SPECIAL EDITION 2023

BIOPROCESSWATCH

BIOPC2022 Meeting Report

mabdesign
THE BIOTHERAPY EXPERT

ABOUT **MABDESIGN**

MabDesign, the French Association of the Biotherapy Industry

MabDesign, the French biotherapy industrial association, aims to support, federate and increase the visibility of the biopharmaceutical industry, foster exchanges, promote the development and competitiveness of companies, and stimulate innovation by encouraging the emergence of start-ups from academic research.

In order to carry out its development strategy and to adapt to changes in the industrial ecosystem, MabDesign's governance has evolved to meet the specific needs of the various companies working in the biotherapy industrial sector. Therefore, the Board of Directors of MabDesign already composed of DBV Technologies, Lyonbiopole, Pierre Fabre and Sanofi, has been strengthened with the arrival of ABL Europe, bioMérieux, Institut Pasteur, Thermo Fisher Scientific and TreeFrog Therapeutics as well as three Qualified Persons with Nicola Beltramineli (Innate Pharma), Hervé Broly (Merck), and Stéphane Legastelois (33 California). Their arrival to the Board of Directors reinforces MabDesign global vision of the current challenges and opportunities of the biopharmaceutical industry.

Moreover, to achieve its goals MabDesign sets up a coherent set of actions promoting exchanges, collaborations and skills development. In this dynamic MabDesign has developed a **national directory** that brings together industrial and academic players in biotherapy and allows to identify online the know-how available in France. MabDesign organizes high-level **international scientific events**, in collaboration with key ecosystem players, to highlight innovation and stimulate exchanges between companies in the sector. With the help of its Scientific Committee (**COSSF**), MabDesign writes summary reports (**ImmunoWatch & BioProcessWatch**) for the biotherapy industry. MabDesign offers specialized and **innovative continuous professional training** solutions to enable companies to adapt their skills to the market evolution and maintain their competitiveness. Finally, MabDesign offers its members a **wide range of services** to help companies of all sizes to optimize their positioning, protect and

Operational since September 2015, MabDesign currently has over **270 member companies** and its diversity is its strength. MabDesign's dynamic network includes pharmaceutical and biotech companies, service providers (eg. CROs, CDMOs, etc), professional training actors, high-tech equipment suppliers and specialized consultants.

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INTRODUCTION

According to our latest information, France is currently at the second place behind United Kingdom, closely followed up by Germany and Switzerland, in Europe as biologic developer with a pipeline of 643 biopharmaceutical drug candidates being developed by French companies. Importantly, these candidates include therapeutic antibodies, recombinant proteins, vaccines, cellular therapies, gene therapies and advanced therapy medicinal products[1]. In more recent news, the French government has announced its 20-by-30 objective for the national biopharmaceutical industry to manufacture a minimum of 20 biopharmaceutical therapeutic or prophylactic drug on French soil by 2030. The need for adequate and timely bioprocessing capabilities for both clinical and commercial batches is thus undeniable.

For several years now, MabDesign has been actively participating in national and regional programmes and organising scientific events and gatherings focusing on bioprocessing. Indeed, since 2016, our annual Bioproduction Congress has gathered so far more than 1380 participants, 194 Speakers and 143 Sponsors/Exhibitors and has allowed for more than 1300 B2B meetings. As such, this event is considered as a major French scientific event where stakeholders from Europe gather together to showcase and exchange the latest innovations in bioprocessing. In parallel, we have also been providing strategic consultancy services together with various training opportunities to key actors of this field, including academia, public bodies, SMEs and biotech and pharmaceutical companies.

BioprocessWatch marks our organisation's latest endeavour and commitment to support the different academic and industrial French stakeholders involved in the field with the hope that through the latter and combined with our various past, current and future services, actions and training opportunities, MabDesign has been making a contribution, however humble it might be, in supporting and promoting the biopharmaceutical and bioprocessing industry.

In 2022 the first meeting report from the Bioproduction Congress 2021 (BIOPC2021) came out as a special edition of the BioprocessWatch. We have recently released the first classic edition of the series focusing on mAb bioprocessing with Alain Beck from Pierre Fabre and Hervé Broly from Merck-Serono SA as invited Chief Editors. You can acces it HERE.

In 2022 Mabdesign also held the 7th Bioproduction Congress(BIOPC2022) on CMC readiness to accelerate Biotherapeutics for patients. Counting with 57 Expert Speakers divided in two parallel tracks: Mabs and Vaccins on one hand and Cell & Gene Therapy on the other track ,as well as holding 4 workshops and 1 round table; it reunited 310 stakeholders to discuss how to advance the field of Bioproduction both in France and worldwide.

[1] Source : GlobalData

In a dynamic and stimulating event of one and a half days, 40 companies showcased their latest technologies and more than 250 B2B meetings took place, thus promoting collaborations and generating new commercial leads.

The scientific program of this edition was set-up by a **Scientific Advisory Board** composed of **LFB Manufacturing** : Roland BELIARD, **Pierre Fabre** : Alain BECK, **Quality Assistance** : Arnaud DELOBEL, **UCB Pharma** : Annick GERVAIS, **CELONIC** : Laszlo PARTA, **Novartis** : Francisca GOUVEIA, **Innate Pharma** : Nicola BELTRAMINELLI, **Merck Serono** : Hervé BROLY, **SANOFI** : Elodie GUIDAT, **Debiopharm** : Olivier COCHET, **EverZom** : Nicolas ROUSSEAU, **TreeFrog** : Michaël FIDALGO, **EGLE Therapeutics** : Bernard VANHOVE, **SANOFI PASTEUR** : Cédric CHARRETIER, **EFS** : Sophie DERENNE, **SANGAMO THERAPEUTICS** : Pierre HEIMENDINGER. We would like to thank them for their efforts for bringing together the experts on the frontline of the development in a unique event to exchange on the future of bioproduction, the current challenges and the new solutions being presented by French companies as well as international stakeholders. Moreover, the success of the congress also comes from the support from our 40 sponsors/exhibitors and our 3 partners of this event.

