European Biotechnology

Spring 2020

Bioprocessing

Special

Growing market for viral vector biomanufacturing

ANTIBIOTIC RESISTANCE With the coronavirus pandemic mounting, experts are already warning of antimicrobial resistance as being the next, hidden crisis. The AMR community still urgently waits for substantial pull incentives. While the US DISARM act was pulled at the last minute from the country's corona stimulus package, the UK's NHS has started stakeholder engagement for its flat-rate model. Meanwhile, Forge Therapeutics has closed a €170m deal with Roche.

The market size for originator biologics, biosimilars, and cell and gene therapies in 2019 of about US$262bn is projected to grow $133bn until 2023 (CAGR of 9.1%), to $371bn. Accordingly, the market share of biologics to the total pharmaceutical market is expected to grow from currently 20% to more than 25% by 2023, a new report from London-based Results Healthcare states. The market for gene and cell therapies is small, and thus, the share of the viral vectors and plasmid DNA manufacturing market size stood at US$368.3m in revenues last year. However, by 2025, it is predicted to grow with a CAGR of 14.5% per year. Driven by market approval of ultra-expensive, advanced therapies, particularly gene and cell-based therapies, such as Novartis' US$2.1m per patient SMA gene therapy Zolgensma, new lucrative markets might materialise. Thus, contract manufacturing organisations, pharma developers, and service providers producing the required DNA plasmids, viral vectors, and transposons, are expanding their capabilities to benefit from this potential, additional business arm.

Currently, around two-thirds of the research in gene therapy is focused on oncology. Furthermore, 350 million patients are diagnosed globally with a rare disease, another key area of interest in gene therapy.

Need for cost-efficienc

While RNAi therapeutics delivery is currently the largest market segment for viral vector producers, the approval of gene therapy products in US is fuelling the necessity for completely scalable, clinical-grade Good Manufacturing Practice (GMP) solutions to develop gene therapies for large patient groups who need high vector doses. In Q1/2019, 372 clinical trials were registered that involved vector-mediated gene therapy production.

In 2019, the FDA announced the drafting of guidelines to facilitate clinical testing and market approval of ATMPs, as many gene therapies provide solutions for ultra-rare genetic diseases and help establish highly personalised treatments for stratified cancer patient populations. Vector manufacturers, such Belgian Univercells SA, know how complex and resource-intensive processes can be, which are needed for GMP-compliant ATMP-manufacturing. In mid-February, the company received a US$50m financing from KKR-subsidiary Gamma Biosciences for a highly-automated, virus production platform with a footprint of only 10 m2. According to the FDA, further progress is needed to improve batch reproducibility and quality assurance for vector production.

While it's not clear if gene therapies are a business case, in the future, gene and cell therapies might become a significant part of the current US$11.7bn contract development and manufacturing market for biologics, which is expected to grow with a CAGR of 13% by 2023. ■

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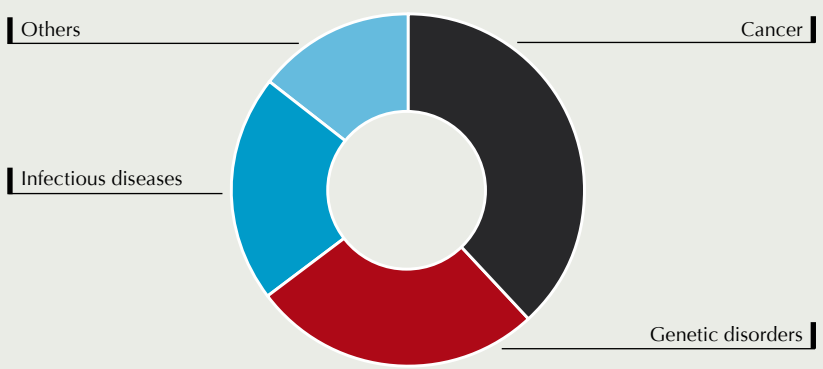
Global viral vectors & plasmid DNA manufacturing market share by disease in 2019



Source: www.grandviewresearch.com

Disease areas mostly affected by the current hype around gene and cell therapies

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Viral vector one-stop-shop for gene and cell therapy

VIRAL VECTORS Many CDMOs have taken actions to meet the growing demand of viral vector development and manufacturing services for clinical trials, as well as for commercial scale production. While capacity is important, there are only a few companies who provide services across the entire supply and value chain. So, what should you expect when choosing a true one-stop-shop as a CDMO partner in the gene therapy space?

