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Genome editing turns biotech upside down

The simplification of targeted cut and paste techniques for whole-genome manipulation has triggered a flood of new developments in both basic and applied life sciences. With researchers now using the new CRISPR/Cas9 DNA-scissors on a major scale, a patent war is also looming. Not surprising, since repairing faulty genes in blood cancers and other inherited disorders is potentially worth billions. And a wide range of other applications could also prove to be game-changers in the global life science economy.
EDITORIAL

Diving into Brussels

Just two weeks after the publication of our last issue, the new European Commission binned the ambitious circular economy package. While MEPs and EU Environment Ministers continue to protest, the new Commission insists that its goal is to improve legislation. EUROBIOTECH has discovered exactly what changes Juncker’s team is preparing to table (see p.8).

Finding biotech processes that improve the recycling of raw materials of strategic interest is another focus of the EC’s strategy. Our reporter Martin Laqua dove deep into the biomining scene to look for projects aimed at overcoming current bottlenecks (see p.52).

Both agri- and pharma biotech are on the verge of landslide changes set in motion by a novel tool for the targeted manipulation of genes and gene networks. EUROBIOTECH asked experts from different fields if and how CRISPR/Cas9 genome editing will improve gene therapies, R&D and drug discovery (see p.14).

The vaccine market is undergoing restructuring, and major improvements are mainly being achieved by innovative biotechs and EU initiatives like IMI and EATRIS. EUROBIOTECH correspondent Bernd Kaltwaßer reports on p.36.

And finally, how financing and the IPO landscape improved for EU biotechs is subject to a new BIOCOM report (see p.24). Happy reading!

Thomas Gabrielczyk
Editor-in-Chief

BIOECONOMY

Europe’s new focus on bioleaching

Mining has traditionally been energy-intensive and not exactly great for the environment. But innovative approaches to one of humanity’s oldest professions is changing both its carbon footprint and the way we approach the acquisition of the metals and minerals our societies depend on.

VACCINES

This won’t hurt a bit

Although the worldwide vaccine market has experienced double-digit growth for years, the vaccine industry faces huge structural changes. Some major players have quit the field completely, others are replenishing pipelines with new techniques and molecules developed by specialised biotech companies.

SPECIAL

IP in Life Sciences

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FREE EXCERPT
Letter to the EC

OFF-LABEL USE Three organisations have attacked Italy for adopting a new law that favours cheaper off-label medicines over market-approved products. In a letter of complaint sent to the European Commission at the end of January, the pharma industry interest groups EFPIA, EUCOPE and the biotech association EuropaBio stressed that they are “particularly concerned of the fact that certain member states [such as Italy] have introduced measures to expand the off-label use of medicines solely for economic reasons, while an [market-approved] alternative is available.” According to the lobby groups, this practice would undermine the EU system of the safety and efficacy assessment of medicines, and would contradict judgements from the European Court of Justice.

Last March, Italy’s antitrust authority fined Novartis and Roche €182.5m for colluding to keep doctors from prescribing Roche’s cancer drug Avastin as treatment for age-related macular degeneration (AMD). Italy’s government stressed that that there is no difference with regard to the safety and efficacy between the companies’ marketed VEGF blocker Lucentis, and its not AMD-approved, but 300 times cheaper, parent antibody Avastin, which has been used extensively off-label for treatment of the eye disease. However, EFPIA, EUCOPE and EuropaBio state that “in addition to posing a threat to patient safety, the off-label use of medicines for economic purposes can disincentivise biopharmaceutical companies from exploring new indications to bring ever more innovative and safe products to patients.”

Heard in Brussels

Europe triumphs at kicking the GM ball into the long grass

BRUSSELS You would have to be blind, deaf and living in a hole for the last twenty years to not know that Europe struggles with the whole GMO thing. Despite a mountain of scientific evidence behind the safe cultivation of genetically modified (GM) crops, the PR bomb dropped by Monsanto all those years ago changed Europe forever, resulting in one of the few areas where a belief in witchcraft seems to carry more weight than scientific evidence.

