European Biotechnology

Autumn 2022

CDMOs & CROs

Special

Technology expansion

CROS/CDMOS With the vaccine business made lucrative by the COVID-19 pandemic, and more and more ATMPs in clinical testing, providers such as CDMOs are also expanding their capacity to produce vectors and alternative tools for delivery. Add to this: After the first eleven approvals of gene therapies for rare diseases and cell therapies for blood cancer, there are a large number of candidates being tested in clinical trials. Digitalisation is becoming increasingly important for both CDMOs and CROs.

With a current value of US$7.7bn, the market for contract manufacturers of gene and cell therapies is still a small fraction of the overall market of over US$200bn shared by CDMOs. But with 10 to 20 gene and cell therapy approvals expected from the FDA by 2026, contract manufacturers' revenues for ATMPs are expected to nearly double by then. At least that is what the CPHI report published in mid-August predicts. Positive for the CDMOs: in this yet small market segment, their services are in demand even more frequently than in the production of biologics in mammalian cells (44%). CDMOs are now responding to the consequences of the COVID-19 pandemic and the already noticeable supply shortages of vaccine and gene/cell therapy vectors by expanding their production capacities. At the same time, triggered by the Ukraine crisis and COVID-related lockdowns, CROs are looking for alternatives to clinical trials in study centres, e.g. through increasing decentralisation of studies and digital monitoring of the study population via wearables.

Proven and new vectors

According to Rob Panting, PhD, Managing Director of Rentschler ATMP, gene and cell therapies still face challenges in terms of manufacturing costs and safety. Upon the launch of the first customer projects in early 2023, Rentschler Biopharma SE's subsidiary in the European gene and cell therapy cluster Stevenage, UK, will focus on process development and cGMP production of proven viral vectors, such as AAV. "In the near future, we also intend to offer other forms of gene vectors and will evaluate newer technologies," said Panting, who calls the increase in preclinical and early clinical gene and cell therapy projects "encouraging".

The German supplier Merck KGaA, which in August presented its vector production platform 293-AAV, which is 40% faster, takes a similar view. The company also offers alternative gene delivery systems.

In August, Switzerland made good on announcements made at the previous year's Swiss Biotech Day that it would expand its capacities for innovative mRNA, vector- and peptide-based active substances and vaccines in an "internationally competitive" manner.

In collaboration with equipment supplier Pall, new laboratories for the production of gene therapy vectors were opened at the Biofactory Competence Center (BCC) in Fribourg at the begin-

More and more gene and cell therapy companies are setting up shop in the Catapult cluster in Stevenage

Picture: © RentschlerBiopharma SE

ning of September. Lonza had previously hired additional staff at the Visp production site to produce Moderna's new mRNA vaccine, which was approved in Europe and the USA at the beginning of September and also provides vaccine protection against the omicron variant.

Vector BioPharma AG, a spin-off from the laboratory of Zurich antibody pioneer Prof. Dr Andreas Plückthun, was already launched in mid-August with first-round funding of CHF30m. With its SHREAD platform, developed largely by Dr Sheena Smith, the company aims to solve several problems of gene delivery at once. With 36Kb, the andenoviral platform offers seven times the gene insert size of AAV vectors. In addition, the bioengineers have built a protein shell around the vector that protects it from liver degradation and attacks by the immune system. It contains target cell-specific DARPins which the vector to home in at its specific site of action. The company's management sees potential for application in the optimisation of cancer immunotherapies, which have many side effects.

Newer forms of delivery include exosomes or completely AAV-free approaches. Recently, US companies AGC Biologics and RoosterBio have merged to commercialise exosomes.

Digitisation at CROs

The digitisation of clinical trials is certainly still a pipe dream given the lack of validation of digital monitoring techniques for vital functions. However, the medical technology industry is already taking the challenge seriously to lower the hurdles for digital patient monitoring and thus more efficient data acquisition. According to an industry survey conducted by Veeva, there's been an acceleration of digital transformation in clinical research, starting with the rapid deployment of decentralised trial models to enable remote execution during COVID-19. While, 87% of companies use decentralised technology, up 59 percentage points from pre-pandemic, there are a lot of technological challenges particularly concerning the validation of systems for remote patient monitoring, before parts of trials can become virtual. In addition, 56% of the respondents said the move to decentralised trials has improved the patient experience, and less than a third have seen improved site engagement, reduced costs, and shortened trial timelines. However, sponsors and CROs seemingly want to establish a connected clinical ecosystem that improves collaboration with research sites, drives better patient engagement, and allows seamless data sharing across study stakeholders, in the longer term. A survey of London-based Dassault Systèmes confirms (see p. 10)that demand for decentralised studies will continue to rise. ■

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Knowledge-based contract services

SCIENCE AND MANUFACTURING To install a newly created Chief Scientific Officer position and to hire a biotech veteran is a signal sent by Rentschler Biopharma, celebrating 150 years.

