of cases, in the at-risk patient population, late treatments were frequently unsuccessful. With patients who are elderly or at risk, if they develop severe flu, it's harder for them to recover.

At Open Orphan, we are now testing antivirals and immunomodulator treatments, as well as prophylactic drugs. We are currently using viral-induced studies in Africa, and hope to do more studies in COPD. I think those are some of the key findings.

Yamin 'Mo' Khan is CEO at **Open Orphan** with over 25 years of experience in clinical research and the CRO industry. Mo previously worked as a Consultant assisting CROs to develop growth strategies, and also held a variety of senior roles at Pharm-Olam. In his time at Pharm-Olam Mo had leading roles in Clinical Operations, Project Management, Business Development and Executive Management functions.

Dose and deliver: How PMDIs are transforming asthma and COPD treatments

Chris Baron, Director of Business Development at Aptar Pharma, explores how pressurised metered-dose inhalers (pMDIs) are continuing to change the landscape of asthma and COPD care

Pharmafile: How do pMDIs aim to treat asthma and chronic obstructive pulmonary disease (COPD)?

Chris Baron: From a pMDI perspective, it's not a new technology; pMDIs have been used now for asthma and COPD for over 60 years. Even though they still look familiar in some aspects, the technologies within the pMDI container closure system and the drug/formulation are very different. It's still using the same delivery methods of trying to treat asthma and COPD. The objective remains to deliver a repeatable and consistent dose to the lungs via aerosolisation of the aerosol, irrespective of the patients' respiratory effort. There are always pros and cons of having a patient wanting or needing to inhale at a specific inspiratory flow rate depending on what type of delivery platform is being used. On a positive note, when you think of a pMDI, if it's a traditional press-and-breathe, the fact that there is a propellant there which is expelling the drug means that even if the patient has very low respiratory efforts, or may be very old or very young, you can still deliver a formulation.

There are other ways – the perfect delivery system, from my perspective, would result in a lower respiratory effort where the patient would use a breath-actuated pMDI. This would help reduce patient coordination errors but would add additional costs.

How do pMDIs compare to traditional treatments for asthma and COPD?

This has been the million-dollar question. When I first came into the business quite a few years ago, we were going through the transition from chlorofluorocarbons (CFC) to hydrofluoroalkane (HFA). In those days, it wasn't global warming or climate change – it was the ozone depletion. People were saying: "Is it the end of the pMDI?" In those days, it was a transition which was mandatory – we had to reduce and then remove all CFC propellants, including those used in medical devices including pMDIs. This resulted in the development of formulations using new HFA propellants. These HFA propellants not only had a zero-ozone impact but they also reduced the actual global warming potential at that time by 300%. It was deemed a win-win for everybody.

At that time, they were thinking, "it's going to be DPIs (Dry Powder Inhalers) that take over". It certainly did not work out like that, and there are reasons for that. The most obvious one is that patients are used to using the pMDI because they are familiar with it. It gives a consistent dose and the patient experience is always the same when you use a pMDI, irrespective of the type of product you're using. Whereas, if you use a dry powder technology platform, it's more likely that you're going to have a very different experience with so many different dry powder inhaler technologies. You have reservoir-type, blister-based, and capsule-based technologies that all offer a different patient experience. This means it's not always easy to switch from one DPI technology to another DPI technology, and probably even more challenging to move from a pMDI to one of the DPIs.

The other thing you must consider if you're taking a rescue medication, like salbutamol, is you could never use a capsule-based DPI. You don't want to be playing with a capsule or putting that capsule into a device when you're having an asthma attack. The other key difference is that the costing aspects of a pMDI per dose are significantly lower than any other technology platform. If you have a 200-dose pMDI, it's much more cost sensitive to the industry versus single dose or multi dose DPIs. It's very difficult to ever replace a pMDI for such rescue medication.

What are the issues with existing treatment options for COPD and asthma?

I think there's an overuse of salbutamol. The challenge we have is that, when patients take medications, including controller medications for asthma & COPD, you may not feel any different for several days, then you begin to feel better, and that's when many patients stop taking their controller medication. With rescue treatments, like salbutamol, delivered by a pMDI, you take the medication and you get an instantaneous hit. The patient

feels like it's doing something, so they continue to take their rescue medication instead of their controller medication. The patient then becomes over-reliant on rescue treatment, as opposed to better managing their symptoms by using an appropriate controller medication. The net result is an over prescription of rescue medication. Perhaps this is maybe more of a communication issue between asthma nurses, physicians, and patients, i.e. not educating the patient enough to ensure that they need to continue with a controller medication. Even when they don't feel that immediate hit or buzz, they need to continuously take the medication in line with the patient instruction leaflet. One could argue that if you are in control of your asthma, then you shouldn't really need to use the rescue medication as frequently.

Another challenge for patients, when we think about the use of pMDIs in particular, some patients historically have co-ordination issues. When you use a conventional press-and-breathe pMDI, you should inhale and press, whilst still inhaling. Some patients may be very old or very young and sometimes patients struggle with coordination issues. To resolve this issue, you could incorporate a breath-actuated inhaler within the pMDI. You inhale through the actuator mouth-piece, which triggers the pMDI and delivers the medication, thus eliminating any coordination issues.

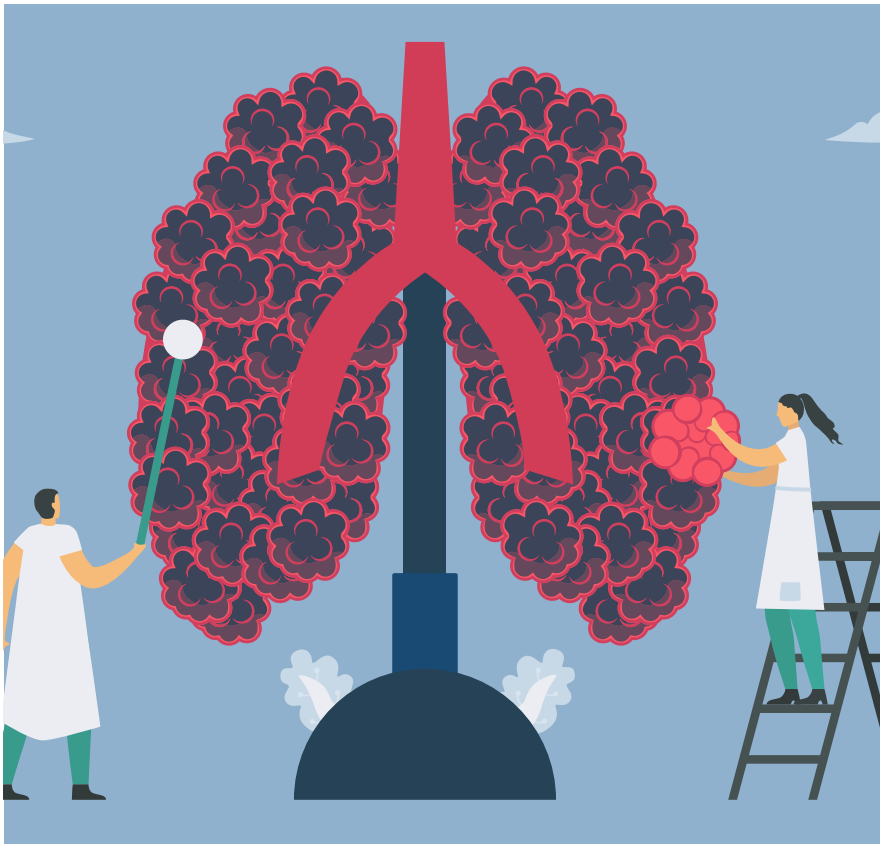
DPIs on the other hand are generally triggered by actually inhaling, which then delivers the dose from the device. This can be considered a pro but there are cons too. Some patients may not have a high enough respiratory effort to trigger the device and deliver the dose to the deep lungs.

The challenge then is cost, because the traditional pMDI is relatively inexpensive versus other technology platforms like DPIs and soft-mist inhalers. These new treatments could be used but it would just mean that the cost is more expensive.

Another key thing to mention is remaining doses. Many pMDIs on the marketplace today still don't incorporate a dose counter. Even though it's mandatory in the US and Australia, it's still not mandatory in Europe, and that's generally due to cost. If the patient knows how many doses are remaining, then they would know when to be in a position to go back to the physician and actually ensure that they've got their next prescription of medication, instead of having lots of pMDIs around the house, some half full, because the patient doesn't know how many doses are left. The final unmet need with pMDIs is that you need to re-prime them if you do not use the pMDI for a period of time (one or two weeks). This means you have waste, and this is a sustainability issue. The other consideration is that most primeless valves are used in conjunction with a BAI (breath-actuated inhaler), which could offer benefits from both a sustainability and a patient compliance perspective. I've just returned from the 2022 Respiratory Drug Delivery Conference, during which there was a significant focus on tackling the sustainability aspects of pMDIs during the Conference. I think the above points are key to meeting those unmet needs.

How can we make them more sustainable?

