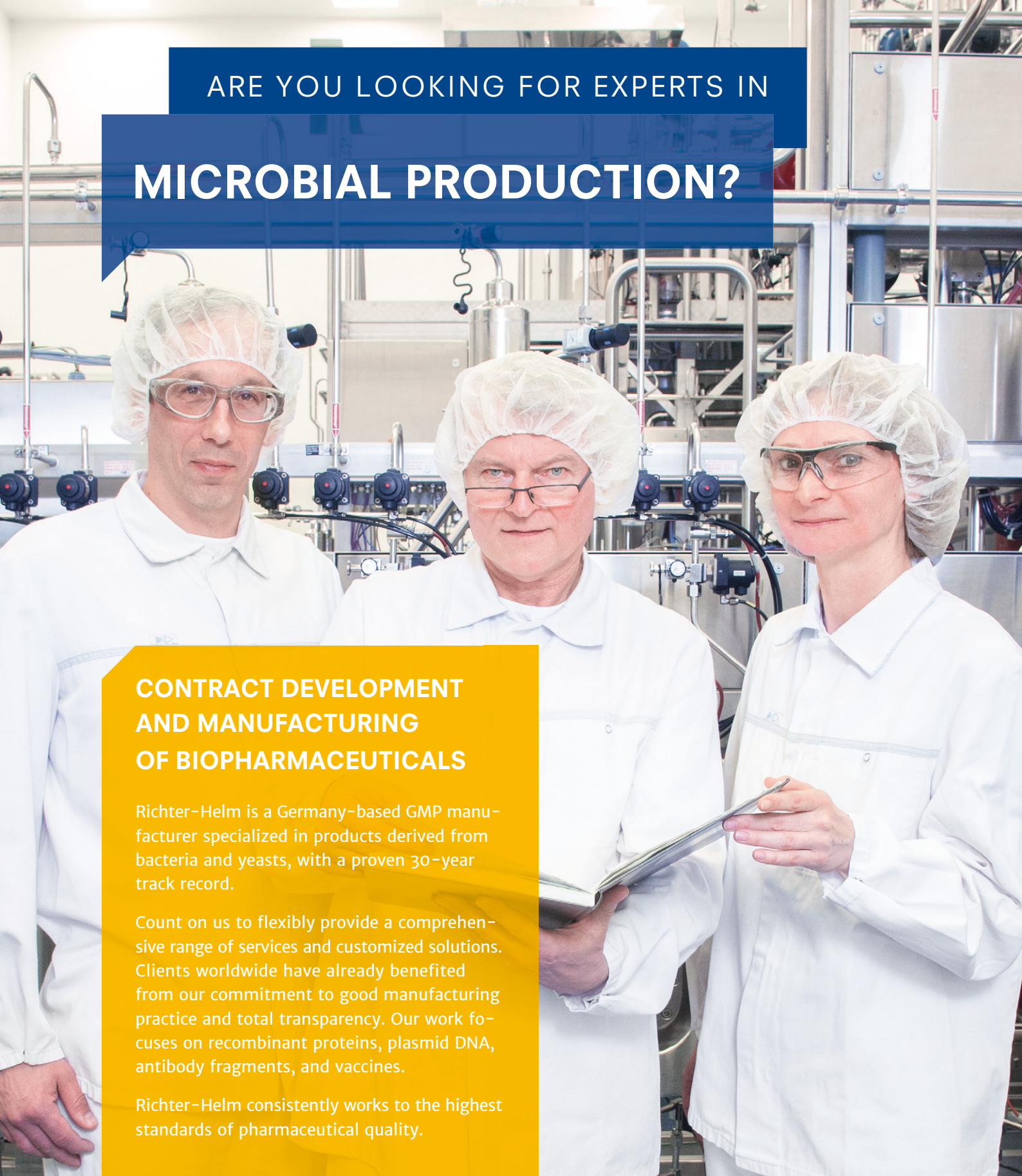
European Biotechnology

Autumn 2019

CMOs & CROs

Special



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CDMOs/CROs: Good time for specialists

CONTRACT RESEARCH/CONTRACT MANUFACTURING While CMOs and CROs are benefitting from steady growth in the biopharmaceutical market, providers are under pressure to qualify as experts in gene and cell therapies, live microbials, and antibody conjugation. In a move to adopt DoE into process development, real time control of purification is getting closer.

Backward and forward integration of services along the biopharmaceutical value chain have dominated the past few years in the steadily growing market for outsourced biomanufacturing and drug development. Following the examples of market-dominating CDMOs such as Boehringer Ingelheim and Lonza, mid-sized companies such as Polpharma, Rentschler, et. al., have expanded their services, partnerships, as well as their geographic footprints, to become "fully integrated" or "one-stop service agencies" to the biopharmaceutical industry.

Price pressure increasing

As cheap biosimilar versions of off-patent antibody blockbusters are flooding the markets, improving biomanufacturing productivity/efficiency – in brief: delivering high quality at low prices – was the top concern of biomanufacturers that Bioplan Associates surveyed last year. Roughly 16% of the surveyed companies said that process efficiency must be steadily improved. About 64% of the surveyed managers said their facility has "implemented programs to reduce bioprocessing costs." Currently, about 165 biosimilars are in human testing, and 380 are being marketed worldwide. Bioplan's projection that biosimilars may outnumber innovative reference drugs or bio-betters within the next few years is fuelled, specifically, by the German government's plan to automatically substitute the expensive biopharmaceuticals with biosimilars at the pharmacy level.

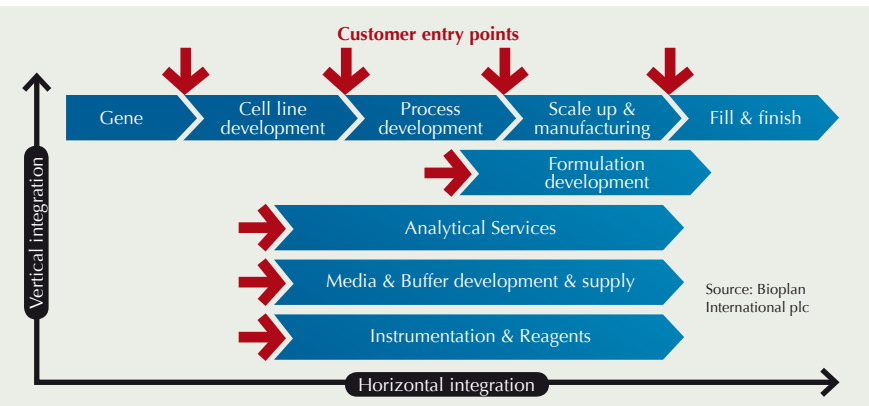
While antibody production titers have tremendously grown over the past decade, downstream processing bottlenecked progress. Thus, biotech leaders, such as Biogen Inc., have piloted continuous DSP facilities to bridge that gap.

