SPECIAL EDITION 2024

BIOPROCESSWATCH

BIOPC2023 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 enhance their innovations, conquer new markets and raise public funds.

Operational since September 2015, MabDesign currently has over **300 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 the latest information, France is currently at the second place in Europe, behind United Kingdom and closely followed up by Germany and Switzerland, 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 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, MabDesign has been actively participating in national and regional programmes and organising scientific events and gatherings focusing on biomanufacturing. Indeed, since 2016, our annual Bioproduction Congress has gathered so far more than 1810 participants, 245 speakers, 190 sponsors/exhibitors and has hosted more than 1800 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, biotechs 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. However humble it might be, MabDesign has been making a contribution to support and promote the biopharmaceutical and bioprocessing industry.

Since 2022 and the publication of the first meeting report on the Bioproduction Congress 2021 (BIOPC2021) in a special edition of the **BioprocessWatch**, we have released several editions of the series focusing on **mAb bioprocessing** and **Analytical tools in Bioprocessing** (accessible HERE).

In 2023, Mabdesign organized the **8th Bioproduction Congress (BIOPC2023)** focused on accelerating BioPharma development for patients. Counting with 57 expert speakers divided in two parallel tracks: mAbs and vaccines on one hand and Cell & Gene Therapy on the other track, as well as holding 4 workshops, it gathered 430 stakeholders who discussed how to advance the field of Bioproduction both in France and worldwide.

[1] Source : GlobalData

In a dynamic and stimulating two days event, 46 companies showcased their latest technologies and more than 500 B2B meetings took place, thus promoting collaborations and generating new commercial opportunities.

The scientific program of this edition was set-up by a **Scientific Advisory Board** composed of Alain BECK from **Pierre Fabre**, Roland BELIARD from **LFB Biomanufacturing**, Nicola BELTRAMINELLI from **Innate Pharma**, Hervé BROLY from **Merck Serono**, Cédric CHARRETIER from **Sanofi**, Olivier COCHET from **Debiopharm**, Arnaud DELOBEL from **Quality Assistance**, Sophie DERENNE from **EFS**, Annick GERVAIS from **UCB Pharma**, Elodie GUIDAT from **Sanofi**, Michaël FIDALGO from **TreeFrog Therapeutics**, Laszlo PARTA from **Fresenius Kabi**, Bernard VANHOVE from **EGLE Therapeutics**, Francisca GOUVEIA from **Novartis**, Oumeya Adjali from **INSERM**. 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 46 sponsors/exhibitors, our 12 institutional partners and our media partners of this event.

Due to the importance of the topics being addressed during the meeting, and following up on the great feedback we got from the first meeting reports we have decided to continue to included the science discussed at the meeting in a special edition of the **BioprocessWatch** so that all the players can benefit from it. We would like to thank all the speakers who took part to the BIOPC2023 and have contributed to the 3rd special BIOPC report edition of the BioprocessWatch. Due to confidentiality and intellectual property issues, 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 delighted to see you later this year at the **9th edition of the Bioproduction Congress, September 25-26, 2024 in Tours.** More information at http://www.biopcongress.com.

Wojciech Nowak
Group Senior Director, Global Governmental and Public Affairs
Novartis, Switzerland

Competitiveness of the European Biomanufacturing in a globalized world

Summary

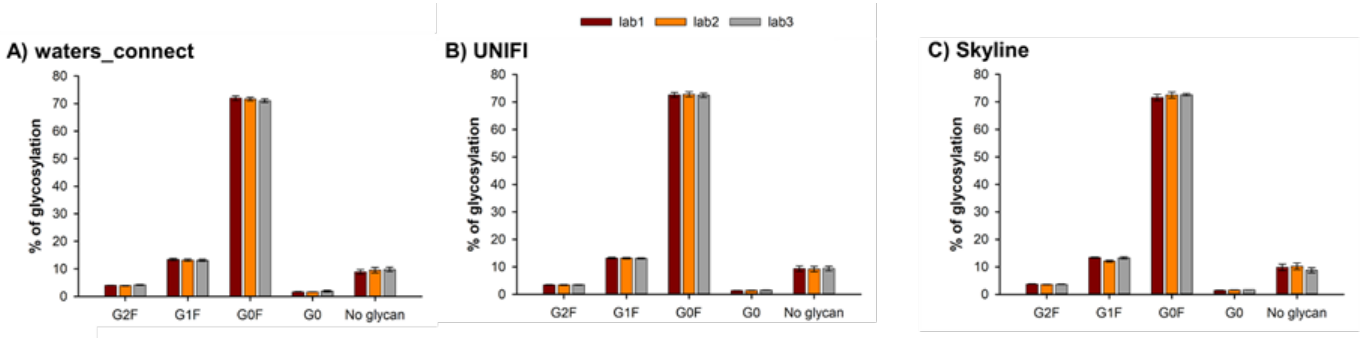
- The European biomanufacturing industry faces challenges in maintaining its competitiveness in a globalized world.
- The most concerning measure is the draft of the new Pharmaceutical Legislation including a proposal of a two-year reduction of the period of Regulatory Data Protection (RDP).
- Other key areas of concern include limited accessibility to financial resources, slow regulatory approvals, and the burden of the new standards such as “Corporate Sustainability Due Diligence Directive”.
- To ensure a bright future for the industry, Europe must preserve existing regulatory and intellectual property protection systems, strengthen platforms through education and efficient regulatory processes, and prioritize the availability of innovations to patients

Arnaud Delobel
R&D and Innovation Director
Quality Assistance, Belgium

Is multi-attribute monitoring ready for QC? Insights from an interlaboratory study

In the quest to market increasingly safer and more potent biotherapeutic proteins, the concept of the multi-attribute method (MAM) has emerged from biopharmaceutical companies to boost the quality-by-design process development. MAM strategies rely on state-of-the-art analytical workflows based on liquid chromatography coupled to mass spectrometry (LC–MS) to identify and quantify a selected series of critical quality attributes (CQA) in a single assay. Here, we aimed at evaluating the repeatability and robustness of a benchtop LC–MS platform along with bioinformatics data treatment pipelines for peptide mapping-based MAM studies using standardized LC–MS methods, with the objective to benchmark MAM methods across laboratories, taking nivolumab as a case study. Our results evidence strong interlaboratory consistency across LC–MS platforms for all CQAs (i.e., deamidation, oxidation, lysine clipping and glycosylation). In addition, our work uniquely highlights the crucial role of bioinformatics postprocessing in MAM studies, especially for low-abundant species quantification. Altogether, we believe that MAM has fostered the development of routine, robust, easy-to-use LC–MS platforms for high-throughput determination of major CQAs in a regulated environment.

Lab1 Lab2 Lab3



Violette Vincent
QC Specialist
ABL, an Institut Mérieux Company, France

Analytics Simplified - Capsid titer and impurities quantification along the Adeno-Associated Virus (AAV) Manufacture Process using ELLA

Adeno-associated virus (AAV) has emerged as a leading vector for gene delivery for treating various diseases due to its safety profile and efficient transduction of various target tissues. AAV, like other viral vectors, are complex molecules leading to challenges in their characterization. ABL's viral vector manufacturing site in Lyon, France is advancing its AAV process development and manufacturing platforms and is becoming an industry leader in AAV manufacturing and control on several serotypes (currently AAV2/5/6/8 and 9). Recently ABL has been able to manufacture AAVs from the harvest stage (from HEK293 cell line) through clarification, tangential flow filtration [TFF] (concentration diafiltration), capture and polishing chromatography (Figure 1.) Those downstream process purification steps have allowed for a reduction of process impurities while enriching the ratio full/empty of AAV particles. Capsid titer and process impurities are some of the main metrics in AAV manufacturing but can be challenging to evaluate.

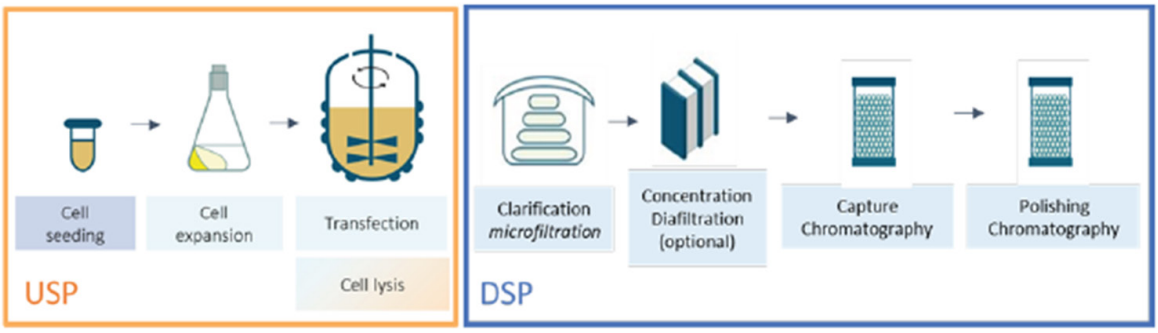


Figure 1. AAV Manufacturing – USP (Upstream) and DSP (Downstream) Steps. The presentation described how ABL is utilizing the benefits of a fully automated ELISA platform (Figure 2.) in its AAV manufacturing process to assess AAV capsid titers on several serotypes and describes initial evaluation of the technology for the measurement of residual process impurities (endonuclease and host cell proteins) critical quality attributes.