And the European Parliament has recently achieved the questionable triumph of ensuring that superstition at national level can override scientific review at European level. In November, it backed a plan to allow nations to ban GM crops on their soil, even if they are given approval to be grown in the European Union. This of course means that Europe can proudly approve crops and foods available to every other farmer in the world, then they will not be able to compete in a very global market. European citizens already use and consume products from genetically modified plants, created outside Europe, and if they make their farmers operate with one arm tied behind their backs, they can expect to eat and use a lot more, because there will be far fewer farmers in Europe.

It comes back to science (as usual) and the big picture behind Europe continuing to resist GM technology within its own agricultural system, despite the fact that it is happy to eat the products. GM crops allow more efficient production, and means fewer resources required in today’s intensive agricultural systems. The environmental impact of farming is immense, whatever the production system, so anything that can reduce inputs required is good for everybody. It is a huge pity that national governments have spoken with a false voice through the European Parliament and put short term votes over the long term positive impact of biotechnology on European agriculture, environment and economy.
The guidebook to rewriting the genome

**GENOME EDITING** The biotech industry was truly born in the early 1970s, when US researchers first invented recombinant DNA technologies. 40 years on, we’ve now opened the door to a new era. Novel tools that simplify site-specific genome editing are allowing labs all over the world to shut down, repair, replace and rewrite human genes. The range of applications for the technology is huge, impacting research into inherited diseases, fighting cancer with edited immune cells, crop improvement, drug development and many areas of academic R&D. Everyone – Big Pharma included – is jumping on the genome editing train.

» Read the full story in the printed issue.
Changing the landscape

GENE EDITING  Since its discovery, the speed at which scientists have adopted the groundbreaking CRISPR/Cas9 technology has been tremendous. Microbiologist and co-discoverer of the system, Emmanuelle Charpentier told EUROBIOTECH that it feels a little like science fiction to her.

EuroBiotech_ There has been a lot of buzz in the scientific world and media about the CRISPR/Cas9 technology. Can you keep track of the wave of publications that you have initiated?
Charpentier_ It is difficult to keep track of the wave of publications. It is just amazing how quickly the technology has been adopted by the scientific community. It feels like science fiction, you believe in the fact that the technology will definitely be attractive for a large number of biologists because of its efficacy, simplicity and versatility, but you want to see it happening. To me, this unusually quick adoption of the technology just shows how desperately biologists were in need of a better tool to manipulate genes in higher organisms.

EuroBiotech_ What makes CRISPR/Cas9 superior compared to other genome editing technologies such as Transcription activator-like effector nucleases (TALENs) and Zinc finger nucleases (ZFNs)?
Charpentier_ The former genome editing tools are artificial systems that require substantial protein engineering to specifically target genomes. The CRISPR/Cas9 system that is now largely used by the scientific community is a natural system originating from the bacterium Streptococcus pyogenes. The technology just uses a simple adjustment of the RNA component of the system and thus involves only a minimal step of engineering. We made this technology available right away to molecular biologists. CRISPR/Cas9 is a democratic tool, cheap, easy to design and it is much faster to implement. It can be done in the range of a couple of days versus a couple of weeks or longer for other systems. CRISPR/Cas9 is also versatile in the sense that one can target more than one gene at a time. One can also develop and use the system to target genes and modulate their expression in various ways in a simple manner and this was a feature that the former tools could not fulfill.

EuroBiotech_ With the rise of CRISPR/Cas9, do you see a future for other approaches – such as Zinc finger nucleases and TALENs?
Charpentier_ Right now, the tendency in the scientific community is to switch massively to CRISPR/Cas9, which is now acknowledged as the method of choice for genome engineering. Zinc finger nucleases and TALENs may still be very useful in certain applications.

