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Interview

Addex co-founder and CEO Tim Dyer talks about his company's roller-coaster history and explains why his outlook is upbeat.



Biosimilars

Innovators are suffering under the EP's taste for the SPC waiver

Fragrances

Cosmetics giants seeking to ride the sustainability wave

Device + Drug

Novel combination products are therapeutic game-changers

Bioprocessing

Synthetic biologists demand global manufacturing standards



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Metastasis

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Encourage development of new antimicrobials



DR COLM LEONARD is a Consultant Thoracic Physician at University Hospital of South Manchester NHS Foundation Trust since October 2000 and, since 2008, spends 50% of his time as clinical adviser to the Centre for Health Technology Evaluation at NICE. He leads the clinical input on the AMR work in NICE. A Graduate of the Medical School at the University of Dublin, Trinity College, Dr Leonard has a very broad experience in clinical care of immune-suppressed patients, basic science research, animal model work, and clinical trials, and his horizon-scanning work with NICE spans across all clinical specialties.

Antimicrobial resistance (AMR) is a global threat, particularly given the modest activity in the pipeline of new antimicrobials in development, and emerging resistance to existing antibiotics. In 2016, Lord Jim O'Neill published a globally-focused review on AMR, which highlighted the lack of incentives for new antimicrobial development and encouraged a worldwide system of 'push' and 'pull' incentives to stimulate new drug development.

Push incentives have gathered pace with combatting antibiotic-resistant bacteria via biopharmaceutical accelerator (CARB-X), global AMR innovation fund (GAMRIF), and other public/private investors funding early-stage research. However, effective pull incentives are still needed. The UK government, in response to the O'Neill report, started working with the Association of the British Pharmaceutical Industry (ABPI), NICE, and NHS England to investigate a novel approach to value assessment of new antimicrobials, which would inform a scheme to pay companies primarily based on their value to the NHS as opposed to the volumes used.

NICE recognised that current health technology assessment (HTA) methods generally do not fully assess the specific value of new antimicrobials beyond the benefit of curing a given patient's infection. It has been argued that the value assessment needs to address additional attributes, such as the impact on transmission, spectrum effect, enablement, and diversity values, while also factoring in the impact of development of resistance to the new and existing antimicrobials. NICE and the Department of Health and Social Care (DHSC) commissioned an academic group at the University of York that carried out an 18-month study researching how to design a new HTA approach using these principles, in order to facilitate such a payment scheme.

Following on from the methodological research, the UK is now planning to test two antimicrobials with the novel HTA value assessment. This will be considered alongside a test of an innovative reimbursement approach that provides proportionate incentives to invest in research and development while supporting antimicrobial stewardship. By testing the feasibility of evaluating and reimbursing antimicrobials in a different way, the UK is sending a clear signal to the rest of the world that workable models can achieve the right sort of pull incentives for these vital medicines. To have a more significant impact on AMR globally, other countries will need to respond to this signal by developing similar incentives in their own domestic markets. ■

I would like to acknowledge my co-authors Dr Nick Crabb, National Institute for Health and Care Excellence, UK, and Tracy Parker, Health Protection Policy, Head of AMR, HCAI, and Sepsis policy at Department of Health and Social Care, UK, for their contribution.

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COVER STORY



Hard on the heels of metastasis

For decades, cancer researchers focused on shrinking primary tumours. But now some pioneers are trying to zero in on what's the most common cause of malignancy and death in those who have the disease: metastasis. Our understanding of the process is still limited, but the technological toolbox is growing. Novel approaches to the problem from different research teams are leading to groundbreaking strategies set to take the fight against cancer to a whole new level.

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BIOECONOMY

Bio-based body care

In the last few years, consumers have increasingly begun to demand greener, more sustainable products. Not just in food and fuel, but in the body care, beauty and fragrance sectors as well. But processes based largely on petroleum are what brought those products to the masses. Can biotechnology help overcome the barriers involved in the mass production of ‘natural’ skin creams, perfumes, cosmetics and shampoos?



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DRUG DELIVERY



80

Drugs and devices

In an age when even toasters are internet capable, it’s proven surprisingly hard to design smart drug delivery devices tailored to people with chronic conditions like diabetes and asthma. Demands from patients and insurers are finally being met, but regulating the field is no easy matter. Not least because of one simple question: Are the new systems drugs – or devices?

EDITORIAL

Don’t break ties!

When this issue went to press, the issue of Brexit remained unresolved. Several scenarios look possible, but there’s still no compromise in sight. So it’s still pretty unclear what the next research and innovation Horizon Europe will look like, particularly when it comes to financing. With the potentially expensive crisis in the UK and another one involving refugees still bubbling away on Europe’s back burner, powerful EU members like Germany and France have made it clear they are unwilling to invest more in the research programme than the around €94bn proposed by the European Commission.

