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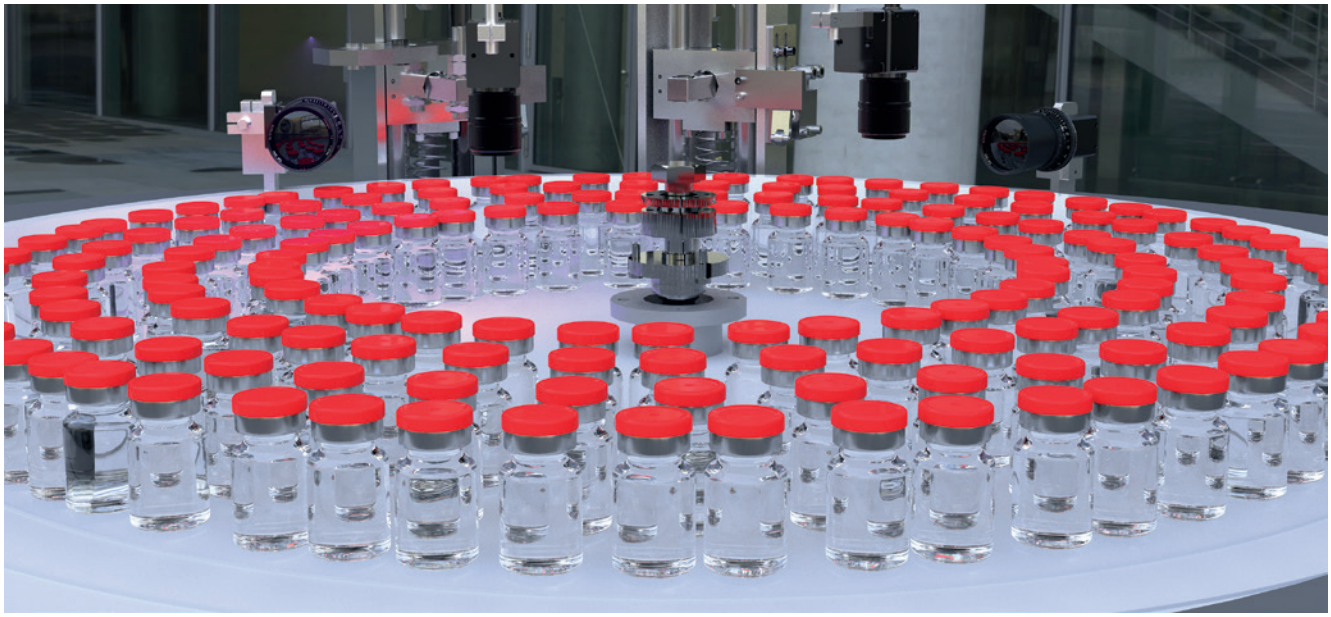

Picture: AdobeStock_Mike Mareen

Big business Bioprocessing

BIOPROCESSING In the past decade, the number of approved monoclonal antibodies raised fourfold. Biologics have become the most delicious piece of the pharma cake. And recombinant proteins and antibody conjugates are just the beginning: Multibillion-dollar markets are opening in the ATMP, DNA/RNA, vectored in vivo CRISPR drugs and cell therapy/redmed markets - CDMOs are adapting their footprint.

The expansion of global biomanufacturing capacity has been the dominant topic not only since the approval of the most successful biotech drug of all time, Pfizer/BioNTech's mRNA-based COVID-19 vaccine Comirnaty.

At an ever faster pace, companies are reporting the upgrading of their biopharmaceutical production capacity, and after gigantic tax revenues from biotech production, more and more governments are following suit, having first recognised the economic potential of biotechnology in light of the pandemic: Most recently, Sweden and Switzerland have publicly declared their intention to lead the world in expanding biomanufacturing capacity for the hyped RNA, cell and gene therapies, innovative peptide drugs and antibodies/conjugates. Although four of the top-5 production sites - the USA, South Korea, Switzerland, Ireland and Germany - are located in the Western world (see table p. 48), Singapore and other fast-growing Asian production sites are already coming close to Germany as a production site, which has been weakening for ten years despite the BioNTech bonus. There, investments and decisions are made unbureaucratically instead of missing the train to the future - at least from the political side. The EU already announced in 2021 that it wants to make Europe less dependent on imports of essential medical goods and raw materials. Whether this includes the creation of additional production capacities with state investment support, however, will not be specified by the EU bureaucracy until 2023. Until then, CDMOs and pharmaceutical developers will have to shoulder the investment risk on their own. Meanwhile, Lilly is creating facts in Boston: the pharmaceutical company is investing US$700m in a plant to produce RNA-based gene therapies.