The most recent innovation in DSP control was announced by Vienna-based acib GmbH, and Boehringer Ingelheim and Novartis Pharma country offices. After three years of testing, they installed a process at Boehringer Ingelheim in Vienna that allows for real-time monitoring of protein purification instead cost-intensive post-analysis of certain DSP steps. "While current methods only allow information on single-quality parameters of a product during a process, our process informs us in seconds about the quality and quantity of a product and about contaminations," said project leader Astric Dürauer. Through this patented progress in process quality control, the companies expect significant cost savings, even for high-priced biopharmaceuticals in the future – a success in a continuous DSP that has been requested by regulatory agencies in recent years.

Bottlenecks

At the same time, pressure on prices of gene and cell therapies and a production capacity crunch in the emerging market for advanced therapies are triggering huge investments and new partnerships. This summer, Pfizer said it will invest US$500m into a new US gene therapy production facility. In Q4/2019, bluebird bio's EU manufacturing partner apceth will start the shipping of Zynteglo (see interview, page 14). However, a lack of production capacity at the level of viral vector production will provide huge growth opportunities for specialised CDMOs in this emerging market area. ■

t.gabrielczyk@biocom.eu



Integration of services in the CDMO value chain

Picture: Bioplan Associates

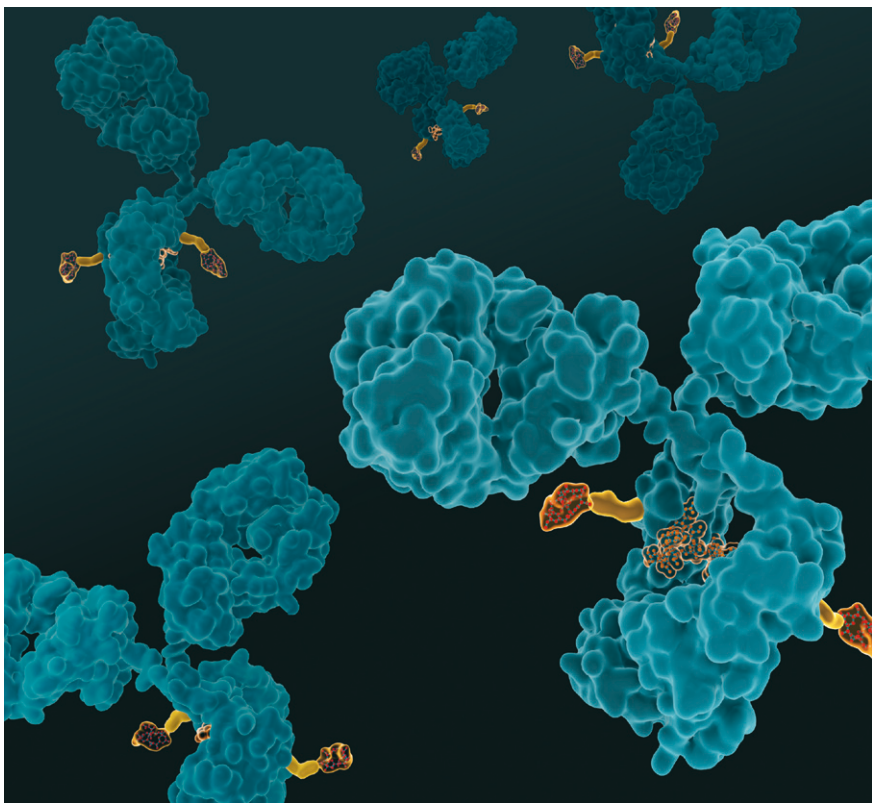
High performance glue for targeted cancer therapy

ADCS Araris Biotech AG is pioneering a novel antibody-drug conjugate linker technology that enables highly controlled and stable enzymatic conjugation ("gluing") of any payload to "off the shelf" antibodies without the need for prior antibody engineering.

› Dr Isabella Attinger-Toller, Dr Dragan Grabulovski, Dr Philipp Spycher

Antibody-drug conjugates (ADCs) consist of an antibody (tumour-targeting), a payload (drug), and a linking-moiety (linker) that connects the drug to the antibody. ADCs selectively deliver drugs to tumours while healthy tissues are spared, a so-called targeted chemotherapy. Although promising progress has been made and five ADCs have received market approval so far, current ADCs and ADC technologies face three major challenges:

- premature loss of the drug leading to unacceptable toxicities and reduced efficacy,
- limited linker solubility leading to non-optimal ADC drugs, and
- time and cost consuming ADC generation.



Schematic illustration of an ADC harboring two drugs stably connected to the antibody through the Araris Linker (depicted in yellow)

Picture: Araris Biotech

In fact, many of the clinical ADC failures are attributed to one or more of the challenges mentioned above.

New concept

Araris Biotech AG is developing a novel ADC-linker technology platform to overcome these challenges through the use of peptide linkers. Using these linkers and a microbial transglutaminase-based enzymatic approach, we are able to conjugate IgGs site-specifically and efficiently with our linkers and any payload of choice (drug, dyes, DNA, etc.). Moreover, peptide linkers offer a great flexibility to incorporate various functional chemistries, e.g. azides, for click-chemistry or sulfhydryl-groups for maleimide-based approaches, enabling the incorporation of two, four drugs, or even two different drugs ("dual-payload" delivery) in one ADC.

The resulting ADCs have favourable physicochemical properties and have shown very efficient anti-tumour responses in efficacy studies compared to conventional ADCs used at the same dosing, payload, and drug load.

