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Interview

By splitting his company, Selvita CEO Paweł Przewięźlikowski plans to catapult his CRO business into the top five.

Malaria

After decades of research, a vaccine is rolled out in Africa

Biomanufacturing

The power and promise of cell-free production systems

Horizon Europe

The EC reduces bioeconomy to its agricultural aspects

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The Art of Biomarker Validation

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Emergency on planet AMR: a vital pipeline to protect

Picture: Summit plc

CLIVE MASON is Senior Director, Anti-Infectives Research at Summit Therapeutics. He holds a leadership role in fully exploiting the Discuva platform to bring forward differentiated, new chemotype antimicrobials with novel mechanism of action against urgent-threat pathogens. Previously, he was founding scientist and Director of Biology at Discuva Ltd. Clive is a member of the BEAM Alliance* Board, where he looks to support and develop incentives for SMEs to deliver the commercial changes needed for innovative products addressing AMR.

The recently released IACG report testifies that the antimicrobial resistance (AMR) problem is now receiving some echo at the political level. Literature exploring ways to fix the acknowledged market failure is growing. Stakeholder meetings deciphering the impact of the proposed models are being organised all over the world. Still, time is against us.

Big corporations have mostly left the field already, and SMEs are struggling to survive, as raising money is highly difficult in the AMR space. If nothing is done quickly, most companies will have gone out of business within the next two years. Who will be left to bring new antimicrobials all the way to the market?

The sooner we come up with practical solutions, the more SMEs (and currently developed products) we can save from vanishing. We won't find one global solution. The complexity of the task upon us calls for a diversity of solutions, whose coordination may take some time. But, we need a first move to give the signal that changes are coming.

Significant progress has recently been made in implementing different PUSH financial incentives (CARB-X, etc.), and we are encouraging further extensions, possibly through the upcoming EU Horizon Europe framework programme. But, the recent failure of Achaogen reminds us that R&D financial de-risking is only one part of the solution. More should be done to attract private investors back to the field and ensure sustainable business.

The salvation may come from a range of PULL incentives. To be effective, the proposed mechanisms should provide a renewed investment profile and allow companies to present a viable business case.

As a first fix, reforms must be engaged to enforce the fair pricing assessment of antimicrobials' societal value. Reimbursement protocols should also be modified to unleash the budgetary constraints that are currently preventing hospitals from delivering the most appropriate treatment to their patients. Finally, some buying commitment mechanisms should help to secure a minimal market uptake during the first commercialization years of the newly approved drugs. Otherwise, the Achaogen story will repeat over and over again.

More is needed to reshape a sustainable AMR market. But, without a quick start, there will soon be no companies left to support. ■

Launched in June 2015, the BEAM (Biotech companies in Europe combating AntiMicrobial Resistance) Alliance is a Network of approximately 60 small and medium-sized European companies involved in developing innovative products and kits to tackle antimicrobial resistance (AMR).

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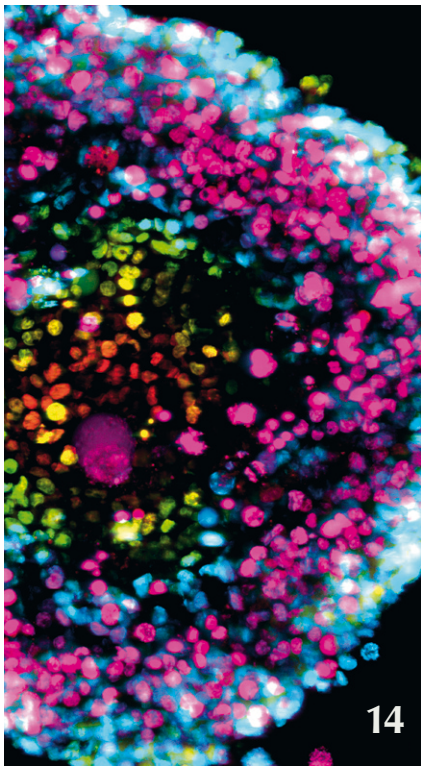
COVER STORY



The hunt for safety biomarkers

Developing safe and effective medications is no easy task. Every year, the pharma industry loses hundreds of billions of dollars due to safety-related attrition during the drug discovery process. For both patients and companies, improving R&D in this area could bring significant benefits. Now novel biomarkers designed to better detect and manage drug-induced organ injury – both preclinically and clinically – have been validated, and are ready to receive the regulatory stamp of approval.

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Picture: Shurong Hou, SLAS Discovery, doi: 10.1177/2472555218766842

MALARIA

Vaccine for a killer

Malaria has a huge impact on patients and national health systems in the tropics, particularly in sub-Saharan Africa. For decades, researchers have struggled to come up with effective ways to prevent it. Now a large-scale vaccination programme is starting, even though the vaccine is far from perfect. Still, it's one step further on the path to stopping an often deadly parasite.