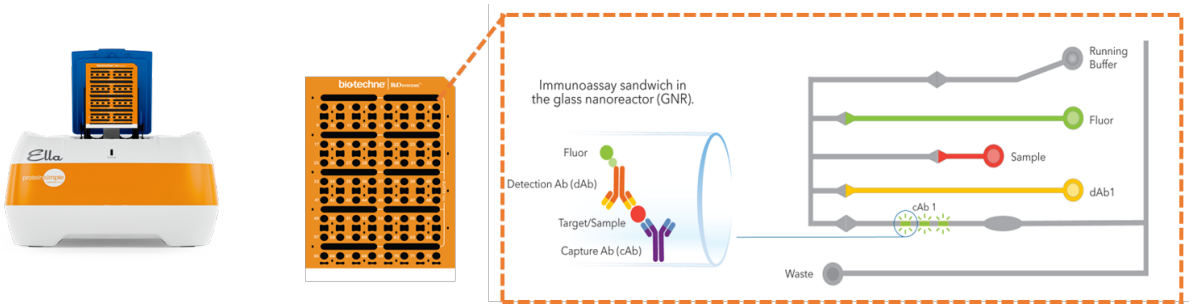


Figure 2. ELLA Equipment and its cartridge. Each sample well Assays are carried out within Glass Nano Reactors (GNRs), which are coated with analyte specific capture antibodies. GNRs and other assay reagents come preassembled into the microfluidic circuitry of the Simple Plex cartridge. Setting up a run simply requires loading the cartridge with diluted and centrifuged samples and wash buffer. Once a run is initiated, Ella automates every step of the assay in less than 90 minutes.

Discover all results in BioprocessWatch - Analytical Tools in Bioprocessing - Edition 2023

About ABL

ABL is a pure play CDMO specialized in the development and manufacturing of gene therapies, oncolytic viruses and vaccine candidates. Our mission is to provide GMP viral vectors from early-stage to market. Our services include manufacturing of bulk drug substance, fill-finish of drug products, process and assay development as well as regulatory support. ABL is a subsidiary of the Institut Mérieux and operates in Europe and the US.

For more information: www.abl-biomanufacturing.com

Alain Beck
Senior Director, Biologics CMC & Developability
Pierre Fabre, France

Pierre Fabre

Advanced Liquid Chomatography tandem Mass Spectrometry Workflows for Host cell proteins Quantification

Corentin BEAUMAL[1], Oscar HERNANDEZ-ALBA[1], Zoheir MOGRANI[2], Alain BECK[2], Christine CARAPITO[1]
[1] LSMBO, CNRS, Université de Strasbourg.
[2] Laboratoires Pierre Fabre, IRPF, Toulouse and Saint-Julien en Genevois.

Host cell proteins (HCPs) constitute a major group of process-related impurities in biological drugs produced using cell culture technology. HCPs are produced inadvertently during the expression of recombinant biopharmaceuticals and secreted from host cells in response to cell stress and/or cell lysis over the course of bioprocessing. Many HCPs are benign, but some are immunogenic. Some may interact with a drug substance, and others (e.g., proteases and lipases) can reduce effective product dosage through direct action on the drug or its stability by interfering with formulation buffers. Because HCPs can pose a risk to patients and affect the efficacy and stability of biological drugs, the quantity and nature of residual HCPs in a drug substance generally are critical quality attributes (CQAs).

HCPs are routinely detected using multi-analyte immunoassays (typically ELISAs) that are designed to measure heterogeneous populations of HCPs. Regulatory agencies around the world have put measures in place to ensure that the HCP ELISA used by a sponsor will be fit for the purpose of monitoring purification process consistency and product lot release.

Orthogonal analytical techniques such as liquid chromatography tandem mass spectrometry (LC-MS/MS) complement HCP ELISAs and enable the comprehensive characterization and identification of HCP impurities. Despite the development of advanced mass spectrometry techniques and optimized workflows, identifying and quantifying all problematic HCPs present at low levels remain challenging. Implementing a High-Field Asymmetric Ion Mobility Spectrometry (FAIMS) separation step in the workflow as well as of the use of Data Independent Acquisition (DIA) combined with a Gas-Phase Fractionation approach to address the challenges of accurate and precise quantification of very low-level HCPs in samples presenting an extreme dynamic range have been explored. As a proof of principle, major improvements towards robust quantification of trace-level HCPs in antibody Drug Products (DPs) have been demonstrated both on the NIST mAb Reference Material standard and two FDA/EMA approved DPs, down to the sub-ppm level (Beaumal C et al, 2023). As a follow-up, the same workflow is applied to more complex antibody-based product such as Fc-fusion proteins or Bi and Multi specific Antibodies (Bs/MsAbs).

Such emerging state-of-art analytical methods contribute to accelerate gene to clinical-grade Biologics Chemistry, Manufacturing and Controls developments (Broly H et al, 2023).

References: Beaumal C, Beck A, Hernandez-Alba O, Carapito C. Advanced mass spectrometry workflows for accurate quantification of trace-level host cell proteins in drug products: benefits of FAIMS separation and gas-phase fractionation DIA. Proteomics, 2023.

Broly H, Souquet J and Beck A. Effects of the COVID-19 pandemic: New approaches for accelerated delivery of gene to first-in-human CMC data for recombinant proteins. mAbs 2023, 15(1): 2220150. Published online 2023 Jun 6. doi: 10.1080/19420862.2023.2220150.

Célia Sanchez
Biological engineer
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Use of Raman spectroscopy for in-line, real-time monitoring of critical process parameters in perfusion cultures

The bioprocessing industry is moving towards automation and monitoring of bioproduction. To achieve this goal, new analytical instruments and tools are needed. For example: Raman spectroscopy has shown good performances in the real-time monitoring of cell culture parameters which allows automation of feeding strategy for example. Raman spectroscopy is an analytical tool that can be used to identify and determine the concentration of molecules in solution such as cell culture media.

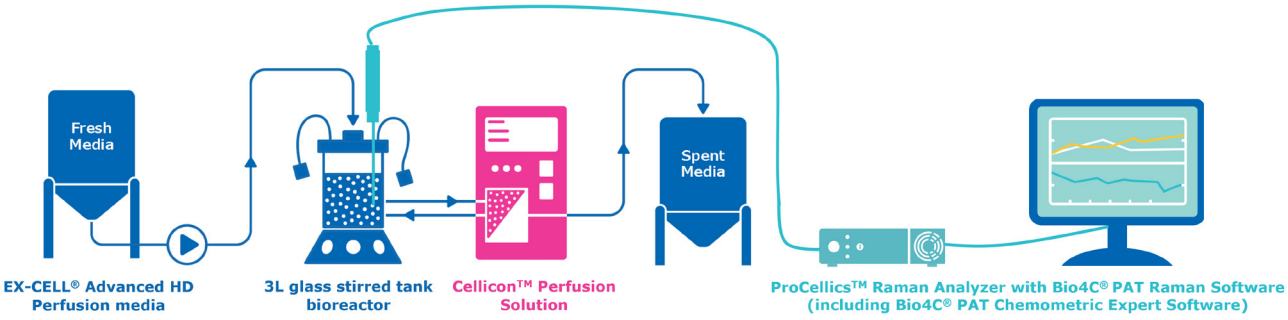

Figure 1: Set up of a perfusion cell culture monitored with ProCellics™ Raman Analyzer

For the experiments described in this use case, the Raman spectroscopy workflow consisted of six steps:

- Collection of Raman spectral data by inserting the probe aseptically into the bioreactor and running a calibration model to collect the spectra.
- Collection of off-line reference data of target variables and association.
- Pre-processing of data to reduce the noise and improve the signal and predictive models.
- Model development using the partial least square model.
- Model validation based on the cross-validation error and the prediction error.
- Deployment of the model for real-time monitoring, optimization, and process control.

The results of real-time monitoring of some of the cell culture attributes are shown in the figure below.