Due to the importance of the topics being addressed during the meeting, and following up on the good feedback we got from the first meeting report we have decided to continue to included the science discuss at the meeting in a special edition of the **BioprocessWatch** so that all actors can benefit from it. We would like to thank all the speakers that participated on the BIOPC2022 and have contributed to this 2nd edition special report of the BioprocessWatch. Due to confidentiality and intellectual property reasons, some presentations from the congress have not been made available here.

We hope you will enjoy reading this special edition of the BioprocessWatch and we will be more than happy to see you this year at the **8th edition of the Bioproduction Congress, October 5-6, 2023 in Lyon.** Check the website at **http://www.biopcongress.com.**

Xavier Berthet
Institut Pasteur de Dakar

Opportunities for European Biotechs in Africa

Africa is a land of opportunity and challenges. On one hand, Africa has the most rapidly expanding population of any region in the world and its population is expected to reach 11 billion people by the end of the century, providing a treasure trove of talented individuals and young leaders. On the other hand, providing food, education, and jobs to the next generation of Africans is an objective of daunting complexity.

In this context, the abundance of unmet needs and market gaps represent an Eldorado for entrepreneurs and start-up builders. In 2021 more than 680 equity rounds have happened raising more than USD 5 billion of funding almost four times more than in 2020. This vibrant ecosystem has also attracted all the stakeholders (incubators, accelerators, seed investors, venture capitalists, etc.) that have coalesced in a limited number of countries having access to high-speed internet. Investment is focus on a selected number of areas such as e-commerce, fintech, agritech, healthtech, biotech, etc.

From the health care point of view, the existence of countless challenges (neglected, infectious and chronic diseases) as well as the political will to promote local biomanufacturing (drugs, vaccines, diagnostic tests, and medical devices) provides a vibrant ecosystem for innovating and transforming the society. The ambition of the African Union and Africa CDC to ensure autonomy by sourcing more than 60% of their vaccine needs from local manufacturers is a clear example of that vision.

The Institut Pasteur of Dakar (IPD) is a not-for-profit Senegalese foundation whose mission is to contribute to the promotion and protection of human health in Senegal and West Africa. This century old organization is undergoing a profound transformation involving the use of innovative education, biomanufacturing for equity and leveraging on the power of communities for epidemiological surveillance. Among the recent endeavours ongoing at IPD are:

- the creation of DIATROPIX, using of the Netflix business model for promoting access to diagnostics to Neglected Tropical Diseases (NTDs). This venture is an example of collaboration of NGOs (Mérieux Foundation, FIND, IRD, MSF) and private partners (BioMérieux, Mologics, BioNote, etc.) to better serve the patients.

- The construction of a vaccinopole in Diamniadio to boost the local vaccine manufacturing capacity of yellow fever and other diseases such as that included in the Expanded Programme on Immunization supported by WHO.

- Innovative projects under development to control the vectors responsible for the transmission of arthropod-borne viruses.

Alain Beck
Pierre Fabre

Pierre Fabre

Risk-based control strategies of recombinant monoclonal antibody charge variants

Alain BECK, Senior Director Biologics CMC and Developability, Pierre Fabre.

Acidic and basic species have drawn substantial attention during the discovery, the lead selection and optimization, the pharmaceutical development, and the commercialization of therapeutic antibodies (mAbs) due to their sensitivity to manufacturing process changes.
Commonly, acidic species are detected as several small peaks when analyzed by Ion Exchange Chromatography (IEX) or by capillary Iso-Electric Focusing (cIEF) based techniques, formed due to modifications such as deamidation, glycation, and sialyation. In contrast, basic species are usually detected as fewer peaks, easier to identified, and formed by modifications such as clipping of C-terminal Lysine or of C-terminal amidation.
It may be challenging to maintain the levels of acidic and basic species within the reasonable ranges defined in specification and comparability acceptance criteria when process changes are introduced during optimization steps, manufacturing scale-up or transfer to different facilities. Candidate selection through developability assessment, early phase process and formulation development are critical steps toward successful late phase development and commercialization. The objective of developability assessment is to select candidates with inherent properties of generating low and consistent levels of acidic and basic species. The inclination towards advancing a program through Investigational New Drug (IND)-enabling toxicology, and early-phase development quickly should be balanced with the need to understand the degree of controls over charge variants. Since characterization of the acidic and basis species at early development stage is not necessary nor is it a common practice, basic understanding of process parameters and their effects on charge profiles is essential to support process optimization, transfer and scale up. Process parameters are further studied, qualified and tightly controlled during Process Performance Qualification (PPQ) to be commercialization ready. Overall, parameters during cell culture have the most substantial effect on charge variants. To a much lesser degree, downstream process, formulation, and storage can be explored to control charge variants. Qualitative difference, such as the appearance of new species, is more concerning compared to quantitative difference. It is more manageable in early phase compared to late-phase development and commercialization. Nevertheless, maintaining acidic and basic species within a controlled range throughout development including animal toxicology, early phase and late phase development and commercialization can ensure product safety, efficacy and overall Regulatory Authority acceptance.
Critical Quality Attributes (CQAs) evaluation evolves along with the program development process. For early-stage programs, with no or limited information on the chemical nature of acidic and basic species, lack of structure-function relationship and clinical experience, acidic and basic species are most likely categorized as CQAs. Although based on the published information, if no difference in antigen binding, potency and pK is observed between acidic, basic and the main species, it may not be justifiable to classify acidic and basic species as non-CQA due to the lack of extended characterization. If not carried out earlier, peak isolation and extended characterization of acidic and basic species must be included in a Biologics License Application (BLA) submission. If necessary, CQA assessment can be re-evaluated. Whether or not classified as an CQA, it is prudent to maintain acidic and basic species at consistent levels. When differences arise, additional peak isolation and characterization are most likely required to demonstrate the presence of the same species and lack of adverse effect on safety and efficacy. Sometimes, in vitro data alone may not be sufficient to justify lack of impact especially for safety.