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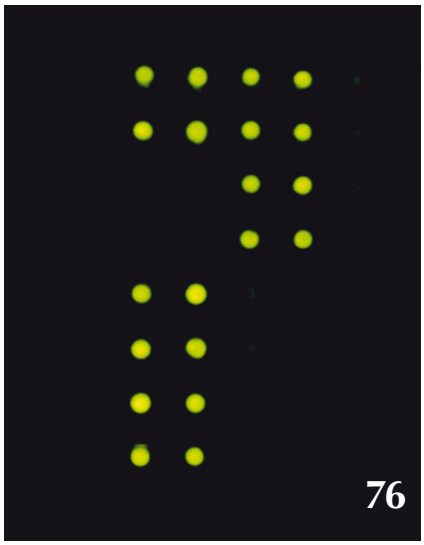
BIOMANUFACTURING



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Cell-free production

Cell-based systems aren't necessarily the best bet for producing biologics on a large scale. Many firms are now turning to lysated cell substrates for their compound needs, because in some cases cell-based production is inefficient. But there are many challenges to overcome in what could be the next big step in protein synthesis.

Pictures: Cell Free Technology (above), Henrik Larsson/stock.adobe.com (left), BIOCOMAG (right), AdobeStock/viperagp (below)

SPECIAL

EU Event Compass

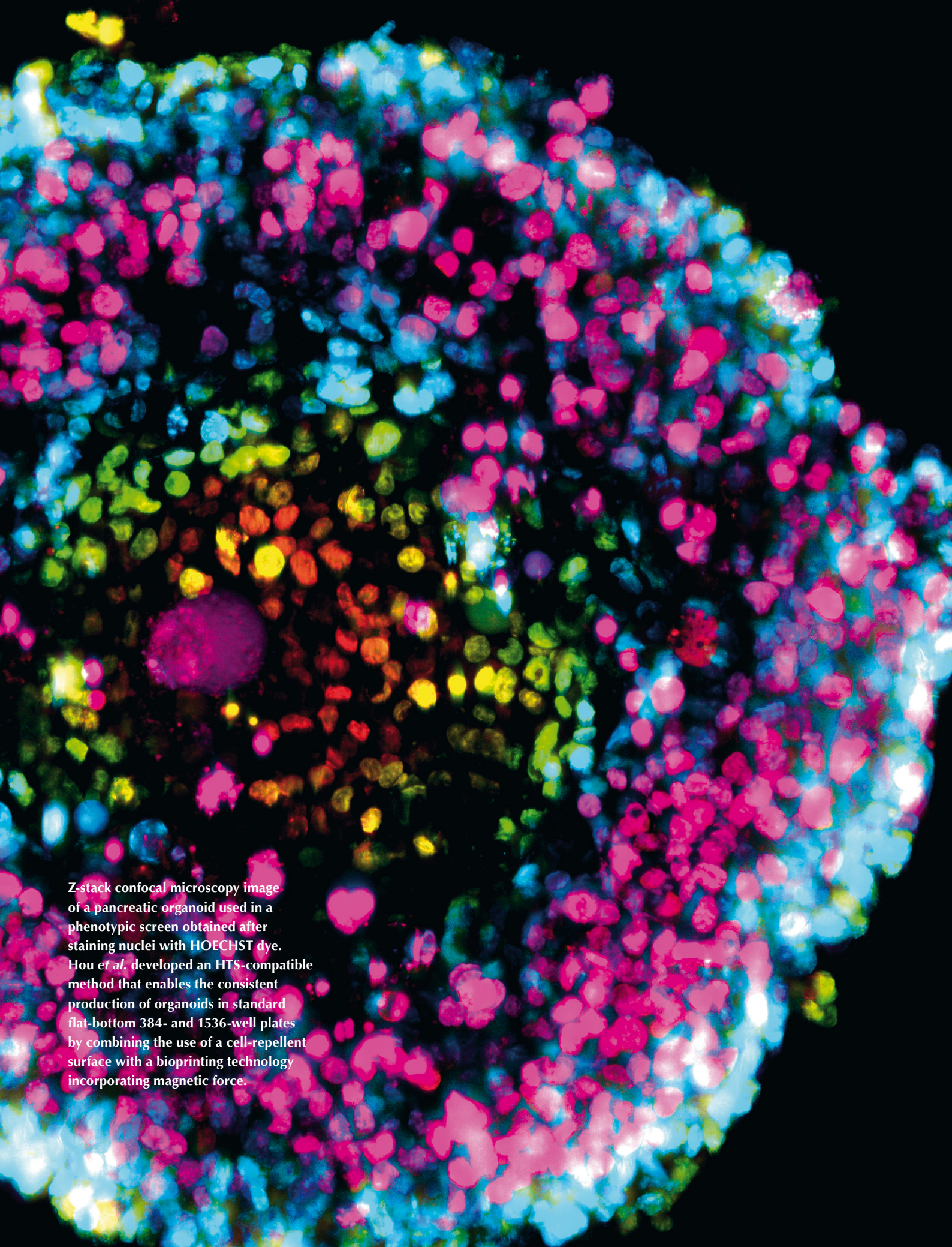
EDITORIAL

Frustrated?