EuroBiotech_Why was the CSO position at Rentschler Biopharma newly created? What has changed since you joined the company?
Christian Schetter_ The position with the actual scope was newly created to ensure that Rentschler Biopharma stays on top of new developments and applies forward-thinking to meet the needs of our clients. This also comprises deciding upon the right level of digitisation, automation and implementation of new technologies for development, analytics and manufacturing. In the last year, we got an even better picture of what we should focus on and where we will implement new initiatives.

EuroBiotech_What topics are you focusing on when defining the scientific orientation of Rentschler Biopharma?
Schetter_ It is an absolute key to appreciate that our prime objective is to service our clients and ensure that we do everything possible so that they are successful. Having said this, the most important aspect is to fully understand their needs and challenges, the stage of development of their product candidate or commercial product and then match this with the areas we should focus on scientifically.

EuroBiotech_There was a time when one thought that engineers are most essential for production processes and new developments. What is your take on this? Is this way of thinking outdated?
Schetter_I do not believe that a premium CDMO can rely on a single expertise or function to be successful. This is becoming even more evident with complexity and focus on faster development cycles dramatically increased. Only a real team approach with many diverse expertise working seamlessly together as one will result in success and meeting all needs of biopharmaceutical clients. This is what we mean to be "One Rentschler".

DR CHRISTIAN SCHETTER
CSO Rentschler Biopharma SE

EuroBiotech_Does the CSO define independent research projects, or are these rather projects driven by clients or in cooperation with clients?
Schetter_ Rentschler Biopharma does not have independent research projects to develop new therapies for specific diseases. This is the expertise of our clients. We do however have projects aiming to identify new solutions to existing hurdles in analytics or manufacturing to enable us to run more efficient processes for the benefit of our clients. For us, innovation has to go beyond the desire to know more, it has to be geared towards a clear purpose and benefit.

EuroBiotech_One hears a lot about artificial intelligence and new possibilities in protein design, due to a new understanding of protein structure and how the building blocks of a protein interact with one another. Does Rentschler Biopharma need to be at the forefront of research in this area, to also be able to produce such molecules, or is that not a challenge at all in biopharmaceutical production?
Schetter_ This is an excellent question and a very complex topic. The answer again is along our desire to provide outstanding services to our clients. As a premium CDMO, we believe it will be key to be strong in bio data processing, which is constantly learning from all the data generated during process and analytical development as well as in manufacturing to constantly improve our processes. Another aim will be to have an even larger understanding of the processes allowing, e.g. predictions about manufacturability or instant adaptation of conditions. Again when it comes to understanding protein structures and how best to drug the relevant targets, it is our client's exper-

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EuroBiotech_Besides this area, which of the recent developments and trends are most important for Rentschler Biopharma right now?
Schetter_ There are several important trends we have identified and incorporated into our strategy and execution plan. Allow me to focus here just on one specific area, which from a CSO's perspective is especially exciting. The emergence of Advanced Therapy Medicinal Products (ATMP) is significantly increasing the space of druggable targets potentially allowing the treatment of patients with serious and rare diseases for which therapies are yet not identified. There is a high demand for CDMOs like Rentschler Biopharma to provide development capabilities and cGMP-capacity to clients focusing on cell and gene therapy approaches. For this, we have established Rentschler ATMP in Stevenage, UK, in 2020. I am proud to state we have made significant progress in the last 12 months and are now on the path offering all relevant services for the development and cGMP-manufacturing of Adeno-Associated Virus-based gene therapies. We will continuously expand our offering in this space also to other modalities.