If you can reduce the number of priming shots, then you're going to have a more sustainable product, and as I mentioned earlier, using dose counters to confirm that the product is nearly empty. Many patients have products that they throw away, which are not empty. The other aspect is the link between digital health and connectivity. You could argue that it will be more expensive, but the patients who are not following their regime, and aren't taking their medication every day, are the ones who end up in the hospital needing emergency care. From a life cycle assessment perspective, this has a significantly higher carbon footprint (more resources in hospitals through emergency equipment) than using a pMDI using existing propellants. If you can have something that is more controlled, and has better compliance and adherence, it will be more sustainable too. It may initially be more expensive for the device, but the final cost to the healthcare system



is more positive, and the burden on the healthcare system is eased. Once a patient requires rescue treatment in a hospital, this becomes very expensive.

From a pMDI perspective there is significant work ongoing to switch pMDIs using the current propellants which have relatively high carbon footprints versus other inhaler device technologies to new low GWP (global warming potential) propellants including P152a & HFO1234ze which have significantly lower carbon footprints.

What are your visions for the future of respiratory treatments?

I've presented at multiple conferences and written various papers looking at improving the sustainability with regards to low GWP propellants. The good news is that low GWP pMDIs are on the horizon, and we can look forward to a much more sustainable future. Several leading Big Pharmacos, including Chiesi, AstraZeneca, and GSK, have all made announcements regarding their new low GWP pMDI programmes.

I think we can have better waste collection centres for used devices and that could include pMDIs, SMIs (soft mist inhalers), and DPIs. We could use more sustainable and reusable resins within the inhaler devices, but this is not going to be a quick thing, because obviously such resins need to be approved to medical grade.

Several major actuator suppliers for pMDIs are looking to utilise such reusable medical grade materials, as and when such materials become available for medical use. It'll just take time for those medical grades to come through and be approved accordingly.

With regards to improving patient experience, then using digital health solutions can make a real difference. Ensuring patient compliance and adherence is crucial, but this needs to be aligned with effective drugs and intuitive delivery devices which the patient will use. As stated previously, I think that, in the UK, there's too much emphasis on rescue salbutamol medication and the overuse of salbutamol, whether that's due to patients being prescribed too many rescue medications, or simply not being in compliance with their medication regimens.

The other thing which I would love to see is the patient coming first. The patient should always be the first thought of the physician, the Pharmaceutical company and the device developer. There are current examples where, after being taught the environment impacts of a product, physicians and Health Care Institutions are provided financial incentives to switch a patient from a pMDI to what they're perceiving is a more sustainable technology. These arbitrary switches may not be what is best in the long-term for the patient or the environment. You are asking a patient to change from a pMDI, which they may be in control of, to another technology without really thinking if this is going to benefit their health. I believe this is a dangerous precedence. A sustainable future is key, but the most sustainable product will be the one which the patient uses correctly and adheres to it. In summary, patient preference should matter as well.

I also think that dose counters should become mandatory in Europe, similar to in the US. Every pMDI should incorporate a dose counter or dose indicator. Why should we be lagging behind other countries purely due to a marginal increase in price? Patients who use products containing dose counters are more likely to be adherent and only replace the pMDI when the product is running out, thus reducing waste and reducing the cost/dose.

Chris Baron is Director of Business Development Pulmonary Category at **Aptar Pharma**. In his role, he is responsible for the global business development activities for Aptar Pharma's inhalation drug delivery devices, as well as their respective services pertaining to the application fields of Asthma and COPD. With an Honors degree in Mechanical Engineering, Chris has gained over 28 years' industry experience in the field of Inhalation Drug Delivery (IDD).

Working daily to improve the health of our patients and our planet

As the market leader in pMDI valve technology for asthma and COPD, Aptar Pharma is committed to improving the environmental impact of our products and ensuring our devices are safe and effective.

That's why we are actively engaged in defining the next generation of pMDIs, finding more sustainable solutions with alternative propellants that align with our sustainability commitments as well as those of our partners and their patients.

To find out more about how Aptar Pharma is advancing pMDI technologies, please visit **www.aptar.com/pharmaceutical/delivery-routes/pulmonary/**

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Improving outcomes in idiopathic pulmonary fibrosis

Hans Schambye, CEO of Galecto, discusses the benefits of inhaled technology in the treatment of idiopathic pulmonary fibrosis, and answers what he thinks the future of therapy for this devastating disease will look like

Pharmafile: **What are some of the current unmet needs within fibrotic disease?**

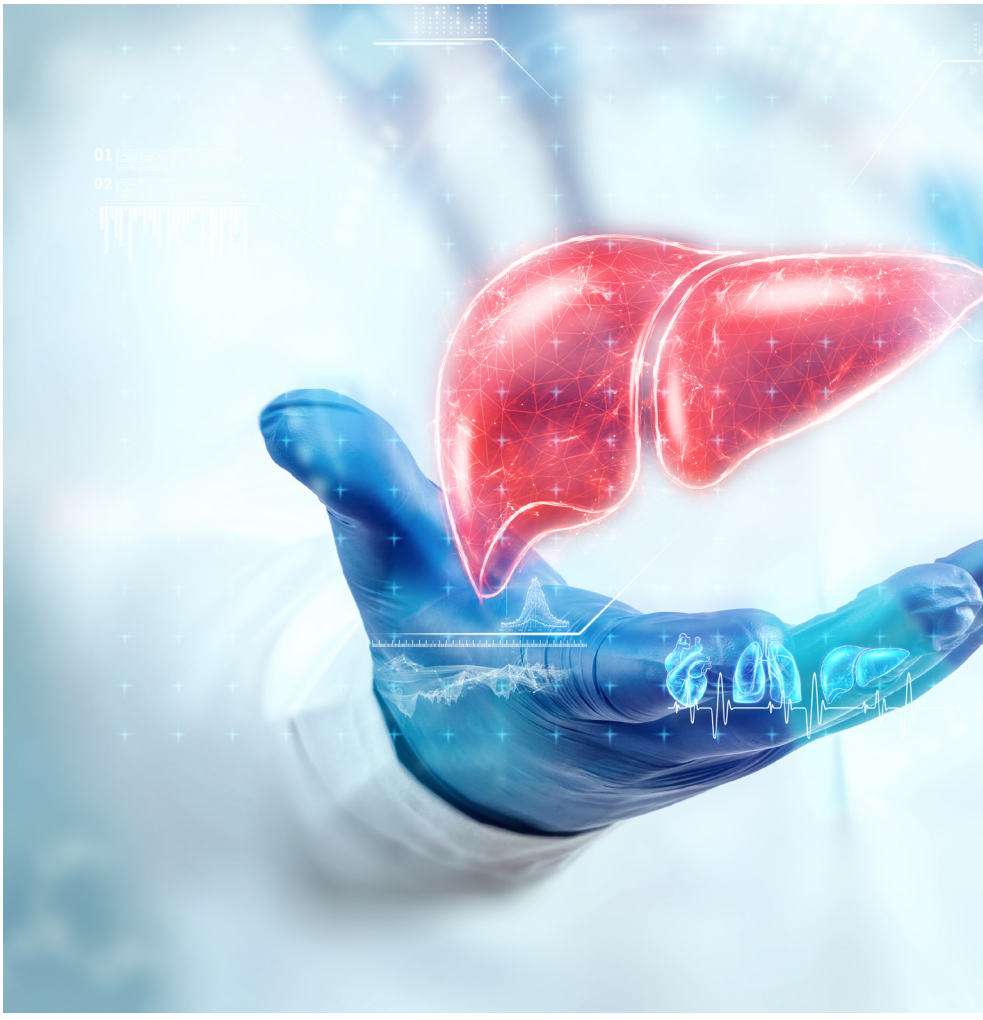
Hans Schambye: Fibrotic disease is a very broad topic, because you can essentially develop fibrosis in any organ, and it's always detrimental to the function of the organ. There are some claims in literature that up to 45% of all people eventually die of fibrosis-related complications.[1]

A particularly clear unmet medical need within this field is that there are no good treatments, and no good prophylaxis, for fibrosis. This is the short answer. If we dive into it more specifically, the only disease where there is some treatment is lung fibrosis. But the treatments available are not very safe, have got very significant side effects, and are not very effective. There is a big need for more efficacious and safe medicines, even in pulmonary or lung fibrosis, where there is treatment available. Beyond that, within cardiac fibrosis for example, there are no treatments; or kidney fibrosis, there are no treatments; or liver fibrosis, there are no treatments. There is clearly a massive need to develop treatments, which could help patients with all of these different diseases within fibrosis.

Why do you think there have been so few effective, safe, and well-tolerated medicines for idiopathic pulmonary fibrosis (IPF) so far?

There's really been a dramatic change in our understanding of fibrotic disease. Ten or fifteen years ago, most experts would say that there's nothing you can do within these diseases, because all treatment attempts had failed. Some of the logical treatment attempts have even proven to be dangerous for patients, like steroids, with the belief that the disease probably has something to do with inflammation, and that's what causes their fibrosis, or the belief that if we deal with the inflammation, it will be effective. But it turned out that this treatment path instead increased mortality for patients.

What we have learned in the last 15 years is that fibrosis is much more dynamic, and that you can actually change the disease with very targeted therapy – but we've also learned that this is very difficult. This is the reason there have been so few medicines developed, alongside the fact that the clinical trials needed in order to demonstrate efficacy in a targeted



therapy are very long, complicated, and therefore very expensive.

There have not been nearly as many attempts at solving this as necessary. But this lack of attempts in the field just reflects the nature of the disease.