To summarise, highly stable and efficacious Araris ADCs are generated in less than 48 hours directly from "off-the-shelf" IgG antibodies without prior engineering. Our ADCs, thus, may offer higher efficacy and lower risk for side effects in patients with highly unmet medical needs. ■

Success through partnership for biologics

ONE STOP SHOP CDMO FOR PROCESS DEVELOPMENT, cGMP CLINICAL MANUFACTURING AND COMMERCIAL SUPPLY

Microbial

Mammalian

- Cell line development
- Tech transfer
- Process development
- Analytical development, qualification & validation
- Scale-up
- cGMP manufacturing
- Process characterization & validation
- Commercial manufacturing

Biopharmaceuticals 3P

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Therapeutic mRNAs made in Hamburg

RNA MANUFACTURING AmpTec GmbH is an internationally active CMO company with comprehensive services for the production of therapeutic mRNAs as a drug substance or active pharmaceutical ingredient (API) for the pharmaceutical industry using mRNAs to develop a new category of medicines. AmpTec's products meet the requirements of the finest international standards

› Dr. Peter Scheinert, Managing Director & Founder, AmpTec GmbH

The two AmpTec founders Dr Peter Scheinert and Dr Guido Krupp

AmpTec GmbH was founded in May 2005 by Dr Guido Krupp and Dr Peter Scheinert and is an international supplier of synthetic nucleic acids for diagnostic and therapeutic applications. A quality managment (QM) system with ISO 9001 had been introduced in 2008, followed by ISO 13485 in 2010. Another milestone was the implementation of requirements of cGMP FDA 21 CFR Part 820 in 2012, a guideline relevant to the manufacturing of products for diagnostic applications. Since then, AmpTec has been supplying customised synthetic long RNAs and DNAs from any sequence as reference material for the development of real-time PCR assays or therapy-accompanying assays, so-called companion diagnostics, for worldwide leading companies, which are active in the field of molecular diagnostics.

In 2016, another big step was taken with the implementation of the requirements of cGMP FDA 21 CFR Part 210 and ICH Q7 (Section 19: APIs for use in clinical trials). The implementation of this guideline was the prerequisite for the production of drug substances or active pharmaceutical ingredients (APIs) for the pharmaceutical industry at AmpTec. Production of APIs are subject to stringent regulations, and the quality of APIs has a significant effect on the efficacy and safety of medications, because the drug substance is mostly composed of the API or the "naked" drug without excipients. The API is what will have a therapeutic effect inside the body, as opposed to the excipients, which serve to package and deliver the API.

AmpTec's key APIs for the pharmaceutical industry are customised, fully functional GMP-grade mRNAs from any sequence at scales from milligrams to grams, produced according to a highly standardised AmpTec workflow. Key applications are highly specific vaccination, individualized tumour therapy with patient-specific tumour neo-antigens, cellular reprogramming, and genome editing by CRISPR/Cas9 technologies.

GMP manufacture

All APIs are produced at AmpTec according to a fully traceable GMP manufacturing process and in a highly regulated GMP environment. AmpTec is working together with academic customers as well as biotech and pharma companies, and the API products are already involved in a number of international clinical trials (*ex vivo*), and preclinical trials (*in vivo*).

Picture: AmpTec GmbH

In 2019, AmpTec's mRNAs were used for the start of the first clinical trial in patients. In August 2019 Gritstone Oncology (Nasdaq: GRTS), a clinical-stage US based biotechnology company, developing the next generation of cancer immunotherapies has published a press release kindly mentioning AmpTec as CMO: „Gritstone Oncology Announces First Patient Dosed with SLATE, its "Off-The-Shelf" Neoantigen Immunotherapy. First patient dosed is a metastatic non-small cell lung cancer patient with a KRAS G12C mutation. [...] the company partners with third-party contract manufacturing organizations such as AmpTec GmbH, a leading provider of RNA technology products and GMP manufacturing, to support the production of SLATE for clinical trial use." Many projects with biotech companies are currently in the pipeline. Due to the strong growth momentum, AmpTec has more than doubled the number of its employees and will have approximately 38 employees until the end of 2019. Also, the lab space has been significantly expanded in order to increase capacity.

Towards the end of 2019, AmpTec will establish a second GMP unit, and, beginning in 2020, additional room can be occupied on a further floor in the building.This will allow AmpTec to meet the rapidly growing requirements for mRNA manufacturing, and it will allow the company to further develop its good position as a CMO partner for the pharmaceutical industry. ■

Picture: AmpTec GmbH

Reshaping the future of adequate care

CRO Multi-collaborative solutions, multiplex programmes, and new generation clinical trials are taking future research forward, and personalized medicine and innovative therapeutic solutions have extended beyond oncology to embrace new areas of development.

› Dr Aldo Poli, CEO, OPIS Srl

The advancement of science has led us to a deeper understanding of disease at the molecular level. Consequently, it is becoming increasingly evident that we need to "re-classify" disease and tackle cures from a very much more personal angle. We have adopted a mind-set of looking at disease as highly individual manifestations of symptoms caused by very complex combinations of enormous sets of variables. The paradigm for treating disease has shifted. Today, we are exploring options where personalised medicines are promising to deliver the correct drug to the right person at the precise time. Highly personalised, rationally designed, and biologically derived therapies are driving the future of adequate care.

Progress

Oncology has led the way by laying the groundwork for innovative translational research. Genomic-based research is now widely applied in various other therapeutic areas, such as neurology, rheumatology, and other auto-immune diseases.

However, due to a number of important factors influencing such an approach, changing the way we do research and clinical trials has become crucial. Optimising resources would probably stand out as one of the most important aspects to take into account.

Picture: OPIS

No more "wasting" patients on control groups, no more "doing it alone": compared to ten years ago, pharma companies have become more transparent and more collaborative, with a much wider sphere of stakeholders. Researchers are sharing data through therapeutic specific platforms; academic institutions form closer relationships with health care institutions; and nonprofit organisations and patient associations are very active in spreading information about the latest R&D and available trials.

Patient participation is precious

Smarter options for finding the right patient to fit the right trial have helped trial retention, and thanks to technology, we are now able to stratify larger patient populations into smaller, targeted populations for integration in clinical trial structures. With the implementation of sophisticated platforms for translational research, as well as genomic-annotated databases, we are able to optimise patient participation.

Involving patients from the beginning, acknowledging their key importance in the process, and treating precious patient data with attention have certainly become exceedingly important aspects to consider.

Conclusion

Precision medicine and new-generation clinical trials are here to stay. Multi-collaborative solutions and multiplex programmes created with state-of-the-art technology are leading the way. Let us responsively and conscientiously build the future together! ■

Nordmark Biotech

Full Solution Provider for Mammalian Cell Culture and Microbial Fermentation

Nordmark Biotech bundles all biotechnological activities of Nordmark. We are offering all-in-one solutions for microbial fermentation and mammalian cell culture based products covering the entire value chain from process development, analytics, production of API and finished drug product up to regulatory affairs and marketing authorisation. Our worldwide customers benefit from this integrated approach, which is based on solid project management, long-standing GMP experience and recurrent EMA and FDA approvals.

Meet us at BIO-EUROPE, November 11 – 13th:

Nordmark will be present at the booth of LifeScience Nord (hall 2, booth 65) and in the partnering program.

www.nordmark-biotech.de projects@nordmark-biotech.de

Further Information

Nordmark Arzneimittel GmbH & Co. KG
Pinnauallee 4 | 25436 Uetersen | Germany | www.nordmark-pharma.de

Nordmark Biotech

Humanisation 2.0 with GlycoExpress®

PROTEIN MODIFICATION GlycoExpress (GEX®) is a well-established human expression platform consisting of a toolbox of glycoengineered cell lines optimised for the production of biotherapeutics with specific glycan profiles desired to improve their clinical performance.