However, the Corona pandemic has helped vaccine providers and their CDMOs to dream profits. For 2021, US mRNA vaccine developer Moderna Inc, which has been manufacturing in Europe mainly through Lonza and Granada-based Rovi, reported sales of $18.5bn and net income of $12.2bn. Pfizer, the marketing partner of German mRNA corona vaccine developer BioNTech, made even more sales: almost $37bn last year, the US group expects another U$32bn this year. BioNTech SE has so far only reported turnover for the first nine months of 2021: €13.4bn, with a net profit of €7.1bn. Numerous CDMO partners such as Rentschler Biotech-

nologie are benefiting from the recent upswing in mRNA production, but above all from the strong demand for viral and other vectors associated with the pandemic and the upswing in approved gene therapies. Pfizer and BioNTech expect their total production capacity to rise to 4 billion doses in 2022. In late February, Moderna Inc announced to expand its commercial network in six European nations: Belgium, Denmark, the Netherlands, Norway, Poland, and Sweden to support the delivery of mRNA vaccines and therapeutics. The companies have already begun to set up programmes in RSV, influenza, malaria and other infectious diseases with unmet medical use. These might be the lower hanging fruits than cancer vaccines that have failed despite massive development efforts in the past 25 years.

Continued stellar growth

For 2022, a CPhI Worldwide survey among 350 biopharma decision-makers suggests 30 to 50 FDA market approvals resulting in a production squeeze at CDMOs and consequentially higher margins and profits for supply side companies – with mRNA, advanced therapies and biologics seeing the fastest growth rates. Overall, the findings suggest a very robust and prosperous year ahead for CDMOs.

As the pandemic has put immense pressure on the global manufacturing capacity, CMC personell, sourcing and consumables such as vials and single-use equipment, manufacturers expect higher prices, limited availability, and delayed deliveries for many raw materials and therefore a continuation of the dynamic supply chain issues prevalent in 2021.

Nevertheless, according to analyses by Markets&Markets and BioPlan International, the market will continue to grow: M&M predicts that the single-use equipment market will grow to US$20.8bn by 2026 after sales of US$8.2bn last year. Further M&M market studies cite gene and cell therapies (2021: US$7.7bn, 2026: US$13.8bn) and regenerative medicine (2021: US$8.5bn, 2025: US$17.9 bn), as well as RNA drugs and genome editing (2021: US$5.1bn , 2025: US$11.2bn), as other growth areas besides the well-known blockbusters.

According to BioPlan International, about 5.5 million litre production capacity for biologics and vaccines were available in 2021, both in the US and Europe at 650 sites, respectively. Global production capacity increased from 16.5 million litres in 2018 to 17.4 million litres in 2021, comprising 67.7% mammalian cell culture and 25.8% microbial production capacity, while gene therapy (0.5%) and cell therapy (0.7%) were only in their beginnings.

Breakthrough research

This might change with a modular automated manufacturing platform developed by Cellino Biotech, a Boston-based company that got a $80m Series A financing by Bayer AG. Its laser photolithography platform combines vector-free, automated reprogramming of autologous stem cells, its expansion, and differentiation in a closed cassette format and may open the market for cheap cell therapy production (see interview p. 54).

BioPlan projects a worsening cell and gene therapies "capacity crunch". The current capacity shortfall for cell and gene therapies is estimated at 500%. So, 5× current capacity would be in use if such capacity were available. That shortfall will increase significantly over the next five years. Despite many new cell and gene therapy facilities and expansions, future shortages will continue. Most developers, including leading CMOs, are working to catch up with early and mid-phase clinical capacity needs, and few developers have scaled up capacity for commercial and GMP manufacturing.

While growth will be significantly hampered by sourcing and personal bottlenecks, according to the CPHI survey, 65% of executives believe mRNA technologies will be the biggest investment opportunities in 2022 followed by cell and gene therapies (45%) and biologics (43%).

Codagenix is already in clinical testing of a completely synthetic coronavirus. ■

t.gabrielczyk@biocom.eu

Result of a survey conducted by the pharmaceutical association VFA and the Boston Consulting Group in the year 2000 on the top global biomanufacturing nations in terms of production volume. It should not go unmentioned, however, that the specialist provider BioPlan Associates, which has been recording global biomanufacturing capacity in a subscription-based database for more than 17 years, states much higher production capacities (USA: 3.2-fold Europe: 4.4-fold), and also includes the 1.35 million litre fermenter volumes of less than 5,000 litres offered at 1,261 locations worldwide, which were ignored in the VFA/BCG survey.

Biomanufacturing capacity/l	2018	2021	2025
USA	1,680,000	1,710,000	1,720,000
South Korea	500,000	520,000	950,000
Switzerland	200,000	420,000	560,000
Ireland	200,000	425,000	400,000
Germany	395,000	390,000	390,000
Singapore	170,000	300,000	300,000
Denmark	100,000	150,000	150,000