We're developing an inhaled therapy that we believe will slow down the disease, and it looks to be very well tolerated. It makes a lot of sense when you have a lung disease to give medication in an inhaled form, so you get the drug to go where the disease is, and not everywhere else. This can potentially lead to fewer side effects, too.

Currently, with many IPF medications in development or on the market, you either have to take an IV infusion, for which you have to go into the hospital every two or three weeks, or you have to take the medication several times a day. A medication which is very convenient, in terms of remembering to take your medication or having it administered,

is definitely needed in this area. Inhaled technologies, where patients take one or two puffs once a day, present a much better proposition, and could really impact the lives of patients. The medications that are out there today, are often required several times a day, sometimes in the form of many pills a day.

What efforts can be made to improve the quality of life for patients living with fibrosis?

The main quality of life impact is, of course, their gradual loss of lung function. The best thing you can do for these patients is to develop medications that slow down the progression, or even reverse, the disease. Equally, you want to achieve this without too many side effects, because today, the patients are faced with a choice between losing their lung function fast, or losing it slower but suffering very significant side effects alongside that slower disease progression. A treatment is needed that is both very safe, well tolerated, and also good at slowing down the negative effects in the lungs.

What are the biggest steps made in the treatment of fibrotic diseases in the last 10 years?

Arguably, that is the approval of the two first drugs (pirfenidone and nintedanib), because the approvals showed that it was possible. It took away the basic doubts around the concept, of "Can you even do this right?". Now we know that you can, with drugs, impact how this disease develops. This was a major breakthrough. Of course, part of that is agreeing with the regulatory authorities, such as the FDA and the EMA, what it is that needs to be demonstrated in order to get a drug approved.

Originally, because there's a high mortality in this disease, the assumption from the authorities was that you need to show that you can reduce the mortality. But it is very, very difficult to run clinical trials while you reduce mortality. One reason is that those patients who are going into a clinical trial are taken much better care of than those patients who are not, so they actually live longer, just by being part of a clinical trial. This is sad, because it shows that if we just treated all patients the way we treat patients who are in clinical trials, we could actually keep them alive longer. However, this just showed it was really too high a bar to assess mortality – it would become infinitely costly, and therefore prohibited. By then agreeing and saying no, we are measuring lung function, and if we can show a difference in how the lung function develops over time, then it is good enough to assume that this is actually good for the patients.

What do you envision for idiopathic pulmonary fibrosis (IPF) therapies in the next 10 years?

I envision that there are going to be developments in combination therapies, just like what we see for cancer. IPF looks like a cancer disease: you have growth in your lung of tissue that really shouldn't be there, and that growth ultimately destroys the lungs. Additionally, in terms of how these patients fare, they have a mortality and morbidity that is as high as with many cancers. Ten years ago, they were not treated, only managed, and it's taken a massive effort to now have most patients actually on treatment. In the future, I expect much more aggressive treatment because we will have better tools, and we'll be able to show that by combining these tools, we can actually extend the life, and improve the quality of life, of these patients.

Reference

1. *Visit: www.ncbi.nlm.nih.gov/pmc/articles/PMC2702150*

Hans Schambye, President and CEO at **Galecto,** is a seasoned biotech entrepreneur with extensive experience in drug discovery and development. Previously, Hans served as the CEO of ReceptIcon from 2006 to 2009, and as the CEO of Gastrotech from 2004 to 2006. Before joining Gastrotech, he was Director of Biology and Pharmacology, and Head of Portfolio Management at Maxygen. Hans has co-founded several biotech companies, including ProFound Pharma A/S, which was acquired by Maxygen in 2000. Prior to this, he had a successful research career at Stanford University and Copenhagen University within the field of receptor biology. Hans holds an MD from Odense University, and a PhD in Medical Sciences from Copenhagen University.

ROCK2 the top: the future of IPF therapeutics

Dr Jane Robertson, CMO of Redx, sheds light on idiopathic pulmonary fibrosis (IPF), the side effects of current availabile treatments, and why the future of IPF treatment might lie in ROCK2 inhibition

***Pharmafile:* Can you tell us a little about idiopathic pulmonary fibrosis (IPF) and its currently available therapeutics?**

Dr Jane Robertson: IPF is a fibrotic disease. Essentially, it's a disease caused by an internal scarring process. This scarring process leads to the progressive replacement of normal lung tissue with collagen and connective tissues, which ultimately reduces lung function. It's a life-threatening illness: we know that there's no cure for this disease, and that patients generally only survive for three to five years after their diagnosis. They have a progressively poorer quality of life as their lung function deteriorates, and often suffer from repeated infective episodes and disease exacerbations.

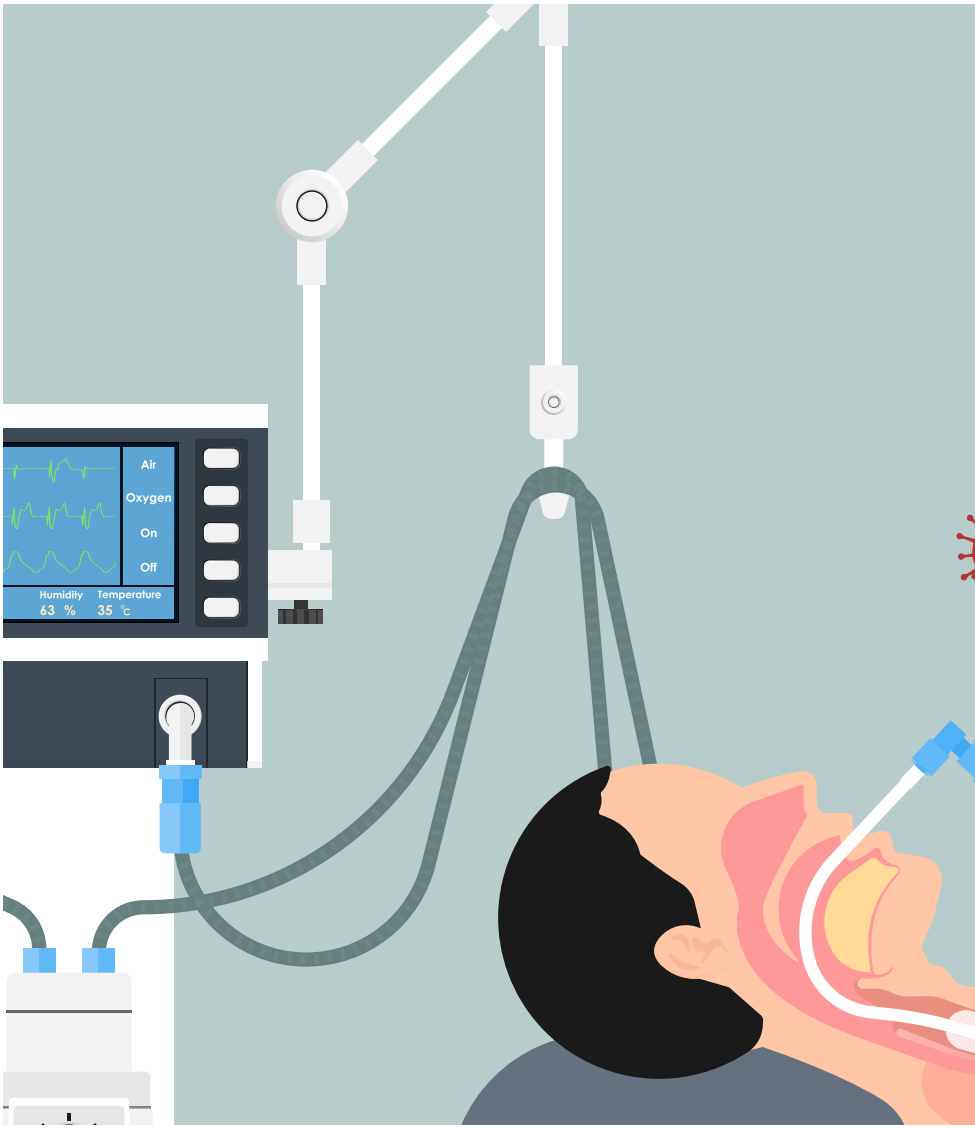
Unfortunately, there aren't any effective treatments to reverse the lung fibrosis, but there are some treatments which can slow it down. There's a clear unmet need, then, to find treatments that can modify this disease more effectively, and improve the quality of life for patients, as well as overall survival.

How can novel approaches potentially modify fibrotic disease processes and improve patient outcomes?

There are only two approved treatments for IPF, and both of those slow the progression of the disease, rather than halt or reverse it. One of these is pirfenidone, which acts in several ways, targeting primarily the TNF alpha and TGF beta pathways. The other one is nintedanib, which is a multi-kinase inhibitor also targeting several fibrotic pathways. Both drugs have been shown to be effective in trials, and were better than placebo in terms of slowing the progression of the disease. This in turn leads to an improvement in survival. However, they don't reverse the fibrosis, Both of these drugs have side effects too, especially in the gastrointestinal system. These side effect profiles can limit usage of the treatments.

With only these two approved drugs, there's a big unmet need for further treatments that will target different aspects of the fibrosis pathways to halt or reverse the process.

What is ROCK2 inhibition, and what is its potential in IPF treatment?