› Dr. Knut Ringbom, CEO, Biovian Oy, Turku, Finland

Currently, global biopharmaceutical companies are facing increasing pressure to develop innovative drugs in faster time and at lower cost. Thus, partnering with a CDMO that offers a comprehensive range of services can be the best policy for the drug developers seeking increased efficiency.

Many manufacturing organisations have adopted a phrase "one-stop-shop" to define their way to operate. However, a deeper look at the processes and operations may bring up some substantial differences between service providers, despite supposedly similar positioning. While there is no one-size-fits-all answer for gene therapy developers, a reflective, mutually transparent gap analysis is an important exercise between any developer and manufacturer when looking for the right CDMO for their specific needs.

Benefits of a true one-stop-shop

Biovian's definition of a one-stop-shop, is to provide clients with services across the supply and value chain. This is facilitated by Biovian's fully integrated infrastructure of resources and capabilities.

Within the supply chain, we cover services all the way from GMP cell bank manufacture to aseptic fill and finish for final products. Further, labelling and warehousing of the drug products at –80°C can be provided within the comfort of our EMA-certified, FDA-inspected facility. When it comes to the value chain, Biovian fully covers the life cycle from pre-clinical, to clinical, to commercial GMP supply of plasmid DNA and viral vectors.

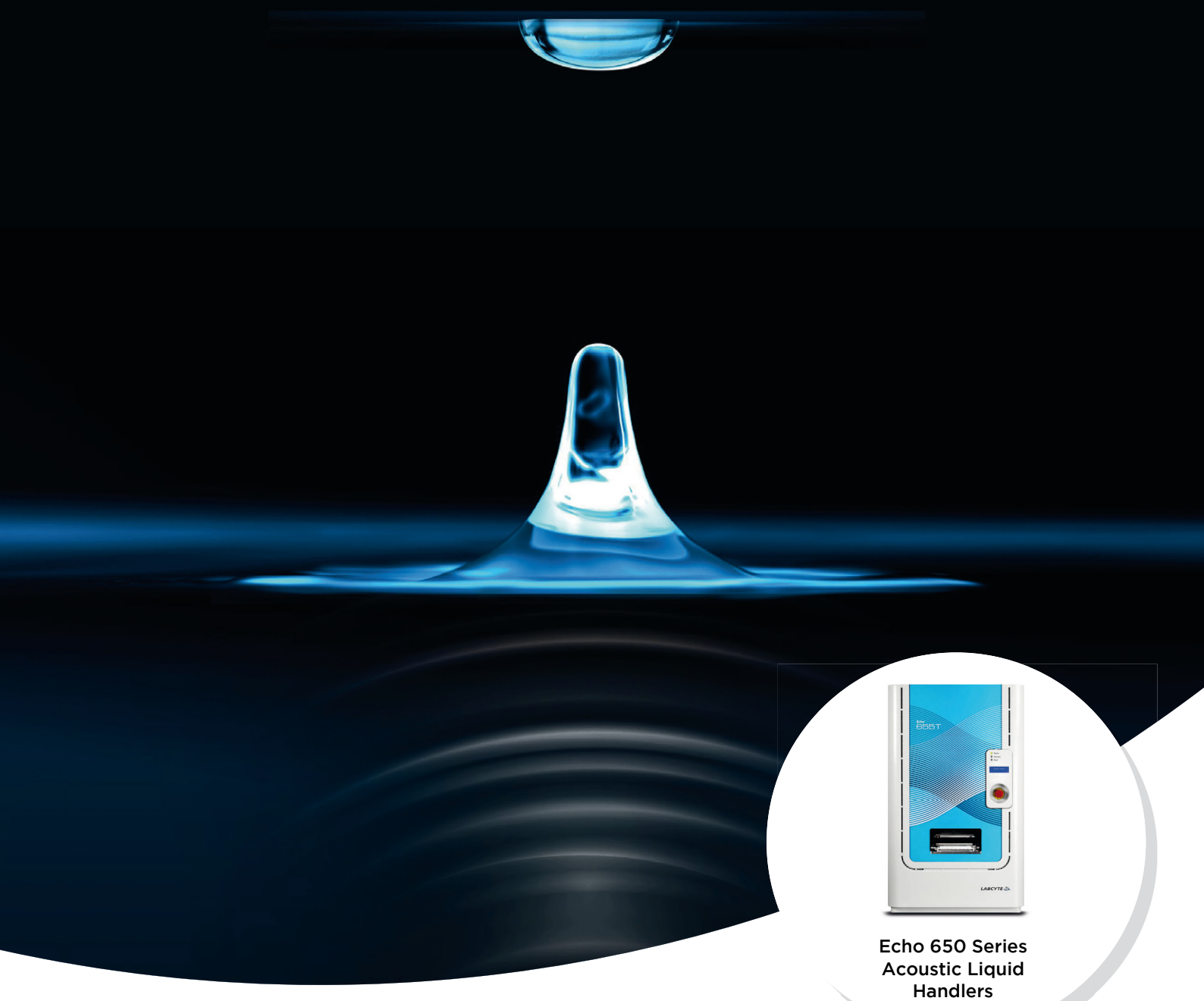
Our new GMP production area includes 200 L scale, single-use bioreactors, which enable efficient manufacturing of viral vectors at a sufficiently large scale for more advanced clinical trials and support of commercial strategies. With this current facility extension, we will more than double our capacity in the production of adenovirus, AAV, and lentivirus, building on over a decade of experience in the viral vector field.

