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# European Biotechnology

Life Sciences and Industry Magazine

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## Interview

Novozymes's New Business Development Head Sebastian Søderberg on the value of open innovation.

T cell therapies

FREE EXCERPT

# CARs crash cancer

## Modern breeding
How the ECJ ruling on genome editing thwarts organic farming

## DNA synthesis
Can a new enzyme approach help solve global problems?

## Photosynthesis
Engineers converge on the Holy Grail of energy production

## CROs & CDMOs
New technologies that trigger pharma outsourcing growth

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# Turning cancer into a "chronic" disease

**PROF. DR. DOLORES J SCHENDEL** is CEO of Medigene AG. From 1998–2013, Prof. Schendel was Director of the Institute of Molecular Immunology of the German Research Center for Environmental Health at the Helmholtz Center in Munich. Previous to this, she served as a university professor for immunology at the Ludwig-Maximilian-University, focusing on human cellular immunology and T cell responses within the field of oncology. Prof. Schendel is the author of more than 200 scientific publications.

*Following last year's approval by the US FDA, the EU's EMA has now also approved the first two T-cell-based immunotherapies against certain types of cancer. This marks the ultimate proof-of-concept for the acceptance of patient-individualised cellular immunotherapies. The regulatory authorities have moved fast, together with the companies and manufacturers, to bring these products to patients as quickly as possible. This is a good start – but what does the future hold?*

*Initially, prices for such cellular therapies have been set at high levels, mainly due to the individualised nature of the manufacturing processes, but we can anticipate that robotics and automation will play a decisive role in the manufacturing of these products over the next five to ten years. Even more, if production sites are located at nearby hospitals where patients are being treated, this should have a positive effect on reducing the enormous logistic infrastructures that are needed today to deliver these therapies to patients in need. Furthermore, it may become possible to treat patients with fewer but more potent cells, reducing time and costs in cellular manufacturing. Taken together, those improvements have the potential to substantially reduce treatment costs over the years to come.*

*Beyond manufacturing and delivery costs, possible severe side effects are still a major concern in T cell immunotherapy. We see a lot of research ongoing to find ways to gain better control over T cell activity – for example, by using inducible T cell receptors that can be turned on and off in patients' T cells as needed. The immunotherapy field shows tremendous growth, and we can anticipate innovation will expand at a rapidly growing pace. Today's first-generation products will be subject to fast evolution. One important consideration is how long a particular product will remain on the market. Also especially challenging from a researcher's point of view is how to optimize T cell therapies for solid tumor indications, where one must ensure that T cells can enter the tumor micro-environment, maintain their functions, and tackle the hostile setting that tumors create for the immune system.*

*Generally speaking, big pharma and big biotech recognise more and more that this is an arena they want to play in, and some are probably already looking for means to acquire expertise and know-how, as well as products and technologies from existing companies. Thus, we will also see many collaborations and probably more acquisitions over the next years.*

*Most importantly, from a patient and medical point of view, cell therapy is on its way to further revolutionize cancer treatment and become a standard treatment option by turning cancer more into a "chronic," if not curable, disease.* ■

Picture: Medigene AG

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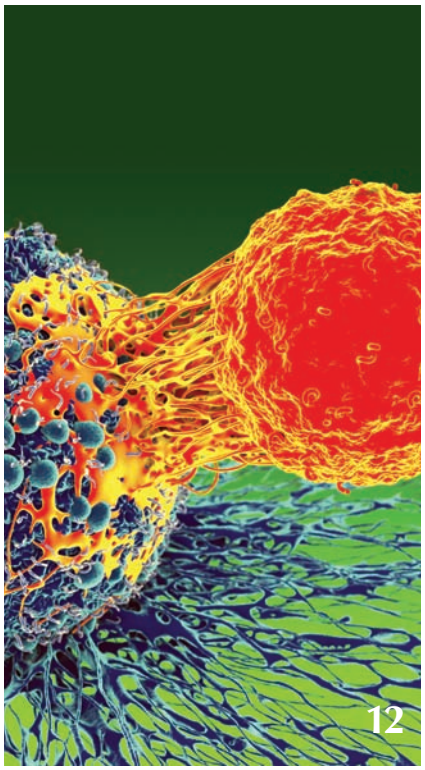
## COVER STORY