› Doreen Weigelt and Lars Stöckl are Senior Directors at Glycotope GmbH, Berlin, Germany.

With the development of the GEX® technology, Glycotope has established a human expression platform verified by a variety of different biopharmaceuticals:

- Antibodies of different isotypes (e.g., IgG, IgM, IgA)
- Defucosylated antibodies
- Bispecific antibodies (e.g., NK cell- and T cell recruiters)
- Alternative antibody constructs (e.g., scFv and diabody constructs)
- Difficult-to-express (e.g., SP-D) and other complex glycosylated proteins
- Coagulation factors (e.g., FVII/FVIIa)
- Protein hormones (e.g., FSH and HCG)
- Enzymes (for enzyme replacement therapy, ERT), e.g. α-galactosidase A)
- Fusion proteins with extended serum half-life (FVII-, FVIIa-Albumin).

The glycosylation of a protein depends on the host cell line and strongly affects properties of biotherapeutics, such as bioactivity (e.g., of ADCC-mediating antibodies) serum half-life (e.g., due to missing sialic acid or terminal GalNAc) and immunogenicity (e.g., due to nonhuman sialic acid). Thus, modification and control of glycosylation are important aspects in developing these products. Glycoproteins produced in hamster or mouse cell lines carry nonhuman glycans that can lead to immunogenic reactions. Because GlycoExpress® cells are of human origin, immunogenic glycans, such as nonhuman sialic acid (NeuGc), the Galili epitope (Galα1,3Gal), or core α1,3-fucose are absent. These unwanted structures are known to cause immunogenic reactions and can increase serum clearance of the glycoprotein. Furthermore, human specific glycosylation features (e.g., bisGlcNAc, α2,6-linked sialic acid) are present while α2,6-inkage is not found in hamster-derived cell lines, such as CHO and BHK. Figure 1 summarises how glycan structures influence protein properties.

Since different products need different glycosylation characteristics for optimal activity, we have generated a set of GEX® cell lines with the following attributes:

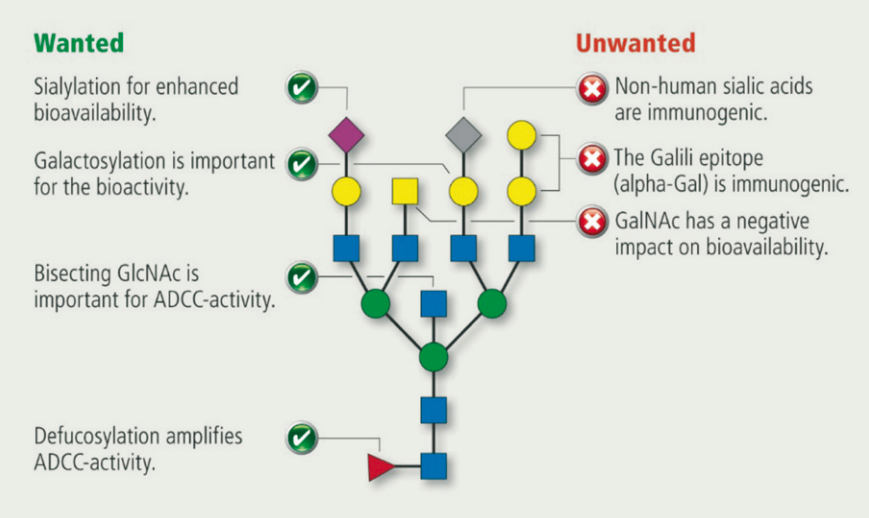

Fig. 1: Possible impacts of glycan structures to properties of recombinant proteins

- **mAbExpress®** is used for antibodies with high sialylation and with core-fucosylation.
- **mAbExpress^{F-}** is used for antibodies with high sialylation and without core-fucosylation
- **SialoMax®** is used for products where high sialylation and high core fucosylation is required
- **SialoFlex®** allows for gradual adjustment of the sialylation degree in screening of the optimal amount of sialic acid in a product.
- **FucoFlex®** allows for the adjustment of the fucosylation degree in screening of the optimal amount of fucose in the respective product.

Further glycoengineered cell lines are being continuously developed. Examples include a cell line for the production of glycoproteins with high amounts of mannose-6-phosphate (e.g., in the field of enzyme replacement therapy) and SialoMax® glycoengineered to eliminate N-glycan-linked GalNAc for products with fur-

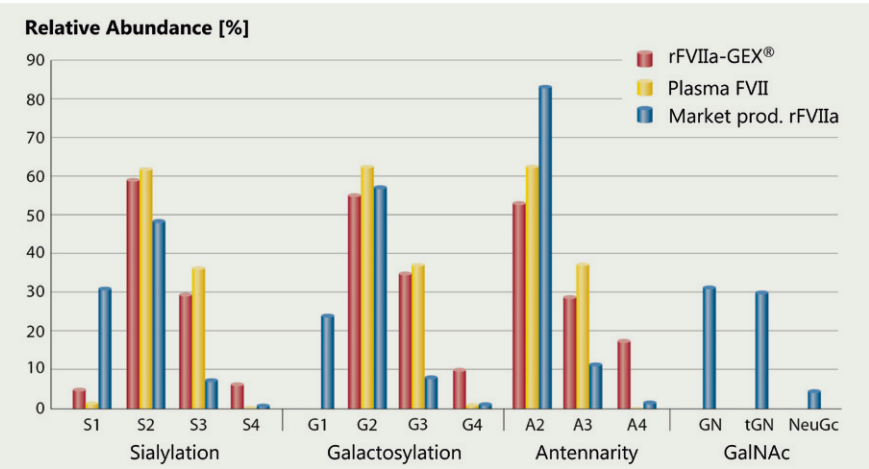

Figure 2: Comparison of N-glycans specific for recombinant FVIIa produced in GEX® (red) and BHK (blue) cells with FVII isolated from human plasma (yellow): The glycans of proteins produced in GEX® and plasma derived FVII show a similar distribution, whereas the recombinant market product exhibits a completely different glycan profile. Especially the appearance of terminal GalNAc may have a negative impact on serum half-life of FVIIa.