MEPs led by Horizon Europe chief negotiator Christian Ehler, however, say that’s far too little to guarantee EU ambitions to remain a global leader in research and development. The bloc will miss its target to raise R&D spending in the EU to 3% of GDP by 2020 (in 2017 it was 2.07%, while emerging countries reported 3–5%). MEPs are calling for a major bump up in the budget to €120bn, and are questioning the effectiveness of the programme’s Public-Private Partnerships.

The UK’s move to propose a new reward mechanism for the development of antimicrobials (see pp. 3, 40, 70) clearly shows that both R&D and business in the EU will be hit by a lack of input from the UK. We’ll need new forms of collaboration to drive innovation in a post-Brexit Europe.

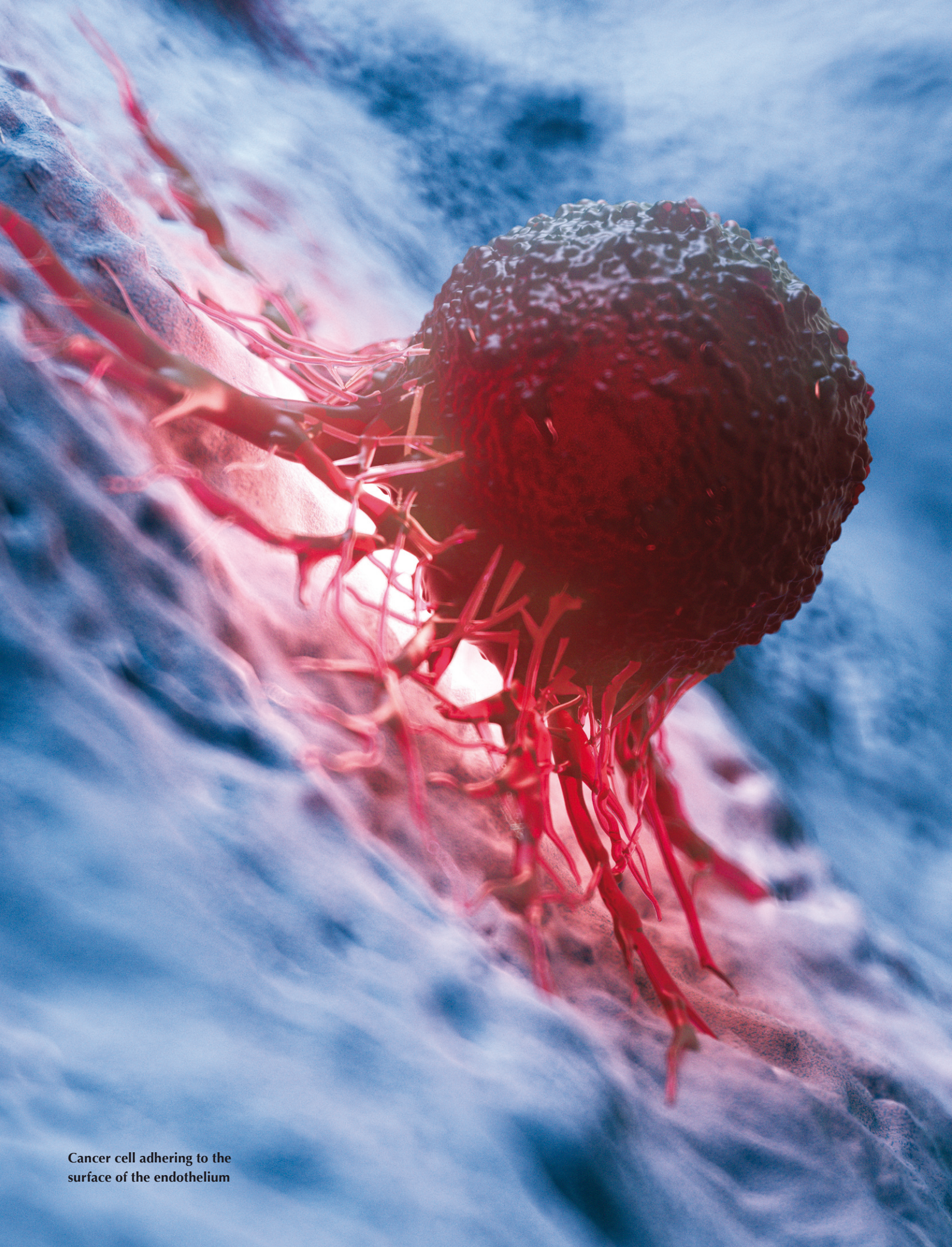


Thomas Gabrielczyk
Editor-in-Chief

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Cancer cell adhering to the surface of the endothelium