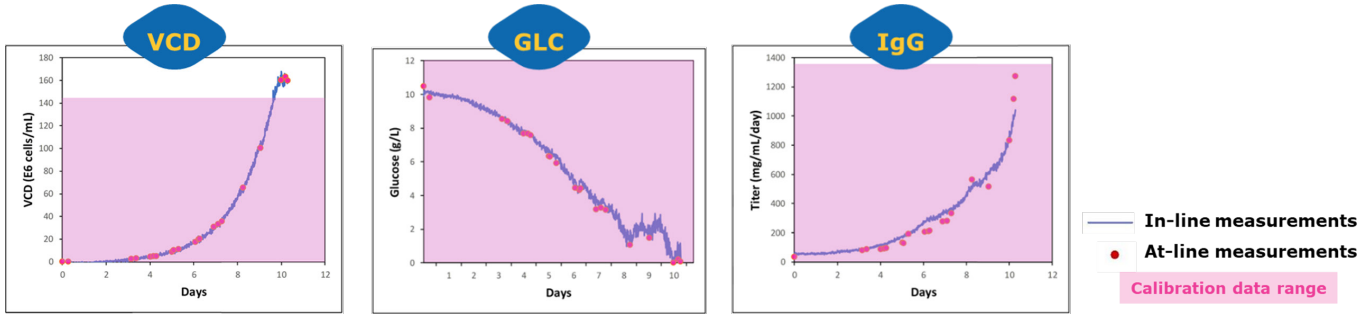

Figure 2: Real-time Raman measurement (In-line) of Viable Cell Density (VCD), glucose concentration (GLC) and antibody productivity (IgG) compared to sample measurement (At-line)

This study demonstrates the integration of Raman spectroscopy-based sensors into perfusion cultures for real-time monitoring of cell culture process parameters.

Véronique Blouin
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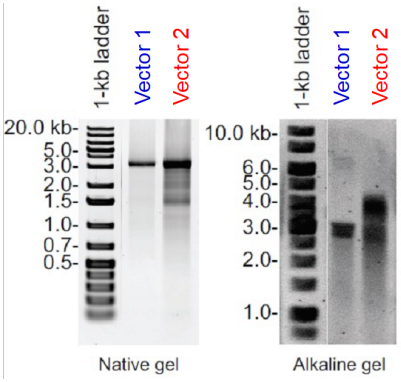
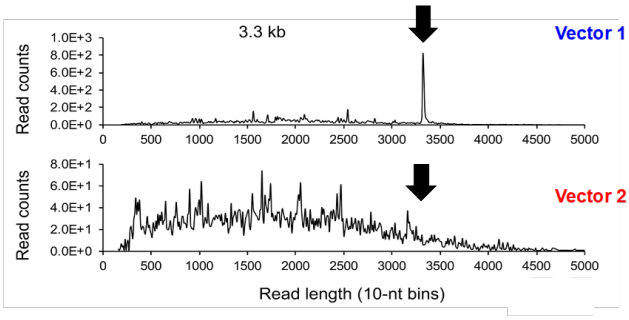
Analytical developments for viral vectors: NGS-based methods for the characterization of DNA contaminants and genome integrity

Recombinant Adeno-Associated Virus (AAV) are viral vectors of choice for in vivo gene therapy with already six products currently approved in the market. However, the manufacturing process to produce large amounts of AAV vectors remains a major challenge in particular with the increasing clinical and market demands, and the necessity of systemic administration of high doses to achieve therapeutic efficiency. Our translational vector core (CPV), "intégrateur en Biothérapies et Bioproduction, France 2030", aims at addressing these challenges from fundamental "vectorology" to preindustrial manufacturing.
The improvement of rAAV processes cannot be dissociated from the characterization of the produced products.
During rAAV vectors production, different sub-populations were characterized. rAAV batches are not homogeneous but composed of full, partially-filled, empty, as well as aggregates. The presence of defective particles can increase the risk of immune response to AAV vectors and reduce their potency. Various methods have been used to characterize these defective AAV particles. At Target-ViVeM, we developed the analytical ultra-centrifugation method which confirms the presence of intermediate particles in rAAV production. We also developed multiplexed digital PCR to characterize more precisely the rAAV genome integrity but it doesn't give us complete information on the integrity of the packaged genome and not allow us to differentiate between 3'ITR and 5'ITR sequences.
To investigate, at Target laboratory we have developed the SSV-Seq method which enables high-throughput sequencing of a large amount of DNA packaged in rAAV particles. Bioinformatics analysis of the sequences showed that more than 85% are rAAV genomes, less than 10% are from the vector plasmid, less than 0,5% are from the helper plasmid and DNA from producer cell. These results are similar to qPCR data. In collaboration with University of Massaschusetts, a long-read sequencing approach able to characterize heterogeneity of vector genomes has been developed. This innovative method, Single Molecule Real-Time sequencing (SMRT) has the capacity to sequence vectors from ITR to ITR without the need for bioinformatic reconstruction of the full genome. We compared two rAAV production platforms and we found that truncated genomes from pTx/HEK293 and rBV/Sf9 production were observed and more abundant for rBV/SF9. The truncated genomes were attributed to mutated and unresolved ITRs. We also show that for empty fractions, particles packaged short reads that map to ITRs.



Vector 1: plasmid Transfection human cells platform (pTx/HEK293)
Vector 2: recombinant Baculovirus insect cells platform (rBV/Sf9)



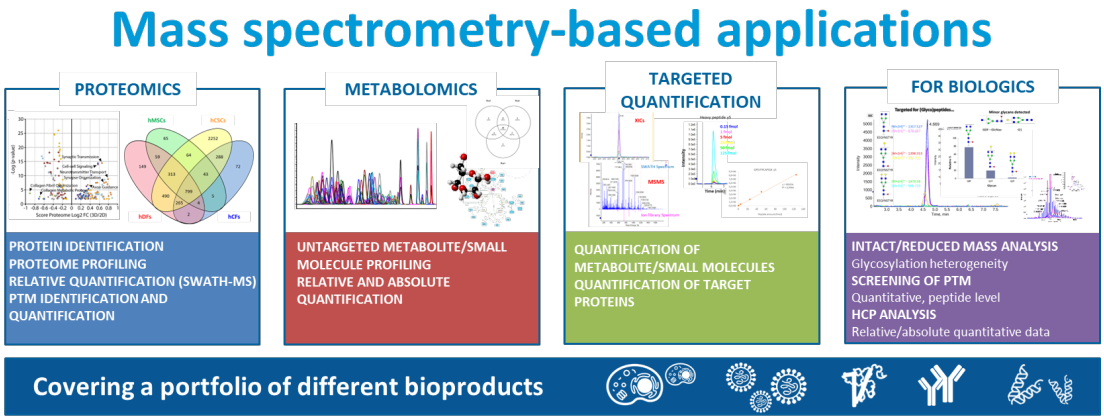
References:
Lecomte et al.; Mol Ther Nucl Ac 2015
Tran et al. ; Mol Ther MCD 2020
Tran et al. ; HumGenTher 2022

Patricia Gomes-Alves
Head of Lab
iBET, Portugal

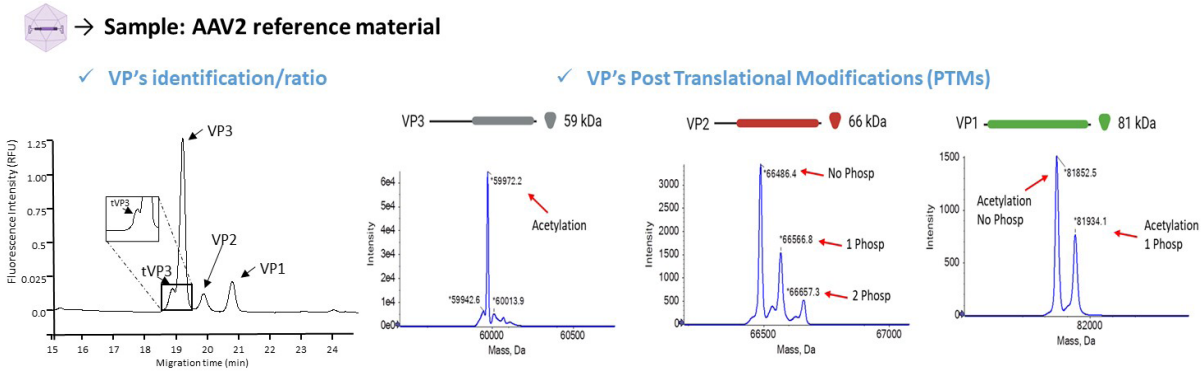
iBET
Instituto de Biologia Experimental e Tecnológica

Bioanalytics development for ATMPs and advanced cell models

The development and clinical use of biologics, in particular advanced therapy medicinal products (ATMPs), is growing at a fast pace. Products such as antibodies, fusion proteins, and antibody-drug conjugates are quite complex and challenging, requiring effective and orthogonal bioanalytics tools for comprehensive molecular characterization. Furthermore, the demand for new and improved therapeutic solutions with increased complexity, such as multispecific antibodies, gene and cell-based therapies has been a driving force for the development of advanced analytical methodologies with increased sensitivity, throughput, and time/cost-effectiveness (1). Mass spectrometry (MS)-based analytics have been emerging as powerful solutions for qualitative and quantitative analysis of such complex products and also for a better understanding of advanced 3D cell models used to test and predict the potency of these ATMPs.