EuroBiotech_Is it also part of the CSO's responsibility to identify potential acquisition candidates whose science and technology could be a good complement to Rentschler Biopharma?
Schetter_ Putting our client's success at the centre of our attention we fully understand the complete development path of biopharmaceuticals starting early with cell line development and going all the way to commercial market supply. We therefore constantly look for partners that complement our offerings. The idea is not necessarily to acquire these partners but rather to form strategic alliances, making it even easier for our clients to experience a full service for all their CMC requirements. Examples are our partnerships with Vetter for fill and finish or with Leukocare in formulation. We are always on the lookout for additional partnerships to expand our offering.

EuroBiotech_The company prides itself in "creating value sustainably" for its employees and clients. Could you elaborate on this from a CSO's perspective?
Schetter_ Thank you for bringing this up. It implies always taking a long-term view on all the things we do not being driven by short-term sparks or hypes which may be over quickly. From the CSO's perspective, a good example is again how we approach our new Rentschler ATMP initiative. We first convinced ourselves that cell and gene therapy will be an important sector to help patients in the long run. We then put in place a long-term plan on how to best enter the space and are now on track to execute this plan, of course with the always necessary adaptations. This will allow us to set up a new business in a sustainable way with the ultimate purpose helping patients in a meaningful way.

EuroBiotech_Rentschler celebrates its 150th anniversary this year. What does this milestone mean for the company?
Schetter_ We are extremely proud of this. It is a long way starting as a pharmacy in 1872 to becoming today's premium CDMO that we are. This outstanding success was only possible by determination combined with creativity and innovative entrepreneurship over the last 150 years. For us, at Rentschler, it is a time to celebrate and take this huge accomplishment as an inspiration to continue our successful journey as a premium CDMO and accelerate into the next 150 years.

EuroBiotech_Thank you. ■

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A spotlight on tomorrow's CRO

CLINICAL STUDIES The CRO industry is predicted to grow considerably over the next five years. Trials are becoming more complex, and technology is becoming increasingly interwoven with processes. The CRO of tomorrow must be tech smart, agile, and environmentally conscious to remain relevant. In this changing landscape, how does a CRO cut through the noise in 2022-30?

› Alan Morgan, CEO, Excelya

As an integral part of the drug development journey, the CRO market is in a period of exponential growth. A symptom of a drug and medical device industry in acceleration mode, an influx of innovation and much-awaited medicines are just around the corner. In addition, trials are getting more complex and require an increasing level of expertise.

With new logistical challenges, market growth and opportunity come new CRO players and established brands hoping to broaden their scope. The pandemic was a double-edged sword for the industry as it demanded increased flexibility and reliance on technology.

Flexibility is paramount

Clients of 2022 and beyond are not looking for a one-trial-fits-all way of working. With protocol complexity and project sizes varying wildly from trial to trial, sponsors are not looking for a one-size-fits-all cookie-cutter service. Instead, a CRO that offers flexibility, (both in terms of service delivery, patient recruitment strategies and technology solutions) will meet the needs of the sponsor of tomorrow.

As a mid-sized CRO headquartered in Europe, Excelya is unique in its ability to provide full spectrum CRO ser-vices across three business models: Full Service, FSP and Outsourcing.

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Delivering excellence

Despite having been founded in 2014, Excelya has quickly grown to over 900 staff worldwide. Built on a wealth of highly specific expertise and long-standing partnerships, our operational and medical teams have decades of experience and, by proxy, many of our clients have been working with us and our subsidiaries for more than ten years.

Right-sized

As a medium-sized CRO, at Excelya we have an impressive knowledge and resource base, an extensive operational know-how and an agile, flexible and responsive way of working that is precisely aligned with customer needs, rising to the challenges of each individual trial. There is also a strong focus on sustain-ability – we scored highly in and achieved a silver EcoVadis rating last year. We have a global footprint, providing scale and reach to patients and sites, with strong local relationships and teams maintaining a human touch. For more information about how Excelya can help you realise your clinical trials goals and accelerate your drug or medical device approval, please email contact@excelya.com. ■

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Transformative innovation in drug development

DRUG DEVELOPMENT The technological and pharmacological advances lead to an increase in the number of molecules for R&D that are challenging and difficult to manufacture. To improve clinical success, pharma and biotech companies are seeking innovative ways to accelerate progress and reduce scientific, economic, and delivery risks.