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Michael Sachpekidis
Optimal Industrial Technologies

Measure, Understand, Control, Improve: How PAT knowledge management utilises CQAs to enhance bioproduction and support digital transformation

Michael Sachpekidis, Business Development Manager at Optimal Industrial Technologies

Process Analytical Technology (PAT) is a key framework to optimise manufacturing operations. It helps ensure that these deliver high-quality products whose properties meet desired critical quality attributes (CQAs) by measuring and controlling critical process parameters (CPPs). This is achieved by generating, sharing, analysing and interpreting data to support decision making.

The use of PAT-driven strategies can therefore deliver two major benefits to bioproduction companies: improving and futureproofing their operations. These are greatly supported by one of the essential elements in such frameworks, the PAT knowledge management platform.

The most advanced forms of this software provide an immediate and intuitive interface for different subject matter experts (SMEs). As a result, they can leverage key insights to support their activities. For example, staff in production lines can quickly identify anomalies and act accordingly to address them to meet quality and efficiency targets. Data scientists can improve their chemometrics and predictive algorithms as well as enhance material and product traceability. Process scientists and engineers can use the information provided to develop and refine their control models as well as implement effective continuous improvement strategies. Regulatory specialists can find support for their activities through the creation of key documentation for quality audits, while resting assured that user management, signature control and data integrity is maintained.

In addition to helping SMEs, a high-quality PAT knowledge management platform can enable the digital transformation of biopharmaceutical manufacturers. By sharing and presenting the data, information and knowledge derived from their operations, it maximises the availability and visibility of products and processes. Also, the ability to communicate with different parts of the enterprise, such as analysers, machines and higher-level software tools, provides the level of connectivity and integration required by Industry 4.0 applications. When applied to different facilities, it enables cross-functional collaborations and standardisation, sharing key insights and best practices across plants.

When automated process control is implemented, the PAT knowledge management platform can prompt immediate changes in CPPs directly to ensure product quality and efficiency is optimised, in line with smart manufacturing practices. Furthermore, when looking at Good Manufacturing Practices (GMP), this solution can provide relevant capabilities even to non-GMP compliant instruments.

Optimal's synTQ is a market-leading, award-winning software for knowledge management that provides an encompassing PAT system that supports its users to create highly effective, future-oriented manufacturing processes, lines, plants and entire enterprises. It can communicate with a wide range of analytical instruments, modelling packages and automated devices to monitor and control CQAs as well as CPPs and it offers an intuitive platform for SMEs to gain key insights.

Thanks to its scalable nature and ability to support Cloud computing, even in GMP-compliant environments, synTQ can ensure regulatory compliant data accessibility to facilitate collaborations across different departments, such as R&D and manufacturing, as well as production facilities worldwide. The software is currently used by over 60% of global majors in the pharmaceutical and biotechnology sectors, driving their competitiveness.

SGS Biosafety Solutions

Health Inspired, Quality Driven.

Our solutions

Our Center of Excellence for biosafety based in Glasgow provides:

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- GMP Sanger sequencing
- Viral vaccines Adventitious agents and species specific viruses
- Replication of competent vectors
- Retrovirus
- Process impurities
- Genetic stability
- Other microbial contaminants

"Most notably, the Biosafety Center of Excellence in Glasgow has participated in the batch-testing and release of over 3 billion doses of COVID-19 vaccine, helping to increase vaccine access and bring the global population out of the pandemic."
Archie Lovatt
Site Manager & Scientific Director at SGS

Contact us

To discuss your biosafety requirements, contact us today.

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Supporting a variety of molecules

Our team of experts can support manufacturers of:

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- Recombinant proteins
- Viral vaccines
- Cell therapies
- Gene therapies

Why SGS?

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- Regulatory compliant and recognized quality systems based on cGMP/GLP
- Accurate and reliable report
- Fast turn around times
- Online digital communication platform (booking GMP slot, protocols, results, invoices...)

WHEN YOU NEED TO BE SURE

Track Critical Quality Attributes (CQA) for Cell & Gene Therapy : new advancements

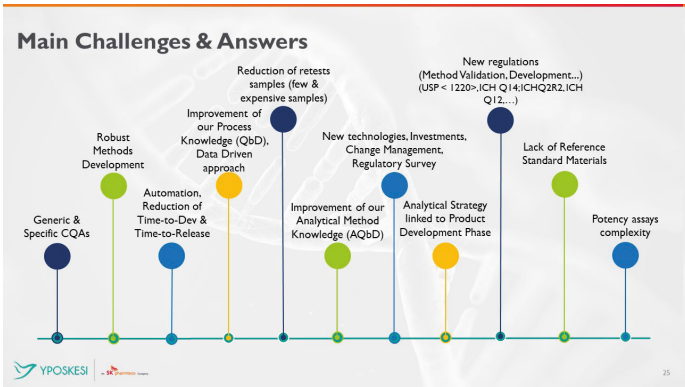
Olivier Maurion
Yposkesi, an SK pharmteco company

