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European Biotechnology

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Interview

Federico Pollano from Rentschler Biopharma on what drives developments in the CDMO market.

Cancer

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The thing about milk...

Structural Proteomics
Breakthrough AI algorithms unravel 3D protein folding

Country Close-up
Biotechnology in Spain is growing in leaps and bounds

CDMOs & CROs
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Europe needs strong incentives for private biotech funding

DR RAINER STROHMENGER
joined Wellington in 1997 and became a Partner in 2000 with responsibility for the life science activities, to date comprising €450m of investment volume. Previously, he was involved in research work in cardiovascular physiology and health economics. Dr Strohmenger holds MD/PhD and MSc of Economics degrees from LMU, Munich, and was trained at the Entrepreneurship Center of MIT, Boston. He is a Member of the VC Council at InvestEurope and a Member of the Senate at BVMW.

The COVID-19 pandemic has demonstrated how vulnerable human beings and societies are to a new infectious disease, and how important the life science industry is to come up with diagnostic and therapeutic solutions. The first and most widely used vaccine was developed in a record time by German biotech company BioNTech, financed with private money provided by highly entrepreneurial investors.

The attention level of politicians in the biotech sector has significantly increased. Following Trump's attempt to secure exclusivity for its COVID-19 vaccine, CureVac received EU grant funding and a €300m investment from KfW, and the European Commission launched the FDI regulation to protect critical life science technology from foreign acquirers. This initiative, however, negatively affects exit processes and increases the hurdles for European companies to obtain private financing.

Even though EU biotech funding has marked a record high last year, the gap behind the US has been opening further. The aggregate investment in US biotech is more than 30 times higher than in Germany, compared to a factor of 15 twenty years ago, although the US population is only Four times larger and relative innovative potential is similar.

In order to alleviate this, the European Commission created the €10bn EIC Fund with 30% dedicated to the life science sector. While the EIC Fund can lead financing rounds and formally provides "private" capital, it does not behave like a private VC. Application for funding is a bureaucratic process similar to an EIC grant application. It is questionable if this is the right financing instrument for biotech start-ups to successfully compete with their US competitors.

The vaccine race won by BioNTech has shown that more private, entrepreneurial biotech financing in the EU is required. If the private sector fails to provide sufficient capital despite the attractive return potential, we need stronger incentives for investors to fund companies across all stages of development. It is not acceptable that the largest asset managers neglect the European life science sector, while simultaneously increasing their allocations for US biotech and other PE fields in the EU.

Tax incentives do not work if investors do not pay taxes in the EU. The strongest incentive would consist in a mandatory capital allocation for European biotech pro rata to their investments in other geographies or PE areas. We have seen EU politicians developing regulations to foster ESG and gender equality as a response to market failure. Now is the time to foster private biotech investments. ■

Picture: Wellington Partners

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COVER STORY

About that milk...

Progress in the search for new treatments for colon cancer and other solid tumours has been slow, but the old adage about an ounce of prevention being worth a pound of cure holds true. Now recent research from German Nobel laureate Harald zur Hausen, who showed that human papilloma viruses cause cervical cancer, has established a causal link between bovine episomal pathogens found in milk and red meat and subclinical chronic inflammation – and subsequent tumour genesis. Food authorities are looking at the issue, but have yet to make regulatory moves.

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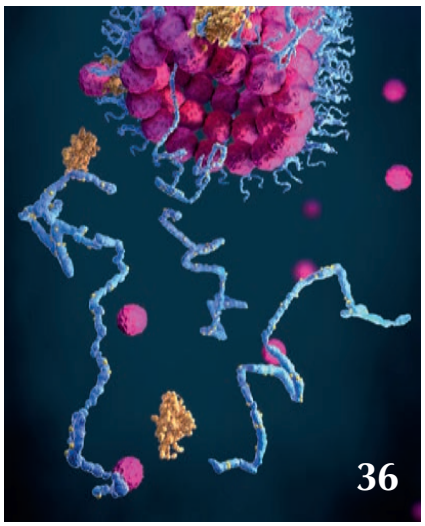
ARTIFICIAL INTELLIGENCE

The next revolution

AI-driven pattern recognition could help biotechnologists design better medicines, engineer more nutritious crops and develop greener enzymes. In June, Alphabet subsidiary DeepMind announced it had solved a protein folding problem that has dogged the field for half a century. Its self-learning protein prediction tool Alphafold 2 can forecast globular protein structures within minutes.



ANTIBIOTICS RESEARCH

Antibiotic boost

After seven years of funding, the European Gram-negative Antibacterial Engine (ENABLE) will be finished in Autumn 2021. Wandrille Ract-Madoux, CEO of French firm Mutabilis, explains how the support helped attract further funding.

