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European Biotechnology

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Interview

Abivax CEO Hartmut Ehrlich on what's needed to establish new approaches to autoimmune diseases.

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Protein Degraders

Molecular Targeting

Industrial Biotech

Bioengineered bacteria that could help stop climate change

Patent Waiver

How the WTO is corroding the roots of biopharma innovation

CROs & CDMOs

How gene and cell therapies are transforming the pharma market

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Biotechnology-driven carbon revolution

DR MICHAEL KÖPKE, is pioneer in Synthetic Biology of carbon-fixing microbes. Michael started his career at the University of Ulm and has over 15 years' or experience in biotech. Since 2009, he is working for LanzaTech, currently as VP of Synthetic Biology. Michael is also an adjunct faculty at Northwestern University and part of the Engineering Biology Research Consortium council. He is an inventor of over 200 patents, has published over 50 scientific articles and is an awardee of the Presidential Green Chemistry Challenge award.

Fossil carbon is in nearly everything we use in our daily lives ranging from power and fuels to fibers, coatings, and materials used in our clothes, packaging, toys, and household goods. Virgin fossil carbon use in these products is not sustainable given the current understanding of the impact of extracted, emitted, and waste carbon on our environment, climate, and vulnerable populations. To achieve our climate goals and mitigate climate disasters, a large-scale, robust, rapid, and sustained effort must be made to re-tool our entire carbon economy. To align with a "Net Zero Path," economies today are investing in innovative carbon transformation technologies that enable a circular carbon economy where carbon is reused rather than wasted.

Aimed to foster that clean energy future, biotechnology is poised to play a major part in a circular carbon economy providing a path to displace products made from petroleum with alternatives from recycled carbon. Biological systems are uniquely suited for this challenge. Life on Earth evolved on transforming CO_2 into more complex building blocks and biology unlike traditional technologies is inherently flexible and capable of processing chaotic input streams. This allows accessing low-cost, regional feedstocks including industrial off-gases, agricultural residues, and municipal waste; CO_2 with the addition of green H_2 can make an unlimited supply of sustainable products. Imagine polyester for a dress made from recycled carbon from a steel mill. This is not science fiction, it's happening commercially today. Global consumer brands are already using recycled carbon chemicals in their supply chain enabled by biotechnology.

As we enter a critical period for energy use and for our climate, we should all take steps to consider how to enable a stronger circular carbon economy. As business leaders, we can use carbon transformation to rethink how we procure, use, and dispose of carbon. And as consumers, we can choose where our carbon comes from. In the quest for innovative technologies, we must ensure they benefit both rural communities and traditional manufacturing centers to support a more sustainable, equitable, and resilient economy.

Carbon transformation technologies offer solutions that can be applied across economic sectors, such as agriculture, industry, and waste management, as an essential strategy to reduce greenhouse gas emissions; meet commitments to reduce fossil imports and support the wider economy. Carbon transformation can address sustainability needs domestically by reducing air pollution, recycling waste, providing clean jobs, generating cleaner burning fuels, and producing low-carbon materials stamped. But we need more industries to adopt the approach. To heal and repair the world takes time. And with innovation and strong partnerships and the support of government leaders, we are ready to make the transition and celebrate a post-pollution future. ■

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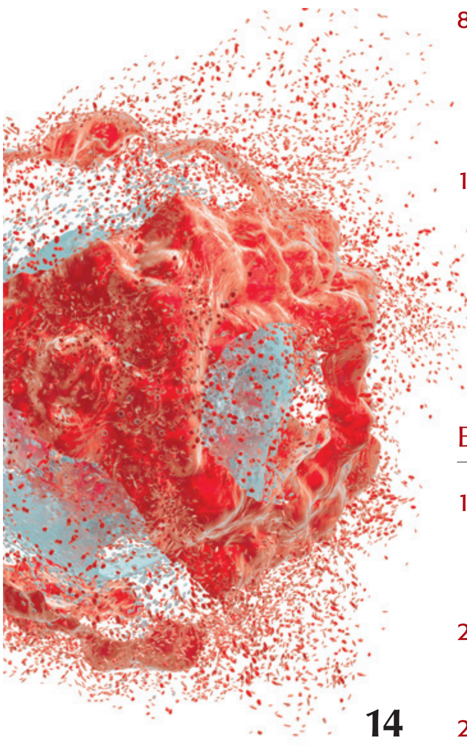
COVER STORY



The new drug class of degraders and glues

The 2004 Nobel Prize for Chemistry was granted for the discovery of the ubiquitin degradation pathway of proteins, while seminal work in the field happened decades earlier. But only recently have over 15 compounds in a new drug class based on ubiquitination truly entered clinical development. What are known as PROTACs and 'molecular glues' are now driving a dynamic field, and the pharmaceuticals industry is throwing a lot of funding at it. The ability to mark disease-causing protein targets for destruction could soon help treat even 'undruggable' conditions.