# CAR-T cell therapy revs up in Europe

Ever since reports that blood cancer response rates to T cells carrying chimeric antigen receptors (CARs) exceeded 80%, investors have been betting big on CAR-T cell approaches. In August, the first two therapies hit European markets in a head-to-head race to be the number one next-gen cancer therapy. But will CAR-T cell treatments lead the pack long term? Or will alternatives like TCR-based cell therapy or multivalent bispecific antibody-T cell engagers leave them in the dust?

## INSIGHT EUROPE



## FINANCIAL MARKETS



## ECONOMY



## REGIONAL NEWS



## SCIENCE & TECHNOLOGY



## SERVICE



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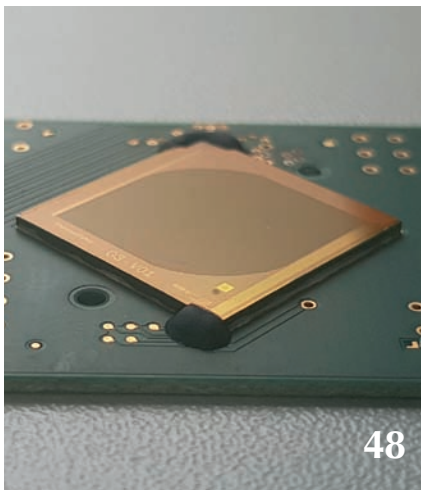
DNA SYNTHESIS

## Building a genome

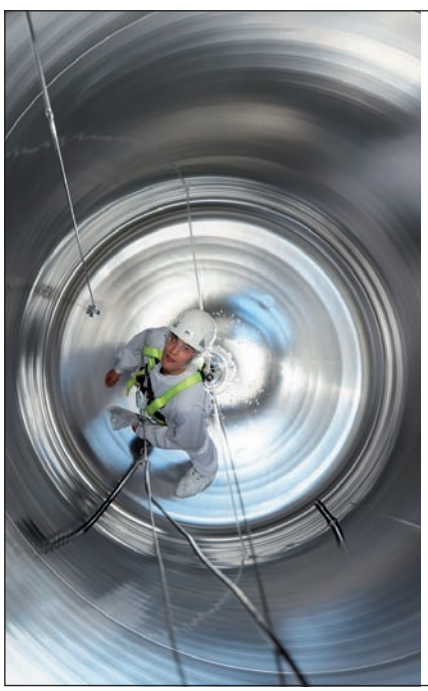
The methods used to make DNA from scratch have been around for well over 40 years, and have drawbacks. They can be inaccurate, slow and the solvents used are bad for the environment. Now startups are looking to develop new methods for building the code of life that use enzymes rather than chemicals. Will they soon gain a foothold in the market?




BIOECONOMY


## The cure for $CO_2$

Levels of atmospheric carbon dioxide nearly doubled over the last century. So why not just take a page out of Mother Nature's book and harness this immense potential energy source with the help of artificial photosynthesis? In the lab, synthetic biology approaches are making decisive progress in the field, and improving on naturally evolved systems.