SPECIAL

CROs & CDMOs

Pictures: istockphoto.com/ Christoph Burgstedt; Mutabilis; istockphoto.com/ filipjelic

EDITORIAL

Prepared for crises?

Shortly before this issue of European Biotechnology went to print, the EU announced it will declare health emergencies on its own in the future. This seems a late if reasonable reaction to the pandemic, as EU institutions reacted very slowly compared to counterparts in the US.

There the former administration gathered industry experts under the aegis of the NIH, CDC and BARDA to identify promising vaccine candidates and medicines to fight COVID-19 without any calls, established an adaptive trial design, and pushed development with a budget of US$12bn starting in March 2020. The first antibody treatment was approved nine months later. Regeneron's antibody mix REGN-CoV is still awaiting EU approval, which will hopefully finally come by the end of this year.

The EU also delayed funding of promising COVID-19 drugs in favour of vaccine development. Now, in Autumn 2021 it finally has decided to copy the structure of BARDA by starting the EU authority HERA from scratch.

The European Parliament has now adopted the appropriate legislative package. MEPs have also decided to enable the existing ECDC to combat cross-border health threats, and to hire qualified staff to monitor crises, as well as to set up an ad hoc team of doctors and nurses to hit the ground fast when needed. Better late than never.

Thomas Gabrielczyk
Editor-in-

Why milk and meat can trigger cancer

ONCOLOGY For years, pharmaceutical companies have made little progress in the search for new treatments for colon cancer and other solid tumours. Now research from Nobel laureate Harald zur Hausen has established a causal link between infection with the bovine episomal pathogens found in milk and red meat and subclinical chronic inflammation, as well as subsequent tumour genesis. Food authorities are asking questions, but haven't yet moved to protect infants from infection.

Harald zur Hausen is used to resistance. After the German virologist published evidence in 1976 indicating certain human papilloma viruses (HPV) cause cervical cancer, he was scorned for years by researchers, authorities and industry experts. Today, HPV antigen-based cervical cancer vaccines such as Gardasil (Merck Sharpe & Dohme) or Cervarix (GlaxoSmithKline), which were approved in 2006 and 2007 respectively, have become widely established preventive measures, even though uptake remains low (30%) considering the vaccine's potential benefits. The merits of the virology pioneer's groundbreaking work have also been honoured with the science world's most prestigious award. In 2008, zur Hausen received the Nobel Prize for Physiology or Medicine together with HIV researchers Françoise Barré-Sinoussi and Luc Montagnier. But as his latest publication (PNAS, doi: 10.1073/pnas.2025830118) shows, history can sometimes repeat itself.

Shaken beliefs

"I am open to scientifically sound criticism, as long as it is based on data," says the researcher, now an 85-year-old early riser who some call stubborn. "On the other hand, rejection of a thesis based only on gut feelings that something can't be just because you don't know it – that is abhorrent to me," zur Hausen told EUROPEAN BIOTECHNOLOGY. What zur Hausen is referring to is what he views as superficial criticism by the German Federal Institute for Risk Assessment (BFR, Berlin) and the collaborating Max Rubner Institute (MRI, Karlsruhe) on the chain of evidence he and co-workers have generated about a novel cancer etiology hypothesis. According to the researcher, one could at least expect such key authorities to study the scientific literature thoroughly.

> "There is a wealth of publications on the fact that the inflammatory reaction and the development of cancer are connected – only the pathogen was not known."

The new hypothesis has been developed and validated by zur Hausen, South African researcher Ethel-Michelle Villiers – who is also his wife – and the research team headed by Timo Bund at the German Cancer Research Center (DKFZ). Published data from the researchers, "soon to be confirmed by groups in San Diego and Maastricht", zur Hausen said, suggest that a number of cancers appear to be caused indirectly by infection of infants with novel, self-replicating mini-chromosome-like DNA pathogens after breastfeeding is replaced by commercial dairy products or cow's milk or beef products are ingested. Called 'Bovine Meat and Milk Factors' (BMMFs), the new class of single-stranded DNA episomal vectors show some similarity to certain viruses and bacterial plasmids, and can act as indirect carcinogens contained in and transmitted by milk products and serum sourced from Eurasian domestic cattle (*Bos taurus*). BMMFs appear to penetrate only the still immature immune system in infants in the first year of life. It remains unclear whether immune tolerance, decreasing maternal antibodies or perhaps other mechanisms are what makes infants vulnerable to BMMF infection. "The consumption of milk products and red meat later in life presumably doesn't matter," explains zur Hausen, whose results prompted the BfR and MRI to issue a statement in 2019. In it, the authorities say that "the consumption of cow's milk without any restriction is still recommended in compliance with the latest available knowledge."

BMMFs express the replication initiator protein Rep, including [...]