ROCK2 is an enzyme that sits at a nodal point of multiple fibrotic signalling pathways. Fibrosis is a very complicated process, involving many signalling pathways. By inhibiting ROCK2, we aim to inhibit several downstream pathways, and ultimately reduce and reverse that build-up of collagen and scar tissue. So we're very excited about the potential of inhibiting ROCK2 to really modify this disease and improve quality of life and survival outcomes ofr patients.

ROCK2 is also upregulated in other fibrotic diseases, not just IPF, because the same sort of fibrotic process occur in several other diseases in the lungs, kidney, and liver, and in the gut as well. If we think of, for example, the fibro-stenotic strictures of Crohn's disease. ROCK2 is a really important target to focus on, with several potential applications.

Why do you think previous therapies haven't gone down this route?

ROCK2 has been quite hard to selectively target. There's another enzyme called ROCK1, which is very closely related to ROCK2. The problem with inhibitors of both ROCK1 and ROCK2, is that they cause quite severe systemic hypotension and vasodilation, so they're not suitable to be used as a treatment option. It's been challenging to design compounds which are very highly selective against ROCK2.

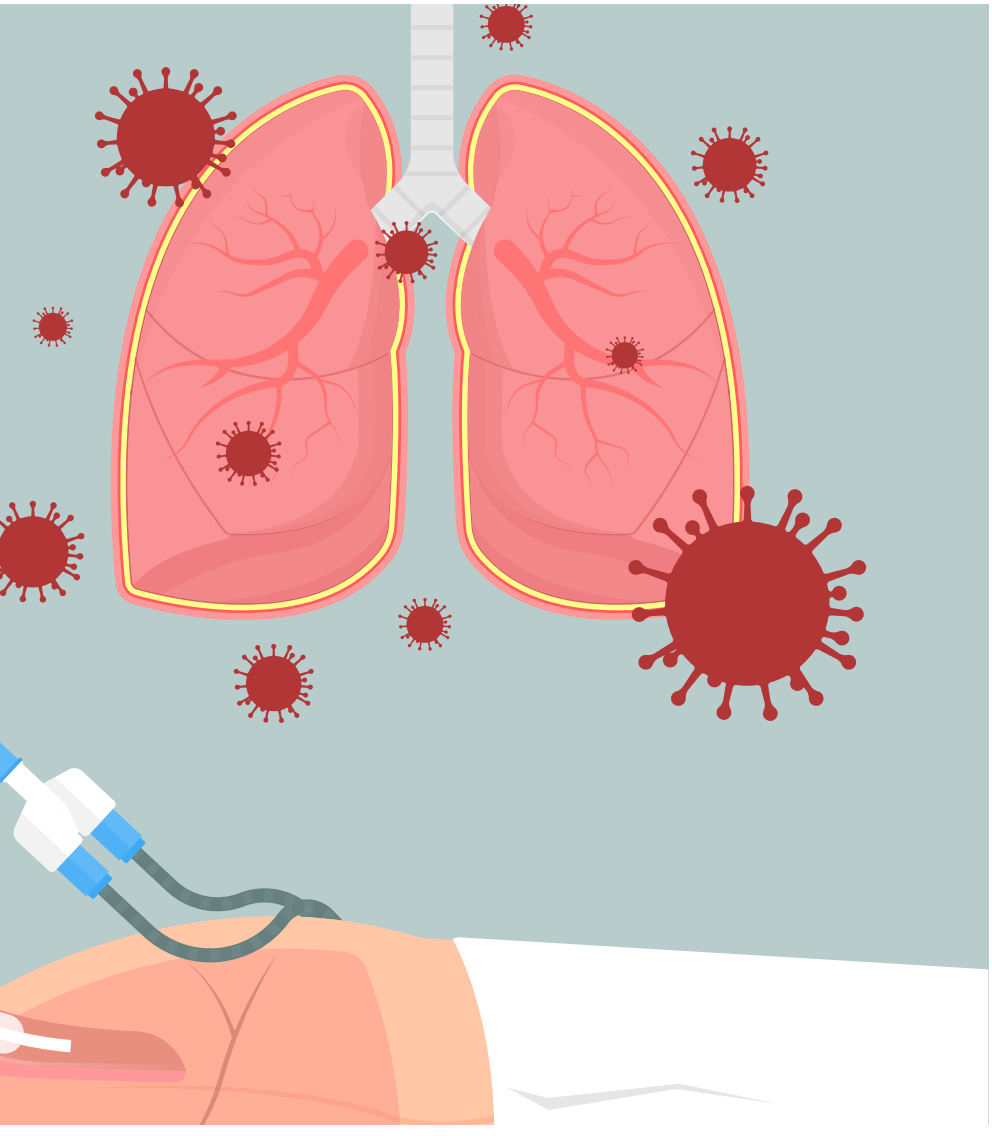
What is the importance of 'de-risking' programmes within IPF?

IPF is a serious and complex disease that is difficult to treat, and has no cure, so we need to be sure we have a validated, relevant target when we are trying to develop novel drugs for this area of unmet need in a timely manner. With ROCK2 inhibition, we are taking a de-risked approached, as we know ROCK2 is highly up-regulated in IPF, so it is biologically validated, and the target has also been clinically validated in graft-versus host disease, a disease that sometimes occurs after bone marrow transplantation that causes fibrosis in several organs including the lungs, skin, liver, and gut. A ROCK2 inhibitor is approved in that setting, so we can be confident that ROCK2 is a validated and relevant target.

What are your hopes for potential future management and treatment of the condition?

IPF is a devastating disease that shortens life expectancy, and causes a progressive worsening of quality of life. As the lung function deteriorates, patients become less able to carry out the normal activities of daily life, and more prone to disabling lung infections. Currently, no cure is available for IPF, with patients having an estimated life expectency of three to five years after diagnosis.

I think patients need medicines that can halt or reverse that fibrosis, and actually restore lung function and improve respiratory symptoms, rather than just slowing the decline, as the symptoms worsen and the lung function deteriorates.



Prior to starting as Chief Medical Officer at **Redx** in March 2021, **Dr Jane Robertson** was CMO at Achilles Therapeutics Ltd. Prior to Achilles, Jane served as the Chief Medical Officer at Nucana Biomed Ltd and at Kesios Therapeutics Ltd. She has previously also held a number of senior R&D leadership roles at AstraZeneca Oncology, notably leading the development of the first-in-class PARP inhibitor, Olaparib (Lynparza). Jane originally trained in general medicine and haematology, working in clinical practice and translational research settings, and sub-specialising in haemato-oncology; she remains General Medical Council registered.

PHARMAFILE SPEAKS TO

Sapphire Clinics

Medical cannabis – The inhaled answer to cancer and non-cancer pain?

Simon Erridge from Sapphire Clinics illuminates the clinical potential of medical cannabis in treating chronic pain, and offers a reflection on how the pain management sphere has changed in the last decade

Pharmafile: **How has the clinical landscape for pain management changed over the past 10 years?**

Simon Erridge: I think there's been a real emphasis to move away from many of the habits of prescribing we've seen in the earlier part of the last 10 years. That period saw a sharp increase in the number of patients who were prescribed opiate medications. Over the past few years, most recently with some of the NICE guidance around primary chronic pain, we've seen a move away from using opiates in the setting of chronic pain, and more of a focus on other medications, such as antidepressants. Even with gabapentinoids, which the medical community has been using with increasing frequency – there's been a little bit of hesitancy around guideline makers recommending those, due to potential harms and the lack of evidence of benefit in chronic pain.

The main shift has been towards firstly working with patients to acknowledge that with the medications and other treatments that we use in chronic pain, things may get better, but there's no certainty or guarantee that whatever we use will resolve that chronic pain. Psychological therapies such as CBT (cognitive behavioural therapy), in combination with physiotherapy, are all first line measures to try and get on top of those aspects of chronic pain.

Are there any areas of unmet need in pain management, or what changes are needed in this field?

I think the real unmet need is with respect to pharmacological management. For lots of patients that I've seen and have referred on to physiotherapists, often I'll get a report back that will say 'this patient is in too much pain to even engage in physical therapy'. Although we recognise the benefits of having a medication that enables people to engage in physiotherapy and psychological therapies, that is not a one stop fix, and takes time. Giving them options, so that they can carry on their day-to-day activities, so that they can sleep well, they can go to work, all these are really important. The real unmet need is identifying pharmacological management methods that can be used.

We have seen some work on more interventional treatments around chronic pain, and that really depends on the individual condition, and the sites, such as joint injections. We need more research into the more interventional measures.

Taking something like chronic pain, which in and of itself is a really heterogenous group of conditions, and affects a wide variety of people, what would probably benefit all patients the most is more identification of novel therapeutics for them to use.

What is the clinical potential of medical cannabis within palliative care?

We've seen a real increase in the amount of evidence surrounding medical cannabis and chronic non-cancer pain, but also in chronic pain related to cancer, whether that's the cancer in and of itself, or the side effects of cancer treatment.

There was a recent, rapid recommendation based off a systematic review and meta-analysis published in the BMJ last year, which suggested that patients who have failed first line therapeutics for chronic pain could trial non-inhaled medical cannabis agents. That's either oils, capsules, or lozenges, as they recognise that there was a small but significant benefit in respect to pain specific outcomes, but also looking at things such as sleep and general health-related quality of life.