A key part of the value chain is, of course, quality and regulatory support from expert teams. We are very proud to have four qualified persons who ensure that clients' investigational, medicinal products are released smoothly for clinical trial use or for sale.

Keeping an eye on the future

To summarise, it is important to keep an eye on the future of the product from the very beginning of the project. When partnering with a qualified, dynamic one-stop-shop CDMO, like Biovian, that accompanies the entire supply chain and value chain, there is no need to change providers, which is often a time-consuming and costly hurdle. We eagerly look forward to Viral Vector-based gene therapy to step out of its niche, and we are ready to serve our new, current, and returning clients with Nordic consistency, reliability, and efficiency. ■

Pictures: Biovian Oy



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Life Sciences

Radiant Precision

RADIONUCLIDES High-Precision Radionuclide Therapy is a promising, new generation of targeted molecular therapy in which the smallest amounts of medical radioactivity find their way through the bloodstream specifically to the tumour cells for diagnosis and treatment of cancer.

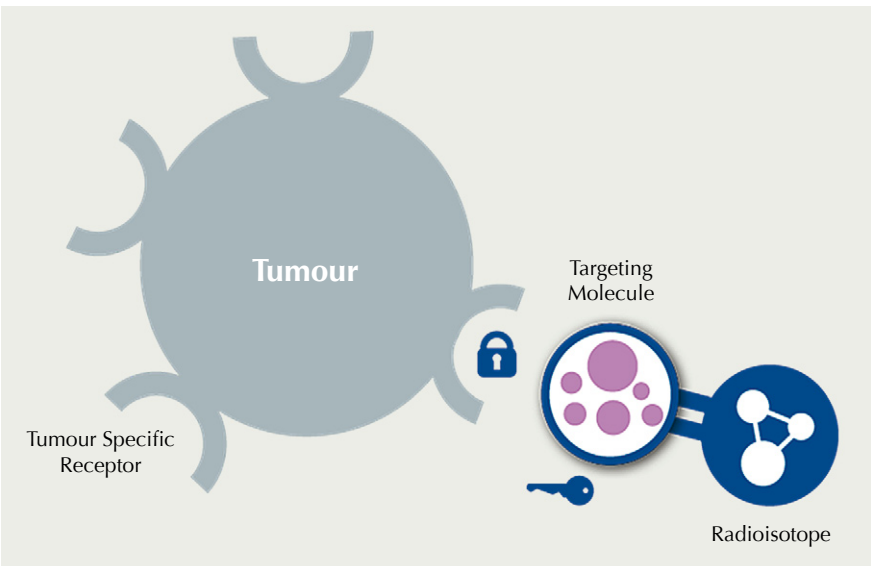
› Dr Tamara Ćiković, ITM Isotopen Technologien München AG

Since the time of Marie Curie, radiation research has been fundamental for the development of nuclear medicine. Furthermore, biomedical investigations on various tumour markers have contributed to the evolution of precision oncology, paving the way for Targeted Radionuclide Therapy.