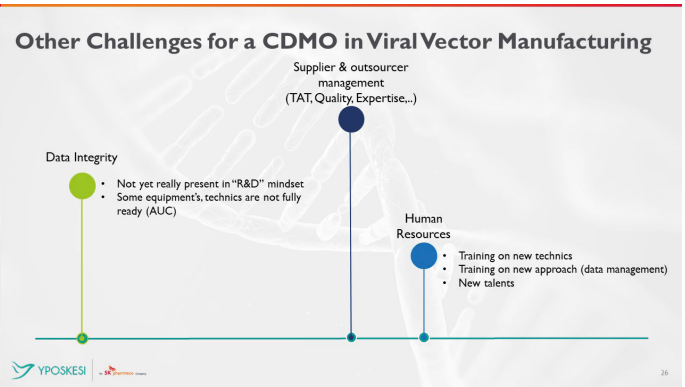
Challenges in Analytic for Viral Vector Manufacturing in Cell & Gene Therapy

Yposkesi, an SK pharmteco company, is one of Europe's largest Contract Development and Manufacturing Organizations (CDMO) for cell and gene therapy viral vector manufacturing. A trusted partner for biotech and pharmaceutical companies seeking to advance clinical trials and commercialize new Advanced Therapy Medicinal Products (ATMPs), Yposkesi offers a full range of services in lentiviral vectors and AAV (Adeno-Associated Virus) cGMP manufacturing.
With a new building extension(5000m² building, equipped with several 1000-liter bioreactor), completed in 2023, Yposkesi will be able to support clinical and commercial batches.
There are 2 main analytical departments at Yposkesi:

- **Quality Control** for mainly cGMP batches testings, stability studies, raw materials testings and environmental testings
- **Analytical eXpertise Center** for mainly non-cGMP batches testings, customer project management on analytical topics, analytical methods development and validation

Main causes of disruption in the development of cell and gene therapies are "CMC issues" and especially "comparability / analytical issues".
Indeed, CGT analytical methods present some challenges from the beginning (early stage) to the end (validation, life cycle): lack of Reference Standard Material, assay variability (understanding requires material but limited batch size...), quick evolution of regulatory guidance, different methods for a same CQA, Process improvement which have an impact on analytic and CQAs…
But some answers exist: AQbD (Analytical Quality by Design), Internal Reference Standard, Lab standardization, Giving justifications for large accuracy to regulatory agencies...
The goal of the presentation was to present all these different challenges & answers, what is already deployed at Yposkesi, and to discuss about the main points that needs to be harmonized in a near future for all actors: reference method to all discuss about the same "specifications" (example: E/F capsids ratio: CryoTem versus AUC), CQA definition for process standard step to all measure the same parameters...





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Emmanuelle CAMEAU
PALL Corporation

Consideration of Quality by Design (QbD) Principles in the Use of Sterilizing Grade Filters for Clarification and Final Sterile Filtration in Adeno Associated Virus (AAV) Applications

Emmanuelle Cameau, Morven McAlister and Alexander Lambropoulos

The development of gene therapy applications using recombinant adeno-associated viruses (AAV) as a gene delivery vector has gained significant momentum in recent years. Although there are numerous applications for potential therapies to treat unmet medical needs, the ability to implement robust AAV manufacturing processes continues to be a bottleneck to fully realizing the potential of AAV based therapeutics. This includes the requirement to understand the characteristics (quality attributes) that are critical to product quality and patient safety, and to define these in appropriate detail for regulatory submissions such as chemistry, manufacturing, and controls (CMC) information.

Sterilizing grade filtration plays an important role in AAV manufacturing, both for drug substance (DS) as well as final drug product (DP). However, to fulfill regulatory expectations for provision of CMC information, it is recommended that the principles of quality by design (QbD) are considered during the early product development stages of the AAV manufacturing process. Both prior knowledge and experimental data should be used to identify potential critical quality attributes (CQAs). Enhanced knowledge should result from increased experience, and ultimately the critical process parameters (CPPs) and critical material attributes (CMAs) that can impact the CQAs can then be defined. The objective is to define a manufacturing control strategy that includes appropriate control of CPPs and CMAs to assure the CQAs of the drug product.

Here, the application of QbD principles for sterilizing grade filtration in both DS clarification and DP final fill steps of a typical AAV manufacturing process is described. Both experimental and data review approaches are included to help understand what a typical design space could look like, from which appropriate controls can be implemented. Ultimately, the expectations from regulatory agencies for assurance of product quality and patient safety are aligned with the requirement for a robust manufacturing control strategy to ensure consistent product quality is achieved.

Guillaume Sirgue
ABL, an Institut Mérieux Company

Process Characterization For Viral Vectors: A Lifecycle Approach In CDMO Context

Guillaume SIRGUE / Head of BioManufacturing and Process Development Operations / ABL Europe

Quality by Design is required by regulations but also needed to create a robust process and then achieve successful product development and validation. But what happens in real life when you simply do not have the time or the resources?

This question is particularly relevant in the field of cell & gene therapies and in the CDMO context. In many cases, availability of historical data is not easy, as the products are at early stage and process ownership can change at a fast pace. Also, there is a certain level of emergency as the molecules are designed for unmet medical needs and clinical proof needs to be obtained quickly to secure fundings. As a result, the balance between process understanding and GMP manufacturing is crucial.