In addition, at Sapphire Medical Clinics, we have generated evidence through the UK Medical Cannabis Registry. We published some data this year, looking at patients prescribed medical cannabis, including oils, and dried flower. In those prescribed for chronic pain, including those with cancer pain and non-cancer pain, we saw that there were statistically significant improvements in their scores for interference with the pain in day-to-day quality of life, and also with respect to anxiety symptoms, and their self-reported sleep quality.

There's an increasing body of evidence to support the use of medical cannabis. The *BMJ* article, *Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials*, makes recommendations towards utilising medical cannabis for those patients where first line therapies haven't been effective.[1]

In other aspects of palliative care, such as psychological components of end-of-life care, whether that's anxiety and low mood, there's very limited evidence directly from the palliative care population. Looking at anxiety disorders as a whole, there's really promising preclinical evidence, and now increasing levels of clinical evidence around its utilisation in anxiety disorders. There have only been a few randomised control trials, and they've mainly looked at social anxiety disorder, rather than generalised anxiety disorder, or PTSD, or anxiety related to health conditions. They've been largely positive, and again, we've looked at patients prescribed medical cannabis for anxiety in the UK through the UK Medical Cannabis Registry. That select cohort of patients in the UK who were prescribed medical cannabis for that indication, we've seen significant improvements in their anxiety, general health related quality-of-life, and sleep.

What are the differences between the use of medical cannabis in palliative care versus for chronic pain management?

The main difference in how it's used is largely in response to whatever symptoms you're trying to treat. In fact, the way medical cannabis is prescribed for cancer and non-cancer pain largely is very similar. You would ideally start out with a higher dose of cannabidiol, and maybe either have no THC, or a very low dose of THC. As people start to tolerate the effects of both of those medications, you'd slowly titrate them up, until they would be receiving the maximum amount of benefits, with the lowest risk of them developing any adverse events from the medications.

With respect to some other symptoms around palliative care, for instance – if they're having difficulty sleeping, or with anxiety and they need something that's more short-acting, in order to manage symptoms quickly, rather than slowly titrating up with an oil, they might be better off taking their medication in the form of dried flower.

That dried flower is vaporised to a lower temperature than it would be for people who would smoke it, and we specifically counsel patients not to smoke medical cannabis because of the associated carcinogenic risk.

However, when it's taken at lower temperatures through inhalation, the onset of action is much quicker, and then drops off much quicker as well. Normally, these would contain a slightly higher dose of THC compared to if they were titrated up solely through oil, so these patients get a quick relief of their symptoms, and then the effects of the medication quickly taper off.

What impact do you anticipate medical cannabis having in five years' time?

At the moment, there are quite a few barriers to medical cannabis in the UK. One is knowledge – the general public really are

> **A lot of patients say to us, they wouldn't be willing to even disclose that they're taking medical cannabis even though whatever they're doing is completely legal**

quite unaware as to some of the legislation changes, even though we're two and a half years down the line from when some legislation changes came into effect.[2]

We did a YouGov survey last year which showed that only approximately 50% of people that were surveyed were aware of the legislation changes. That's obviously a big barrier for those people who it may otherwise be appropriate treatment for, with these people not understanding that medical cannabis is even a possibility for them. To some degree, that problem exists amongst clinicians as well. It's to a lesser extent; lots of clinicians are aware of its legal status – but for many, when they were coming through medical school and their training, medical cannabis wasn't on the curriculum. Because of this, they have less of an understanding of what it is, what it does, how to prescribe it effectively and safely. Therefore, they're more reticent to either recommend or prescribe it themselves.

Knowledge and education is a big barrier. Another major barrier is stigma. A lot of patients say to us, they wouldn't be willing to even disclose that they're taking medical cannabis, even though whatever they're doing is completely legal. They find it really difficult to share that, whether that be with members of the criminal justice system, police courts, the other health care providers, or family and friends. Some people really find that quite difficult, because of the stigma that's still associated between recreational cannabis use and those being prescribed it for medicinal reasons.

Finally, cost is a barrier: it's not available on the NHS. Apart from a very small number of patients – I believe only three to date – have managed to get medical cannabis prescription through the NHS. But how do I think it's going to change from that point? Things will slowly change in terms of education, and this will help address stigma. The key to unlocking all of this is more research, as we do more research, and more specifically, do randomised control trials that compare medical cannabis against first line therapies for some of the conditions in which it's being prescribed. We can more clearly find out where this sits in our treatment arsenal for any specific condition, because at the moment, you need to have tried first-line licenced therapies before you can even be considered to start medical cannabis treatments. Once we have that extra data, we can perhaps say that actually for chronic pain, it might be a first line treatment, or that for some of the other conditions that it's been prescribed for currently, there are better things out there, and we probably shouldn't be using it. I think that's how things are going to change: we'll see medical cannabis being more widely used in individual conditions, hopefully within the NHS if they can demonstrate cost effectiveness as well as through health economic analyses. But alongside this, in some conditions, we may in fact see medical cannabis's use being far less.

What makes cannabis useful for pain management?

When you look at the cannabis plant, and how it gets distilled down to what causes its effects, you have what's thought to be over 400 potential active pharmaceutical ingredients in the plants. The two main ones that we understand are THC and CBD. This is what the prescription is made up of. But there are over 100 potential cannabinoids, and then many more terpenes and flavonoids, which are all purported to have individual effects on many receptors across the body. We understand that those three compounds are actually quite low potency, in that they don't elicit really strong effects in receptors across the body.

With respect to chronic pain, we have evidence that the major compounds in cannabis-based products dampen down the response at peripheral pain receptors. Chronic pain is really complex, and a lot of the experience and severity of pain can also be modulated by your own central nervous system. For instance, we all understand that if you're laughing, you're really enjoying yourself, and you don't feel the effects of chronic pain as much as you would do if you're stuck inside on a grey rainy day. We understand that the cannabinoid receptors in the brain have lots of particular roles in terms of modulating anxiety, and other emotions, and this has a really clear role in heightening or dampening down the effects of your interpretation of chronic pain. If we look at those people who have high levels of anxiety with their chronic pain, those people can have an even greater response than those where anxiety doesn't do much of a role in their experience of chronic pain. That's one of the main points: you have so many compounds, and so many different receptors that can potentially be acted upon.

If you can find the right formulation for the right patient, then there's a multitude of possibilities, but obviously it goes without saying that medical cannabis may not be the right thing for them at all.

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Simon Erridge is a medical doctor who graduated from Imperial College London in 2018, also completing an intercalated BSc in Surgery and Anaesthesia. He is the Head of Research and Access at **Sapphire Medical Clinics**, an award-winning medical cannabis clinic in the UK. Simon leads on the development and analysis of the UK Medical Cannabis Registry, the largest bespoke clinical registry for patients treated with medical cannabis in Europe. Since 2019, he and colleagues have published outcomes in chronic pain, anxiety, and palliative care in several prestigious journals.

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Pain management and pharmaceutical compounding

Treatment of pain is often at the forefront of both healthcare professional and patient's minds. How might compounding medication aid in treatment?

Pain is an unpleasant bodily sensation that causes mild-to-severe physical and emotional distress, usually deriving from an injury or illness. Pain can be classed as one of the most common reasons patients seek healthcare worldwide, and is a significant contributor to healthcare costs. It is difficult to define the epidemiology of pain, because of the subjective nature of the symptoms, and the lack of consensus for specific diagnosis and conditions. It is, therefore, hard to talk about evidence for the true incidence of most pain conditions.[1]

Pain can vary from acute, intermittent, or chronic, depending on its duration and severity. Acute pain is generally a shorter duration, lasting up to six months, and is resolved when the bodily distress is healed by itself. Examples of acute pain can range from a broken arm, cosmetic procedures, or healing from a surgery. Pain that comes and goes is called intermittent pain, and an example of this is toothache. On the other hand, chronic pain lasts longer than six months and can vary from patient to patient. Some chronic pains can be a result of nerve damage pain, lower back pain, or even from cancer treatment. Due to the long-lasting duration, chronic pain produces anxiety and emotional distress, interferes with functional capacity, and hinders the ability to participate in family and social events. It is hard to diagnose chronic pain due to its complexity and, in some cases, it is misdiagnosed.

Therefore, the optimal management of pain, either acute, intermittent, or chronic, is imperative for a patient's wellbeing.[2] A good pain management treatment plan will provide the patient with the pain relief they need, while also offering them the ability to regain their range of motion and mobility as quickly as possible without injury.

Current pain management treatments

Current pain management treatments primarily aim to reduce or eliminate pain with minimal side effects through pharmacological and non-pharmacological therapy.