› Sanjay Konagurthu, Senior Director, Science and Innovation, Thermo Fisher Scientific

One of the most promising channels for doing so is in-silico modelling, both in early development and across the product lifecycle, including drug substance, drug product, and clinical trials.

In-silico modelling

Thanks to the availability of high-quality datasets and new strategies for data analysis, in silico approaches can streamline drug product development and reduce the risks associated with trial-and-error experimental methods. For example, computational models can be used to characterise drugs more accurately and predict the best path for development. They can be used to inform formulation development and clinical trial design, including dose selection and optimisation. They can support the evaluation of critical regulatory review considerations, including evaluation of in-silico absorption, distribution, metabolism, excretion, and pharmacokinetics (ADME-PK). They can identify process development and optimisation issues. They can accelerate stability determination. And they can aid in the development of life cycle plans in the post-approval setting.

As in all settings, data is knowledge, and knowledge is power – but only if it is actionable. Predictive modelling has the potential to aid in developing robust drug development and manufacturing platforms. However, realizing the full potential of the technology requires careful selection and application of in-silico strategies and a deep understanding of how to interpret and derive the most valuable insights from the data.

In-silico modelling has evolved from being a nice-to-have alternative to real-world data sources to a must-have tool for drug development. When informed by real-world data and guided by a deep understanding of the interplay between all aspects of drug development, in-silico modelling is positioned to accelerate the industry approach to drug development and clinical research.

Speed up and de-risk development

This report provides a framework for that understanding by outlining some of the processes that stand to gain the most from computational modelling and identifying the in-silico capabilities that can be used to accelerate and de-risk each phase of development. Some of the key modelling capabilities that will be discussed include:

- Predictive modelling for solubility and bioavailability enhancement
- Accelerated stability modelling for shelf life and packaging determination
- Materials science, compaction simulation, and process modeling
- ADME-PK modelling to predict the effect of API physicochemical properties and pharmacokinetics.

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Bringing virotherapy forward

VIRAL VECTORS Whether it´s oncogenic viruses or vectors for cancer therapy or modern vaccines, the demand for development, production or filling capacities is rising rapidly. To keep pace with this rise in customer demand, Vibalogics, which recently became part of the Recipharm Group, is investing around US$50m in the expansion of its Cuxhaven site by the end of the year, and even more in the US site near Boston.

› Stefan Beyer, President & Managing Director, Vibalogics, a Recipharm Group company

Vibalogics, one of the world's leading CDMOs for the supply of viral vectors, is expanding its services in cancer immunotherapy with oncolytic viruses and viral vectors for vaccines both in Europe and the USA. The company, which became part of Recipharm Group last year, helps customers develop and manufacture oncolytic viruses that open up promising possibilities for cancer immunotherapy. The natural properties of the virus to multiply in cancer cells in particular and to lyse them can be enhanced many times over by use of recombinantly integrated immunostimulatory factors or the combined administration with immunomodulatory factors.

Shortly after its foundation in 2002 in Cuxhaven, Germany, Vibalogics' focus was on providing oncolytic viruses for customers in Europe and North America. Several production platforms have been established since then. The development of manufacturing processes using different cell substrates for the propagation of enveloped and non-enveloped DNA and RNA viruses are part of the offering. GMP clean rooms of classes A,B,C and D allow us a completely aseptically managed production, which in many cases allows the use of cell substrates growing in suspension as well as adherently.

In Cuxhaven, manufacturing processes are developed for the provision of oncolytic viruses to subsequently produce test material for clinical trials by GMP standards. Two lines with 200 or 500 litre volumes are available, as well as two production suites for the production of viruses for aseptic vector production on adherently growing cell substrates. There is also a filling line with a capacity of more than 25,000 units per batch.

Vibalogics virotherapy manufacturing facility in Boxborough

What began with the establishment of a modern, virus-specialised filling plant for the finished products, and continued with the expansion of bioreactor capacities, was again accelerated from May 2019 onwards following the acquisition by the American growth-oriented investor Ampersand Capital Partners. The strategy proposed by Vibalogics to expand the site in Cuxhaven, but in particular the establishment of a second site with significantly larger capacities in the USA to better serve North American customers, has been consistently implemented over the past three years. With the establishment of the facility in Boxborough/Boston, Massachusetts, USA, the Vibalogics headquarters also moved. Together with Cuxhaven, Vibalogics now covers the entire value chain for the production of oncolytic viruses, viral vectors for gene therapy and virus vector-based vaccines for clinical trial phases and approved market products.