In contrast to radiotherapy, where radiation is applied from outside the body, Targeted Radionuclide Therapy is defined by the injection of a radiopharmaceutical, which precisely recognizes tumour cells. Radiopharmaceuticals consist of a medical radioisotope conjugated to a tumour-specific targeting molecule that binds specifically to a tumour antigen according to the lock-and-key principle. A very small amount of medical radiation is sufficient for this therapeutic approach. Due to the efficacy and specificity of Targeted Radionuclide Therapy, healthy tissue is minimally affected, and side effects are maximally reduced.

In many cases, the targeting molecule can be used for both diagnosis and therapy, the only difference being their conjugated radioisotope. Radioisotopes with shorter half-lives are used for diagnosis, while therapeutic ones have slightly longer half-lives.

The biotechnology and radiopharmaceutical group of companies ITM Isotopen Technologien München AG (ITM) develops, produces, and globally distributes a new generation of radiopharmaceuticals for Targeted Radionuclide Therapy. They have established a method to produce a highly pure, no-carrier-added (n.c.a.) Lutetium-177, which does not contain impurities, with metastable, long-lived Lutetium-177m. This ensures economical waste management and environmental sustainability. Recently, ITM received the "German Medical Award" for their dedicated work in this field and the prestigious support of the European Investment Bank. ITM's goal is to achieve a sustainable medical benefit with their therapeutic approach and to significantly improve the quality of life for cancer patients.



Targeted Radionuclide Therapy uses radiopharmaceuticals, which are conjugates of a medical radioisotope and a tumour-specific targeting molecule, recognizing the tumour cell precisely according to the lock-and-key principle.

How to improve outcomes?

"We are currently conducting the clinical phase III trial COMPETE, which is investigating the efficacy and safety of the radiopharmaceutical Solucin®," says ITM's CEO Steffen Schuster. Solucin® is comprised of a somatostatin analogue as the targeting molecule and ITM's highly pure n.c.a. Lutetium-177 and is used for the treatment of somatostatin-positive neuroendocrine tumours (NET) of gastroenteropancreatic origin. NETs are rare diseases, thus exacting a high demand for effective therapies. "We are confident that COMPETE will confirm the promising results of our Phase II study and will give many NET patients the opportunity to benefit from this new generation of Targeted Radionuclide Therapy," added Mr. Schuster.

In addition to Solucin®, ITM is working on further product candidates for the diagnosis and therapy of bone metastases and other cancer indications, thereby actively shaping the progress of radiopharmaceutical research and development – a "radiant" contribution to treating cancer. ■

Picture: ITM Isotopen Technologien München AG

Contract Development and Manufacturing of Biopharmaceuticals

Biovian has 17 years of experience in biopharmaceutical GMP-production and a solid track record in tailored services from early development to finished vial.

ONE-STOP-SHOP

- Virus production for gene therapy and vaccines
- Microbial production of recombinant proteins and plasmid DNA
- Process development
- Formulation
- Fill & Finish
- Analytical quality control
- Cell and virus bank preparation

BIOVIAN

www.biovian.com

Phages as a promising alternative to antibiotics

PHAGOMED The Vienna-based biotech company Phagomed wants to establish therapies with phages – viruses that infect bacteria – as an alternative to antibiotics. For 2020, a Series A financing round is planned to proceed with the three drug programs. Currently, the start-up is focusing particularly on advancing a new treatment for Bacterial Vaginosis (BV), based on phage lysins. The highlight of this approach: They target the pathogenic bacteria without harming the rest of the microbiome.

Since its foundation in November 2017, Austrian Phagomed has specialised in developing phage-based drug candidates for the treatment of severe bacterial infections in humans. "Phages and endolysins offer effective alternatives to antibiotics blunted by bacterial resistance, and they work very precisely without destroying the natural microbiome. What's more, they can combat bacteria in impenetrable biofilms, where antibiotics are ineffective independent of resistances," explains PhagoMed's co-founder and co-CEO, Lorenzo Corsini.