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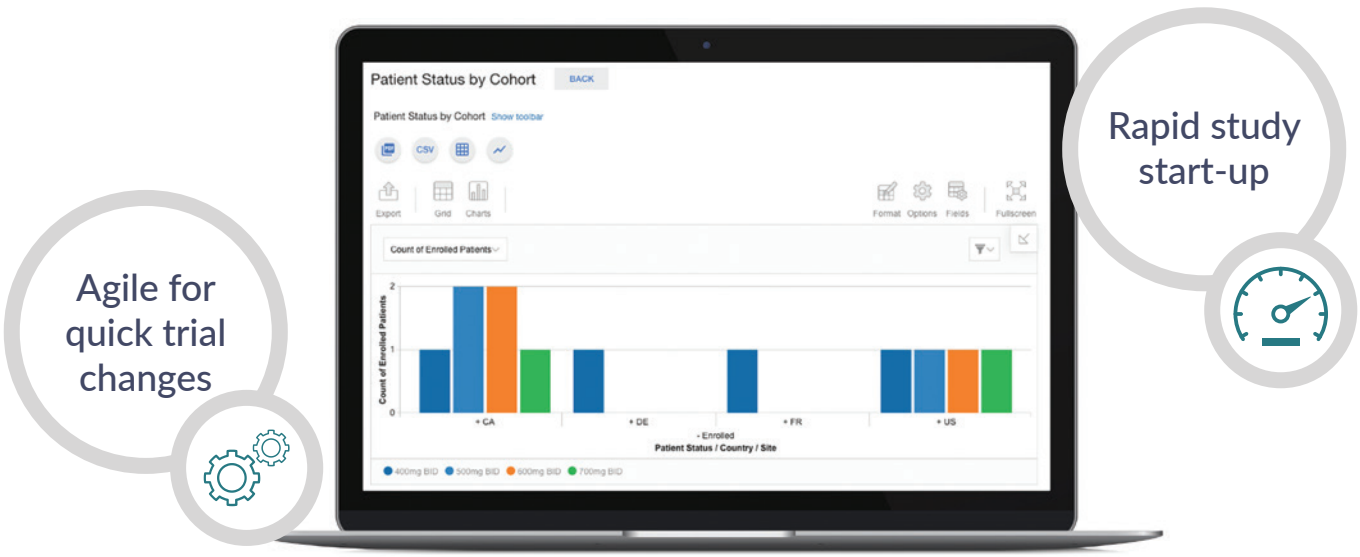

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Mastering the data revolution of clinical trials

CRO Data Management has been a hotbed for development and innovation, correlating primarily with the changing digital landscape. Clinical trial management has been significantly impacted, with the electronic data capture and GDPR-compliance-led industry now unrecognisable from the paper-document administration methods of the past. This development process extends beyond COVID-19 and has a noticeable impact on clinical trials.

› Géraldine Mercier, Head of Data Management at Excelya

Having worked in the world of Data Management for over 23 years, it's safe to say that I have witnessed the industry change and evolve a lot, from the nearly entirely analogue methods of the 1990s to today's almost exclusively digital approach.

Data management used to be very expensive, paper-based and inefficient, with most tasks devouring multiple human hours and being prone to human errors and other vulnerabilities.

Flash forward to now - thanks to the Digital Revolution in the early 2000s-2010s – when we have shifted from paper forms and manual data entry to electronic data capture.

As a result of these changes, instead of waiting for weeks for results, users can access databases directly, update data digitally, which can be validated immediately, then extracted and analysed as needed.

Constant change and adapting processes to meet new industry regulations and client expectations have had a real and meaningful influence on clinical trials at Excelya. The fact that Data Managers, CRAs, PV, stats and sponsors alike can easily and quickly see data in real time, accelerates the way we can perform clinical research. Decisions can be made in reaction to real-time data, improvements can be realized more efficiently, and lifesaving drugs can make it to-market, sooner.

Thanks to data storage protection and the arrival of GDPR, patients can now be confident that they are completely safe and anonymous when participating in clinical trials.

At Excelya, we take user management very seriously. For every study, everyone who needs access to data must be tracked and monitored and can only have access to the precise data they need to perform their work. Passwords are reset very frequently. We review matters regularly for each study, ensuring our list of users is up to date.

This strict approach to compliance allows Excelya to execute internal audits frequently and with ease. This ensures that we are ready for external audits whenever necessary.

Picture: Excelya

The Excelya DM future vision

We are very confident in our operational projections for the coming years and aim to have as much influence and global traction outside of Europe as we currently do within it. We have placed a real strategic focus on Asia and The Americas, and have big ambitions there, already seeing a lot of very positive developments.

These exciting advancements give Excelya the ability to grow faster and diversify our personnel, offering increased flexibility and forming a solid foundation on which to build our increasingly international team.

Some other areas for development in Excelya's future include expanding into machine learning, business intelligence and data science. We don't intend to rest on our laurels and have big ambitions when it comes to innovation and new tech. ■

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Lead optimisation – the sequence is the key

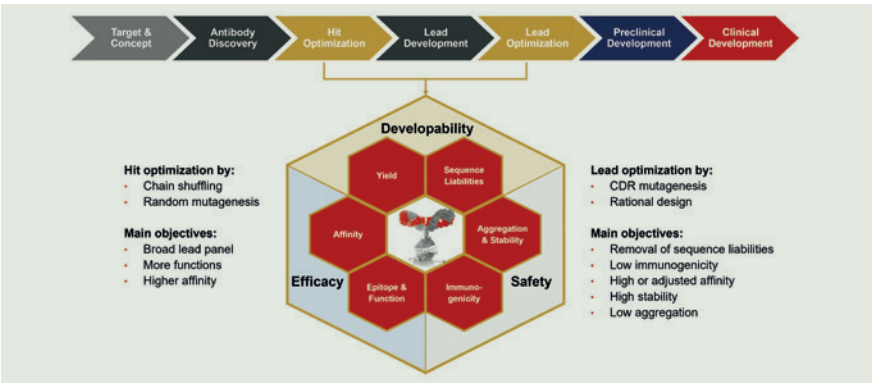
ANTIBODIES The efficacy of therapeutic antibodies is defined by their primary amino acid sequence. After discovery, antibody candidates often profit from protein engineering and sequence optimisation. Different technologies can improve the functional properties of antibodies as well as their biochemical and biophysical characteristics influencing manufacturing, process development, formulation, and other parameters of the final drug target product profile.