EuroBiotech_ Are there any weak spots in the CRISPR/Cas9 system that need to be resolved?
Charpentier_ Toxicity is low and not detectable in assays used so far. The issue of specificity and the problem with off-target effects has widely been addressed by the scientific community. Specificity with CRISPR/Cas9 was already high compared to former technologies on the market, and steady improvements have been seen as applications increase. For most lab applications, scientists seem satisfied with the specificity of the tool and rely on further validation of the targeted genome modification by sequencing. If a researcher applies known rules for the design and use of CRISPR/Cas9 that includes adjustment of the expression level for selected applications, they have a technology in hand that is very precise. An area of ongoing interest, for CRISPR/Cas9 and other systems, relates to improved delivery tools to further enhance their uses in regenerative medicine and human gene therapy.

EuroBiotech_ Are you addressing any problems with the CRISPR/Cas9 system…

Read the full interview in the printed issue.
The IPO wave continues

**IPO** It’s time to get used to biotech IPOs in Europe. The first two listings of 2015 successfully took place in Europe. A wave of further six IPOs is expected in the coming weeks. In addition, a couple of European companies plan to tap US or Asian investors with overseas IPOs.

French diabetes specialist Poxel SA kicked off the rally by successfully raising €26.8m in its IPO on Euronext Paris at the beginning of February. The latest drug candidate of the ex-Merck Serono unit is Imeglimin, a new class of oral antidiabetic agents. With almost synchronous timing, Belgian Bone Therapeutics SA made its IPO on Euronext Paris and Brussels. The regenerative medicine company raised €37m. Both companies not only priced within their target ranges, they also sold out their over allotments. On top of that, their share prices took off impressively during the first few days of trading.

**Plans aplenty**

It is unlikely that this is the end of the line. At least another six companies have announced plans for a listing on a European stock market in the upcoming weeks. Two of them – Evgen and Redx – intend to enter the Alternative Investment Market (AIM) in London, where both aim to collect €27m. Antibiotics developer Motif Bio Ltd is also planning to go public on AIM, albeit taking the backseat with the goal of bringing home a modest €5.4m.

There have also been some stirrings in Scandinavia: Norwegian Nordic Nanovector ASA has applied for a listing on the Oslo Stock Exchange, Swedish Cantarga AB plans to launch an IPO on NASDAQ First North in Stockholm and also Danish NNIT A/S is seeking an IPO on its home turf, the NASDAQ OMX Copenhagen. NNIT is an IT service provider, which has, amongst others, a life sciences unit and biotech roots: it is the fully-owned subsidiary of Danish insulin specialist Novo Nordisk A/S. It could be valued in an IPO at up to a whopping €670m.

Other European biotech companies still feel safer in the tried-and-tested US waters. Danish clinical stage biopharma company Ascendis Pharma successfully raised US$110m (€96m) with its upsized NASDAQ IPO at the end of January, while Irish-Australian animal health specialist Nexvet was less fortunate in ear-rasing US$3m. Neurovive now plans for its subsidiary’s IPO to take place in Asia as “the market for the biotech and pharmaceutical industry in Taiwan is currently favourable,” Neurovive CEO Mikael Brännegard said.

**Euronext and AIM in the lead**

This year kicked off where last year ended. In 2014, the European biotech industry experienced a stock market boom. According to a report from Berlin-based market analyst BIOCOM, a total of €2.4bn was poured into fresh off-the-shelf biotech companies in Europe via the stock exchange, an increase of 25% compared to the previous year (€1.9bn). The number of biotech IPOs in Europe tripled to 15. A total of seven companies opted for a listing in the US.

The BIOCOM report also states that at the end of 2014, a total of 150 biotech companies with a market capitalisation of €66bn were listed on the 15 most important stock exchanges in Europe. The majority of companies were traded in London (33) and Paris (32). In the aftermath of the crisis years 2011 and 2012, all indicators are now showing signs of a significant upswing throughout all trading centres. “The cross-border exchange Euronext and the AIM in London are obviously the most attractive. They are at the top of our ranking,” says Boris Mannhardt, CEO of BIOCOM. The cross-border exchange NASDAQ OMX and the Swiss Stock Exchange follow in 3rd and 4th place.

For now, it seems that the US biotech IPO boom has spilled over the Atlantic, and that investors continue to have faith in European biotech ideas.