Picture: Thermo Fisher Scientific (left, above), Roche (left below), temmuzcan/istockphoto.com (middle), BIOCOM AG (right)

SPECIAL

## CROs & CDMOs



EDITORIAL

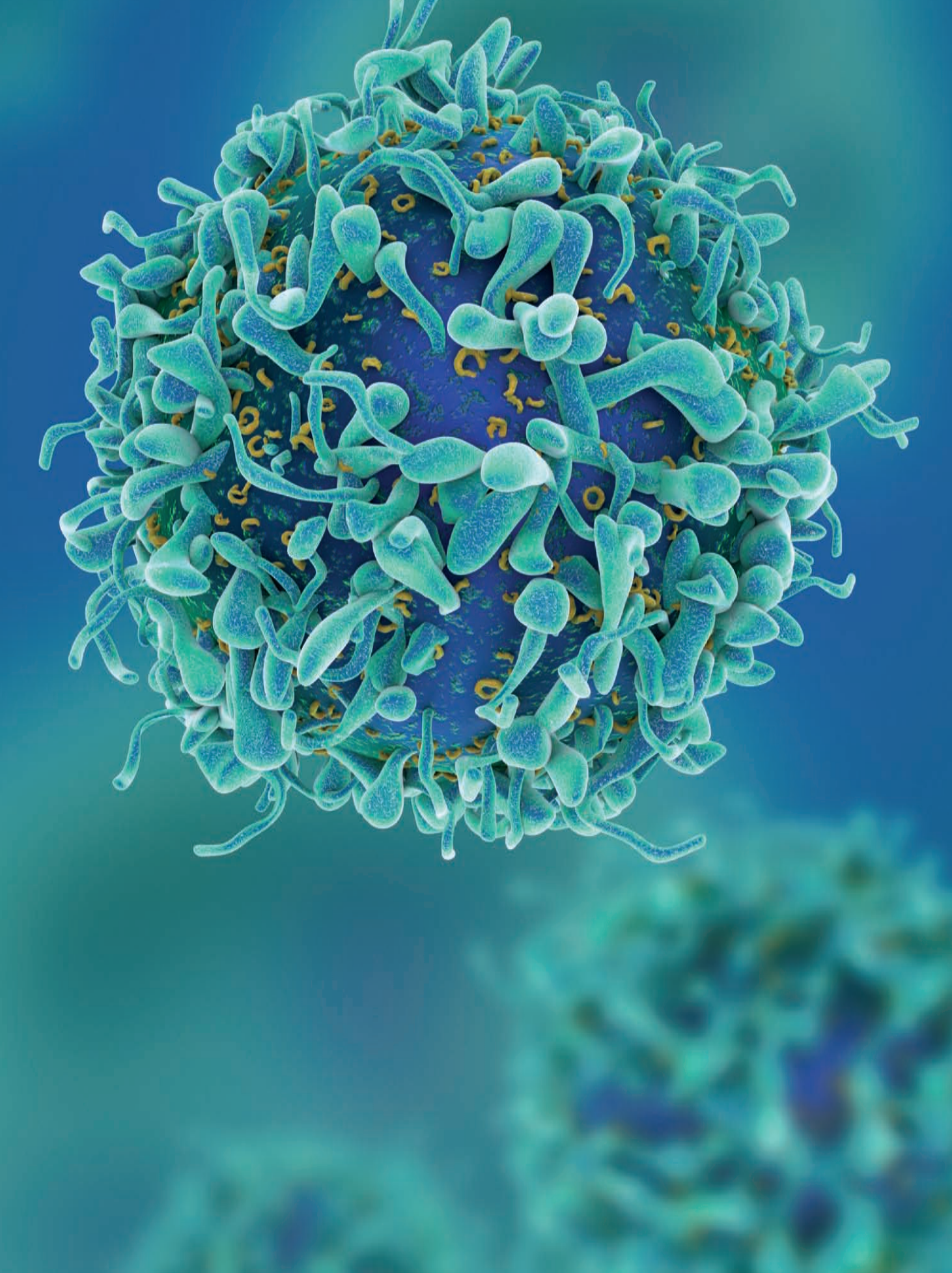
## Counterstroke

*For years, cancer immunotherapy has been celebrated as a new treatment paradigm. In September, however, the first hints of possible long-term effects surfaced. A team from the reowned Gustave Roussy cancer centre reported that PD1- or PD-L1 blockers actually cut overall survival in a subgroup of NSCLC patients by pushing proliferation and metastasis (see p. 71). And reports published prior to that analysis indicate the phenomenon of hyperproliferative disease isn't limited to lung cancer.*