› Dr Thomas Schirrmann, CEO, YUMAB GmbH

Therapeutic antibodies are the most important class of biopharmaceuticals, and they are indispensable for the treatment of many diseases. Fully human antibodies can be directly generated by different technologies such as in-vitro display technologies from libraries (phage, yeast, mammalian display) or by immunisation from transgenic animals endowed with human antibody genes or by both in combination. Selection and screening of early antibody candidates already define many properties of the final drug such as high target specificity and selectivity, or even special features such as cross-reactivity with animal models to facilitate preclinical development. However, it is unlikely, that early antibody candidates combine all favourable features in one molecule to already develop an optimal drug.

Lead optimisation

Hit and lead optimisation can help to improve functional properties of the antibody candidates such as affinity or stability, and they can also address issues concerning manufacturing or formulation relatively early in the development process. Therefore, it is important to consider and plan these optimisation steps at early stages of drug development, because they can save valuable time and high costs at the later development stages. Moreover, they de-risk the drug development programs before critical decision points, for example, before cell line development, when the antibody lead sequence is defined and cannot be changed anymore.



The exchange of single amino acids can strongly influence the functional properties, stability, expression levels, trend towards aggregation, and immunogenicity of an antibody, which means it can be decisive for the fate as a suitable therapeutic compound. Many properties are interdependent, for example higher stability can improve expression levels and can facilitate process and formulation development, or lower aggregation propensity may allow high-dose formulations, a prerequisite for subcutaneous administration route, and reduction of the likelihood of immunogenicity.

Hit optimisation soon after discovery can help to obtain larger lead panels with a broader range of functional properties to choose better early lead candidates. Here, random mutagenesis or chain shuffling can increase affinity and/or new functional properties, respectively. Top lead candidates often require additional protein engineering, which is tailored to the individual molecule. Bioinformatic approaches support many if not all steps of antibody development. Prediction of sequence liabilities does not only help to select or deselect lead candidates in the screening process, but also to identify sequence liabilities, which may interfere with later development steps. There is no one solution for all, but the combination of bioinformatical and molecular genetical technologies provide optimised solutions to improve almost any antibody molecule. ■

Picture: Yumab GmbH

Automating patient-derived cell production

REGENERATIVE MEDICINE In mid-February laser photolithography specialist Cellino Biotech Inc. raised €71m in a Series A financing led by Leaps by Bayer, German Bayer SE's funding arm. European Biotechnology spoke with CEO Nabiha Saklayen about the company's groundbreaking technology.

EuroBiotech_Dr Saklayen, Cellino Biotech - built by yourself, Dr Marinna Madrid and Matthias Wagner - could revolutionise the costly engineering, reprogramming and scaling of production of autologous cell therapies due to an automated non-invasive high throughput process. Could you please describe the workflow and physical principles behind?
Sakalyen_Cellino is on a mission to make stem cell-based regenerative medicines accessible for all eligible patients. Stem cell-derived therapies are poised to prevent, treat, and potentially reverse diseases for which no options are available today or the current standard of care is insufficient. Currently, large scale production of stem cell therapies is challenging due to extensive manual handling, high variability, and expensive manufacturing costs. Our next-generation manufacturing platform combines artificial intelligence (AI) and laser technology to automate cell therapy manufacturing thus reducing expenditures and overcoming scaling limitations. Cellino's next-generation process combines label-free imaging, high-speed laser editing, and artificial intelligence (AI) to automate cell reprogramming, expansion, and differentiation in a closed cassette format. The groundbreaking approach has the potential to reduce production costs by an order of magnitude and expands patient access to cell therapies.

Nabiha Sakalyen, PhD, is the CEO & co-founder of Cellino Biotech Inc (Cambridge, Mass.). Nabiha was selected as a Pioneer in MIT Tech Review's 35 Innovators under 35 list for her patented inventions in cellular laser editing. She received her PhD in Physics from Harvard University as a Howard Hughes Medical Institute (HHMI) International Fellow. She is also the inaugural Tory Burch Foundation Fellow in Genomics at the Innovative Genomics Institute led by Nobel Laureate Dr Jennifer Doudna. Nabiha is also a TED speaker and co-creator of I Am A Scientist, an educational program running in 50 states that inspires children to explore science. She grew up in Saudi Arabia, Bangladesh, Germany, and Sri Lanka and considers herself a global citizen.

EuroBiotech_In which markets or indications do you see the most potential for your platform technology?
Sakalyen_Stem cell-derived therapies offer significant value across a variety of therapeutic areas, from Parkinson's to muscle disorders and more.