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VACCINES  For several years now, the global market for vaccines has seen double-digit growth. But despite the favourable economic outlook, the vaccine industry faces huge structural changes. Major companies are consolidating their vaccine business around blockbuster products, and some big players have dropped out of the field completely. Others are replenishing pipelines with a range of new techniques and molecules developed by specialised biotech companies. Only sound European research funding will ensure that great new ideas are implemented.

Health systems around the world prefer prevention to treatment. But although the outlook in the vaccine sector is bright, it’s in the midst of a major restructure. Big Pharma companies are still consolidating business around blockbuster products, and kicking out vaccines with smaller revenue streams. “Small companies can pick up these niche products and bring them back to success with a small and dedicated team,” says President and CEO of Valneva SE Thomas Lingelbach (see interview, p.41). There’s no question that the market is in disarray. Swiss leader Novartis is preparing to swap practically its entire vaccines business unit (valued at over US$7bn) for GlaxoSmithKline’s (GSK) oncology franchise (around US$16bn). So far, only its flu vaccines – which GSK has already produced on its own for some time – have been sold to biotech giant CSL. The Australian company says combining its existing flu vaccine operations with the Novartis range will create the second-largest player in the US$4bn global flu-vaccine industry. GSK has arisen as a mighty competitor to Sanofi-Pasteur. The French company prides itself to be the world’s largest company entirely dedicated to vaccines.

Baxter drops out, Crucell divests

Vaccines major Baxter International has announced that it will be exiting the vaccines business as well. The US-based company completed the divestment of its unit in December 2014 when preparing its split into Baxter International (Medical Products) and Baxalta (Bioscience). “Our commercial vaccines were sold to Pfizer, and we sold our Vero cell platform to Nanotherapeutics in December 2014. There are no further commercial vaccines at Baxter,” reports Brian Kyhos, the company’s Global Communications Director.

One of Johnson & Johnson’s Janssen Pharmaceuticals companies, Crucell began to reorganise business early in 2014. The Dutch company has decided to phase out commercial operations relating to its influenza and hepatitis A business. Along with its Swiss production site, the firm sold its proprietary typhoid vaccine (Vivotiv) altogether to US speciality pharma company Paxvax Inc. Then early in 2015, French-Austrian vaccines specialist Valneva SE acquired Crucell Sweden AB and all assets related to cholera vaccine Dukoral (see p. 44). Crucell says it will now focus on transformational immunisation candidates to fight diseases like HIV/AIDS, influenza, respiratory syncytial virus (RSV), polio and numerous other viral and bacterial diseases.

While Big Pharma companies are …

» Read the full story in the printed issue.
BIOECONOMY

Miniature miners making it big

BIOMINING  For millennia, microbes have been invisible little helpers in the area of mining. Since the discovery of their impact on processing ore in the middle of the last century, mining companies have been trying to capitalise on this fact. Most metals today are still extracted using conventional methods. But with primary resources growing scarcer, the age of biomining lies just around the corner. The German-French project Ecometals is now trying to overcome some of the biggest hurdles.

Read the full story in the printed issue.
Join the European Biotechnology Network!

The European Biotechnology Network is dedicated to facilitating co-operation between professionals in biotechnology and the life sciences all over Europe. This non-profit organisation brings research groups, universities, SMEs, large companies and indeed all actors in biotechnology together to build and deliver partnerships.

Do you want to know more about the advantages of a (free) membership? Just have a look at our website: www.european-biotechnology.net
The Swiss Biotech Day is the leading biotechnology conference in Switzerland. The upcoming event will bring together around 400 senior executives from the life science industry across Europe.

Programme highlights will be keynotes by Joseph Jimenez (Novartis AG) and Holger Zinke (BRAIN AG), as well as the presentation of the Swiss Biotech Report.

The parallel sessions in the afternoon will focus on: Innovations in Healthcare, Regulatory Affairs, Listed Biotech Companies (Investor & Analyst Track) and Hotspots in Biotech.

Additionally, there will be an exhibition and extensive networking opportunities throughout the day.

More information on the conference, the complete agenda and a registration form can be found on: www.swissbiotechday.ch
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