Pharmacological therapy is done by administering a range of analgesic drugs, and can be divided into:

- Non-opioid analgesics
- Opioid analgesics
- Adjuvant analgesics

Non-opioid analgesics include paracetamol and non-steroidal anti-inflammatory drugs. Opioid analgesics can be divided into those used for mild-to-moderate pain (such as codeine phosphate), and those used for moderate-to-severe pain (such as morphine or oxycodone hydrochloride). Adjuvant analgesics include drugs such as antidepressants, antiepileptics, benzodiazepines and other muscle relaxants, bone-modulating drugs, corticosteroids, topical capsaicin, lidocaine, and rubefacients.[3]

Non-pharmacological therapy is the management of pain without medications. This method utilises ways to alter thoughts and focus concentration to better manage and reduce pain. Methods of non-pharmacological pain therapy include

neurostimulation, hypnosis, comfort therapy, education and psychological interventions, and physical therapies.[4]

Pharmaceutical compounding can offer better results

Throughout the years of pain management research, we can see that the art of compounding medication and personalising dosage forms for an individual patient can potentially become an optimal solution for patients. Pharmaceutical compounding is the creation and dispensing of tailor-made medications, and can be used as a pharmacological approach to benefit patients suffering with pain. Compounding allows the pharmacist to work with the patient and the prescriber, to customise pain medication to meet the patient's specific needs.[5]

Pharmaceutical compounding offers a much wider choice of pain-relieving ingredients than mass produced, single-dose medicines, and the ability to target pain in a multitude of ways. A prescriber working closely with a pharmacist can prescribe a range of active ingredients, each of which may target a specific mechanism in the body. As a result, compounding usually results in smaller concentrations of each medication, and more overall targeted pain management.[6]
While single-ingredient analgesics are preferred to allow for independent titration of each drug, fixed-dose compounded analgesics may be considered for those with stable chronic pain. Sometimes analgesic preparations that contain multiple analgesics, such as aspirin or paracetamol with an opioid component, reduce the scope for effective titration of the individual components in the management of pain of varying intensity.[3] In some instances, chronic pain sufferers are likely to be placed on a variety of medications to help address the symptoms associated

with their condition. With compounding, multiple medications can be combined into a single dose of a specially prepared compound either as a capsule or topical treatment, providing greater convenience for the patient, and therefore improving overall compliance.

Many patients experience stomach irritation or other unpleasant side effects from taking pain medication. Some patients have difficulty taking the medication in its commercially available form, and this is where compounding provides patients access to personalised medication, which can lead to less displeasing side effects and a more palatable formulation.

Compounding also allows patients to choose how the medicine is delivered and absorbed into their body. This is particularly useful if you have difficulty taking or swallowing capsules and need an alternative solution, such as topical preparations, custom-flavoured troches that dissolve buccally or sublingually, sublingual drops, rapid dissolve sublingual tablets, nasal spray, or a suppository. Such dosage forms may bypass the gastrointestinal tract, providing optimal results with less gastrointestinal irritation, reducing pain, and overall removing another source of aggravation.[7]

Patients, particularly those who suffer from allergies, can also benefit from compounded pain medications. As well as active ingredients, medications can also contain inactive ingredients such as binders, fillers, and dyes. Some people are allergic to these ingredients, which can make a medical treatment potentially fatal. Commonly used allergens include peanut oil derivatives, gelatine, corn, dairy, wheat, coconut, and potatoes. If there are allergens in a prescription medication, a compounding pharmacist can reformulate the drug, removing the non-essential ingredients to which a patient is allergic.

Lastly, a considerable number of patients with long-term pain management treatment may have the issue of their drug becoming discontinued. This often occurs not because the drug is unsafe or ineffective, but simply because it is no longer cost-effective for large pharma companies to manufacture. Compounding pharmacies can recreate the exact formulation of the original drug, and deliver it in the precise dose required by the prescriber for a truly personalised pain management option.[6]

Compounded pain medication

Compounded analgesics can be created by compounding pharmacies and customised to patients' specifications, to help develop an effective pain management treatment plan. The compounded formulations can include ingredients such as amantadine, amitriptyline, benzocaine, baclofen, clonidine, diclofenac, lidocaine, ketoprofen, and tetracaine, to name a few. These can be formulated to deliver a concentrated analgesic at the site of application. Low-dose and/or multi-drug formulations can be prescribed to reach multiple pain pathways optimising and targeting pain relief for patients.

Either combined or alone, active pain medications can be compounded into a topical cream, gel, or ointment, which can offer tailored, effective pain management, whilst also providing the opportunity to reduce adverse side effects, increase efficacy, reduce opioid use, and improve patient compliance.[8] Furthermore, expert compounding pharmacists can compound low-dose naltrexone primarily used to help reduce pain and inflammation, in any strength ranging from 0.5mg to 6mg in different formulations. Capsules tend to be the preferred formulation; however, other formulations can be compounded such as buccal lozenges, topical creams, and sublingual drops (depending on patient preference with swallowing difficulties or allergies/intolerances).[9]

Summary

Regardless of advanced research and scientific development, many patients are still taking pain medication, which may not provide optimal results. Compounding pain medication can help reduce these cases and create a unique medication specific for the individual. Each compounded analgesic medication is patient specific, and the ingredients can also be altered for dietary requirements such as lactose or glucose intolerance, or allergies to dyes found in the commercial drugs. Compounding opens a new avenue for prescribers who in the past were not able to prescribe medication due to the various reasons discussed above. Since traditional compounding practice might be the only viable option to meet individualised patient needs, more healthcare professionals should be encouraged to publish case reports and participate in small or large investigational studies to further the data we can gather on compounded pain medications. Having all experiences gathered and shared may benefit the growing, yet important, practice of compounding personalising the treatment of pain.[7]

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Embracing transdermal technologies

A number of challenges exist within the delivery of quick, effective pain management which doesn't deliver significant side-effects. Pharmafile spoke to Ken James of Futura for insights into the effective delivery of drugs to relieve pain, and alternative technologies

Pharmafile: **What are the therapeutic benefits of transdermal delivery in pain management?**

Ken James: The benefits are there, but it's worth highlighting that there are certain drawbacks and potential limitations as well. The obvious benefit is that higher systemic exposure of drugs is avoided when a patient takes drugs orally. It's not a particularly selective mechanism; an oral drug has to be dissolved, it enters the systemic circulation (it can go anywhere in the systemic circulation) and interacts with various parts of the body. Then, it takes a tortuous route, and eventually gets to the site of the pain. In that tortuous journey, systemic side effects can occur, such as, with oral non-steroidal anti-inflammatories, gastric upsets.

There's additionally been a lot of work done recently to show that there are potential cardiovascular side effects that can occur with orally administered, anti-inflammatory drugs: it's not a very selective way of administering the drug. The benefit of an effective transdermal system is that this tortuous, circuitous route just to get the drug to the side of pain is avoided – it gets there through a more direct route. In other words, you apply the drug directly to the skin. If you formulate it properly, you can get the drug directly to the site of pain, minimise the amount of drug in the systemic circulation, and avoid the stomach, and so on and so forth.

The drawback is that the art of delivering drugs locally or topically isn't as well developed as the oral route. Therefore, there's a lot of skill that is now being devoted towards the effective delivery of drugs topically.

What difference does it make for anti-inflammatories to be non-steroidal?

Steroids are very potent drugs – they're all chemically related to hormones in the body – and they can lead to quite significant side effects. If you take them orally, you can get this 'moon face'. You can get skin thinning, if you apply them locally. You can get a worsening of the condition over time, if you use steroidal injections for arthritis. They're highly effective, but they do have quite significant side effects, particularly if you use them over long periods of time.

The non-steroidal anti-inflammatory drugs are quite effective if they're delivered effectively, but a lot of them aren't. If you can deliver them effectively, the side effect profile is much better, particularly for topical delivery as opposed to oral delivery. There are some local side effects that can occur: you can get some irritation, either as a result of using excessive amounts of drug, or harsh penetration enhancers. They're not devoid of side effects, but, in comparison with steroidal anti-inflammatories, the side effect profile is much better.

What are the challenges of transdermal technology being utilised for pain management?

Two main challenges exist. First off, the skin is meant to be a barrier to the elements – it's there for a purpose: to stop things attacking the body. The two challenges that exist with transdermal delivery are, firstly, breaking through the skin barrier – that is, getting the drug through the epidermis. That penetration relies on having a good partition between the vehicle that the drug is in, and the skin layer, so you effectively want to make the drug want to get into the skin, as opposed to remain in the cream. You do that through partitioning. For example, the skin surface has a number of lipid layers, so an environment that is conducive to partitioning more into that lipid layer needs to be created.

The second difficulty is, once you've got it through the epidermis, that's still not where the site of the pain is for many pain conditions, such as soft tissue rheumatism, arthritis, or sports injuries. The drug must be enabled to diffuse through the dermis to get to the sites of the pain. Therefore, it must be formulated with that second objective in mind. To get to the actual sites of pain, a combination of a partitioning to get it through the outer layers of the skin, and then diffusion into the lower layers, is needed.
Those are the challenges, and it is quite a skill to balance those two factors and to come up with effective formulations that work.

How do CBD products differ from other pain relief products?

Not everything is known about CBD, but it does seem to work through a different mechanism. It seems to work through binding to cannabinoid receptors and other receptors in the body to block neurotransmission – so effectively blocking nerves that transmit the pain. That's a different mechanism to non-steroidal anti-inflammatories, which block an enzyme called cyclooxygenase, which is responsible for producing prostaglandins. It's prostaglandins that cause the pain and the inflammation, so this is an entirely different mechanism.

Since with CBD products, you are binding to the body's cannabinoid receptors – which are natural receptors in the body. It could be argued that this is a more natural mechanism to treating pain, rather than a "chemical" mechanism which some would regard as undesirable. The naturalness of blocking neurotransmitters, is what I think is attracting people more towards the products that contain CBD.