The presentation detailed a project recently carried out by ABL. The process was a typical manufacturing process for Viral Vector, based on HEK293 suspension cells, with two chromatography steps for purification and one TFF step for formulation. The challenge came from the timeline but also the product ownership. The product moved from a university in 2020 to a Big Pharma spinoff in early 2022 and the process knowledge was transferred along the way.

ABL performed the Tech Transfer at 10L scale and manufactured 5 Drug Substances batches at 200L (Engineering and GMP runs) in parallel of Viral Seed batches manufacturing and development work. Development activities were split between different parties and process upgrades were successfully implemented during GMP manufacturing for clinical supply.

Before moving to Phase III batch manufacturing, several concerns were still not fully addressed - including Product Titer and residual impurities content. Considering the fast pace of the project, very little time was available for deeper process understanding studies and DoE. By organizing the data and analyzing changes between batches, the project team was able to supply a proposal for prioritization.

Examples were shared during the presentation of relevant analysis of data on Upstream and Downstream steps. Several recommendations could be made about process operations that need additional process development work and about parameters to focus on during process robustness studies.

In conclusion, this case study highlighted the need to balance the project strategy between expected QbD principles and GMP supply requirements.

Furthermore, ABL identified several key principles to ensure the success of the development:

- Time must be allocated to process characterization during process transfer to CDMO;
- All Product Attributes should be tested all along, and results shared with all the parties involved in the development;
- A robust change management process can make a difference when preparing CMC package for submission;
- A strong analytical package, in terms of robustness and scope, is essential.

Track Process Characterization and Validation for Cell & Gene Therapy : Case-Studies

William Small
CRODA

CRODA
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Croda Pharma is a leading partner for the development of excipients and the supply of high purity materials for pharmaceutical formulations. Croda Pharma's formulation and regulation expertise enables the next generation of drug delivery systems. We offer high purity pharmaceutical excipients to enhance delivery, efficacy, and stability of actives as well as highly performing vaccine adjuvants and in-house formulation expertise to aid in navigating drug and vaccine formulation challenges.
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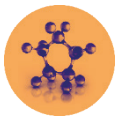

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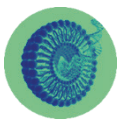
- Collaborating with customers to provide tailored excipient solutions to speed-up time to market.



Nucleic Acid Delivery

Developing and manufacturing highly specialised lipids used in Lipid Nanoparticle (LNP) delivery technology to solve the stability and delivery issues associated with mRNA-based vaccines and therapeutics.

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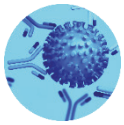
- Formulations division to develop custom lipid-based drug delivery systems for a range of pharmaceutical applications.
- Expertise on development and scale-up and manufacturing of lipids under cGMP.
- Contract manufacturing of proprietary lipids.



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• Extensive expertise in immunology and formulation of adjuvant systems, proving quality and support through vaccine research and development.
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Scan the QR code to visit our website, or visit: www.crodapharma.com

Anja Müller
IRUBIS

IRUBIS

Mid-infrared spectroscopy to monitor excipients and protein concentration in downstream processing

Anja Müller[1], Géraldine Baekelandt[1], Sarra Boutaieb[1], Vitaly Mozin[1], Ariana Peredo[1]
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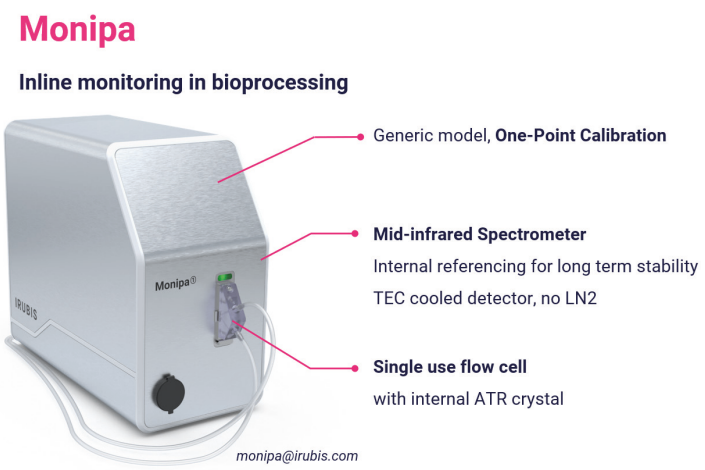
In recent years, there has been a crescent need for the improvement of bioprocesses, more specifically in the biopharma industry. Faster, safer, and more efficient drug development and production are imperative to bring these medications faster to patients.

To achieve this goal, the use of process analytical technologies (PAT) has increased, with an important role in advancing bioprocesses. The complex nature of downstream processes requires monitoring techniques that are continuous, fast, robust, and non-destructive. Spectroscopy methods fit all these requirements, providing inline monitoring of the components of interest. At IRUBIS we have developed Monipa, a PAT device based on vibrational spectroscopy operating in the mid-infrared (MIR) region. Comprising a single-use flow cell, it is capable of monitoring continuously many components simultaneously and inline. Also, the One point calibration method saves its user time and money by avoiding the development of complex calibration models. The measurement intervals befit classic downstream processes for the purification of active substances.



We have demonstrated monitorization of protein concentration with a protein dilution study, where accurate measurements were performed in the range of 0.5 to 200 g/L.

Another displayed application resides in the monitoring of protein and excipients, namely bovine serum albumin in a PBS solution containing sorbitol and mannitol. Differences in spectra were found for the complex mixtures, allowing for the identification of similar components together with changes in their concentration. A collaboration with Alvotech has established proof-of-concept for the detection of protein aggregation. By evaluating changes in protein secondary structure, more specifically in the increase of β-sheet structures, we have observed differences in spectra after the aggregation of monoclonal antibodies.