INSIGHT EUROPE

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INDUSTRIAL BIOTECH

Solving the gas crisis

Fossil fuel use is driving climate change. Almost 80% of today's anthropogenic CO_2 emissions can be traced back to the burning of oil, coal or natural gas. To help preserve existing infrastructure, bioengineers are working to make combustion in cars, aircraft and power plants CO_2-neutral. We took a look at the most advanced technologies in the field.

INFLAMMATION

Final track for Abivax

Paris-based public company Abivax SA has bagged €50m to push development in its promising Phase III candidate obefazimod in autoimmune diseases, starting with ulcerative colitis. We spoke with CEO Hartmut Ehrlich about how despite the cash injection, the trials still face financing challenges.

SPECIAL

CROs & CDMOs

Pictures: © AdobeStock/tilialucida; Abivax SA (right), Gingko Bioworks (upper left), BIOCOM AG (right)

EDITORIAL

Industrial Biotech

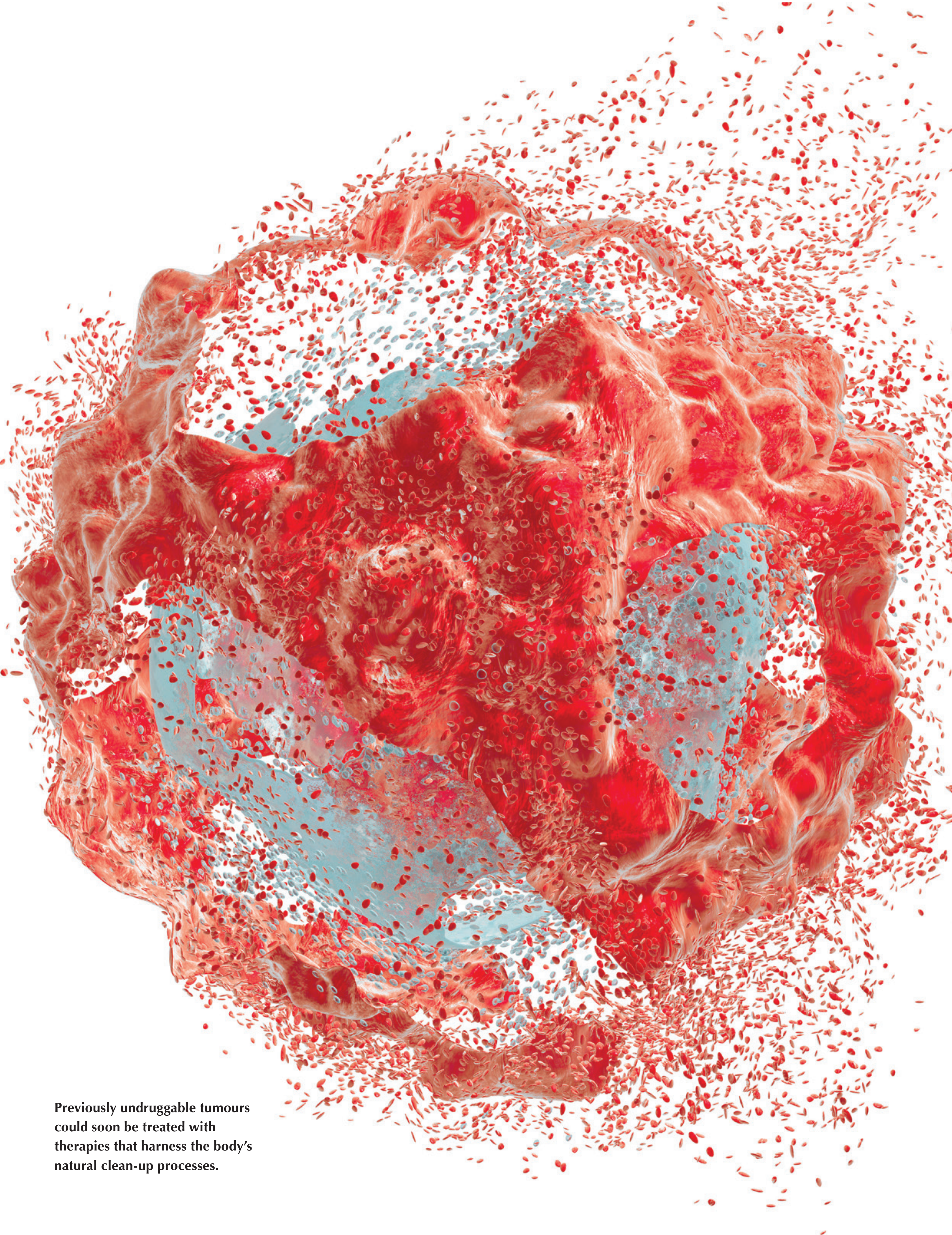
The EU climate change service Copernicus recently determined that in 2022, the months of June, July and August were warmer in Europe than at any time since records began. In addition, August this year was generally much drier than average in Western Europe, and some areas in the eastern part of the continent as well. Few people continue to think we're just living through capricious weather. The climate catastrophe has begun, and industrialised countries are desperately searching for ways to lower dependence on fossil fuels.