It's derived from hemp, but it doesn't cause any high – you don't get any CNS effects. CBD itself does not cause this, particularly if you can control the level of THC in the formulation. The natural benefits of the cannabinoids are delivered without the high that is normally associated with hemp- or cannabis-derived products.

What are some of CBD's grey areas at the moment, and what is still unknown?

Our understanding is increasing, but the science is really only just emerging at the moment. I think it's because of popular opinion – anecdotal evidence of these products suggest they work in a variety of conditions. What is lacking is large-

scale clinical studies, and, in fact, some of the basic safety work that you would normally carry out in a drug development programme. This is what I think is holding things back at the moment, because, as things currently stand, the regulations do not allow for any medicinal claims for CBD creams to be made. Whilst the products can be sold, any medicinal claims would make them illegal. There's also been a number of enforcement actions that have been undertaken in Europe, the UK, and in the US, against companies who try to make medicinal claims for products that, at the moment, are classified as cosmetics. They're classified as cosmetics because the basic science to underpin all this kind of anecdotal evidence just frankly hasn't been done. You won't find any big Phase III clinical studies, for example, studying the pain-relieving effects of CBD, and therein lies a big opportunity. If a company were to garner the resources and actually conduct all this work, that's a winning proposition because there is a weight of anecdotal evidence – people believe that it really works.

The science needs to catch up a bit, and then if companies go through the drug registration route, I think it puts it on a much better ethical footing. I would say, from our studies, that the plethora of cannabidiol creams, gels, and so on that are on the market, in general, are very poorly formulated from a pharmaceutical perspective. This comes back to what I was saying: just taking an ingredient and shoving it into a cream or a gel isn't really going to cut it. That won't get it through the outer layers of the skin, the epidermis, and won't achieve the diffusion that's necessary to get it to the lower layers and, therefore, effectively treat conditions such as pain and other topical conditions such as pruritus (itchy skin).

There's a lot that can be done, and this is work that we've been researching. It is possible to formulate the products more appropriately, and, therefore, make them more effective. The other thing to note is that, as we've studied the many products on the market, there are clearly problems of instability with the CBD in the formulations: they discolour over time, they go brown; when you measure the level of chemical present, often it drops below the declared level on the tin. As it's a fairly labile chemical, you have to formulate it properly to get a stable formulation. There's a lot of scope for developing superior CBD formulations – they'll work better, and they'll be more stable through the course of their shelf life.

What work needs to be done to improve the quality of life for those suffering local pain?

There are various ways of treating local pain; I could write an encyclopaedia to answer that question. But it's all about offering people greater choices. Coming back to the question of more natural therapies like CBD, there are great advantages if you can formulate the ingredient properly, using a product such as this, because it's a more natural action working with the body, rather than using heavy-duty steroids, or some of the side effects that you get from the non-steroidal anti-inflammatories.

Offering people greater choice is how we can improve things. The next step would be to do some proper clinical research on it to prove that the formulation really does deliver CBD to the deep tissue, where you want it to work. We can put the icing on the cake by conducting proper clinical research on that, but these are the greater choices we can offer people to improve their quality of life.

You speak a lot about how the weight of evidence in favour of CBD is real-world data, and evidence that's not clinical trial based. What is needed to launch CBD in clinical trial settings?

You should really go through a systematic drug development programme. There's a reasonable understanding as to how CBD actually works. Therefore, what you need to do next is conduct proper Phase I, then Phase II, and Phase III clinical studies. Typically, Phase I would look at the pharmacokinetics: how much gets where. Phase II would try to optimise the dose. At the moment, you go into the marketplace and can find any number of doses. But what's the proper dose to be delivered? People don't know that yet, to treat the various pain conditions. Phase II studies, which are typically dose ranging, look at a range of doses against a suitable pain model. Phase III studies have established a dose and go into multi-centre, possibly multi-country studies, using hundreds or thousands of patients, and a placebo control, to prove ultimately that the product works. That's really what regulators expect out of Phase I, Phase II, and Phase III trials.

Then, in the course of that, you really do need to show that the products are safe, particularly in a drug delivery system that treatments haven't been delivered in before. In the case of CBD, it's a drug delivery system delivering much higher concentrations. It needs to be proven to be safe – and just because something is natural, it doesn't mean that it's safe, which is a common fallacy. There are many toxins and poisons which are natural, but people ultimately jump to the false conclusion that natural means safe. No, it doesn't. What is needed is to support good clinical evidence with good safety data as well.

Finally, I'd like to express my enthusiasm for CBD pain therapies. It's nice to see an emerging area, something that's got a completely new mechanism, and it's exciting having the opportunity to explore and research it, and underpin it with some good clinical research. Some companies do have a winning proposition in my view, because CBD has obvious theoretical benefits over steroids and non-steroidal anti-inflammatories. It's great to see a new field opening up. Over the next few years, we're going to see some real breakthroughs in this area, as the science catches up.

Ken James is the Head of R&D at **Futura Medical**. He oversees the development, regulatory and manufacturing strategies for the Group's existing pipeline and the evaluation of early-stage pipeline, opportunities with over 40 years of experience in the research, development, and commercialisation of consumer health care products. Ken is an experienced global R&D leader, and Non-Executive Board Director in multi-category Consumer Healthcare and Pharmaceutical Technology industries. He has a strong track record of innovation delivery, and senior executive and non-executive leadership.


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Rare diseases and exceptional solutions

Antonio Payano, Bayer UK & Ireland CEO, explores the advancements that have been made within the field of rare disease in recent years, touching upon the potential of gene editing and viral delivery strategies

***Pharmafile*: The advances made in the life sciences in recent years has been dubbed 'The Bio-Revolution'. What have been the key advancements in rare disease research during this period?**

Antonio Payano: The life sciences have made great recent advances. Biology, life sciences, and the megatrend of digitisation, are growing closer together, enabling new inventions that impact our daily lives. We call it the 'Bio-Revolution'. This revolution is reinforced by rapid increases in computing power, and the emergence of new capabilities in AI, automation, and data analytics. These trends are further accelerating the pace of innovation, and the potential for higher R&D productivity in the life sciences.

All this has led to new ways of understanding and exploring biology. The range of life forms on earth is incredibly complex and diverse. However, the methods of analysing them can be remarkably similar. Technologies and methods are transcending disciplinary boundaries even faster.

The implications across the life sciences can be enormous: for human health, for example, a deeper understanding of the relationship between genetics and disease has led to the emergence of precision medicine, which can potentially be more effective than the one-size-fits-all therapies of the past. In the future, new technologies could help the healthcare industry not only treat, but cure, or even prevent, diseases. New gene and cell therapies, for example, aim to cure genetic diseases, potentially enabling sustainable organ replacement, or reversing autoimmune diseases.

What can you tell us about your journey at Bayer for the past 25 years, preceding your appointment as CEO?

I recently celebrated my quarter-century with Bayer, joining the organisation when Schering was merged with Bayer in 2006 – so I have been reflecting on what a significant milestone it is for me personally and professionally. My current role as Senior Bayer Representative and Country Division Head (Pharma) for Bayer UK & Ireland is a truly natural progression, and I can track the influence that each step and each role has had, leading me to where I am now. For example, after moving to Germany from the Dominican Republic as a child, then starting with my under-graduate studies there, a subsequent scholarship to Stanford, an MS degree from the University of Colorado, US, and a PhD in Industrial Chemistry at the Technical University Berlin, Germany, while also being engaged in a management trainee programme at Schering, travels around the world started early.

Observing how the industry operates from a young professional's point of view, and with the perspective of different countries' modus operandi, I have been able to draw on a depth and breadth of knowledge, through roles encompassing diagnostics (contrast media) during my traineeship:

general medicine and specialty therapeutics in the pharmaceutical businesses working in the US, Spain, Peru, Mexico, Czech Republic, and Slovakia; I have also had responsibilities as Business Unit manager; in regional and global assignments and working in the corporate offices of Bayer AG in Leverkusen; being in a Managing Director and Country Division Head role and sub-region Head Pharma EMA (Turkey, Ukraine, North & Central Africa, and Middle East), as well as heading Bayer Pharma's Global Healthcare Programs group. Through this long and varied experience of Bayer globally, and my connections to our Headquarters in Leverkusen, I aim to bring all the threads together and maximise our opportunities to harness science for the future, using all available technologies. I look forward to seeing the outputs of our Bio-revolution in the next phase of my journey.

What is your long-term vision for Bayer in the area of rare disease treatment/ innovation advancement?

Induced pluripotent stem cell (iPSC) technology, gene editing, and viral delivery strategies are combined at Bayer under its cell and gene therapy platform, which we launched at the end of 2020. The team is enabling the development of innovative treatments to augment regenerative medicine strategies – Bayer scientists are currently looking at gene circuits to formulate iPSCs, which can sense and respond to identified disease markers around them. iPSC-based therapies have potential to change the way we treat the loss of motor controls resulting from the death of neurons that affect dopamine production in Parkinson's disease, or the regeneration of retinal tissue damaged by macular degeneration. The science is there, and our commitment to it is profound.

Bayer's LifeHub UK, in partnership with Sensyne Health, focuses on AI imaging solutions to optimise drug discovery. How will this technology help advance research into rare genetic disease?