These applications show the ability of Monipa to be integrated into diverse downstream applications, providing continuous inline monitoring of protein and excipient concentrations, and protein aggregation, whilst following a plug-and-play approach.

Track stability studies of cell lines to speed up first in human trials: new technologies & approaches

Regina Grillari
Evercyte GmbH

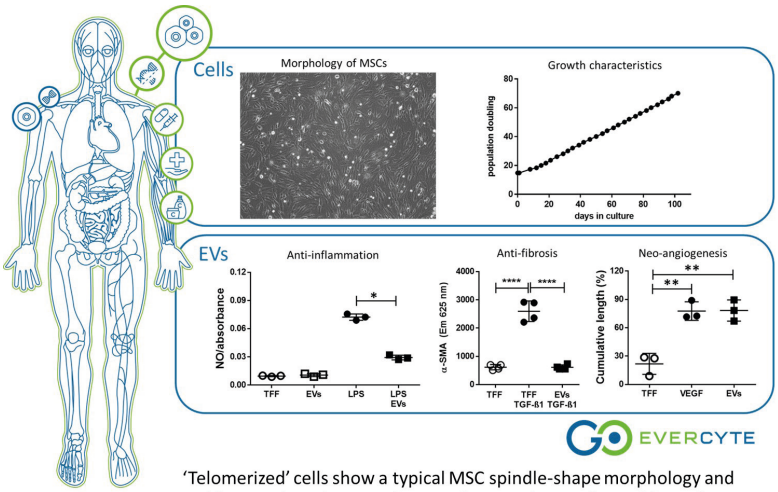
Human mesenchymal stromal cells for production of extracellular vesicles

Mesenchymal stromal cells (MSCs) have been extensively exploited in regenerative medicine and tissue engineering due to their therapeutic effect. However, reports have revealed that MSCs hardly engraft in vivo and the observed beneficial effects are due to paracrine effectors. In recent years, more studies shed light on these secreted factors attributing the regenerative and immunomodulatory activity of the MSCs to extracellular vesicles (EVs). EVs are small circulating messengers that encapsulate specific information derived from the parental cells and deliver them to recipient cells. MSCs-derived EVs are considered to have enormous therapeutic potential in tissue regeneration, treatment of age-associated and inflammatory diseases.

However, the use of primary MSCs for EV production is limited due to the cells' finite replicative lifespan. To circumvent this limitation, we at Evercyte, have put the focus on the implementation of tools for lifespan extension of MSCs without altering the cells' primary-like phenotype by overexpressing the catalytic subunit of human telomerase (hTERT). The ectopic expression of hTERT extends the cellular life span and does not change the cell morphology, or the expression of cell-type specific markers and functions nor induces tumorigenicity.

At Evercyte, we have established an extensive catalogue of 'telomerized' cells derived from different human tissues e.g. adipose tissue, bone marrow, placenta, Wharton's jelly, , under xeno-free conditions with full documentation of any manipulation step and non-viral gene transfer methods. Hence, these cell lines represent valuable cell factories to produce clinical-grade EVs when transferred into GMP environment. Moreover, EVs derived from 'telomerized' cells have been characterized; they carry expected biomarkers, are biologically active in in vitro assays showing anti-inflammatory, anti-fibrotic, wound healing, and pro-angiogenic potential and do not carry hTERT protein nor full-length hTERT mRNA. Moreover, secreted EVs have been characterized for their miRNA cargo, which is stable throughout production using a hollow fibre bioreactor.

In addition, due to the infinite lifespan, our extensive catalogue of cells can also be genetically engineered to express additional proteins, which are naturally incorporated into the EVs and impart specific functions such as tissue targeting, tracing in vitro and in vivo and selective purification.



'Telomerized' cells show a typical MSC spindle-shape morphology and stable growth under xeno-free conditions. The EVs derived from these cells have anti-inflammatory, anti-fibrotic and neo-angiogenic potential.

Track mRNA, a new platform technology and therapeutical approach: pros & cons

Jose Castillo
Quantoom Biosciences

Quantoom Biosciences – Unlocking Global Access to RNA Medicines

Manufacturing challenges: mRNA vaccines have come a long way since COVID-19; however, production means still have room to improve to meet the growing demand for these novel therapeutics. When observing mRNA production, scaling up requires process development and successive investments in capacities to match larger volumes. Purification is typically lengthy, requiring multiple steps, hence decreasing yields.

Technology: To address these bottlenecks, Quantoom developed Ntensify™, a solution for mRNA production with three models covering needs from R&D to commercial production. Typically, DNA inputs are fed into the machine, then the template is transcribed into mRNAs, and finally purified, and ready for formulation.

Figure 1 Ntensify Mini

Ntensify™ Mini is suitable for both drug discovery and pre-clinical development. For Drug discovery: the system can accommodate up to 192 different DNA templates in parallel; while for pre-clinical: a single DNA template can be transcribed in each well and pooled after purification.

Ntensify™ midi is a GMP-grade RNA production system available for the manufacturing of mRNAs or saRNAs at a scale that is ideal for clinical phases I and II. Modules are available to upgrade effortlessly from the Ntensify Midi to the Ntensify Maxi.

Figure 2 Ntensify Midi

Key benefits:
Each system is designed as a ready-to-use solution to produce high quality material for your mRNA-based product.

The innovation focuses on four aspects. First, the **process** was optimized by our partner eTheRNA and redesigned based on intensification and chaining of operations, for a small footprint and automated processing. The performance is improved in both yield and quality, for the purification to be carried out in a single step. Second, the **reagents** are ready-to-use in pre-mixes at the right concentration and right ratio. Third, the **disposables** enable manufacturing by increments of 1 mL (mini) or 20 mL (GMP-midi or maxi) for manufacturing without the need for scaling up. Finally, the **equipment** offers an automated process for ease of use.