Expansion in three phases

In Cuxhaven, this is a three-phase expansion. With the first phase, an additional building was constructed and the capacity for viruses growing on suspension cells was more than doubled. The new facility consists of two rooms for growing the cell substrate and one room each for the so-called upstream and downstream processes (USP, DSP). The facility is equipped with state-of-the-art control and monitoring systems especially for the production of viral vectors up to biological safety level 2. Customers particularly like the ability to follow USP and DSP production via large window areas.

Vibalogics Cuxhaven now operates two complete lines for the production of oncolytic viruses, whereby the customer can choose between two different single-use bioreactor platforms (SUB). It is easy to switch between the two systems using tech transfer and available standard operating procedures. With the new 500L line, Vibalogics also offers customers smooth 1:1 tech transfers "at scale" between the two sites in Cuxhaven and the USA. The technical systems are the same, and the employees are trained on the same tech-

nical systems and work instructions. Standard operational procedures and a quality management system rolled out across both sites, which is currently being supplemented or replaced by the implementation of an electronic system, allowing Vibalogics' customers to freely choose whether the manufacture of their product is to be monitored by the FDA or EMA. This applies to both the so-called drug substance and the sterile-filled end product for clinical testing. Both sites operate the appropriate qualified filling facilities.

In addition to the expansion of GMP manufacturing capacity for suspension-based cell substrates, both process development and quality control have been equipped with additional systems.

Vibalogics offers its customers additional capacity, more flexibility and agility at both sites to provide viral vectors for cancer and gene therapy as well as for preventive and therapeutic vaccination in a more timely manner.

Phase 2 will take approximately additional approximately 550 m2 of laboratory space for quality control and process development by the end of 2022, after Vibalogics took ownership of the entire building complex in August.

Phase 3, which will follow shortly after, will increase infrastructure capacity to accommodate more than 200 employees by the end of 2023, create additional storage capacity, material preparation and post-processing areas, and build further redundancies of critical systems. This will further expand the overall capacities.

In phases 2 and 3, attention will also be paid to very close cooperation between the two sites. Training the staff of both locations on the same systems offers the customers flexibility, but above all also risk minimisation in case of short-term additional staff requirements. A joint warehouse and logistics system increases the ability to deliver in times of uncertain supply chains.

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Growing within Recipharm

In April 2022, Vibalogics was acquired by the Swedish Recipharm Group, which, as a global CDMO with more than 9,000 employees in more than 30 locations worldwide, will form the advanced therapy medicines (ATMP) service area together with the companies Arranta Bio (USA) and Genibet (Portugal). This will open up synergies that will allow Vibalogics to serve its customers better and more sustainably on a global basis in the future. From now on, clients will be offered a very broad range of services, allowing them to develop and commercialise microbiotic as well as viral and nucleic acid-based products under one roof. ■

Non-viral is better

CELL THERAPY Immunogenicity and limited gene transfer capacity can negatively affect the outcome of cell and gene therapies. European Biotechnology magazine spoke to Dr Dimitrios Laurin Wagner, Berlin Center for Advanced Therapies (BeCAT) and "Gene Editing for Cell Therapy" group leader at Charité, on new approaches that promise to overcome some limitations of current virus-based gene therapies.

EuroBiotech_Just recently, co-infections with AAV2 vectors were identified in studies by UK scientists as the cause of unusually clustered infantile hepatitis this summer. What are the advantages of tailored vector-free transfection systems for primary cells in gene and cell therapies, and what is the current state of development in this area?

Wagner_Virus-free gene transfer has been of interest for many groups for a couple of decades, because it would be much cheaper than conventional replication-deficient retroviruses, which are complex biological organisms and require extensive purification and quality control. I believe that the first alternative technology promoted to replace retroviruses in T cell therapies were transposon-transposase systems such as PiggyBac or Sleeping Beauty. However, they have not been broadly adopted, because many groups struggled to establish stable manufacturing processes in the early days. First, the enzymes were not efficient enough, then there were the toxicities associated with conventional DNA plasmids. With the advent of mRNA technologies and improved plasmid manufacturing, transposases have seen somewhat of a revival, but recent reports of malignant transformation show that random transgene integrations may actually be a safety risk in differentiated cell types, such as T cells. Previously, this was something we had only observed in clinical trials with hematopoietic stem cells. Therefore, gene editing and its targeted mode of action may have a major advantage moving forward: By combining a programmable nuclease and template DNA, we can use homology-directed repair to integrate our therapeutic transgenes in a precise location. This can be achieved with viruses that deliver the template, but also in a completely non-viral fashion using synthetic DNA templates. In my opinion, this is one of the most promising virus-free platforms to engineer immune cell therapies at the moment.