For the European Medicines Agency, Brexit – no matter how it pans out – was a tough blow. The Agency's relocation to Amsterdam in March now looks like it could end in financial disaster. Not only does the EMA expect to lose 25% of its over 900 staff by the move. It could also be out £500m due to obligations in the 25-year lease it signed for its London headquarters before the Brexit vote back in 2016.

In February, the UK's High Court handed down its first-ever judgement on the question of whether Brexit can constitute a "frustrating event". Under English contract law, a contract is "frustrated" if an event occurs that neither party could have foreseen when contemplating a contract – an event that so radically alters the parties' fulfillment of the contract that it would be unjust to continue. The court's ruling that Britain's plan to leave the EU did not prevent the Agency from continuing to use its London office has blocked the EMA's plan to break the lease on its former headquarters with the Canary Wharf Group, the landlord of London's financial district. The Agency is appealing the ruling, arguing it cannot operate from an ex-EU country. The case may define whether Brexit could be used as grounds for breaking a contract. For the Agency, an additional €20m in costs annually from its €333m budget would mean further loss of financial flexibility and independence.

Thomas Gabrielczyk
Editor-in-Chief



Z-stack confocal microscopy image of a pancreatic organoid used in a phenotypic screen obtained after staining nuclei with HOECHST dye. Hou *et al.* developed an HTS-compatible method that enables the consistent production of organoids in standard flat-bottom 384- and 1536-well plates by combining the use of a cell-repellent surface with a bioprinting technology incorporating magnetic force.

FREE EXCERPT

Making every cent in testing count

DRUG DEVELOPMENT It's no easy task to develop medications that are effective and safe to use. The pharmaceutical industry loses billions every year due to safety-related attrition during the drug discovery process. For both patients and companies, improving productivity in the area would bring significant benefits. Now novel biomarkers designed to better detect and manage drug-induced organ injury – both preclinically and clinically – could make the process faster, safer and cheaper.

Did you know that in Britain alone, up to 500,000 patients every year are hospitalised after taking medications – like acetaminophen – that are generally considered harmless? 500 of them will die from toxic effects to the liver. In the US, the same medicines are responsible for an estimated 2,500 deaths per week. Taking properly prescribed drugs is the country's fourth most common cause of death.

The problem is that serious drug safety issues often occur only rarely, meaning drug developers can easily miss them until late-stage clinical testing or right before market authorisation. Matters are complicated by the fact that our ability to monitor areas like drug-induced organ damage remains limited. The biomarkers that are currently available aren't sufficiently sensitive, specific or predictive. In worst-case scenarios, this leads to potentially life-saving drugs having to be withdrawn at the last minute, ruining development work that has often gone on for more than a decade – it takes an average 13 years for a new medicine to make it from bench to bedside. And then the huge development costs have to be written off.

"Even a Phase III failure can mean a waste of €1bn or more," says Dr. Michael Merz. The industry expert in preclinical and clinical drug safety from the University of Zurich is coordinating a five-year project (see interview, p. 20) aimed at identifying drug-induced safety issues much earlier in the drug development process – ideally during preclinical or Phase I development. Even if it has only moderate success, the €28m TransBioLine project that was launched by the Innovative Medicines Initiative (IMI) in April 2019 could have a huge impact. Analysts estimate safety issues in the industry lead to costs in excess of a hundred billion dollars annually.

TORSTEN HOFFMANN, PHD
Senior VP Drug Discovery, Taros Chemicals GmbH, Dortmund

? How much money is the industry losing annually due to drug safety issues?