In this work, we describe the implementation of an advanced analytical toolbox, including MS-based workflows, for the characterization of biologics, cell- and viral-based products (2), and advanced cell models (3), streamlining the improvement of the bioprocess and product understanding and design.



References: (1) Escandell JM et al. (2022), Current Opinion in Biotechnology; (2) Fernandes R and Escandell JM et al. (2022), Viruses; (3) Sebastião MJ et al. (2020), Translational Research.

Developability in Biomanufacturing: Process Modeling & Digital Twins – Stream Biologics

Brooke Tam
Process Engineer
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Cell culture digital twins enabling efficient scale-up and tech transfer

Digital twins are valuable for efficiently transferring complex processes from the laboratory to manufacturing scale and ensuring consistent results at different manufacturing sites. By bringing together models of the scale-dependent and scale-independent aspects of cell culture processes for the production of biomolecules, we are able to simulate key parameters throughout the duration of the cell culture process, predict the differences that will be observed, recommend any required equipment or control strategy changes to ensure the process is successful, and develop a plan for monitoring the process and detecting the early signs that an intervention may be needed, all before the first vial is thawed in the manufacturing suite. This increases confidence in process scale-up and reduces the need for costly and time-consuming experimentation at scale, which allows us to meet aggressive timelines and better serve the patients who need our products.

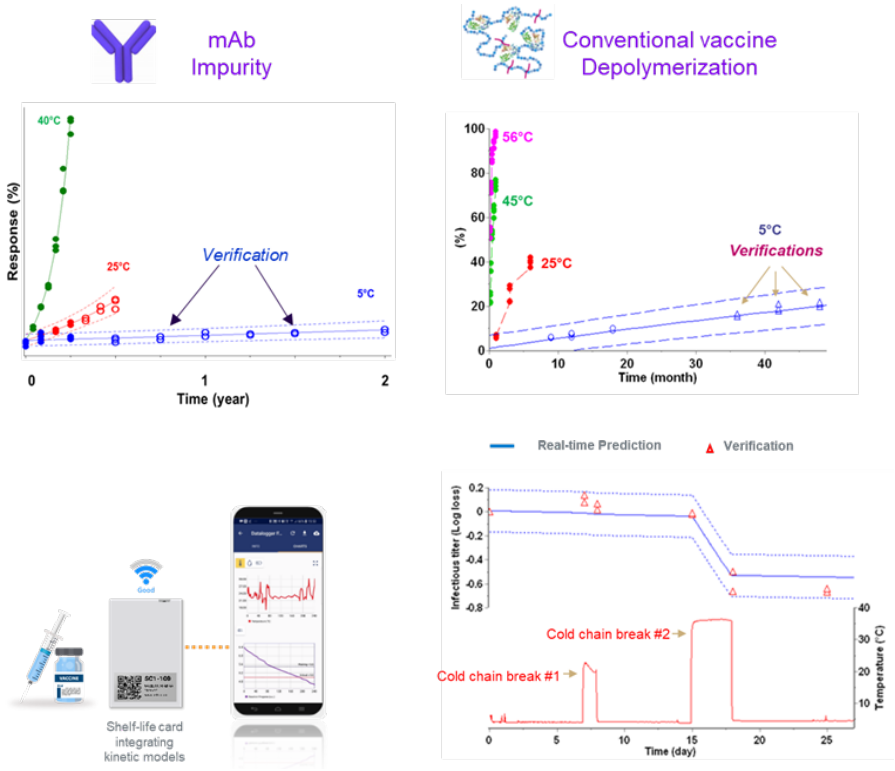
Digital twins are an important component of right-first-time tech transfer. In one example, we have used digital twins to take a process from small-scale to pilot scale and shown that the process met all expectations in the very first batch with no intervention or automation changes. We have also used digital twins to move a process into a new manufacturing facility with only a single engineering run prior to launch of the process qualification campaign. Digital twins already have value, but as process analytical technology improves and becomes more commonplace in the industry, the opportunities for applying digital twins and the impact they have will greatly increase. More complete data sets will allow for improved understanding of the complex interactions of parameters in cell culture, leading to more robust models. Faster access to data will also improve the links between the physical and digital twin, leading to quicker detection of events that may require intervention.

Disclosures: Brooke Tam is a Sanofi employee and may hold shares and/or stock options in the company

Didier Clénet
Research Scientist Formulation & Stability
Sanofi, France

A Universal Tool for Stability Predictions of Biotherapeutics, Vaccines and In Vitro Diagnostic Products

It is of particular interest for biopharmaceutical companies developing and distributing fragile biomolecules to warrant the stability of their products during long-term storage and shipment. In accordance with quality by design (QbD) principles, advanced kinetic modeling (AKM) has been successfully used to predict long-term product shelf-life and relies on data from short-term accelerated stability studies that are used to generate Arrhenius-based kinetic models that can, in turn, be exploited for stability forecasts. The AKM methodology was evaluated through a cross-company perspective on stability modeling for key stability indicating attributes of different types of biotherapeutics, vaccines and biomolecules combined in in vitro diagnostic kits. It is demonstrated that stability predictions up to 3 years for products maintained under recommended storage conditions (2-8°C) or for products that have experienced temperature excursions outside the cold-chain show excellent agreement with experimental real-time data, thus confirming AKM as a universal and reliable tool for stability predictions for a wide range of biological products.



References: M. Huelsmeyer et al. A Universal Tool for Stability Predictions of Biotherapeutics, Vaccines and In Vitro Diagnostic Products, Sci Rep, 13, 10077, 2023

Clément Glace
Life Sciences Industry Solution Experience Consultant
Dassault Systèmes, France

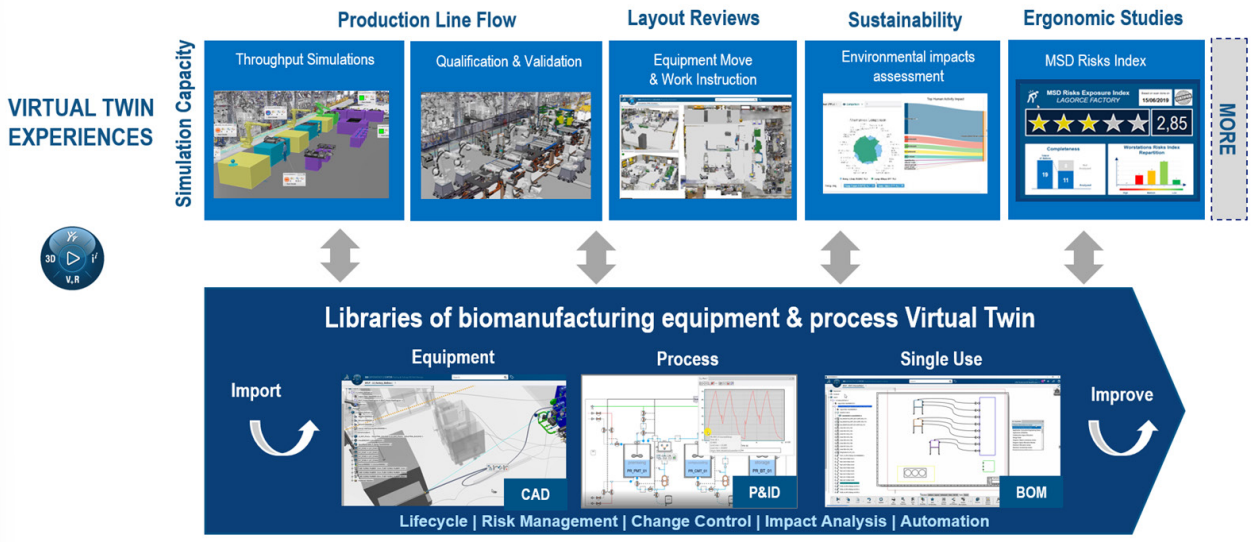
The Virtual Twin of processes and equipment to support manufacturing of innovative therapies

The Life Sciences industry has changed significantly over the last number of years. With a view to developing new, novel, more effective, quality, precision treatments, industry leaders are exploring new therapeutic areas and approaches, leveraging the latest technology advancements to gain the competitive edge and deliver sustainable scientific innovation.