DR DIMITRIOS LAURIN WAGNER is Head of R&D, Berlin Center for Advanced Therapies (BeCAT) Junior Group Leader, BIH-Center for Regenerative Therapies (BCRT), University Hospital Charité, Berlin.

EuroBiotech_What transfection efficiencies and immunogenicities do DNAs generated by genome editing show in comparison to lentiviral and adenoviral gene shuttles, and what about the translation of such platforms by partners with complementary know-how into medical practice?

Wagner_Viruses usually exploit membrane receptors on cells and endocytosis-mediated uptake, which can be very efficient in certain cell types. In fact, viruses are evolutionarily selected to do this very well. On the other side, human cells have evolved strategies to detect such viral components as well using pathogen associated pattern receptors. For example, recognizing foreign non-self-motifs in viral RNA or DNA. Non-viral approaches usually involve transfection with electroporation, chemicals or nanoparticles. Electroporation is the current gold standard and we have very efficient protocols, which reliably deliver virus-free CRISPR-Cas components, mRNA and synthetic DNA templates in more than 90% of T cells or hematopoietic stem cells in a single electroporation. Of course, large amounts of synthetic nucleic acids can also trigger the innate immune pathways in cells, which others and we have demonstrated in T cells too. For mRNA, we can avoid much of this by making the mRNA look similar to normal human mRNA and replacing uracil with less-immunogenic versions, such as pseudouridine. DNA is a bit trickier. Flooding the cells cytosol with large amounts of double-stranded DNA can be very toxic. We tested whether blocking intracellular DNA sensors after transfection can avoid this, and there is a partial impact of individual path-

Picture: © Dimitrios Laurin Wagner

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ways, but we cannot prevent toxicity at larger doses required for higher gene-transfer efficacy. I believe that removing impurities in synthetic DNA templates as well as reducing physical stress during the transfection by removing the DNA size or using single-stranded DNA templates are promising options to reduce toxicity and improve gene transfer efficacy using gene editing. I have recently seen other physical transfection methods that is squeezing cells through small pores in the presence of nucleic acids or use microinjections to deliver them and the needed CRISPR components. It will be exciting to see how the recent hype in mRNA therapeutics and accompanying technologies, such as lipid nanoparticles, will influence how we will transfect T cells in the future.

EuroBiotech_Are there already examples of clinical use of the synthetic DNA platform in TCR-T or CAR-T approaches in blood cancers or beyond, or is this planned and what are the data?

Wagner_On 31st August 2022, Jiquin Zhang and colleagues published the first clinical study using CAR T cells produced by virus-free using CRISPR-Cas9 and synthetic DNA in Nature. The first results in lymphoma patients are very encouraging, because manufacturing was feasible, and most patients benefited from the treatment. Aside from that, others and we are working very hard to bring other TCR-T or CAR-T therapies to patients using similar manufacturing approaches but other diseases. Recently, there has been a major update from one of the frontrunners around Dr Alexander Marson with an updated technology, that uses CRISPR and modified single-stranded DNA. They already demonstrate large-scale manufacturing of CAR T cells for multiple myeloma, and I assume we can expect clinical data from them or one of their associated spin-outs soon.

EuroBiotech_What about cost projections and supply constraints for the synthetic DNAs versus vector-based approaches used?

Wagner_In theory, synthetic DNA is much more flexible, less costly, very stable and thereby a serious contender for vector-based engineering. The waiting times and costs for commercial vector production are slowing down early-stage academic investigations with novel CARs or TCRs. For personalised approaches, where the transgene is customized for each patient, vector manufacturing is simply cost- and time-prohibitive today. Customised DNA synthesis has become much more affordable over the last ten years, and I am expecting that we will see more innovation and growing manufacturing capacity in the synthetic DNA/RNA space. This will likely cause competition and increase quality and price of synthetic DNA.