Unfortunately, biotechnological solutions are hardly being discussed at all in the current climate and energy crisis, even though it should be clear that our global economy urgently needs to be adapted to the natural cycles of our planet. The best way to do that is to biologise industry. Why aren't decisionmakers talking about it?

A new event aims to remedy the situation: INDUSTRIA BIOTEC, *which will take place on 7 October in Berlin. This European convention is dedicated to the most important areas of application and impact of biotechnological solutions in five forums: Nutrition (Food), Energy, Waste, Chemistry and Capital.*

In addition, there will be a range of other information and communication offers, such as partnering, a start-up pitch, company presentations, an exhibition and – of course – plenty of opportunities for personal exchange. And all of this at a sensational venue from the 1920s. We look forward to seeing you there!

Andreas Mietzsch
Publisher



Previously undruggable tumours could soon be treated with therapies that harness the body's natural clean-up processes.

FREE EXCERPT

Breaking down diseased proteins

UBIQUITINATION The Nobel Prize for Chemistry was granted for the discovery of the ubiquitin degradation pathway of proteins back in 2004, while the seminal work in the field happened decades earlier. But only recently have over 15 compounds in a new class based on the mode of action truly entered clinical development, mainly in cancer. What are known as PROTACs and molecular glues are now driving a dynamic research area, and the pharmaceuticals industry has begun to throw serious funding at it.

Fans can storm a football pitch for a couple of different reasons. It might be after the final whistle, or a serious foul, or perhaps a bad call on the part of the referee. In the game of drug development, however, Big Pharma spectators don't leave their seats very often. So when you see them running out onto the field eager to join forces with promising companies, it's a pretty good bet blockbusters won't be far behind.

The pioneering work behind it

That's what's happening for instance in the field of 'targeted protein degradation' (TPD), which has been evolving and maturing since the early 1980s, when Aaron Ciechanover, Avram Hershko and Irwin Rose published studies on ubiquination that would eventually lead to their jointly-received Nobel Prize. An important milestone along the way was work published by Craig Crews and colleagues in 2001. It described the first hetero-biofunctional degrader – a novel use of the ubiquitin system through external addition that for the first time seemed to put targeted degradation reactions within reach. But it took another decade until Crews was able to move into concrete application and development. He only founded the startup Arvinas in 2013, after it could be shown that a synthetic protein degrader also works *in vivo*.

At that time, the field was still pretty sparsely populated, and not many spectators were scattered throughout the bleachers. But progress at Arvinas and other firms on the pitch was gradually awakening interest. Interestingly, the start-up's first major partnership with Bayer in 2019 was in the agricultural sector, where a joint venture called Oerth Bio was set up to test the functionality and usability of PROTACs in a kind of side-show. After Arvinas launched a clinical trial the same year and started presenting proof-of-concept for their two degrader projects (ARV-471 and ARV-110) in 2020, the field turned into a pretty popular pie. Suddenly, it seemed, everyone wanted a slice.

In the years since, many more companies have brought related projects into the clinic, and a lot more lucrative deals between biotech start-ups and Big Pharma have been struck.