*Another area of successful activation of T cells against cancer has also inspired investor fantasies of hitting the jackpot. In August, two CAR-T cell therapies were okayed by the European Medicines Agency, and are now in the midst of a race to dominate the European blood cancer market. On p. 12 we get you up to speed on the competing technologies, and explain which offer price advantages. After all, payors are now having to shell out swingeing amounts for one-time treatments.*

*In oncology, it's nearly always two steps forward and one back. But real progress has been reported from the field of artificial photosynthesis (p. 84) and gene synthesis (p. 48). And finally, for all our readers dealing with company performance, this issue for the first time includes a wide-ranging finance and capital market section (p.20). Hope you enjoy it – and give us some feedback!*

Thomas Gabrielczyk
Editor-in-Chief



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# CARs right on track

**ONCOLOGY** Since reports that blood cancer response rates to T cells carrying chimeric antigen receptors (CARs) exceed 80%, investors have been laying bets on CAR-T cell approaches. In August, the first two therapies hit European markets in a head-to-head race to be the number one next-gen cancer therapy. So will CAR-T cell treatment really take pole position? Or will alternatives like TCR-based cell therapy or multivalent antibody-T cell engagers leave them in the dust?

The story of eight-year-old Kaitlyn from Dallas sounds like a Hollywood screenplay. After being diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) in 2011, she was one of the 15% of patients that relapse from chemotherapy. After two and a half years of chemo, with every recurrence bringing a worsening prognosis and drop in quality of life, she was given a one-time CAR-T cell infusion within a clinical trial. Previously, her own T cells were engineered outside her body to carry a receptor activating them to attack cancerous blasts upon binding the cell-line specific CD19 surface marker. When reinjected, they proceeded to wipe out her cancerous and healthy B cells. In September 2017, according to US broadcaster CNBC, she had been in remission for almost three years.

It's still too early to know whether Kaitlyn is an isolated case. But clinical data from two FDA- and EU-approved CAR-T cell therapies, as well as results from late-stage clinical trials, suggest she might not be. According to Seeking Alpha analyst Bill Koski, over 80% of the 75 children with chemo-recurrent B-ALL responded to Novartis' Kymriah™ (tisagenleucel) in the pivotal ELIANA trail. 60% of those exhibited a complete response (CR). The therapy was greenlighted by the FDA in August 2017, just five years after Novartis licensed it from Carl June at the University of Pennsylvania. Just a year later, the EMA followed suit.

The short time-to-market and low patient numbers (well below 100) required for accelerated market authorisation have helped trigger a wave of company foundations, multi-billion M&As, licensing deals, and a burgeoning crowd of CAR-T cell candidates. 354 are currently in pipelines, 76% of them in preclinical testing. The pricing for CAR-T cell therapies has contributed to the surge. (For a company/programme overview, see fig. 1, p.14).

Kymriah, which is made individually for every patient, has an outcome-based price tag of $475,000 in the US. "If we don't see a complete response by 30 days, they don't pay for the therapy," explains Liz Barrett, CEO of Oncology at Novartis, adding that "there haven't been very many cases where it didn't work". According to her, "there are about 300 patients in the relapsed, refractory patient population" in the US. A further 300 patients per year are in other target markets. In early September, the British National Health Service (NHS) agreed to reimburse Kymriah at "well below the European list price of US$363,000 per B-ALL patient," a spokesman at the UK's health technology assessor NICE told European Biotechnology.

**MICHAEL ELLIOT**
**VP Medical Affairs Europe, Gilead Sciences**

? Will hospitals offer both EU-approved CAR-T treatments to treat DBCL?