As pharmaceutical manufacturing lines transition towards small batch production to produce precision medicines, manufacturers need to effect end-to-end manufacturing line optimizations to produce these therapies more sustainably. To do this, manufacturers look to connect systems, people and data — leveraging digitalization, automation, virtualization, modeling and simulation and Artificial Intelligence (AI) and what we call the Virtual Twin. The Virtual Twin, is a digital replica of real-world pharmaceutical processes, products and plants from end-to-end. When leveraged with a platform based approach, it delivers the agility manufacturers need with science-based tools that can be leveraged to develop novel therapies.

The Virtual Twin for BioManufacturing can be leveraged to achieve the following goals:

- Define, develop, optimize and validate recipes and the associated industrial setup by building the Virtual Twin of the manufacturing environment. Improve production flexibility with "What if Scenarios" to simulate, and analyze multiple production and process engineering scenarios, in a realistic 3D environment, optimizing the production workflow and resource utilization.



- Unify manufacturing operations with warehouse processes, and experience full continuity between recipe authoring and recipe execution on the shop floor and in QC laboratories to minimize waste. Quickly adapt and scale up the production with fast refitting of processes and layouts to deliver flexibility and improved overall equipment effectiveness.

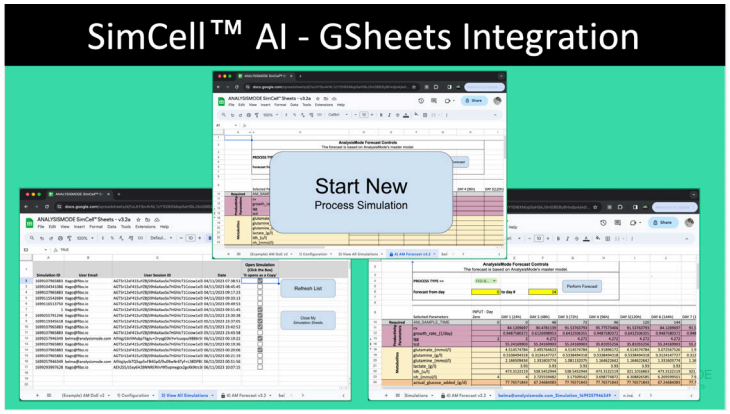
- Experience process control and optimization insights based on simulation, real time data gathering and data prediction with virtual twins. Understand and monitor the process to improve quality, sustainability and increase yield. Ensure safe batch release by monitoring production to identify out of control trends before failures occur and provoke waste of materials.

- Coordinate all plants to optimize full planning activities with the supply chain Virtual Twin experience. Using “What-if” scenarios, compare and optimize planning based on world-class KPI optimizations and experience increased flexibility enabling adaption to demand fluctuations to ensure ontime delivery.

Developability in Biomanufacturing: Process Modeling & Digital Twins – STREAM ATMPs

Belma Alispahic
Head of Business Development
Analysis Mode, Finland

How AI can transform the bioprocessing industry?



SimCell is an AI-driven tool that simulates upstream bioprocess parameters in mere seconds, creating in-silico wet-lab conditions with unparalleled accuracy. By drastically reducing the need for physical experiment, SimCell minimizes costs, optimizes resources, and decreases time-to-insight. It's not just a tool; it's a strategic partner in transforming how bioprocessing is conducted.

SimCell doesn't just optimize processes; it revolutionizes the very essence of experimentation, offering scientists more time for meaningful work and paving the way for a new era in biopharmaceutical research.

Digital Process Twin Paradigm shift

A switch from top-down to bottom-up approach

«AI can help scientists approach problems from the bottom up instead-

measure lots of data first, and use algorithms to come up with the rules, patterns, equation and scientific understanding later.»

[source: https://www.economist.com/science-and-technology/2023/09/13/how-scientists-are-using-artificial-intelligence]

In bioprocessing, Artificial Intelligence (AI) transforms into a collaborative force—ushering in collaborative intelligence. This partnership accelerates decision-making by merging AI's analysis with human intuition, streamlining the navigation of complex challenges.

Amidst the intricate landscape of bioprocessing, collaborative intelligence becomes a catalyst for innovation. The synergy between AI and human understanding unlocks concealed insights, propelling the industry towards unprecedented advancements. This collaboration signifies a paradigm shift, where the convergence of AI and human ingenuity drives groundbreaking discoveries in bioprocessing.

Christophe Bonneville
Co-Founder & President
Dillico, France

All-ScaleFlow™ Technology for Flexible mRNA Manufacturing

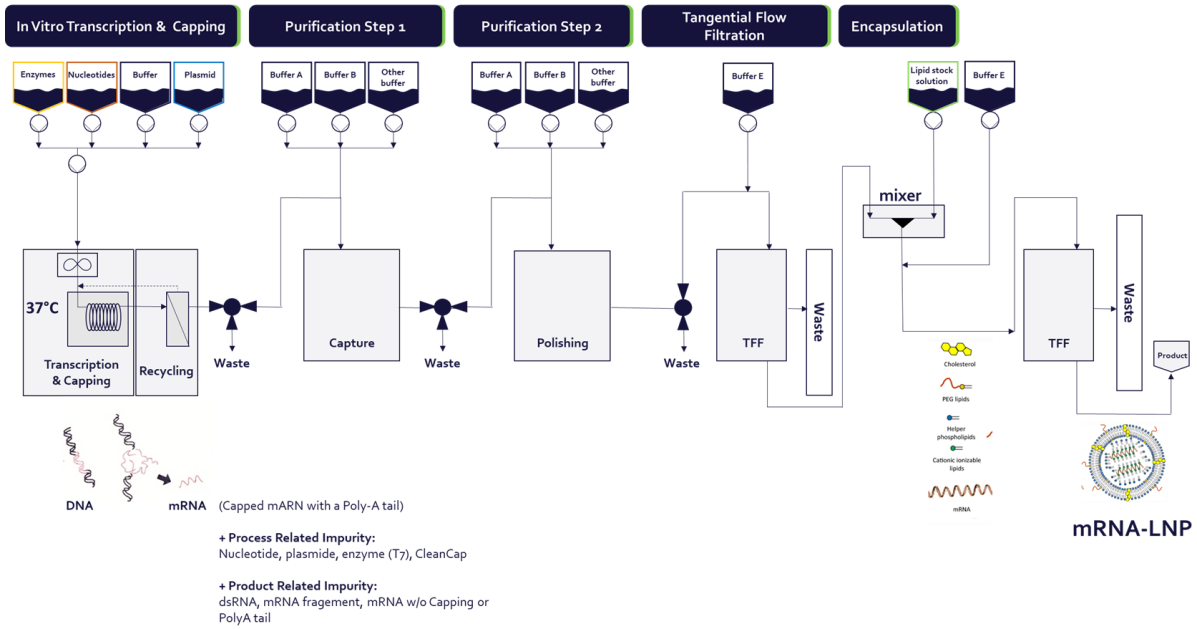
Messenger RNA technology, discovered by the general public during the Covid-19 pandemic, represents a genuine paradigm shift in terms of both therapeutic mechanisms and the development of vaccines and biomedicines. Recent clinical studies confirm its applicability for indications far beyond vaccines for respiratory diseases, notably in treatments for various forms of cancer.

The implementation of mRNA technology in the context of the pandemic was carried out in record time, using manufacturing solutions already available and developed for conventional vaccines, but with numerous drawbacks and not taking full advantage of the benefits of this new modality.

Dillico proposes to revolutionize the way mRNA pharmaceuticals are developed and manufactured with an innovative integrated and digitized solution. All-ScaleFlow™ technology based on a continuous manufacturing approach enables the production of formulated mRNAs, from very small quantities for pre-clinical phases to commercial scale, with the same equipment.

The core of the All-ScaleFlow™ technology solves the substantial drawbacks of the currently implemented batch production mode, and enables to remove the scale-up activity that has hitherto been extremely costly and time-consuming. This is made possible through a continuous flow chemistry approach on a meso-fluidic scale, combined with digitization of the fully automated and modeled process.

This innovation leads to other very significant gains: superior quality of mRNA products (real-time control, confined processes, elimination of hold times), great flexibility in terms of capacity, a reduction in the cost of raw materials through recycling, facilitating the regionalization of production thanks to highly integrated (4 m²) and highly automated equipment, which will enable the reduction of the carbon footprint linked to the distribution chain in refrigerated conditions and the reduction of logistics for plastic consumables.