›› Read the full story in the printed issue.

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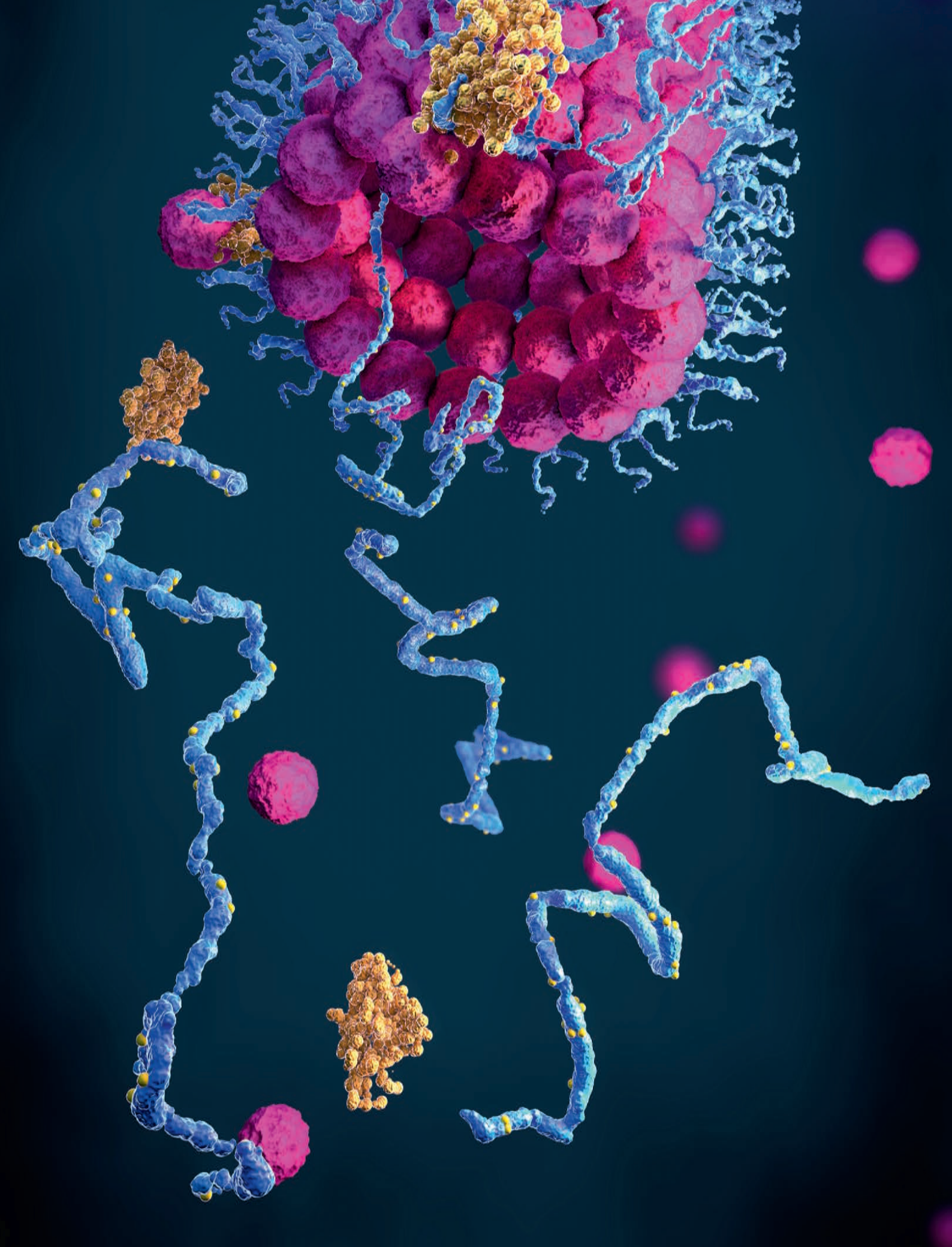

FREE EXCERPT

Protein Intelligence

AI In the EU's Horizon Europe innovation programme, combining biology with artificial intelligence is high on the agenda. The hope that AI-driven pattern recognition can help biotechnologists design better medicines, engineer more nutritious crops and develop 'green' enzymes that can break down plastic waste got a boost in June. That's when DeepMind, a UK subsidiary of Alphabet, claimed to have solved the 50-year-old protein folding problem. Its self-learning protein prediction tool Alphafold 2 can forecast any globular single protein structure within minutes, which could have big implications for technical applications.