EuroBiotech_In which fields of application will you apply Cellino Biotech's technology first? Where do you see challenges and opportunities for your laser-based delivery method compared to established methods such as electroporation or vectors?
Sakalyen_We are currently in discussions with the National Institutes of Health (NIH), where senior investigator Dr Kapil Bharti is leading the first autologous induced pluripotent stem cell (iPSC)-derived clinical trial in the US in ophthalmology, to validate Cellino's manufacturing approach.

EuroBiotech_In 2017, a throughput of 50,000 cells per minute was reported. What is it today, and which factors limit throughput?
Sakalyen_We are currently around 50,000 cells per minute, with plans to increase to 500,000-1,000,000 cells per minute for our GMP facility. Factors limiting throughput in terms of cells per minute include: speed limitations in optical systems that accurately aim and modulate laser pulses per cell; and density of cells to be treated in a particular area of a cell culture vessel.

Pictures: Cellino Biotech

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EuroBiotech_By what factor could your technology reduce the production costs of autologous cell therapies?
Sakalyen_ We believe we could reduce the production costs of autologous cell therapies by an order of magnitude.

EuroBiotech_You founded your company in 2017 with help of four seed investors and just recently closed a US$80m Series A financing round. How will Cellino Bio use the assets? Does the technology still need optimisation or is it ready to use?
Sakalyen_ Proceeds from the Series A financing will considerably expand Cellino's software, machine learning, and hardware capabilities for end-to-end manufacturing of both autologous and allogeneic stem cell-based therapies. We are augmenting our software and hardware teams to optimize our technology and drive considerable value for patients.

EuroBiotech_How about interest and partnerships with biopharmaceutical companies since the latest financing?
Sakalyen_ We can't comment on ongoing discussions with biopharmaceutical companies but can say that we are currently building a long-term collaboration with the National Institutes of Health (NIH), where senior investigator Dr Kapil Bharti is leading the first autologous induced pluripotent stem cell (iPSC)-derived clinical trial in the US to validate our manufacturing approach. The company also plans to build early-stage GMP capabilities to support clinical trials.

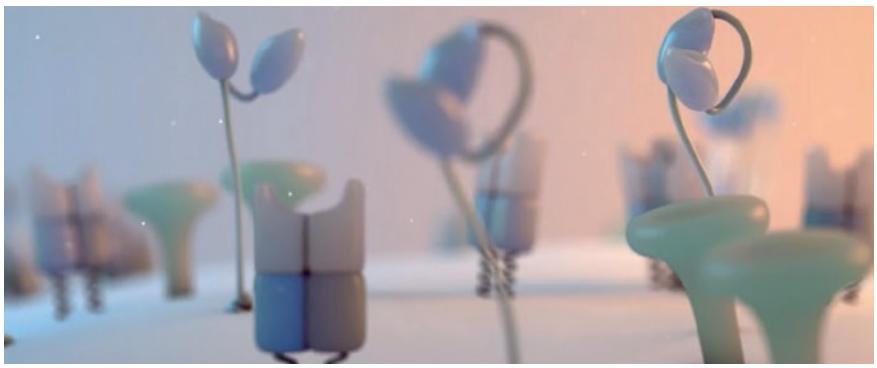
EuroBiotech_What are Cellino Biotech's next strategic goals?
Sakalyen_ Cellino's approach enables the parallel processing of thousands of patient samples in a single facility, which is vital for scalable manufacturing. Inspired by the semiconductor industry, our goal is to build the first autonomous human cell foundry in 2025. ■

Going for allogeneic cell therapy

Cell therapy In January, the FDA lifted its clinical hold from October 2021 on Allogene Inc.'s ALPHA2 Phase II clinical trial because a report of a chromosomal aberration in ALLO-501A CAR T-cells from a single patient did not correlate with the allogeneic cell therapy. The US licensor of Paris-headquartered Cellectis SA's off-the-shelf TALEN-based allogeneic CAR-T technology has announced to continue its pivotal study in mid-2022. Allogene announced to run separate tests on ALLO-501A as well as an experimental, immunosuppressive antibody drug, ALLO-647, the company is using to prepare patients with relapsed/refractory large B-cell lymphoma for treatment.

ALLO-501A is an allogeneic anti-CD19 CAR T cell product whose disrupted TCR-alpha gene may reduce GvHD risk, and edited CD52 gene may permit use of ALLO-647 (a humanised anti-CD52 mAb) to selectively deplete host T cells.

Allogeneic CAR-T cell therapies address logistical/manufacturing challenges inherent in autologous CAR-T therapy. Allogene's allogeneic CAR-T programs utilise Cellectis' technologies. ALLO-501 and ALLO-501A are anti-CD19 products being jointly developed under a collaboration agreement between Servier and Allogene based on an exclusive license granted by Cellectis to Servier. Servier granted Allogene exclusive rights to ALLO-501 and ALLO-501A in the U.S. while Servier retained exclusive rights for all other countries.