This approach allows:

1. **Speed** -> No scale-up needed, (pre-)clinical development is already at final scale, which accelerates your process and product development
2. Single **low-footprint** system integrating all process steps from IVT to DS
3. **Standardized process** but also adaptable to sequence-specificities.
4. **Reduced CoGs** thanks to minimized labor and RNA expertise
5. In vivo validated with multiple constructs to de-risk product development

Track mRNA, a new platform technology and therapeutical approach: Pros & Cons

Arslan Akmammedov
CELONIC

Celonic Group (hereafter Celonic) is a quality Swiss-based CDMO with state-of-the-art manufacturing facilities in Switzerland and Germany. With over three decades of experience, Celonic offers mammalian expression solutions for clinical and commercial development and manufacturing. Most recently, Celonic has built expertise in ATMP modalities, which include cell and gene therapies, exosome and extracellular vesicles (EVs) as well as mRNA. Even before the COVID-19 pandemic began, the company expressed interest in mRNA therapeutics and consequently, Celonic was well-positioned to address the challenges of mRNA manufacturing for vaccine and therapeutic applications.

Celonic's Expert Insight

Validated processes: The DNA template used in the in vitro transcription (IVT) reaction is a critical starting material and its quality has a direct impact on the mRNA quality (e.g. dsRNA, product-related impurities, poly(A) tail length) and yield in the IVT process. At Celonic, we established and validated plasmid vectors delivering stable ca. 120A long poly(A) tails, reduced dsRNA content and obtained low-to-no product-related impurities. These vectors can be used for the manufacturing of GMP-grade plasmids or synthetic DNA templates for IVT.

Client-tailored approaches: The materials used in the IVT also affect the mRNA quality and yield. In order to get an in-depth understanding of this impact, we evaluated IVT materials from different suppliers. The major outcome of this evaluation showed that there is no single IVT material supplier that delivers the best overall performance. Therefore, we can tailor the IVT process to meet the client's requirements. Below, find the examples of our tested criteria.

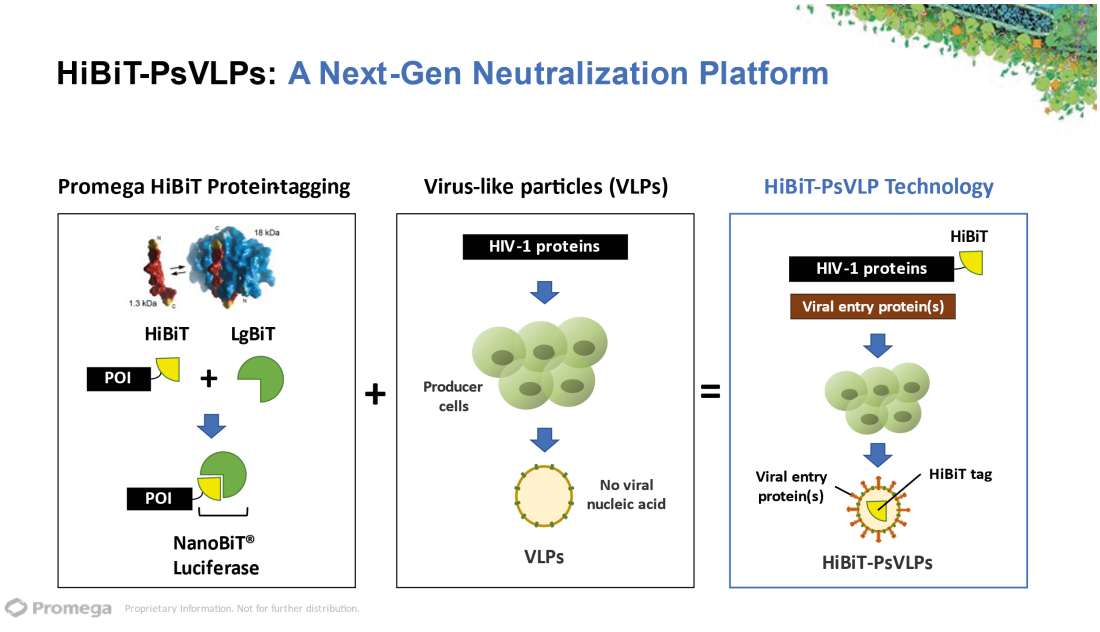
	Supplier A	**Supplier B**
RNA yield/ IVT volume	4x higher than supplier B	4x lower than supplier A
Fold-amplification (DNA -> RNA)	150-fold	660-fold
Cost of IVT/ g of RNA	6x higher than supplier B	6x lower than supplier A

Insightful analytics: mRNA therapeutics are still in an early phase and the knowledge concerning the critical quality attributes (CQAs) that impact the drug's safety & efficacy as well as the methods used to evaluate these CQAs is constantly evolving. For example, the importance of capping efficiency has been known for decades, and thus several different methods were developed to evaluate this attribute. The particular challenge while selecting a suitable analytical method is the accurate understanding of the mechanisms and the relevant assumptions and caveats of each one of these methods. Unfortunately, this insight into the analytical methods is hard to achieve given the "fast-paced" mindset which is predominant in the mRNA field. Consequently, there is one prevalent analytical method that can surprisingly measure up to 400% capping efficiency. Such values either highlight the invalid nature of the assumptions or disregard for the caveats associated with the method resulting in an overestimated value. Clearly, even the values falling within the expected range may be grossly overestimated using this method. Needless to say, such failures will have a catastrophic impact on the drug's efficacy in the clinical trials and the overall success of the project.