Anastasiia Halushkina
Research Engineer
Kimialys, France

Kimialys

SEQRET: Innovative analytical tool for efficient cell therapy development and production

Halushkina A.[1], Delplanque A.[1], Nogues C.[1], Gilbert C.[1], Olmos E.[2,3], Schiavi-Tritz J.[2,3], Loubière C.[2,3], Chebil L.[2,3], Bensoussan D.[3,4], Laroye C.[3,4], Morello J.[3,4], Arnaud L.[5], Niberon Y.[5], Bruyant A.[5], Benoit P.[5]

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Introduction: As cell and gene therapies advance towards clinical and commercial stages, the need for effective quality control in bioproductions intensifies. The secretome plays a crucial role in this, offering insights into molecular mechanisms and stem cell bio-functionality. However, current quality control methods, mainly indirect functional tests, are time-consuming, prone to human error, and carry contamination risks. The **SEQRET project** addresses this challenge by developing an 'online' automated quality control system that leverages real-time secretome analysis of mesenchymal stem cells (MSCs) during production. By correlating secretome characteristics with cell bio-functionality, it aims to optimize and fine-tune cell culture conditions in real time. A key objective is to create a versatile quality control module that can integrate seamlessly into various cell production lines, offering significant advantages: **reduced costs** and simplified logistics, **real-time analysis** and the enhanced ability to **study multiple cellular functions simultaneously**.

Technology: We utilized **Surface Plasmon Resonance** (SPR) and SPR imaging (SPRi) technologies for real-time, label-free analysis of multiple biomarkers in the MSC secretome. The **selectivity** (retaining only the biomarkers of interest) is based on the way in which the ligands are immobilized on the surface of the biochip. Hense, to **prevent non-specific interactions** we utilize our patented **surface chemistry K-One®** which significantly enhances the sensitivity and specificity of biosensors in complex mediums like serum and supernatants.

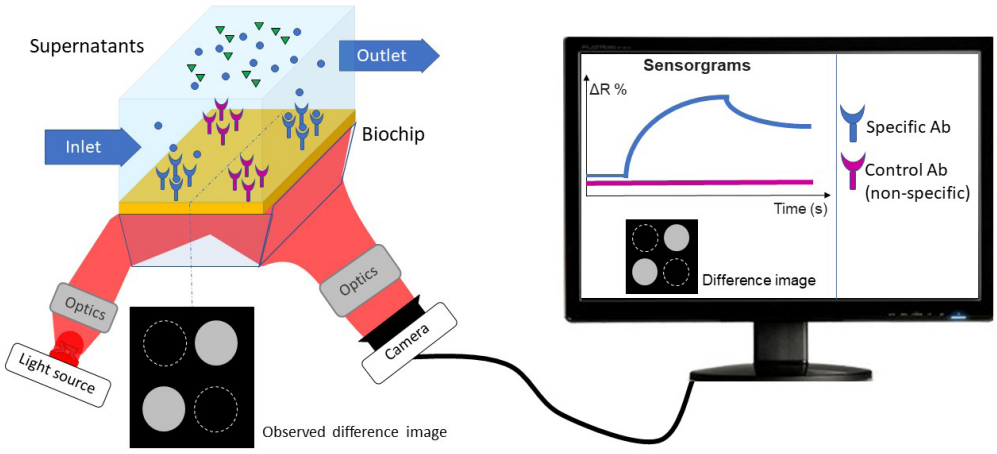


Figure 1: Schematic representation of the multiplexed detection of selected biomarkers via Surface Plasmon Resonance imaging (SPRi)

Results: In our study, we analyzed various supernatants under different culture conditions, comparing the levels of pre-selected biomarkers relevant for this cell culture type. **Our surface chemistry enabled the direct detection of two distinct biomarkers, bypassing the need for revelation antibodies** required in traditional methods like ELISA and ensuring specific detection without cross-reactivity between species.

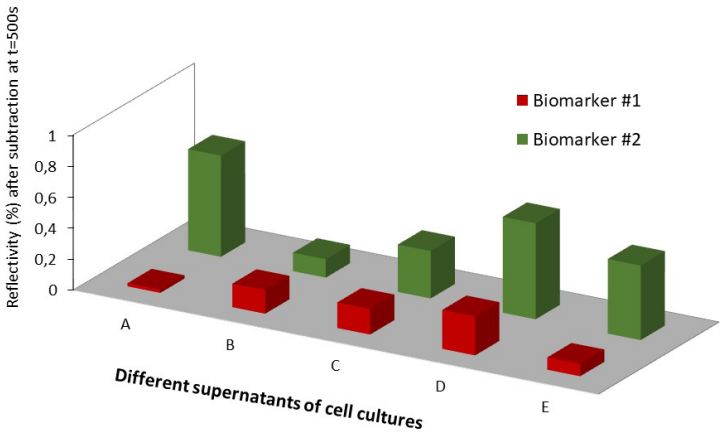


Figure 2: Histogram of detected biomarkers; levels in various supernatants (A-E)

Conclusion: In the frame of SEQRET project we have successfully detected various biomarkers in cell culture supernatants using SPRi, enabling detailed profiling of supernatant compositions under varying conditions. Obtained data will be used for the correlation of supernatant composition to the stem cell bio-functionality allowing further optimization of the culture conditions. **This method represents a significant advancement in terms of cost, time efficiency, and simplicity over traditional quality control methods in bioproduction.**

Sébastien Légaré
Systems Biologist
Deeplife, France

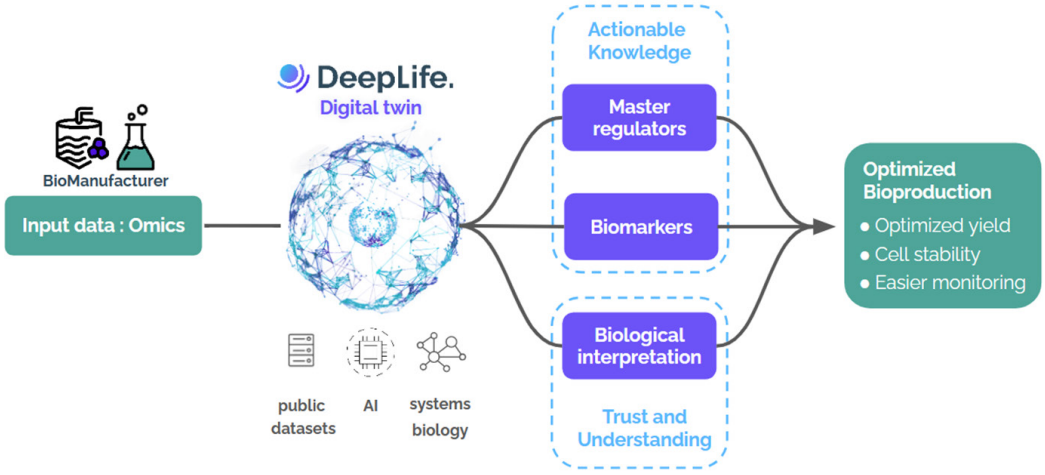
DeepLife's AI-augmented engineering tool for bioproduction

Sébastien Légaré, Thomaz Dias, Elie Hatem, Kevin Carvalho, Jonathan Baptista, Jean Baptiste Morlot

DeepLife SAS 42 Rue de Glatigny 27200 Vernon headquarters / Watt-Biopark, 8 Rue Jean Antoine de Baïf, 75013 Paris, France Lab

Integration of Artificial Intelligence methodology will revolutionize bioproduction processes particularly for biologics like next generation antibodies, vaccines, gene therapy products, and cell-based therapeutics. Enhancing bioproduction efficiency is crucial for minimizing costs, reducing development time, and expediting commercialization.

While traditional cell lines have established advantages in bioproduction aligned with good manufacturing practices (GMP) on a large scale, challenges persist in ensuring consistent quality across large-scale and long term cultures. Indeed, generating high-producing cell lines involves a complex and time-consuming multi-step process with labour-intensive clone identification. **At DeepLife, we develop and deploy digital twins of cells to meet these challenges**. Our AI-augmented bio-engineering tool identifies molecular triggers that determine cell state to guide experimental work. These solutions tackle crucial aspects of bioproduction, including target and biomarker identification, cell engineering, and optimization of cell lines.



Within the framework of the standard CHO-K1 cell line, where clones exhibit diverse production outcomes, our primary objectives include unraveling the biological determinants influencing these variations in biologics production and suggesting interventions for improvement based on this comprehension. To initiate this process, DeepLife leverages bulk RNA-seq data for each clone under various conditions using our proprietary workflow detailed figure 1. This workflow incorporates standard computational biology techniques, such as differential expression testing (DET) and pathway enrichment analyses (PEA). Subsequently, an AI-driven approach was employed to **prioritize key genes distinguishing clones**, and a systems biology strategy, supported by our AI capabilities, was utilized for **causal analysis, pinpointing master regulators as potential intervention targets**.