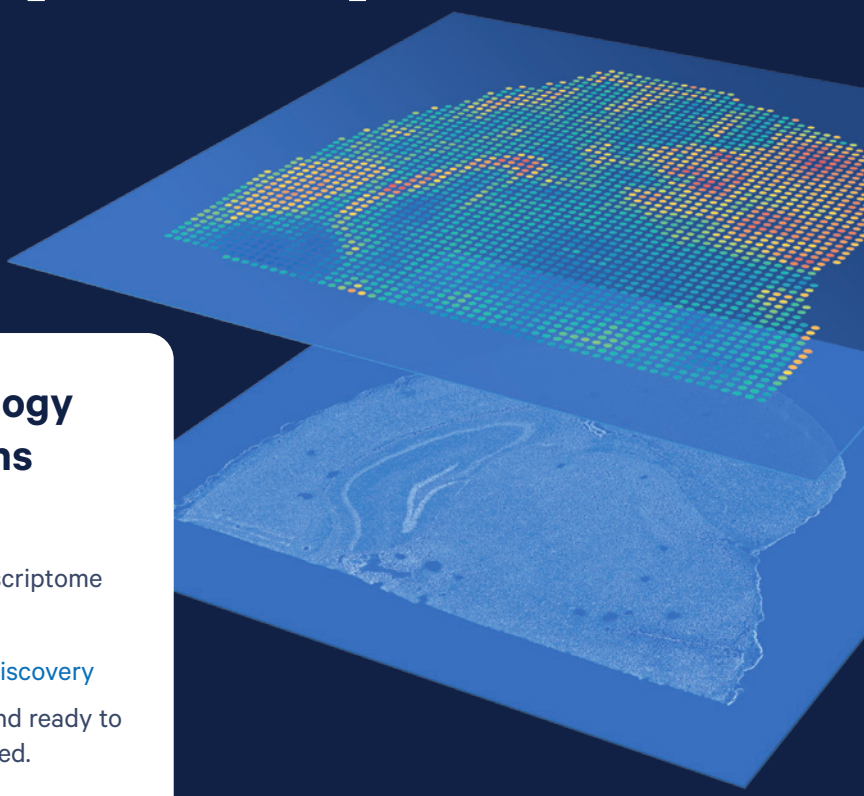
Competitors coming closer

Meanwhile, Swiss CRISPR Therapeutics SA reported positive results from a Phase I trial of CTX110™, in the same indication. In 23 patients receiving CTX110 58% showed an overall response and 38% a complete response in large B-cell lymphoma with a single dose of CTX110.

Further competition is coming in from companies that use NK cells instead of T cells, which have a worse safety profile concerning cytokine release syndrome and neurotoxicity. In November, Fate Therapeutics reported an overall response rate of 72% in patients treated with FT516, an off-the-shelf NK cell therapy manufactured from a clonal master engineered induced pluripotent stem cell line. FT516 expresses a high-affinity, non-cleavable CD16 Fc receptor in combination with an anti-CD20 monoclonal antibody. No dose-limiting toxicities, FT516-related serious adverse events, or FT516-related Grade ↗3 adverse events (AEs) were observed. No CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) of any grade were reported. Eight of the 11 patients treated with 90 million FT516 cells achieved an objective response, seven achieved complete response. ■

Pictures: Allogene

Gain a new perspective on tissue complexity



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RTSM benefits: configuration versus customisation

CONTRACT RESEARCH In the 1990s, the first clinical IVR systems (Interactive Voice Response Systems) were developed in order to randomise patients over the phone, and later, to dispense drug and resupply sites as well.

› Josée Leach, Senior Marketing Manager, EMEA, 4G Clinical

The first IRT systems – Interactive Response Technology – were completely custom-coded. Each application was built from scratch and therefore could meet all the sponsor's needs for a study because it was 100% customised. End-users used them since they met their study needs, but they took forever to build and were very expensive.

In the early 2000s, the first parameter-driven, web-based systems were introduced. They were less expensive to build and saved time but only if the system fit the sponsor's needs out of the box. So, the industry went from 100% customisable (coded) systems to partially configurable systems. Those systems were off-the-shelf, meaning that the end-user needed to take the system as it was and force-fit it to their internal processes, or even more disruptive, change their internal processes to fit the technology.

These systems were more than likely considered "enterprise" systems and were so ingrained into the organisation there was a very high probability an organisation would stay with older systems purely for the change management it would take to free themselves from the status quo.

Thankfully, technology continues to evolve, either driven by regulatory shifts or scientific breakthroughs. As an example, just think about all the new technologies that were spurred on by remote trials or the shift toward biologics and immunotherapies. They can no longer be implemented into the fabric of the organization, but rather need to ebb and flow with the needs of clinical trials.

This brings the discussion back to the partially configurable, off-the-shelf concept. The core of the system stays the same, but certain features can be customised to fit the needs of the specific organisation and study. From an operational perspective, that may sound great. However, it is important to understand that any amount of customisation involves coding. Coding requires more time and resources and ultimately limits future use

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of that product for anything beyond that specific study. Users can't just "flip a switch" and turn off the new add-ons when they don't need them. It also makes future changes both cumbersome and costly. Companies often customise so much that they lose sight of the core function of what is really needed from the system.

Benefits through configurability

How can the industry achieve the benefits of customisation with the flexibility to adapt to changing study needs as well as the introduction of new requirements (driven by science or regulatory)? The answer is 100% configurability.