From bench to bedside

By the end of 2022, around 15 degraders will have entered clinical trials, and it's past time to explain how they work. Unlike conventional drugs, which often block the action of a protein by binding to a specific site, targeted degraders use the cell's natural waste disposal system (in which ubiquitin plays a key role) to remove harmful proteins by marking them up for destruction. The principle could also be applied to treat disease, especially for illnesses previously considered untreatable.

A major advantage with degraders is that they can destroy target proteins that can't be addressed with conventional drugs. There are currently two different classes of protein degraders in use: PROTACs (PROteolysis TArgeting Chimeras), and 'molecular glues' (also called 'molecular glue degraders'). Both utilise small molecules that can pass through barriers in cells. PROTACs are made up of two protein-binding molecules joined together by a linker. One of them binds specifically to the protein targeted for degrading. The second molecule recruits the E3 ubiquitin ligase. It's a special enzyme that can transfer the regulatory protein ubiquitin to other proteins, which marks them up for destruction by the proteasome.

Conventional small-molecule drugs require a defined binding site on the surface of a target protein, but molecular adhesives don't. This opens up a completely new possibility – intervening with proteins that were previously consid-

>> Read the full story in the printed issue.

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Future energy: Biology strikes back

SYNTHETIC BIOLOGY When it comes to climate change, combustion is the new scourge of humanity. Almost 80% of today's anthropogenic CO_2 emissions can be traced to the burning of fossil fuels. More than a third of all emitted carbon dioxide is due to power generation, while industrial combustion and transport are each responsible for another fifth. Bioengineers are racing to make combustion in automobiles, aircraft and power plants CO_2-neutral while preserving existing infrastructure. It's a tricky path to tread.

In March of this year, Jason Kelly, the CEO and co-founder of the SynBio company Ginkgo BioWorks, posted an astonishing message. "The best time to address climate change was decades ago," he wrote, then asked when the next-best time would be. "Limiting warming to below 1.5°C will require us to reimagine our industrial landscapes to eliminate emissions and to sequester carbon from the atmosphere," he said. "Decarbonising our energy, materials, chemicals, and food production will require massive shifts in how we make stuff." The way forward, according to Kelly, must definitely be rooted in what he sees as the most advanced manufacturing technology on the planet: biology – particularly, synthetic biology. The code of life of microorganisms, enzymes and cell factories will have to be rewritten to produce energy, fuels, chemicals and food without CO_2 emissions. According to Bill Gates, synthetic biology will soon be one of the enabling climate technologies that will create companies that generate trillions of dollars.

In the midst of the currect energy crisis, some biotech companies are finally ready to make the old combustion technology – decried as a climate disaster but still a pillar of private and industrial transport – more acceptable. After all, their advanced biofuels already cut CO_2 emissions by 60-90% by harnessing gas fermentation of cellulosic waste or combustion gases from steel mills, oil refineries or aluminum smelters. Even natural gas can now be produced in fermenters with help from pathway-engineered microorganisms, without using any agricultural land at all. The tank-or-table debate actually ended long ago. Together with overdue, binding regulations on energy conservation, the widespread use of biotechnology promises a reprieve from annual CO_2 emissions that, according to the International Energy Agency (IEA), doubled globally between 1970 and 2010.

PROF. DR PETER LINDBLAD
Head Microbial Chemistry, Ångstrøm Laboratory, Univ. of Uppsala, Sweden

? How can SynBio contribute to the mitigation of CO_2 emissions?

! *By combining advanced genetic engineering and synthetic biology, we can design microbial cells that are capable of performing entirely new functions. Our team is trying to demonstrate how you can take modified cyanobacteria that produce isoprene and, by using solar energy and photochemistry, get aviation fuel directly.*

Carbon-negative manufacture

Using the chemolithotrophic bacterium *Clostridium autoethanogenum* as a chassis strain for AI-supported metabolic pathway engineering, Illinois-based Lanzatec Inc. has established a continous production process that can produce drop-in biofuels and over 100 commodity chemicals with a negative carbon footprint. The company licences its carbon capture and transformation (CCT) plants under the product brand CarbonSmart™ to industrial customers.

For commercial-scale, next-generation bioethanol production, the company runs two plants in China that convert steel mill combustion gases. Already in pilot-scale seven years ago, the continuously optimised process produced bio-ethanol that emitted 70% less CO_2 than gasoline – a result similar to second-generation cellu-

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