! *I think maybe the preference would be to work with one company and their system, but it may be that some units want to do their own internal comparison.*

## A huge and hopeful market

However, Novartis and other CAR-T cell players – like Celgene, bluebird bio or Gilead – are focusing on blood cancer indications with much higher patient numbers, because they translate into better profits. "It's important to keep in mind where CAR-T is going. You start in the later lines of therapy, because that's where the highest unmet medical need is," says Barrett. "But we're planning clinical studies in earlier lines of therapy where patient populations are much larger. Catching patients earlier will hopefully prove better for everyone," she remarks.

And of course the real hope is not only to treat blood cancers – which make up just 10% of all cancers – but solid cancers as well. They're already being targeted by companies like Eureka Therapeutics, Celyad NV, Minerva Biotechnologies, Autolus Ltd and others. A range of academic […]

›› **Read the full story in the printed issue**.

Pictures: gtoolbox/istockphoto.com (left), Gilead Sciences (right)

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# Sustained optimism

REPORT

**ANALYSIS OF EUROPEAN BIOTECH COMPANIES ON THE STOCK MARKET**

Biotech stock markets are still appreciated by investors. Whereas the number of IPOs significantly decreased in the first half year of 2018 compared to 2017, follow-on financings doubled. This is particularly true for European stock exchanges. Nurtured by the further progress of breakthrough technologies such as CAR-T for cancer therapies, listed European biotech companies profit from a sustained optimism among investors.

›› **Read the full story in the printed issue**.

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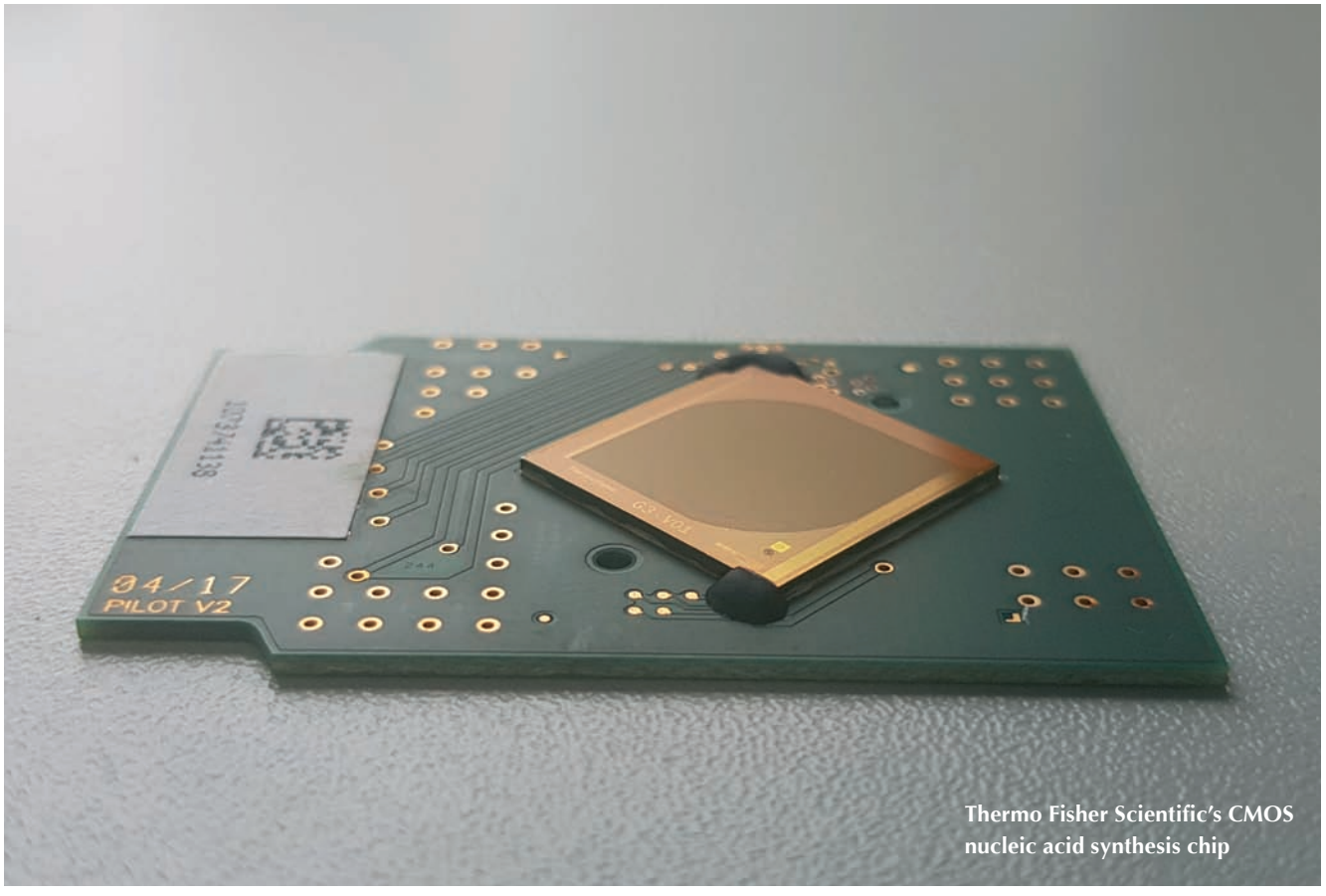