The outcome is the identification of targets for modulating biologics production, along with early secreted markers that enable tracking of production and cell state throughout the growth phase. **DeepLife's proprietary AI-based platform not only provides a profound understanding of standard cell lines for optimizing bioproduction yield, as demonstrated with CHO-K1 cells, but is also universally applicable to diverse cell lines, including HEK-293 and BHK-21**. The synergy between AI and bioproduction not only accelerates research timelines but also holds the promise of unlocking new frontiers in the biotechnology industry with the Help of DeepLife.

Philippe Thomas
Downstream BioProcess Expert - MSAT
Sanofi Vaccines, France

How modelling can bring even more confidence in viral inactivation step?

Viral inactivation is a critical step for any inactivated virus-based vaccine. In a few words, to inactivate viruses, an inactivation agent (chemical molecule) is introduced in the virus solution. Some specific conditions of pH, temperature, mixing are defined, and we let the reaction occurs at least twice the time needed to obtain a conform inactivation control test. The conformity of the step is verified few weeks after its completion. To secure the success of this step, we want to build a model able to track the decrease of the virus infectious titer during the first hours of reaction. To develop this tool, we need:

- New scale-down model
- New analytical method
- A mathematical model

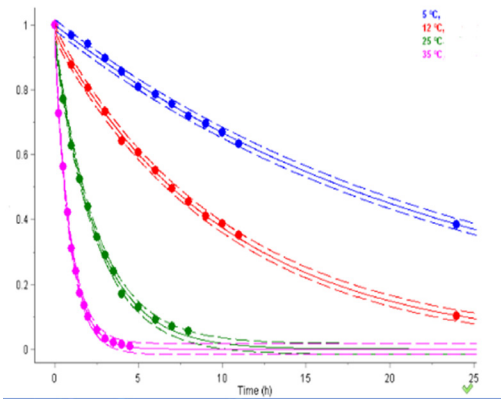
1. New scale-down model

The objective was to change the current SD model (a 1L SCHOTT Bottle) to a 2L stainless steel, with a design closer to the industrial tank used for viral inactivation, a closed processing, and the possibility to add probes for analytics. The inactivation process performed side by side between the two models reach the same results: conform and comparable results, meaning no live viruses detected at mid-period of inactivation total duration. It will be necessary in the future to ensure the robustness of this new model, and to consider the automatization of sampling.

2. New analytical method

The objective was to move from a manual and offline method to an at-line automated method. The historical method used implied the use of hazardous reagents, and various manual steps that were not compatible with our objective. Titration of the inactivation agent by HPLC has been implemented with success: in addition not to use any pre-treatment, a method run lasts 35min and allows the quantification of other species than the inactivation agent only. The method is now qualified and used in manufacturing.

3. A mathematical model



A mathematical has been designed to correlate the degradation of the inactivation agent along the time. After performing the mass balance of the reaction and identifying the chemical reactions, lab data have been generated, with a focus at first on the secondarty reactions (degradation of the inactivation agent in the matric, without viruses). A correlation, based on Arrhenius-like equations, has been developed. The next step will be to perform the same work with viruses, to determine the equation for the primary reaction.

The mixing of these 3 topics will allow to reach the objective to correlate the degradation of the inactivation agent with the decrease of the infectious titer.

This work is a result of a transversal project that implied Bioprocess, analytical and modeling team.

Quentin Bazot
Head of Innovation & Viral vector Development
ABL, an Institut Mérieux Company, France

Accelerate AAV process development and characterization with the mass photometry technology

While adeno-associated virus (AAV) has emerged as a leading vector for gene therapies, there is still an urgent need to improve AAV associated analytics. As a matter of fact, AAV manufacturing processes generate empty capsids, which greatly complicates vector purification and affect product safety and quality. Several analytical techniques have been established for the AAV full/empty ratio, however they still face great limitations such as cost, accuracy, sensitivity, lead time and sample consumption.
Mass photometry is a novel, fast, and easy method to determine these full/empty AAV ratios, as it measures the masses at the single particle level by quantifying light scattering from AAVs in solution (see figure below). Refeyn's mass photometer for AAVs characterization, the SamuxMP, can then easily differentiate between empty, partially filled and full capsids based on mass differences.
In the presentation given during the 8th Bioproduction congress we showed how the mass photometry technology can be used for AAV early full/empty characterization as well as for the optimization of the polishing step. This new technology is used in our Process Development lab for early AAV capsid characterization after production. This has proved to be particularly useful for AAV production screening where any changes in the process (specifically during the transfection step) can greatly affect the quality of the AAV produced.

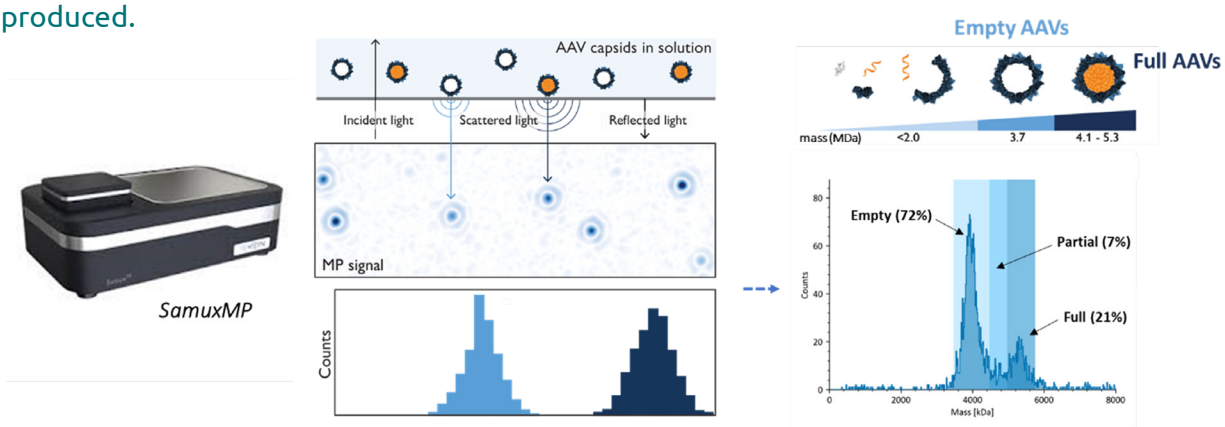


Figure 1: Principle of Mass photometry (Part of the figure was provided by Refeyn)

The mass photometry is also of great interest during downstream process development, particularly during the polishing step where full AAV capsids are enriched. The SamuxMP allows us to quickly assess the full/empty ratio after the polishing step leading to the acceleration of AAV process development.
In summary this new analytical technique is ideal as it does not require sample preparation, works in any buffer, uses only a small amount of sample (1 to 20µl) and is very quick (result in less than 2 minutes per sample). The mass photometry is a game changer in the AAV field and will soon become a gold standard in AAV characterization along with AUC and Cryo-TEM.

ABL, an Institut Mérieux Company – www.abl-biomanufacturing.com

Laure Robert
Global Product Manager
Polyplus, France

Polyplus®
Now Part of Sartorius

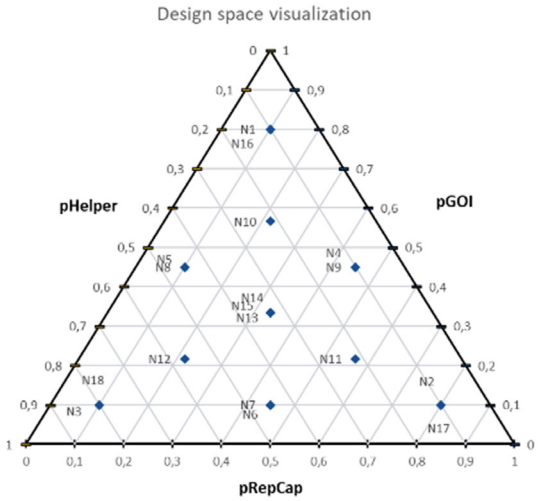
Enhancing AAV productivity through plasmid ratio optimization

To produce rAAVs, the most established method requires a co-transfection of three plasmids:

- Transgene: contains the Gene of Interest (GOI) for therapeutic effect – Flanked by two ITRs to enable expression in the host cell
- pRep/Cap: encodes for proteins needed for viral replication (Rep proteins), capsid structure (VP1, VP2, VP3) and accessory proteins (AAP, MAAP)
- pHelper: encodes for « helper » functions needed for viral replication

Process optimization can be achieved through Design of Experiment (DoE). In the case of introducing new plasmids for transfection, using a Mixture Design approach is recommended to find out what is the optimal plasmid ratio.