My dream would be a bench top-like device that can be set up in GMP labs around the globe, which would enable groups like ours to synthesise single-stranded or double-stranded synthetic DNA for diverse applications. There are the first research-grade machines to make small oligos, but it is still science fantasy for clinical applications now because it would require almost perfect fidelity and long nucleic acids are still hard to make. Until then, we will rely on DNA synthesis companies around the globe to increase their manufacturing capacity and come up with protocols to enable very small scale and very large synthesis scales to accommodate the needs of a highly innovative and changing field.

EuroBiotech_How long do you think it will take to translate this approach and where do you see opportunities and challenges?

Wagner_As Zhang and colleagues demonstrated, the future is already here. Identifying the best genomic regions that enable the generation of potent CAR or TCR T cells using non-viral knock-ins is an interesting question. More studies are needed to answer the question of whether the DNA double-strand breaks are a problem for the safety of non-viral knock-in based cell products. To date, we still need DNA double-strand breaks to trigger the repair mechanisms that integrate our transgenes at our location of choice. This will be a big topic in projects where multiple genes are targeted at once, for example for allogeneic cell therapies.

In a universal off-the-shelf CAR T cell product, we want to edit additional genes to increase the persistence or functionality of CAR and TCR T products. With conventional editors, this is very likely to lead to translocations between break points. Novel CRISPR editors such as base editors or prime editing may circumvent DNA breaks in the future, but they must also be carefully evaluated regarding undesired off-target effects on the genome.

EuroBiotech_How is your research progressing and where do you want to be in a year?

Wagner_Overall, we have started the first scaling attempts and established processes to optimize cell yields for allogeneic CAR-T cells. Unfortunately, many of our clinical programs were slowed by the pandemic and there is a backlog of cell products that await clinical testing. For example, we are finally planning to start a first trial with CRISPR-Cas9 gene-edited regulatory T cells in patients with kidney transplantation. Here, we use CRISPR-Cas9 to force a gene knock-out and induce drug resistance.

This is an important project for us and the IND process guides us in preclinical studies and may help us to finalize our process for the CAR knock-in platform using synthetic DNA. I hope that by the end of next year, we will have perfected manufacturing for our first CAR-T product candidate using non-viral knock-in. Due to the regulatory requirements in Europe, it will be important to identify partners to provide the synthetic DNA and other gene editing components made in a GMP environment. ■

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CDMO excellence in phytocannabinoid products

CDMO CB21 Pharma Ltd announces that it entered a global strategic collaboration to combine its leading expertise and clinical research program in phytocannabinoids with world-class pharmaceutical strategic consulting and business development services of NorthStar Corporate Finance Ltd and Krüger Beteiligungs GmbH, forming a new company called CB21 R&D.

› Jan Storch and David Wolfe, Directors CB21 R&D

CB21 R&D is a contract development and manufacturing organisation (CDMO) developing treatments for medical pathologies based on standardised refined cannabis extracts produced from cGMP medical cannabis strains, while applying science and principles of evidence-based medicine for final pharmaceutical products. Nonregulated hemp products containing cannabinoids are used by the public for various reasons and are commonly perceived to provide medical benefits, especially regarding pain relief, anxiety, and sleeping disorders. By conducting preclinical and clinical trials, CB21 R&D is focusing on finding conclusive data regarding successful targeting of health concerns using cannabinoids.

R&D network

CB21 R&D's mission is to help produce pharmaceutical drugs using natural ingredients extracted from the cannabis plants to supplement or substitute chemical pharmaceutical drugs, especially those with harmful side effects including addiction. It partners with the University of Aachen, the University of Freiburg, the University of Olomouc, the University of Brno, Nedcann Severna DOOEL and its shareholder J&K Consulting to support such research. The parent company CB21 Pharma has already successfully developed and registered medical devices and cosmetics using cannabis active ingredients. It is considered one of the most experienced and regulatory advanced EU companies for CBD (Cannabidiol) and other cannabinoids while producing all cannabinoid raw materials in-house, employing EU-GMP Part II compliant processes.

To translate research into practical applications, CB21 R&D has a cooperation agreement with the genetics laboratory at the cultivation centre at Nedcann, a producer of medicinal cannabis dried flowers. Nedcann holds Global GACP and EU-GMP certifications, embodying 33,000 m^2 of flowering rooms and laboratory facilities. The founders have archived over 25 years of data from the recreational market in the Netherlands.