Thermo Fisher Scientific's CMOS nucleic acid synthesis chip

# Pioneers in the synbio revolution

**DNA SYNTHESIS** Is synthetic biology on the cusp of unlocking the next industrial revolution? A major roadblock is the ability to synthesise DNA for R&D in ways that are both cheap and efficient. Established players in the field believe the answer lies in miniaturising standard chemical processes and running them in parallel systems. But the new kids on the block are betting on a completely new process that involves enzymes.

›› **Read the full story in the printed issue**.

Picture: Thermo Fisher Scientific

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# Copying nature to save the planet

**SYNTHETIC BIOLOGY** Levels of atmospheric carbon dioxide almost doubled over the last century. So why not just take a page out of Mother Nature's book and harness this immense potential energy source with the help of artificial photosynthesis? Researchers around the world are now trying to produce fuels using just $CO_2$, water and light. The technology has a long way to go to reach large-scale viability, but in the lab researchers are making decisive progress.

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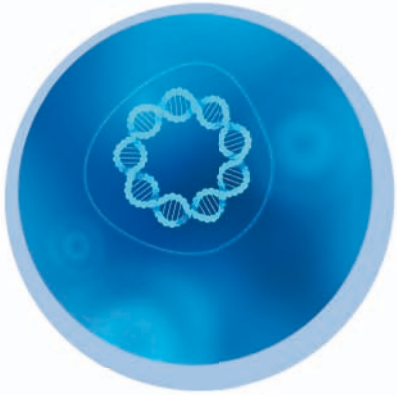

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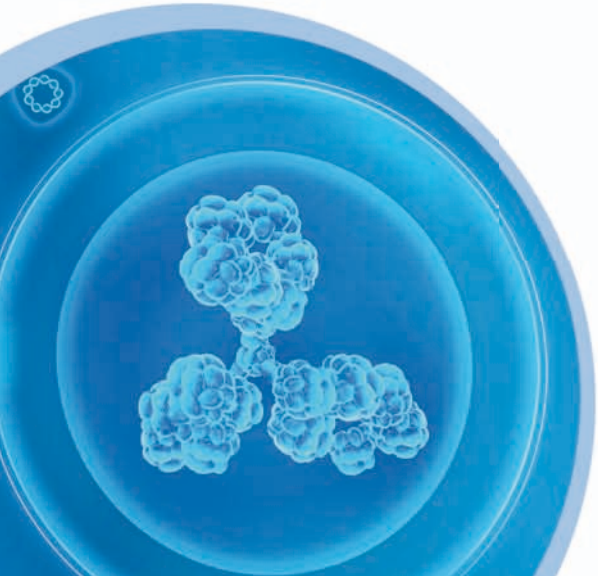

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