Pictures: Glycotope

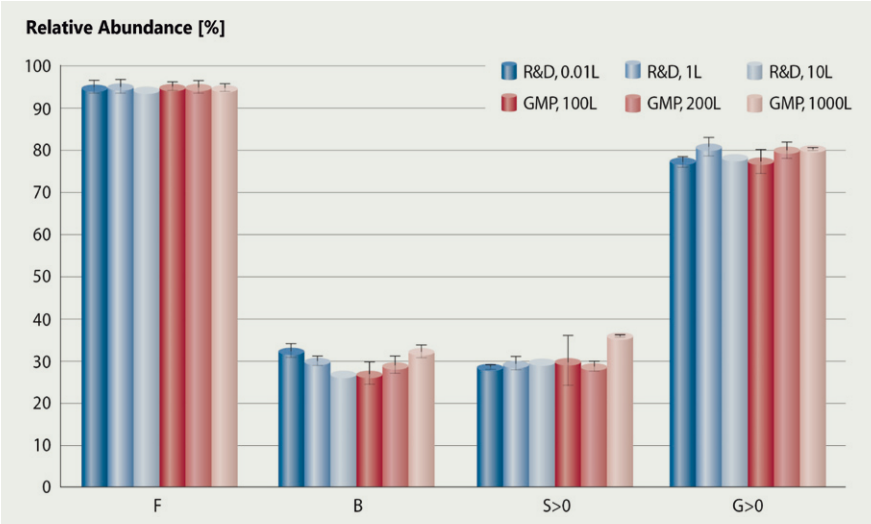

Figure 3: Glycan profiles of an IgG produced in different scales under R&D (blue) and under GMP conditions (red); F: Fucose, B: Bisecting GlcNAc S>0: sialylated and G>0: galactosylated structures

ther reduced serum clearance. By using this toolbox of cell lines, we can mimic the glycosylation of the respective human endogenous protein, for example, for coagulation factor VII (see Figure 2).

GlycoProcess

Production Yield: The preferred production technology for the GlycoExpress® platform is based on perfusion processes leading to high productivity and stable product quality across all scales and batches. Table 1 shows current yields for different molecule classes. In two customer projects, we compared the productivity of difficult-to-express proteins in CHO and GEX® cells and found up to a 10-fold increase in productivity. Furthermore, the product quality was dramatically improved by expression in GEX® cells.

Product Quality: As shown for an IgG antibody (see Figure 3) and a glycoprotein (not shown) produced in several production scales, glycan parameters are nearly identical, even when produced in glass, stainless steel, or single-use bioreactors. For those reasons, regulatory authorities allowed production in different bioreactor sizes and run times, reflecting high reproducibility, due to favourable features of GEX® cells, including:

- exceptionally high stability of production clones in terms of productivity, even without selection pressure
- high cell densities
- high shear force resistance of the cells, which originate from robust blood cells
- low cell doubling time.

Regulatory and safety: The GlycoExpress® production platform and derived products were approved for clinical trials by regulatory agencies in the US, Russia, and several EU countries. ■

Yields of different product classes

Product Class	Productivity*
IgG (high and low core fucose)	15 – 30 g/L
IgA	10 – 15 g/L
IgM	~3 g/L
FSH	~4 g/L
Factor VII	~2 g/L

*Yield per 30 – 40 day perfusion run per litre bioreactor volume

Pictures: Glycotope

Total Solutions for your Microbial Biologics Development & Production Needs

(Cell-line to Commercial Manufacturing)

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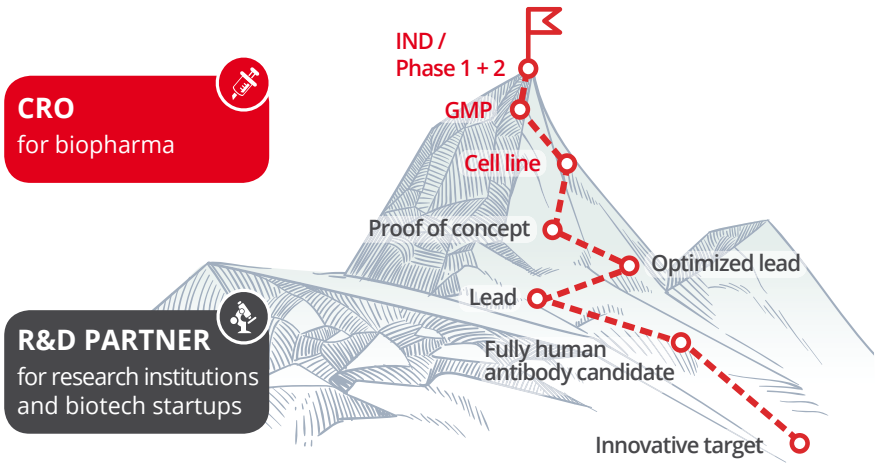
Fully human antibodies for advanced immunotherapies

ANTIBODY GENERATION Answering the increasing demand for novel fully human antibodies in immunotherapy, German biotech pioneer YUMAB GmbH accelerates drug discovery and development with a comprehensive and versatile technology platform.

› Dr. Thomas Schirrmann, CEO, YUMAB GmbH



Immunotherapies based on fully human monoclonal antibodies have been extremely successful since their first approval in 2002 (AbbVie's Humira®, adalimumab), and today, the majority of newly approved antibody drugs are of human origin. This trend calls for a paradigm shift in antibody discovery and development of an advanced process that enables flexible drug design and accelerates translation into clinics. YUMAB is a pioneer in fully human antibody development that offers an optimised discovery process tailored to the needs of the pharmaceutical industry for a rapid, robust, and reliable generation of novel drug candidates.

Diverse and safe antibody leads

The YUMAB® platform generates fully human antibodies that are the closest to the natural germline among those available on the market. Unlike animal-derived, chimeric, humanised, or synthetic antibodies, each YUMAB® antibody combines the maximum epitope diversity of very large universal antibody libraries with minimal immunogenicity. This approach is also efficient for difficult targets, such as G-protein coupled receptors (GPCRs), ion channels, and even whole cells or virus particles. Additionally, YUMAB optimises antibody properties, such as affinity, stability, or interspecies X-reactivity in early discovery. First antibody candidates are identified within weeks and the versatility of the technology allows for flexible manipulation and variable drug formats. YUMAB's advanced human antibodies cover a broad therapeutic spectrum. Tailored to customer needs, YUMAB also generates custom libraries and offers antibody engineering in fee-for-service or attractive licensing options.