! *In light of the fact that pharma revenues since 2014 have exceeded US$1tn – and that failure rates in Phase III studies hover around 30% – failure rates due to safety issues during clinical development globally can be estimated to account for unrealised revenues in the triple-digit billion dollar range.*

Drug safety: a complex task

Overall, 20% of all clinical trial failures – and more than 65% of post-launch withdrawals – have been attributed to clinical safety issues like organ-based, mechanism-based or off-target toxicity. A recent analysis of the attrition of 812 candidates developed by AstraZeneca (AZ), GlaxoSmithKline (GSK), Pfizer and Takeda revealed that "non-clinical toxicology was by far the highest cause of attrition, accounting for 40% of drug failures, while Phase I safety issues contributed to a further 25% of failures." The industry experts stressed that "although minimising safety-related attrition has been a significant area of investment across the industry in the past decade, it remains a key area for improvement that could only be addressed by collaboration and development of new assays tackling the complex problem." In 2014, the FDA estimated that just a 10% improvement in the ability to predict drug failures before clinical trials could save US$100m in development costs per drug.

According to Dr. Joanne Bowes from […]

›› Read the full story in the printed issue.

Picture: Shurong Hou, SLAS Discovery, doi: 10.1177/2472555218766842 (left), Taros Chemicals GmbH, Dortmund (right)

Making biotechnology more accessible – that's the idea behind the Bixel project initiated by Irish-British company Cell-Free Technology Ltd. A central component of its approach is a cell-free system to make green fluorescent protein in test tubes arranged in an 8 x 8 grid.

FREE EXCERPT

Leaving the cell behind

BIOMANUFACTURING Many biologics are difficult to express with cell-based production systems, which is why cell-free expression systems have claimed a niche in the market for years. But all these technologies based on plant, insect or bacterial cells have drawbacks that impede large-scale production. Some recent advances might be about to change that.

Cell-free biology sounds like a misnomer. After all, isn't the cell the basis of life? That may be true, but for certain applications in biotechnology that rely on cells as production units, the whole process is just not cost-effective. That's because maintaining all of the cell's metabolic processes requires a considerable investment in both material and energy. Many believe that to make bioproduction faster, cheaper and better, we have to move beyond the cell.

The essence of a cell

By getting rid of cell walls and membranes, the cell's own DNA and many other cellular components, cell-free systems boil down to extracted, protein-making matrices. By adding doses of new DNA to the mix, proteins of interest can be made without the constraints imposed by cell-based systems. Biologists have actuallly been working with cellular extracts for years. These so-called cell-free protein expression or protein synthesis (CFPE/S) systems are used by synthetic biologists to understand biological networks. In drug and industrial enzyme discovery, they're used to rapidly turn genetic material into protein products that can be screened for desired properties in a high-throughput manner. There are hundreds of protocols out there for growing, harvesting and lysing cells. Of course, such CFPS kits are commercially available as well. While CFPS systems have not been implemented for large-scale production by biomanufacturers so far, drugmakers are aware of some inherent limits that all their well-established cell-based systems have in common. The biggest is that many pharmacologically attractive molecules can't be made in sufficient amounts with cell-based systems – often because of toxic effects the products have on the cells that are churning them out.

Picture: Leniobio

REMBERTO MARTIS, PHD
Co-Founder, CEO & CSO, Leniobio GmbH, Dusseldorf, Germany

? What's the unique selling point of Leniobio's technology?

! *About 20% of all protein production projects are shelved because expression in cells cannot be established at yields needed for creating a viable business case from a cost perspective. While cell-free protein expression today can quickly deliver small amounts of proteins when screening DNA libraries, there is a need for higher protein expression yields. Our CFPS technology serves this need.*

Entering clinical stage

Arguably the first company to attempt to make difficult-to-express therapeutic proteins using a cell-free approach was Sutro Biopharma. Employing the company's proprietary platform technologies, the US-based firm developed an antibody drug conjugate (ADC) that entered clinical trials in 2018 – as the first candidate ever produced with a cell-free technology. In March of this year, Sutro started a second clinical programme (also an ADC). The chief scientific officer at the Californian company, Trevor Hallam, explains why cell-free production of ADCs gives Sutro an edge over competitors: "We incorporate non-natural amino acids into specific positions on the generated antibody for site-specific conjugation of cytotoxins with a linker and warhead to enable consistent, stable, pinpoint placement of toxic payloads." Linking toxic payloads to biologics reliably is indeed a challenge, and utilising nonnatural amino acids may be a good way […]

›› Read the full story in the printed issue.

FREE EXCERPT

The Dawn of Malaria's Doom

VACCINE DEVELOPMENT Although it has only been shown to provide partial protection, the first-ever malaria vaccine is in testing in Africa – and there are many more hopefuls in the pipeline. Will we soon eradicate one of the most deadly pathogens in human history?

›› Read the full story in the printed issue.

For this report, the research trip to Ghana has been supported by GAVI, the Vaccine Alliance.

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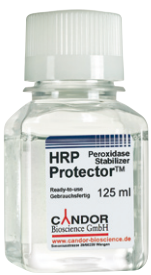

Picture: Candor Bioscience GmbH

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Picture: Andreas Zimmermann

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