With Prancer RTSM®, 4G Clinical's Randomisation and Trial Supply Management software, the pendulum has swung all the way from 100% customisation to 100% configurable. This is because configurable systems are designed to adapt to client needs. Flexibility is literally built into the system itself.

Configurable systems DO allow users to flip a switch. So, if there's a need for a feature in study A, but not for study B, it's simple to adjust. Likewise, if users want the system flow and vernacular to match internal SOPs and processes, it's just a few clicks away.

That said, not all configurable systems are created equal. For the above to work, the system needs to be 100% configurable, not just employ a configurable tool, because that is where custom coding creeps back into the picture. Even if the system is 80–90% configurable, the remaining 10–20% is custom-coded, or customisable. If this was an industry in which the parameters needed on Day 1 were exactly what was needed on days 10, 30, 90, and so forth, there would be no issue. But this is a rare occurrence.

One of the key benefits of working with 4G Clinical's 100% configurable Prancer RTSM® is that typically "added on" features are already implemented into the core product. If a feature is built for one client, it is not only available for that client's multiple studies but is also available for all other clients. Each can have its own flavour of that feature – again, that flexibility is built right in. And since users can turn them on and off whenever needed, changes are no longer a disruption to a study.

4G Clinical, a global leader in RTSM and clinical supply optimisation solutions for the life sciences industry, has offices in the U.S., (Boston, Portland), and in Europe: Amsterdam, Basel, Brussels, Copenhagen, Dublin, Nottingham, and Rheinbach, as well as Tokyo and Tel Aviv. To learn more about our fully cloud-based, 100% configurable, and flexible solutions for accelerating clinical trials visit www.4gclinical.eu. ■

Picture: 4GClinical

A new purification workflow

PROTEIN PURIFICATION Biologicals have shown significant success for more complex diseases, whereas small molecule drugs have not been that effective. New biologicals are mostly highly purified proteins or antibodies, which require the development of technologies for the preparation of a large number of drug candidates with high purity and speed. A high throughput magnetic beads-based system is a game-changer for biologics discovery.

› Roumen Bogoev, GenScript Inc.

According to The Business Research Company market report, the biological drugs market was $258bn in 2018 and continues growing at a CAGR of 12.4%. It was made possible by the invention of the chromatography separation techniques allowing researchers to purify antibodies and proteins to high purity with various separation methods like affinity chromatography, ion exchange, hydrophobic interaction, size exclusion, and others. Although these types of separations are extensively used in the production of biological drugs, they typically require multiple steps that are time-consuming and difficult to automate.

A new purification methodology has recently started gaining popularity, minimising the need for extensive sample preparation – a method based on magnetic beads instead of packed resin columns.

Magnets can quickly pull the beads or re-suspend them as needed, increasing the purification speed and simplifying the instrument design, leading to more cost-effective high throughput instrumentation. In addition, this method can be easier to scale up or down due to adding more or fewer beads to the sample as needed.

GenScript as the game changer

GenScript, Inc. partnered with Amgen to license their internally developed magnetic beads-based technology and offer it commercially. The newly launched

AmMag™ SA Plus semi-automated system uses magnetic beads for purifying proteins and antibodies.

AmMag® SA magnetic beads-based system extends the higher throughput purification capabilities to larger volumes of up to 50 ml and can purify up to 80 mg of protein or antibody per sample. The instrument can purify 12 samples in about 40 minutes and has a throughput of more than 60 samples per day. This system has much lower requirements for sample preparation and does not require samples to be centrifuged or filtered before purification, saving researchers a great deal of time and labour.

While magnetic beads-based systems are used in genomics research and diagnostics, they have not found wide adoption in the protein and antibody purification area.

One of the roadblocks has been that protein work requires capturing a larger amount of target due to the lack of amplification techniques for proteins, that are commonly available for nucleic acid. Part of the problem is that the magnetic beads used for the separation have typically been with limited capacity and reusability, leading to the high cost of the purification. GenScript has several types of magnetic beads with high capacity and reusability and that can sustain NaOH cleaning procedures for eliminating cross-contamination.

High capacity beads

The AmMag protein A magnetic beads targeted to purify antibodies and Fc-labelled proteins can be washed with NaOH and re-used 30-40 times. The AmMag Ni magnetic beads targeted to the purification of 6xHIS-tagged recombinant proteins can also be washed with NaOH and re-used more than 100 times without stripping and re-charging. This allows beads-based purifications for larger target amounts at a competitive cost.

Scaling up protein purification

The availability of the newly launched magnetic beads-based products can help further increase throughput and improve efficiency. These new advancements can significantly accelerate the screening of new drug candidates and help companies launch new cures faster. ■