Enleofen – a success story

In early 2016, YUMAB started a cooperation with Stuart Cook and Sebastian Schäfer at the National Heart Centre, Singapore and Duke-National University Singapore Medical School to generate novel antibody candidates that target interleukin-11 (IL-11) in fibrotic disease. Their research revealed the critical role of IL-11 in fibrosis and set the stage for potential anti-IL-11 therapies that could transform the treatment of fibrosis of the lung, heart, liver, kidneys, and other organs[1]. In April 2017, Cook and Schäfer founded Enleofen Bio Pte Ltd with a focus on the development of first-in-class antibody therapeutics for the treatment of fibrotic diseases. Using YUMAB's expertise in antibody engineering, the startup rapidly generated high-quality antibodies as a basis for the development of antifibrotic therapies. "Owing to YUMAB's rapid and reliable antibody platform, we could shorten preclinical development and are now confident to accelerate the translation of a novel antifibrotic antibody candidate from bench to bed," said Stuart Cook, Enleofen Bio's director. "Successful drug development requires interdisciplinary expertise and technologies that are most easily accessed through collaborations," added André Frenzel, CSO of YUMAB. "Being able to support our colleagues in Singapore in their quest to rapidly translate their new insights in fibrosis into a startup company was very rewarding for us, and we are excited to have played a small but crucial part in that process." ■

Reference [1] Schäfer, S. et al. Nature 552, 110–115 (2017)

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Rentschler
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Linking tradition with cutting-edge technologies

CMO In November 2019, the Bio-Europe conference in Hamburg will prove again the place to be when it comes to partnering and showcasing latest technological advances and capabilities in biomanufacturing. As one of only four regional host sponsors, Nordmark Arzneimittel GmbH & Co. KG will present their expertise, which includes challenging technologies, like the manufacturing of live biotherapeutics.

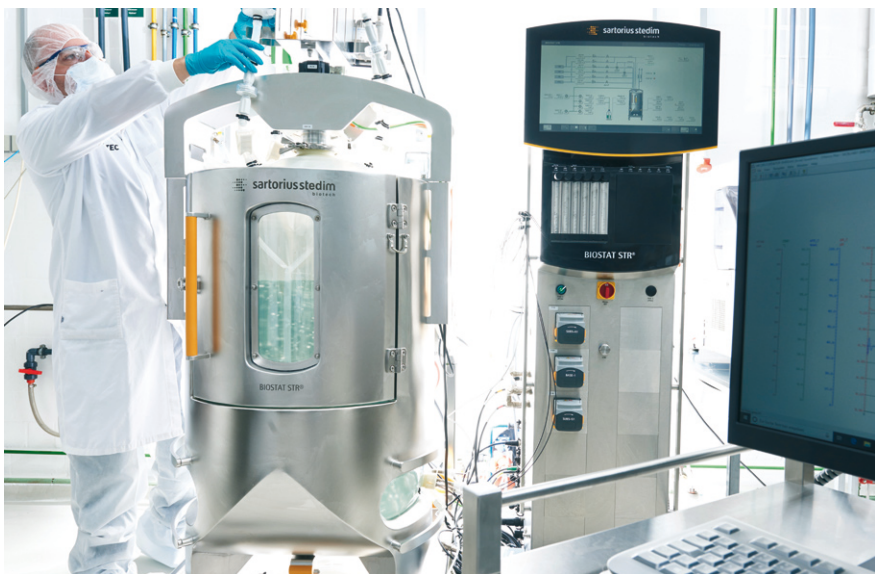
› Dr Jan Heyland, Head of Biotech Development; Volker Kahrmann, Head of Marketing

Headquartered in the Hamburg metropolitan area, Nordmark oversees a company history of more than 90 years. What started in 1927 as a drug maker business for organ extracts has developed over time into a global business of biopharmaceutical APIs and finished drugs. Nearly 600 employees are driving this organic growth, based on a set of GMP production platforms:

› The extraction of animal organs, such as pancreas enzymes for replacement therapy in patients with cystic fibrosis and acute and chronic pancreatitis (very few manufacturers supply the global demand – one of them is Nordmark with a strong foothold in the US market and dominant positions in Europe).

› Microbial fermentation: Microbial fermentation development is conducted in our development laboratories with aerobic and anaerobic cultivation capacities (biosafety level 2). Core competencies are the cultivation of microbial organisms, such as bacteria and yeasts for the high yield production of protein-based pharmaceutical ingredients. This makes Nordmark one of the world's largest manufacturers of collagenase, which is used both as an active pharmaceutical ingredient in wound debridement ointments, and as a biopharmaceutical, helping research and medical care with cell isolation.

› Cell culture: Upstream development of mammalian cell culture-based processes at our site in Bielefeld (Germany) ranges from lab scale (←1 L) for the development of novel production processes to pilot scale (up to 200 L) for GMP manufacturing of preclinical and clinical supplies. In one particular case, Nordmark entered into a joint venture with a strategic partner for the market supply.



Biochemical reactor

Three solid technology pillars

"It is worth mentioning that our organisational set-up goes far beyond the obvious production systems," says Detlev Baumeister, CFO and head of Nordmark's Biotech division. "Today, we are a fully integrated, pharmaceutical company, providing service and expertise along the entire value chain." This includes not only process development (USP, DSP), GMP-compliant production, but also formulation: (virus) analytics, stability testing, regulatory support during approval processes, and project management can be offered, according to the individual customer's needs.

Picture: Nordmark Arzneimittel

AmpTec
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Therapeutic mRNAs
made in Hamburg.

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the quality you need.

Or visit us on the web:
www.amp-tec.com

"We take pride in long-standing business relationships with our global customers," Baumeister adds. Apparently, the individual approach and attention to every project differentiates Nordmark from other players in the market.

Microbiome: Live Biotherapeutics

According to global market analysts, production systems like microbial fermentation and mammalian cell cultures were used by around 48% and 79% of biopharmaceutical manufactures in 2018. In addition to these established technologies, Nordmark successfully made inroads into a innovative niche market: live biotherapeutics, which target the human gut microbiome.

There is a growing understanding that a huge variety of micro-organisms (bacteria, fungi, and viruses) live on and in us. Their combined genetic material, containing hundreds of millions of genes, is known as the microbiome, with the highest concentration of microbes found in the gut. On this basis, the scientific community is hoping to provide a more personalised approach to diseases like IBD (irritable bowel syndrome) in the future.

With their broad experience in microbial fermentation, anaerobic bacteria, spores, and prevention of cross-contamination, Nordmark has stepped in to the field of live biotherapeutics, a medication designed to restore the balance in the human gut microbiome. In this pharmaceutical area, it is crucial to manage the production challenges of consortia of different types of sensitive, living bacteria, including spores and anaerobes. Most recently, a major achievement was the supply of biological API in a conventional formulation (e.g., capsules) for a clinical study.