A Holy Grail in the quest to end cancer

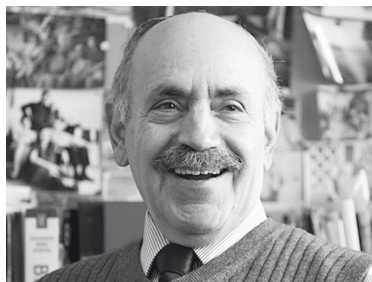
METASTASIS Targeted therapies and chemotherapeutics have helped cut cancer deaths dramatically in the last few decades. In the US, the overall mortality rate of 251/100,000 patients in 1991 had fallen by 2016 to 156/100,000 patients. Engineered (multispecific) antibodies, cell therapies and combination therapies are expected to continue to increase success rates with primary tumors. And research groups are turning their big guns on what is now the biggest killer – metastasis.

When he went in for a routine check-up, Peter Widener discovered he had pancreatic cancer. It's one of the worst diagnoses a doctor can hand out. At Peter's stage of the disease, most people are dead within a year – but he didn't have any symptoms. In fact, the 75-year old retired architect still enjoys sports and meeting new people. So he was glad when his oncologist said he didn't want to conduct a "10-hour surgery that is going to make you feel like you've already died" as long as the "tumour is as inactive as it seems to be at the moment."

Peter was luckier than most patients with his diagnosis, because their primary tumour generally spreads early and returns – in a much more malignant form – at distant sites. In breast cancer, in around a third of the women with the still apparently localised form of the disease, cancer cells have already spread to distant sites by the time they are diagnosed. Many women relapse 12–18 months after surgery.

While cancer survival rates overall have dramatically improved thanks to better diagnoses and drugs that stop tumour proliferation, survival rates for people with metastases have improved little. About 50 years after US President Richard Nixon kicked off the 'War on Cancer' by signing the National Cancer Act of 1971, metastasised bone, brain, lung or liver cancer still leads to over 90% of all cancer deaths,

stressed researchers from the German Cancer Research Centre (DKFZ) at a workshop on metastasis in late January. While there's no drug on the market that can prevent it, a small number of oncologists have left mainstream research – which mainly targets primary tumours – and turned to



ROBERT WEINBERG Director of the Ludwig Center at MIT (Cambridge, US)

? What impact could your finding that NSAID in mice can prevent metastasis have?

! Mice are not people, and therefore this may not translate into clinical practice. Our paper is only intended to alert people to this possibility, and to explore whether the mechanism operates as well in humans – as we think it might.

unravelling the mechanisms behind metastatic dormancy, metastasis, and its triggers, adding a couple of preclinical candidates to pipelines along the way.

When it comes to metastatic cancer, most drugs that are prescribed target primary tumours instead of metastasis formation. The only real market currently out there is not for causative therapies, but for symptom treatments – including medications aimed at pain control, preventing fractures or improving functional disabilities. Inkwood Research projects that market will continue to grow between 2018–2026 at a CAGR of 7.13%. As metastasis is currently the leading cause of death for the 14 million patients newly diagnosed with cancer annually, the focus is now turning to approaches that target metastases directly. Most of the work being done in the field, however, is still very much in the discovery stage.

Signals that guide metastasis

Among the pioneers seeking to understand the roots of metastasis is the head of the Ludwig Center at MIT's Whitehead Institute. Robert Weinberg discovered the first oncogene, and co-authored CELL's most-cited paper 'Hallmarks of Cancer' (see p. 19). "We are just beginning to [...]"

» Read the full story in the printed issue.

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Mixed picture

REPORT

ANALYSIS OF EUROPEAN BIOTECH COMPANIES ON THE STOCK MARKET

Biotech stock markets are still appreciated by investors; however, the second half of the year 2018 was very painful. This mixed picture is reflected in the overall numbers: Whereas the number of IPOs significantly decreased in 2018 compared to 2017, follow-on financings were three times higher. This is particularly true for European stock exchanges. However, nurtured by the further progress of breakthrough technologies such as CAR-T or gene therapies, listed biotech companies – be they from Europe or not – are an attractive target for investors.

» Read the full story in the printed issue.



The formula for sustainable success

BIOECONOMY Many manufacturers in the cosmetics industry are responding to consumer demands for greener, more sustainable lotions, creams and shampoos. But until now, a number of limits hampered the large-scale production of natural compounds and fragrances that are key elements in body care products. Now biotechnology is helping overcome those barriers.

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Many drugs are administered with the help of trusted devices like inhalers. With digital technology, designs are getting smarter and smarter.

A grey zone in regulation

COMBINATION PRODUCTS There is a growing demand for more patient-centric drug delivery and improved health-care cost management via self-administration and smart devices. The global drug device combination market is projected to reach nearly US\$140m by 2025. It's where the two different worlds of pharmaceutical (GMP) and standardised medical devices collide. Each needs to learn from the other in order to facilitate the regulation process in Europe.

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