Due to the ease of controlling chemical production as opposed to biological production, pharmaceutical companies have been reluctant to invest in medicinal cannabis. The process of cannabinoid pharmaceutical production, from the genetics and growth process to their cultivation and extraction, requires expert guidance and knowledge. It is necessary to provide pharmaceutical companies with consistent and controlled ingredients and processes. CB21 R&D is a CDMO assisting pharmaceutical companies by providing research conclusive data within the phytopharmaceuticals, especially using phytocannabinoids. ■

Picture: © CB21 R&D Pharma Lab

Fill & Finish of phytocannabinoid-containing products

Vector BioPharma: the future of gene delivery

CANCER Precision gene delivery remains one of the greatest challenges in modern medicine. A Basel-based biopharma company, Vector BioPharma, has accepted the challenge and, with cutting-edge technology from the University of Zürich, is developing a revolutionary new way to deliver the right genes to the right place at the right time. Vector BioPharma aims to be the pioneer in delivering future medicines with this technology, now under development in multiple areas of urgent medical need.

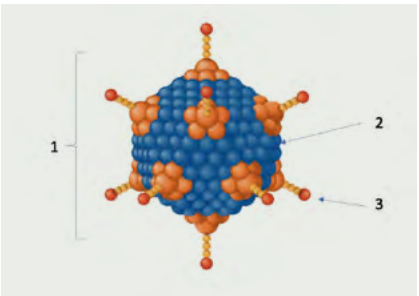
› Nik Barbet, Head of Operations, Vector BioPharma

The field of gene and genetic therapies has exploded in recent years, with hundreds of companies keen to exploit the emerging technology. The grand challenge in the field, however, remains to be solved, namely the precise, efficient and robust delivery of genetic cargo to the target cell and organ. Founded in 2021 and based in Basel, Switzerland, Vector BioPharma has stepped up to address this challenge. With a US$ 30m series A funding from venture capital firm Versant Ventures, the company has grown to 45 employees, 70% of which are PhD-level scientists.

Founded to solve problems

Vector BioPharma is a platform-based company. The technology at the heart of the enterprise comes from the laboratory of Prof. Dr Andreas Plückthun at the University of Zürich, an internationally recognised protein engineer and serial entrepreneur with more than 500 peer-reviewed publications to his name. Prof. Plückthun and Versant formed Vector BioPharma together with Lorenz Mayr, a seasoned biopharmaceutical executive and investor, now CEO of the company.

The technology employs an engineered high-capacity virus-like particle (VLP) that has been stripped of all viral genes. This particle has an incredibly high loading capacity, with the potential to deliver up to 36 kb of DNA payload. The VLP is further engineered to permit evasion of the immune system using a proprietary protein shield that dramatically enhances pharmacokinetic properties and further limits immune clearance. Finally, the fiber knobs of the VLP are engineered with a trimeric protein cap with interchangeable adaptors that alter the natural tropism of the VLP and permit targeting to virtually any cell type. These three components result in a gene delivery vehicle with an unprecedented cargo capacity and exquisite cellular targeting.



Vector BioPharma's proprietary technology consists of a virus-like particle (VLP) with a genetic cargo capacity of up to 36Kb (1), a protein shield (2) and modular, interchangeable retargeting adaptors decorating the fiber knobs (3).

Given the huge flexibility of Vector BioPharma's system, the potential application areas are manifold. The company is looking to initially exploit the technology in the fields of immuno-oncology, cellular therapies and by delivering genome editing machinery to tackle multiple diseases across the field of medicine. Other applications and opportunities are within reach.

"It is gratifying to see the work that started 10 years ago is now being translated into new therapies," said scientific founder Prof. Plückthun. "I look forward to working closely with the Vector team to bring these treatments to patients." "Our platform has significant advantages thanks to the unprecedented size of cargo that can be delivered, our proprietary capsid shielding technology and our ability to precisely target virtually any cell surface epitope," said Vector BioPharma CEO Lorenz Mayr. "We are confident that our approach will offer patients therapies with improved safety, efficacy and specificity. Vector BioPharma: Precision Gene Delivery." ■

Further reading

[1] Bioconjug Chem., doi: 10.1021/acs.bioconjchem.2c00346.
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