Needless to say, currently, there is a steep learning curve with all parties involved: big pharma, authorities, and biopharmaceutical contract manufacturers. Major challenges of bacterial consortia in the drug product include:

- characterisation of each bacterium (cell count, viability, and activity)
- no established production platforms
- multiproduct
- sophisticated analytic tools are needed to differentiate between closely related strains, to distinguish between living and dead cells, and to ensure homogeneity in the drug product.

Most of these challenges are unknown in the mainstream world of small molecules. However, the therapeutic expectations within the scientific community seem to justify such efforts. At this stage, it appears that big pharmaceutical companies prefer to outsource such complex projects to specialists.

From cell isolation to cell expansion

Unsurprisingly, the next generation of projects is already visible on the horizon. At present, several project partners are approaching Nordmark regarding ATMPs, particularly cell therapy (which is one element under the umbrella of "Regenerative Medicine").

With Nordmark's broad experience in different types of collagenase (technical grade, GMP grade), there is quite some market insight with regards to the isolation of stem cells and islets of Langerhans, both for research and clinical applications. In the light of state-of-the-art production capabilities and expertise, it is a relatively small step to cell expansion for therapeutic use.

With flexible decision-making based on market insights, Nordmark is geared to prepare for these types of development projects, leading to commercial supply as the next step on GMP level and with FDA-approved production facilities.

Bio-Europe will be a perfect opportunity to discuss business prospects in person. Nordmark will be present at Booth 65 (Hall 2) and in the partnering program. ■

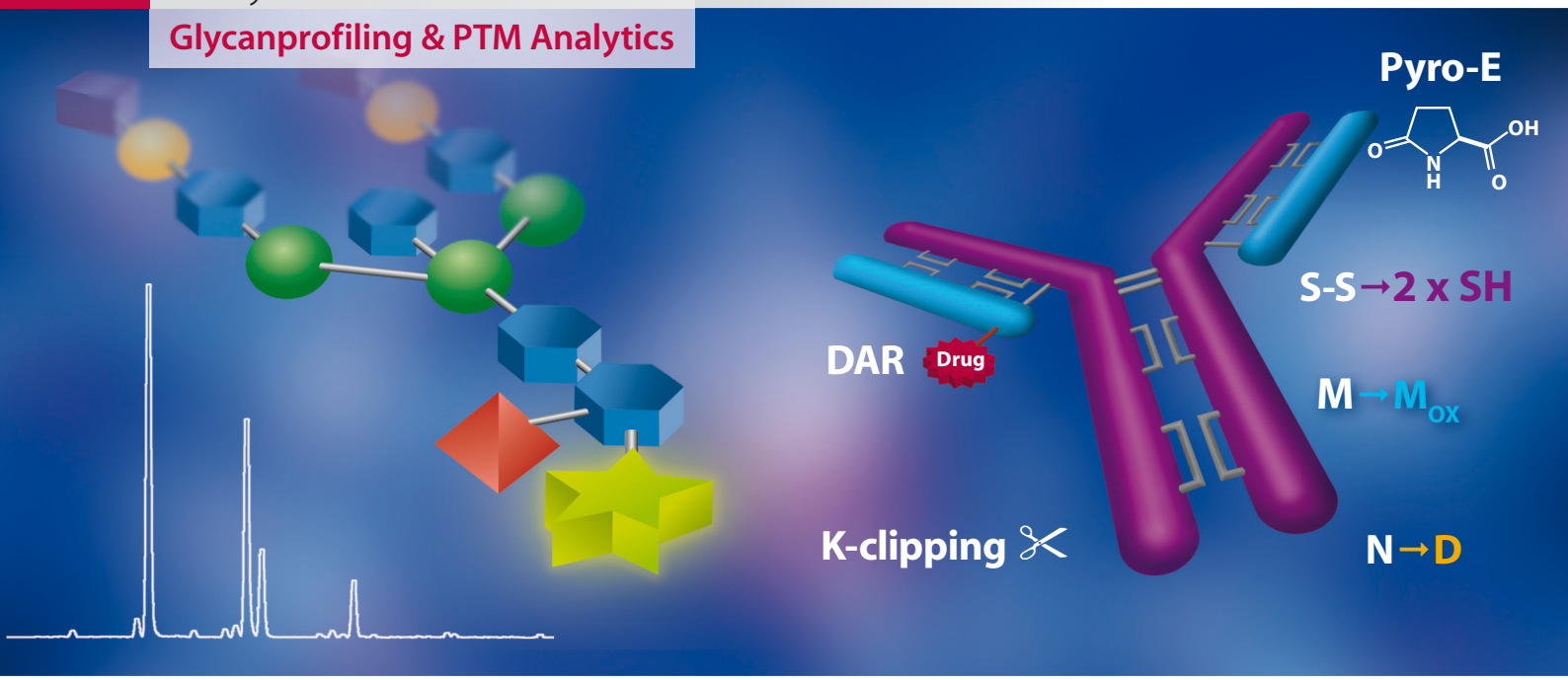
Fermenter

Picture: Nordmark Arzneimittel

GLYCOTOPE

Analytical Services

Glycanprofiling & PTM Analytics



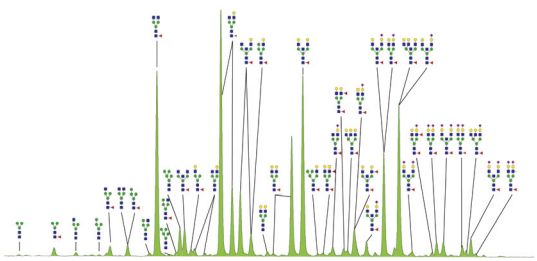
Assessing Protein Modifications

Glycanprofiling

N-Glycans
- MS/MS based identification
- Precise quantification (FLR)
- Highly complex profiles (HILC-FLR-MS)
- > 20 N-glycan parameters assessed
- Site-specific N-glycan analysis

GlycoFiler™
- Software for automated N-glycan profiling

O-Glycans
- Sites of O-glycosylation (RP-MS/MS)
- Profiling of released O-glycans (HILIC-FLR-MS)
- O-glycopeptide analysis
- Monosaccharide composition (FLR)



Glycotope – your competent partner for analysis of glycans

Integrity of proteins and PTMs

Top-Down: UHR-ESI-QTOF-MS
- Molecular mass of intact protein
- Protein truncation and fragment analysis
- Degrees of conjugation (DAR)

Middle-Up: RP-UPLC-UHR-ESI-QTOF-MS
- High resolution MS of subunits
- Fab/Fc analysis including glycoforms

Bottom-Up: RP-UPLC-ESI-QTOF-CID-MS/MS
- Peptide mapping
- Multiple attribute monitoring (MAM)
- Oxidation
- Deamidation
- Integrity of disulfide bridges
- C-terminal Lys clipping/N-terminal pyroglutamate
- Glycation, sulfation, phosphorylation etc.