Determining the 3D shape of a protein used to take years – and sometimes proved impossible. Now the British start-up DeepMind, which was purchased by Google in 2014 for US$500m, has turned the world of structural biologists upside down. With a second generation of the self-learning algorithm Alphafold, the AI specialists at the company – in the space of just a few months – predicted 350,000 spherical protein structures based only on their amino acid sequence. To gain more traction in the scientific community, the firm also released Alphafold 2's source code in July, and announced that by the end of this year it will publish 130 million additional protein structures in the Alphafold Structure Database, which is run by the European Bioinformatics Institute (EMBL-EBI) in Hinxton (UK).

Alphafold 2 works 14 times faster than its predecessor, and achieves an accuracy and partly sub-angstrom (Å) resolution previously reserved for experimental methods like cryoelectron microscopy, NMR and X-ray crystallography – the methods used to determine the 180,000 protein structures known to date.

Progress that stunned the field

"We believe this is the most significant contribution AI has made to science to date, and it is a great example of the benefits AI can bring to humanity," announced company CEO Demis Hassabis. In the past two biennial CASP competitions (Critical Assessment of Protein Structure Prediction), DeepMind has also edged out rival protein prediction tools. "It marks an exciting moment for the field," added Hassabis, who was also a co-founder of the firm. "These algorithms are now becoming mature and powerful enough to be applicable to really challenging scientific problems." In fact, only one other AI-driven protein prediction program, developed by researchers at the University of Washington (Science, doi: 10.1126/science.abj8754) – dubbed RoseTTAFold – compared favourably to Alphafold 2 in terms of performance at the CASP. The competition is viewed as a kind of Olympics for protein prediction tools.

PROF DR ANDREI LUPAS
Max Planck Institute for Developmental Biology, Tübingen (Germany)

? What impact do you think Alphafold 2 will have?

! *It's a game-changer. This will change medicine. It will change research. It will change bioengineering. It will change everything.*

How does it work?

Contest metrics (GDT) ranging from 1-100 reflect the percentage of amino acid residues correctly predicted within a threshold distance from the experimentally verified position within a protein chain. Alphafold 1 and all other protein prediction tools build a multiple sequence alignment (MSA) of homologous protein sequences, then extract roughly speaking how strongly co-evolving every residue is with respect to every other residue. This summarised information is then fed into a neural network to predict a "distogram" – a matrix of the probabilities of pairwise distances between all C- atoms.

Alphafold 2 works in a completely different way. It no longer summarises the MSA. Instead, it keeps all raw sequences and iteratively decides which sequences are worth looking at and which can be safely ignored. Those decisions provide the basis for its distogram. The self-learning program starts out building local structures within individual protein domains, then branches out to more global features like the relative orientation[…]

›› Read the full story in the printed issue.

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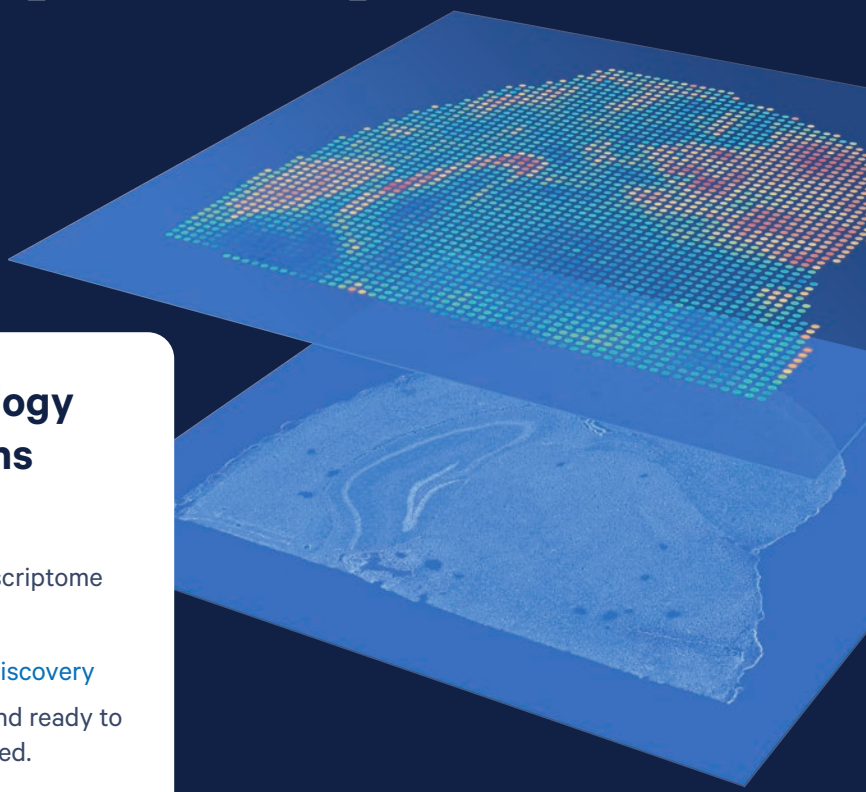

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