Florian Mignot
Promega

New psVLP neutralization assay using bioluminescence: Proof of Concept on SARS-CoV-2

Promega offers several assays and enabling technologies for SARS-CoV-2 drug discovery and vaccine development. One of them, using pseudotyped virus-like particles (PsVLPs), the SARS-CoV-2 HiBiT-PsVLP Assay was developed to measure the activity of small molecule inhibitors and neutralizing antibodies that block viral entry into the host cell. It permits to detects differences in antibody neutralization between variants. The assay uses innovative HiBiT bioluminescence technology to tag PsVLPs that contain the Spike protein on their surface and no viral genetic material. This new technology provides a fast, and biologically-relevant method for assaying SARS-CoV-2 entry without need for cell culture and virus production because of the Thaw-and-Use format. The SARS-CoV-2 HiBiT-PsVLP Assay permits rapid assessment of entry inhibitors with the measures of biologics and small-molecule inhibitors potency and specificity. It can detect differences in antibody neutralization between variants and enables rapid screening of human sera for SARS-CoV-2 neutralizing activity. This flexible technology HiBiT-PsVLP platform can be adapted for other priority viral pathogens.



Stéphanie Colloud
ABL, an Institut Mérieux Company

Guests Speakers:
Kristell Lebozec (ACTICOR Biotech), **Valérie Griffond** (SANOFI), **Cécile Billa Nys** (MaaT Pharma), **Nicole Brument** (COAVE Therapeutics)

Choose the right strategy and the right partner for Innovative Therapies Manufacturing: return of experience & Case Studies of CMC Leaders of Biotech Start-ups & Pharma Companies

ABL moderated the workshop. ABL is a pure play CDMO specialized in the development and GMP manufacturing of virus for vaccine candidates, gene and cancer therapies. With over 25 years of experience, ABL offers a one-stop-shop and end-to-end CMC including bulk drug substance, fill/finish of drug products, process and assay development, as well as bioanalytical testing.

Acticor Biotech - a biopharmaceutical company that develops a first-in-class treatment for cardiovascular emergencies - presented their vendor selection process, which includes the identification of several vendors; the RFP; a bid presentation meeting and a technical visit. The parameters of their selection process include track record; location; price / Research Tax Credit; qualifications; technical and scientific skills; regulatory support; capacity, availability and organization of the team; flexibility and adaptability as well as experience sharing within their network. Acticor Biotech also shared advice on key issues to consider when assessing potential vendors: ease of access to site (shipping, certification and release of batches for vendors based outside of the EU); use of English language in documentation (including operational documents); anticipation of issues by using the adequate documentation (e.g. QP to QP agreement); knowledge of the vendor (size, company structure, management team); assessment of staff turnover and training; long term plans for site's sustainability strategy.

Sanofi - a world leader in vaccines with a strong history of innovation - establish world-class partnerships not only with universities, research institutes and government bodies but also with Biotechnology companies, Contract Manufacturing Organizations (CMOs), Contract Development and Manufacturing Organizations (CDMOs) or Contract Research Organizations (CROs). During the workshop, Sanofi presented how they have adapted their outsourcing strategy to the mRNA Center of Excellence.

MaaT Pharma - a microbiome therapeutics company that focuses on life-threatening diseases in oncology and hematology with high unmet needs - shared an assessment grid to help identify the most adequate type of partnership. Over the past 2 years, in an effort to anticipate the launch of phase 3 clinical studies and the subsequent increase of production volume, MaaT Pharma has been working on the evolution of its production tool. As the product is based on fecal microbiote, the transfer of production activities to CDMO is not easy and after a successful partnership with ABL, it has been decided to repeat the strategy of a collaboration.

	Pros	Cons
Internal capability	- Full control (process, quality, COGS, know-how, IP) - Reactivity/agility - Ongoing asset development	- Higher CAPEX - Limited fixed costs optimization inherent to GMP/Pharma process - Larger organizational needs - Broad expertise in non-core activities
Collaboration / Joint venture	- **Benefit from two parties experience** - Shared cost	- Know-how transfer - Risk access IP - Limited CAPEX
CDMO	- No CAPEX - Little commitment - Expertise	- Oversight - Higher COGS - Reactivity - Potential loss of know-how and Innovation

Coave Therapeutics - a gene therapy biotech company that specializes in rare ocular and central nervous systems diseases - shared the key considerations of their CMC strategy: mitigate development risks by reducing the dependency on CDMOs and limiting the costs; control the process development as PD and GMP capabilities are key assets for small biotech companies.

The plenary presentations were followed by a Q&A session. The main takeaways were the importance of:

- A strong collaboration is absolutely crucial, the CDMO and the customer need to work as one team to lead the complex journey of developing a new, innovative drug;
- Flexibility and adaptability are a necessity for innovative therapies development - from preclinical to clinical phases;
- Quality, reliability and transparency of the CDMO partner are prerequisites to build trust and a long-term partnership.

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Upcoming Events

8TH BIOPRODUCTION CONGRESS

5-6 October 2023 - Lyon - France

http://www.biopcongress.com

mabdesign

PARTNERING EVENT

MAY 2023 - TOURS

https://mabdesign-partnering-day.mabdesign.b2match.io/

https://aiscongress.com/

https://www.i4id.org/

Upcoming Watch Series

- **ImmunoWatch: RNA-based drug products**
- **BioProcessWatch: Analytical tools in Bioprocessing**
- **ImmunoWatch: Therapeutic Cytokines**

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