For further information please contact us

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Celonic pioneering the way with perfusion

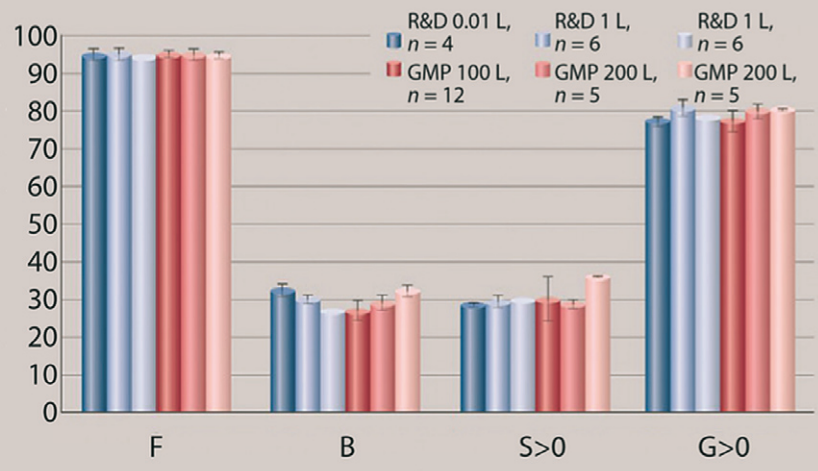
CDMO Celonic has created a niche with their thoroughly researched and developed cell lines, to the advanced technologies and processes to produce novel therapeutics: Biopharma-Business Excellence.

› Hiromi Kessler, Celonic Deutschland GmbH & Co. KG, Heidelberg and Sebastien Lalevee, Celonic AG, Basel, Switzerland

Celonic, a biologics contract development and manufacturing organization (CDMO) with end-to-end capabilities, is one of the selective bio-solutions providers in the world that can offer perfusion culture processes at a large 1,000 L bioreactor scale when working with more complex and hard-to-express molecules. Celonic, the Swiss-based CDMO with facilities in Germany and Switzerland, has been long been developing and manufacturing recombinant proteins expressed on mammalian cell lines with fed-batch processes, as well as a perfusion processes platform for monoclonal antibodies and hard-to-express proteins.

Advantages of perfusion

Continuous bioprocessing using the human GEX® cell line platform enables Celonic's clients to produce complex biologics with consistent product quality profiles. Continuous cell culture ensures stable molecule quality and reduces the risk of product degradation, unlike a classically fed-batch process, where the molecules typically stay in a bioreactor for two weeks. In short, the advantages of perfusion using human GEX® cell line platform enable Celonic as a CDMO to offer clients consistent product quality, rapid scale-up of optimised perfusion processes, and shortened development timelines. Furthermore, Celonic's perfusion process capabilities enable clients to reduced capital expenditures and tech transfer, while providing development and continuous biomanufacturing expertise and service.



(F – Fucosylated; B – Bisected; S – Sialylated; G – Galactosylated structures)

Reprinted from: Production of Biotherapeutics Using GlycoExpress® Expression Platform Technology, by R Stahn and L Stöckl, 2017 – 2018, BioProcess International Industry Yearbook 15 (7), pp 24 –25. Reprinted with permission.

Glycan profiles across various scales for an IgG antibody

Celonic as a premium CDMO

Celonic is pioneering the way with perfusion and at a large scale of 1,000 L bioreactors when working with more complex, multi-specific, hard-to-express, or unstable molecules. Celonic recognises the growing interests and benefits of continuous bioprocessing and has plans to dedicate GMP suites in the upcoming commercial supply facility with perfusion process capabilities, thereby joining the relative few CDMOs that can offer such capabilities. Coupled with the experience and expertise on continuous bioprocess development and manufacturing, Celonic is on a trajectory of becoming a premium CDMO.

Producing biotherapeutics to improve clinical performance

GEX®, or GlycoExpress®, developed by Glycotope and licensed by Celonic, is a human cell line expression platform for difficult-to-express molecules with fully human glycosylation. GEX® cells are adapted to animal component free media for GMP compliant manufacturing. GEX® offers a diverse toolbox of cell lines, dependent on the product to be expressed, to mimic different glycosylation characteristics. GEX® provides an established expression platform for different biopharmaceuticals:

- Antibodies of different isotypes (eg, IgG, IgM, IgA)
- Defucosylated antibodies
- Bispecific antibodies/fragments
- Difficult-to-express and complex glycosylated proteins
- Blood factors
- Protein hormones
- Fusion proteins
- Enzymes

Perfusion and productivity with GEX®

Combining GEX® cell lines with a perfusion biomanufacturing process provides an improved volumetric productivity for complex proteins. Perfusion enables homogeneous glyco-patterns and results in less product degradation. This leads to stable protein quality, as shown, for example, in an IgG produced in several production scales where glycan parameters are nearly identical, even when produced in glass, stainless steel, or single-use bioreactors (see Figure 1). Scale comparison between 1 L and 200 L bioreactors indicates that the glycan-profiles do not vary by increasing the production scale.

The productivity of difficult-to-express proteins using CHO and GEX® cells, as demonstrated in a case study, demonstrates that a perfusion process can be competitive versus a fed-batch process. When produced in GEX® cell lines and combined with perfusion, the perfusion run found higher productivity, with an up to 10-fold increase and dramatically improved product quality, as compared to fed-batch runs.

Celonic's offerings

Celonic provides a seamless, end-to-end package for a Chemistry, Manufacturing, and Controls (CMC) service starting with their cell line platforms, like GEX®, to enable its clients projects into successful clinical studies and beyond. The preferred production technology for GEX® is the perfusion process facilitating consistent product quality over full run time for R&D and GMP. Celonic's state-of-the-art facilities are equipped with bioreactors up to 1,000 L (2,000 L bioreactor capacity available 2020) with in-house Fill & Finish. GEX® cell line has regulatory approval for usage in clinical trials by the FDA and EMA (German regulatory authorities: PEI and BfArM).

Celonic Group is a privately owned Contract Development Manufacturing Organization (CDMO) offering two cell line development platforms: its CHOvolutionTM CHO K1 cell line and human expression platform GEX® developed by Glycotope GmbH and licensed by Celonic AG. In combination with fed-batch and perfusion processes, these platforms facilitate the manufacturing of complex proteins, thereby enabling clients to achieve scalability, consistent product quality, and cost savings.

Celonic experts can help select which GEX® cell lines are suitable to bring clients' biologics from development to commercialisation.

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