Currently, the company has three active development programs in the fields of implant associated infections, urinary tract infections, and Bacterial Vaginosis (BV). In Autumn 2019, the BV candidate was added to the pipeline. PhagoMed has isolated Gardnerella-specific phage lysins based on the company's phage biology platform, optimised them by genetic engineering, and filed a patent application for this class of recombinant endolysins.

More precise BV treatments are urgently needed

For Corsini, BV is an attractive indication, because it affects between 10% and 30% of women worldwide, making it not only the most frequent vaginal infection with a more than 50% recurrence rate, but also one of the top reasons for antibiotic prescriptions and antibiotic resistance. Werner Mendling, a professor and gynaecologist at the German Center for Infections in Gynecology and Obstetrics in Wuppertal, Germany, is convinced that new treatments are urgently needed. "Millions of women suffer from recurrent BV – despite the widespread use of antibiotics. We need to find more precise solutions for combating the biofilm that forms on the vaginal epithelial cells," he says. To advance the program, in late 2019, Phagomed received a €1m grant from the Austrian Research Promotion Agency. In addition, the company has set up a new development team for BV, which is cooperating with vaginal microbiome specialists at Ghent University, and has recruited the previous Head of Pre-Clinical development at Austrian Affiris AG, Christine Landlinger-Schubert, as the director of the lysin program. According to Corsini, "phage lysins are able to specifically target Gardnerella without harming the microbiome, and they are able to attack resistant bacteria, making them prime candidates to treat BV." Mendling also believes that such a strategy could be a promising approach: "Next generation BV therapies should combine precision with efficacy. Killing facultatively pathogenic bacteria, such as Gardnerella spp., while preserving the vaginal microbiome could become the new gold standard for BV therapy."

For 2020, the company seeks further capital to proceed into the clinical phase over the next two years in its lead programs. So far, Phagomed has raised more than €6.5m in private funding and public grants. "Now, we are raising a larger Series A," says Corsini. ■

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Phagomed has a team of 15 scientists focusing on its three programs, 11 of which work at the Campus Vienna Biocenter in Vienna, Austria.

Picture: Phagomed

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Corporations are boosting packaging innovation

SUSTAINABLE INNOVATION In March, food and beverage companies signed on to the European Plastic Pact and pledged to increased support for innovation. Earlier this year, food giant Nestlé announced that it will invest up to two billion CHF to lead the shift from virgin plastics to food-grade, recycled plastics and to accelerate the development of innovative, sustainable packaging solutions. French water brand Perrier, part of Nestlé, announced the support of three start-ups within the Next Packaging Movement.

Picture: Nestlé

The European Plastics Pact is a public-private coalition that aims to accelerate the move towards a circular economy for plastic packaging in Europe. Launched in March in Brussels, 15 governments and 66 companies have signed on to the pact, including large food and beverage companies such as Unilever and Nestlé. This is also the first regional pact to join the Ellen MacArthur Foundation's global Plastics Pact network. The pact was initiated by the French Ministry of the Ecological and Solidarity Transition, the Dutch Ministry of Infrastructure and Water Management, and the Danish Ministry of Environment and Food, in consultation with more than 80 organisations from across Europe. Its members will cooperate across the value chain on a European scale to boost the development of smarter techniques and approaches, harmonise guidelines, standards, and national supporting frameworks, and connect to share best practices and lessons learned across Europe.

Sustainable packaging fund will invest CHF 250 million

In addition, many food companies that have signed the pact have set themselves further sustainability commitments. Many of these goals include increased availability of products that come in sustainable packaging. Marco Settembri, Nestlé CEO for Europe, Middle East, and North Africa said: "We are pleased to sign the European Pact. One of our joint objectives is to create a circular economy by improving collection, sorting, and recycling schemes across Europe." Building on its 2018 commitment to make 100% of its packaging recyclable or reusable by 2025, Nestlé already announced in January its aim to reduce its use of virgin plastics by one third in the same period. Thus, to create a market, Nestlé is committed to sourcing up to two million metric tons of food-grade recycled plastics, allocating more than CHF1.5bn to pay a premium for these materials between now and 2025. In addition to its in-house research through the Nestlé Institute of Packaging Sciences, the company launched a CHF250m sustainable packaging venture fund to invest in start-up companies that focus on these areas.