Pictures: Genscript Inc

Onk Tx partners with Intellia Tx

CELL THERAPY US genome editing specialist Intellia Therapeutics in-mid-February has licenced its ex vivo CRISPR technology and LNP delivery platform to Irish ONK Therapeutics Ltd, an allogeneic cord blood-derived NK cell cancer therapeutics start-up that raised $21.5m in January in a Series A financing to move three lead programs into preclinical proof-of-concept. Under the contract, Onk Therapeutics has the right to use, develop and commercialise up to five guide RNAs provided by Intellia to engineer proprietary NK cells that include gene edits and a TNF-related apoptosis-inducing ligand variant (TRAILv) targeting the death receptor pathway via DR4 or DR5. Intellia will be eligible to receive up to $184m per product in development and commercial milestone payments, as well as up to mid-single digit royalties on potential future sales. The US company will have the right to co-commercialise two of the resulting therapeutic programmes in the US, excluding ONK's CD28-targeting lead product ONKT-102, which is being developed for the second-line treatment of patients with multiple myeloma, for which ONK retains sole rights. If Intellia chooses to exercise the co-development and co-commercialization option on an investigational product, in lieu of the potential royalties and milestones, Intellia will share 50 percent of any future profit and loss generated by the product. ■

Picture: Univercells Technologies

Vesicles as RegMed vectors

BIOMANUFACTURING Vaccine and gene therapy vector manufacturer Univercells Technologies NV in January partnered with RoosterBio Inc. to advance scalable and continuous exosomes manufacturing in a RoosterBio's scale-X™ continuous bioreactor, which features a 2.4 m² surface for cell growth, to deliver cell-based regenerative therapies at reduced timelines and costs. The partnership with the leading US supplier of human mesenchymal stem/stromal cells (hMSCs), highly engineered media, and hMSC bioprocess systems will optimise the manufacturing of extracellular vesicles (EVs), said Univercells Technologies. ■

Preventing CAR-T relapses

Dutch university spin-out Lumicks recently moved to new headquarters in the south of Amsterdam. Its z-Movi measures the avidity between immune cells and their targets without compromising cell viability.

CAR-T CELL THERAPY Relapse to CAR-T cell therapy is thought to be partially caused by both low antigen density and reduced persistence of CAR-T cells. To address both of these mediators of relapse, a team headed by Maria Themeli from University Hospital developed chimeric costimulatory receptors (CCRs), which bind to a second tumour-associated antigen and provide intracellular signalling to support CAR-T cell activation. Using a BCMA- or CD19-directed CAR and a CD38-directed CCR, the researchers at the end of January reported increased tumour cell killing in vitro – using a cell avidity analyser developed by Lumicks NV – and in vivo in xenografted mice – even against tumour cells with very low antigen density (Sci. Transl. Med., doi: 10.1126/scitranslmed.abh1962). This was associated with improved CAR-T cell persistence.

These results suggest that combining CARs and CCRs may improve clinical outcomes for patients receiving CAR-T cell treatments. ■

New vectors

DELIVERY Despite a €250,000 seed financing, Vector Biopharma AG is still flying under the radar of many investors. But as early as this year, experts expect the spin-out from University Zurich to take off internationally with its new adenovirus vector-based delivery technology. What Andreas Plückthun and Markus Schmid, the serial Swiss entrepreneurs, have succeeded in doing could take cancer therapy a giant step forward: They can package the DNA of several anticancer agents at once – such as checkpoint inhibitors and several interleukins – in the viral vector that acts as a Trojan horse. At the same time, the vector reaches its targets better by means of a kinetically stable, trimerised hexagonal scFv fragment and therefore deliver higher doses than cancer antibodies (doi: 10.1073/pnas.2017925118). But it also effectively shields the vector from rapid degradation in the liver, which greatly improves half-life and tumour penetration. Once the novel vector has penetrated a cell of the tumour or tumour stroma, it becomes a factory for anticancer agents such as antibodies, or proinflammatory cytokines. So, as with ADCs, systemic effects are attempted to be reduced by better targeting of Shielded, Retargeted Adenovirus (SHREAD) vectors. ■

Picture: Lumicks NV

Huge financing in Spain

PROTEIN SPLICING SpliceBio S.L. (Barcelona) has raised €50m in the largest Series A financing Spain has seen so far. The round was co-led by UCB Ventures and Ysios Capital with participation by New Enterprise Associates, Gilde Healthcare, Novartis Venture Fund and Asabys Partners. The company was seeded two years ago by Ysios Capital and Asabys Partners. SpliceBio wants to use its unique protein splicing platform to improve delivery of large genes with adeno-associated vectors (AAV) and advance the company's lead in Stargardt disease. Juvenile macular dystrophy is affecting more than 80,000 people in US and EU. The disease is caused by a loss of function mutation in the ABCA4 gene. In the company's approach, engineered inteins catalyse highly efficient protein trans-splicing to reconstitute the desired full-length therapeutic. ■

Management team of SpliceBio SL: Gerard Caelles, CEO; and co-founders Miquel Vila-Perelló, PhD, and Silvia Frutos, PhD

Remote control

GENE THERAPY MICA Biosystems has partnered with Europe's major advanced therapies hub, CGT Catapult. Mica has developed functionalised magnetic beads that can activate specific stem cell receptors in situ through application of an external magnetic field. The company shortly aims to clinically assess its first application in spinal fusion, a type of spinal repair. Plans for future applications include arthritis, tendon repair, osteoporosis, spinal cord repair, and a treatment for neurodegenerative diseases. ■

Gene therapy hub

DELIVERY Sharp, a global leader in contract packaging and clinical supply services, has completed the construction of new production suites of gene therapies, at its facility in Heerenveen, The Netherlands. ■

Picture: SpliceBIO