Our LifeHub UK initiative taps into one of the global challenges in Life Sciences – that is that some problems are too big to tackle alone. Ecosystems boosting the innovation capability of the pharma community and Bayer's ongoing collaboration with Sensyne Health is an example of how progress in data science can disrupt and uncover solutions. Sensyne Health is partnering with Bayer on developing AI-enabled radiology to enhance patient outcomes, and is also investigating how to accelerate the development of new treatments for cardiovascular disease using clinical AI.

The UK is the third biggest market in the world for AI investments - behind only the US and China – and access to academic talent is extensive, including a quarter of the world's top 25 universities. The incredible resource that is the NHS also provides the largest single-payer healthcare system in the world, and one which offers the best data granularity, representing an opportunity for AI solutions to optimise drug discovery and disease diagnosis/therapy, and lead the way in advances in healthcare.

How was Bayer's research impacted by the pandemic?

I would say the pandemic only fuelled Bayer's commitment and fervour. Our development portfolio of cell and gene therapies already comprises eight advanced assets in different stages of clinical development. These are applicable in multiple therapeutic areas with high unmet need, such as neurodegenerative, neuromuscular, and cardiovascular indications. With over 15 preclinical assets in the cell and gene therapy field, the pipeline is expected to grow steadily year by year, and the pandemic has driven our vision in these fields.

On a less clinical note, it is almost too early to learn lessons from this global pandemic, as we are still in the middle of it. It has presented us with many difficulties, yet, faced by this common challenge, the scientific community has come together in unprecedented ways in the search for solutions. The Bio-Revolution has the potential to help address some of the most critical global challenges, from climate change, to pandemics, chronic diseases, and worldwide food security. Experts estimate that a significant portion of the economic impact of biological applications will be in health care, agriculture, and consumer products.[1]

What are some of the major challenges in researching and creating treatments for rare genetic diseases?

One of the great challenges in 21st century medicine is to try and reverse the impact of age on the body; age ravages the body – sometimes unfairly so – generating hard-to-treat, or even hard-to-identify, conditions. Wouldn't it be great to turn back the clock by replacing the damaged cells with new ones? Pluripotent stem cells (PSCs) self-replicate, and have the potential in the human body to develop into almost any cell type. PSCs hold potential in the development of regenerative medicines, but having a readily available supply of PSCs continues to prove challenging for a number of reasons – mainly because they are derived from human cells, an issue identified in the development of COVID-19 adenovirus vectored vaccines using genetically modified human embryonic kidney 293 cells. Science has shown that you can reprogramme adult cells into a pluripotent state – iPSCs – which could be converted into different cell types. Fifteen years on from this scientific discovery, iPSC technology is seen as a potential solution to the major challenges in drug development, in tandem with the ongoing ethical discussions.

Reference

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Antonio Payano joined **Bayer** with Schering in 2006, becoming head of the Oncology BU for Bayer/Schering in Spain. He then became head of the Hospital BU, and later head of the BU General Medicine, before becoming General Manager, Bayer Health Care Head and Country Cluster head for Pharma Czech Republic and Slovakia. From Czech Republic, Antonio moved to Bayer's Headquarters in Leverkusen, Germany, as Head of Regional Co-ordination Europe. Antonio returned to Global Pharma in Berlin to lead the Elevate programme to develop a new go-to-market model, after which he was appointed to lead Bayer's EMEA Sub-region EMA comprised of Turkey; Ukraine; North and Central Africa, and the Middle East and Bayer Pharma's Global Healthcare Programs. Antonio completed this role before taking up his current role as CEO Bayer UKI; MD Bayer plc, and CDH Pharma UKI.

The combination treatment challenge

Dr Emma Roffe, Oncology Country Head, UK & Ireland, Takeda UK, illuminates the role of combination treatments in the realm of rare diseases, and discusses the potential solutions to make them more accessible

Pharmafile: **What has fuelled the high demand for combination treatments in the rare disease landscape?**

Emma Roffe: Combination treatments are becoming more common as the understanding of complex diseases increases, especially in areas such as cancer, HIV, rheumatoid arthritis, hepatitis C, and rare disease. This is because using multiple medicines in combination helps to simultaneously target different pathways that can drive a disease.

These treatments have the potential to offer significant clinical benefits to patients, including improving their health outcomes and quality of life. For example, in cancer, there is broad consensus that combining different treatments, with different modes of action, may improve upon the efficacy of just using a single medicine.

Combination treatments have also been revolutionary in infectious diseases, such as HIV and Hepatitis C, where viruses can quickly adapt and become resistant to single treatments.

Rare cancers, like multiple myeloma, are currently treated through daily use of corticosteroids. What potential do combination treatments have for patients with rare disease?

Rare diseases are particularly complex, and we are continuing to discover diverse ways to tackle them, particularly rarer cancers. Due to the nature of many rare diseases, there is a need to use a combination of treatments to help improve patient survival and quality of life. This is particularly evident in the treatment of rare cancers, such as multiple myeloma, where doublets, triplets, and even quintuplets are used to tackle different biological pathways of the disease. Many of these combinations include corticosteroids administered in combination with other treatments that have different modes of action.

What are the main challenges in making combination treatments available for the wider population in the UK?

Despite potentially offering significant clinical benefits to patients, the availability of combination treatments remains a significant challenge as they often face cost-effectiveness barriers even if one of the medicines were to be given away at zero price.

Combinations are usually made up of two or more parts: a 'backbone treatment' which is often the current standard of care, and a new 'add-on' treatment which is given in combination with the backbone. As the use of combination treatments extends the time before a patient's disease worsens or progresses, the backbone treatment is often used for longer. This alone can increase the cost of the combination treatment to the healthcare system, even before the cost of the add-on treatment is considered. This is made even more challenging due to strict competition law, which prohibits and restricts discussions between pharmaceutical companies on commercially sensitive topics, such as pricing and reimbursement of their treatments.

There is also no mechanism to apportion value to the component parts of a combination treatment, and the full responsibility falls on the 'add-on' treatment manufacturer to bear all the cost-effectiveness burden. It is also the case in the UK that we do not have indication-specific pricing. This means that any price negotiated for the treatments used in combination would also apply across all indications for those treatments, whether prescribed as a single (mono) therapy or in another combination.

Until now, the challenge of combination treatments has firmly sat in the 'too hard to fix' box, despite there being consensus within key national and international stakeholder groups that solutions for accessing combination treatments need to be found quickly for the benefit of patient outcomes.

Takeda's proposed solution suggests ways to tackle the primary barriers in making combination treatments accessible, such as improving cost effectiveness and encouraging dialogue between companies. What does this proposal entail?

In partnership with experts from the patient, academia, clinical, and competition law communities, and with input on key challenges from experts from the NHS and NICE (National Institute for Health and Care Excellence), Takeda has developed a proposed solution for improving access to combination treatments. This solution is proposed in two Whitepapers: An Attribution of Value Framework and The Voluntary Arbitration Framework.

The Attribution of Value Framework proposes an economic methodology that aims to define a fair division of value across the treatments in a combination. It does this by assigning a

relative value to each treatment, based on its health benefit.

The Voluntary Arbitration Framework proposes a standard operating procedure to support compliant dialogue and agreement between pharmaceutical companies, on the value attributed to each treatment within a combination.

Takeda's solution takes into consideration the current processes used by NICE and NHS England in making decisions on access to medicines and competition law. It aims to contribute to the options being explored by other stakeholders, to find effective and implementable solutions that align with current health technology appraisal methods.

We also propose that any solutions that are implemented to address the combination treatment challenge, become embedded into the existing 'voluntary scheme for branded medicines' to encourage universal participation of the pharma industry, the NHS, and the wider healthcare community.

Takeda welcomes feedback, critique, and debate of the two whitepapers so that we can contribute to finding a solution that, not only ensures patients can benefit from the scientific innovation and promise of combination treatments, but is also accepted by all stakeholders.

What are Takeda's hopes and visions for the future, in improving patient outcomes for those with rare disease?

Takeda is guided by an unwavering commitment to put the patient first in everything we do and in the decisions that we make. As part of this, we have a long history of collaborating with healthcare systems, regulatory agencies, health technology appraisal bodies, payers, and the clinical and patient communities, to find solutions to complex challenges that enhance patient access to effective and well-tolerated treatments.

The cost-effectiveness challenge faced by combination treatments is a significant and growing issue that has for too long sat in the 'too hard to fix' box. As a trusted partner, we were well positioned to bring together numerous stakeholders to develop a proposed solution that aims to ensure patients benefit from the potential of combination treatments as quickly as possible.

We hope that a solution, whatever that may look like, is quickly embedded into the healthcare system for the benefit of patients now and in the future.

Dr Emma Roffe was appointed Oncology Country Head for **Takeda UK and Ireland** in 2018, joining the company's Senior Leadership Team. Her appointment followed a 15 year career at Takeda, working across a number of its portfolios, having joined in 2003 as a Scientific Adviser.

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Thank you for a well-organized FlyPharma Europe Conference in Copenhagen. We believe the participants found the presentations and discussions very interesting and valuable. The conference outlined new interesting perspectives on collaboration and digitalization

Leif Rasmussen, President & CEO, SAS Cargo

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