Some brands within the Nestlé group also launched their own initiatives, such as Perrier with its Next Packaging Movement. Through this programme, Perrier will invest in three startups: Biotic, Flexikeg, and PlastiSkul. The startups were selected from among 90 submissions, following an application process launched in April 2019, which evaluated key factors, such as the breakthrough dimension of the proposed solutions, potential environmental and social benefits, and the ability to scale across the sparkling water market and the broader beverage industry. The three winning start-ups will receive technical, operational, and financial support to help bring their solutions to market by 2025. ■

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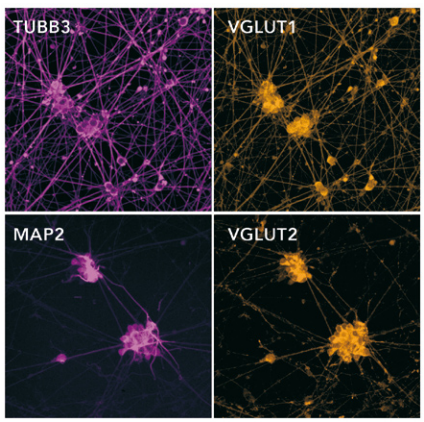
Human iPSC-derived glutamatergic neurons

CELL PRODUCTION Widespread use of human-induced, pluripotent stem cell (hiPSC)-derived, mature cell types is restricted by complex differentiation protocols and inefficient reprogramming methods. By applying a novel gene engineering approach, opti-ox™, to cellular reprogramming, these restrictions have been largely overcome. This proprietary technology enables precise reprogramming and homogeneous differentiation of entire stem cell cultures into any desired cell type.

Opti-ox1 (optimised inducible overexpression) cellular reprogramming enables tightly controlled and homogenous expression of selected transcription factors. The result is the consistent manufacturing of homogenous and mature hiPSC-derived functional cells within days, offering access to the highest quality of cellular models with simple protocols. Glutamatergic neurons (ioNEURONS/glut) are derived from hiPSCs through Neurogenin-2 (NGN2)-driven opti-ox reprogramming.

Human stem cells rapidly convert into functional neurons, providing a reliable model for the study of neurological activity and a robust platform to advance CNS drug discovery programs in a relevant human cell type.



Immunofluorescent staining on post-revival day 11 demonstrates homogenous expression of pan-neuronal proteins (MAP2 and TUBB3) and glutamatergic neuron-specific transporters (VGLUT1 and VGLUT2). Cells exhibit neurite outgrowth.

Picture: Bit Bio

Reliability

ioNEURONS/glut are well characterized and defined, consisting mainly of glutamatergic neurons (more than 80%). The minor remaining fraction of neuronal cells express marker genes of cholinergic neurons. Cells have a rostral CNS (central nervous system) identity and express the classic cortical marker genes FOXG1 and TBR1. These cells form functional neural networks, and spontaneous activity is observed after three weeks of differentiation when cultured in BrainPhys™ neuronal medium.

Consistency

Batch-to-batch reproducibility and homogeneity create a stable, human model for excitatory neuronal activity and disease.

Speed and Scalability

The cells are ready for experimentation as early as two days post revival and form functional neuronal networks at 17 days. Industrial-scale quantities allow the cells to be utilised in a range of applications, from research to screening purposes. Cells are compatible with plates ranging from 6 to 384 wells and validated for HTRF® and CellTiter-Glo® assays.

Ease of Use

Cells arrive programmed to rapidly mature upon revival with only one medium required in a two-step protocol.

Employing a combination of screening and machine learning, Bit Bio has developed a high-throughput discovery platform to identify optimal transcription factor combinations for the direct reprogramming of target cell types. By applying opti-ox, Bit Bio achieves controlled and unprecedented homogenous expression of identified transcription factors in all stem cells. Bit Bio aims to solve some of the most pressing challenges facing medicine through democratising access to consistent and functional human cells. This will improve research and drug discovery, as well as lower the cost and extend the application of cell therapies. Our range is constantly expanding, and human induced skeletal myocytes, the ioMYOCYTES/skeletal, will launch in Q2/2020.

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