In this case study, the pPLUS® AAV-Helper was evaluated by a third-party company. Experiments were done with VPC2.0 cells and Viral Production Medium from ThermoFisher in which rAAV2 were produced with pALD-AAV2 from Aldevron.
In a first experiment, pPLUS® AAV-Helper performance was assessed against pALD-HELP at three different standard plasmid ratios (expressed as mass ratios Transgene:Helper:RepCap): [2:0.5:2] ; [2:1:2] ; [1:1:1]. In this first experiment, similar genomic titers (measured by qPCR on ITRs) were obtained with the two helper plasmids, whichever ratio was used. However, empty to full ratio (measured through the ratio between VG titers and VP titers) were significantly increased when using pPLUS® AAV-Helper.



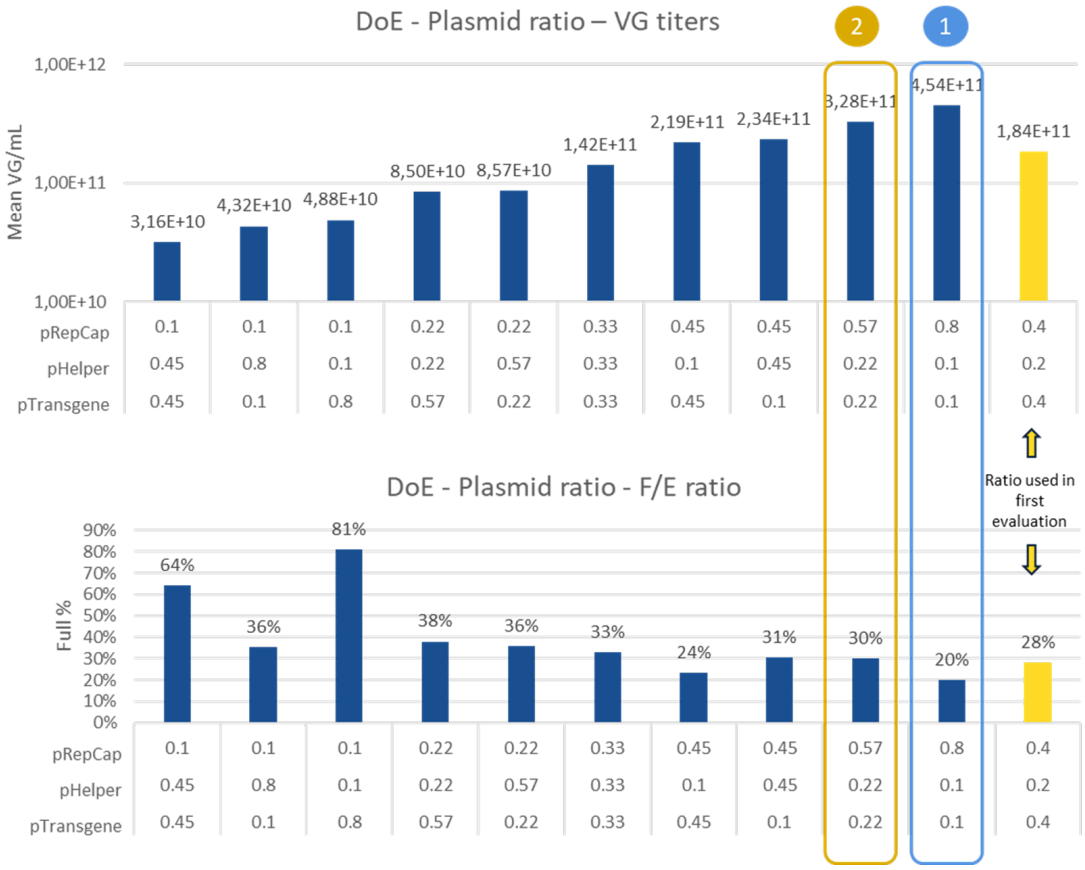
Through a Mixture Design approach, 10 different plasmid ratios were evaluated. Both VG titers and VP titers were measured for each data point.

The contour plot obtained from this DoE highlighted an optimal zone for VG titers corresponding to a ratio 1:1:8, highlighting a need for more RepCap plasmid than transgene and GOI in those testing conditions.

Based on VG and VP titers, the contour plot for empty to full ratio was also generated from MODDE Software.

Interestingly, the best ratio for VG titers does not give the best Empty to Full ratio, and the trends are in the opposite way confirming that there is a tradeoff relationship between VG titers an Empty to Full ratio.

This case study confirmed the need for plasmid ratio optimization when implementing a new plasmid and the need to assess different quality attributes to find the best compromise for an enhanced AAV productivity.



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More robust process and reduced batch failure, thanks to data driven development

Cell Culture Media
Monitoring of cell culture composition & changes & metabolism

Automation
Automated high throughput sample tracking and analysis of bioreactor & cell culture samples

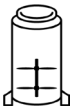
Process Insights
Data analysis tools to correlate cell media & product attributes with process outcome

Intact Drug Substance
Direct analysis of drug substance identity, modifications & variants

Sample Preparation
Simplified sample preparation for in depth product & process monitoring

PQA Monitoring
Site specific multiple attribute characterization of critical quality drug features

Integrated at-line solutions for routine product quality and spent media analysis



Bioreactor samples
Cell culture samples from bioreactors or upstream formats

Sample Preparation
Automated sample tracking & preparation for analysis

Analysis
LC-UV & LC-MS analysis of critical process and product attributes

Data processing
Streamlined data processing and reporting using compliant software

Connected Bioprocess
Connected bioprocessing interfacing bioreactor data in a single software

Accelerated Development
Accelerated cell line and process deveopment at point of need

Streamlined access to results, with automated sample preparation and data transfer

Compact
Robust integrated LC-MS System with with ease-of-operations

Compliance-ready
Ready for use in regulated development and GMP environments

Standardized
Deployable and scalable solutions with reduced training requirements

Workflow driven
Apps to automate sample preparation, data acquisition, processing and reporting

Optimized
Performance for proteins, peptides, released glycans and oligonucleotides

DISASTER RECOVERY/CONTINUITY PLAN

bioKryo

WHY YOUR BIOLOGICAL RESOURCES DESERVE BEING TAKEN INTO ACCOUNT

Air Liquide HEALTHCARE

The Disaster Recovery/Continuity Plan principles are the result of the Hyogo framework for action meeting organised by the UNDP (United Nations Development Program) in 2005, and followed by the Sendaï Conference guidelines in 2015.
They defined 5 to 7 priorities to improve countries resilience and **ability to recover** in case of natural disaster. It has influenced all our countries, agencies, norms and standards. For our bioproduction network, the results of it are significantly integrated into **GMP guidelines.**

DR/CP aim to identify the risk and mitigate it. It concerns IT tools and information recovery, building saving, human safety… BUT DON'T FORGET YOUR BIOLOGICAL RESOURCES.
They represent :

- your IP - your technology, assets and capital (value of your company - cell banks, seeds, standard and reference samples)
- the proof of your results and development programs (clinical patient samples libraries, retaining and in-process samples…)
- your tools and results of your daily work (starting materials, reagents, raw materials and products)
- the resources for your future projects (availability of specimens for translational research…)

"From United Nation to your freezer"
Unbreakable traceability and infaillible temperature stability

At this point, think to the **means and manners** to prevent risks and plan how to recover your activity.

-196°C
-80°C
-20°C
+4°C
+20°C

"Think redundancy"

Double source your power supply system

Double source your energy provider

Set-up redundancy for monitoring

Set-up redundancy of staff on stand by

Set-up reduncancy of records and data

Identify your risks :

*floods, electricity cuts, pandemics, fires, power supply failures, lack of staff or storage unit failures ("**your freezer!**") …*

Mitigate your risks :

Take preventive actions

***Duplicate** your IP and manufacturing products by outsourcing secure storage to a dedicated provider.*

***Set up an action plan** to recover and save your commodities in case of emergency*
= Emergency Saving Plan

BRC: BIOLOGICAL RESOURCE CENTER TO OUTSOURCE YOUR BIOLOGICAL STORAGE

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UN BÂTIMENT DÉDIÉ DE 600 m²

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Upcoming Events

9TH BIOPRODUCTION CONGRESS
25-26 September 2024 - Tours - France

http://www.biopcongress.com

ICGT
22 May 2024, Paris, France
mabdesign
Société Française de Thérapie Cellulaire et Génique SFTCG

https://www.b2match.com/e/innovations-for-cell-and-gene

mabdesign
PARTNERING EVENT
17 May 2024 – Grand Paris

12TH AIS
JUNE 20-21 2024
MONTPELLIER, FRANCE
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I4ID 2024
November 27-28
Lyon, France
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https://www.i4id.org/

Upcoming Watch Series

- **ImmunoWatch: Exosomes and Extracellular vesicles** (Mid-S1)
- **ImmunoWatch: Immuno-Oncology** (End of S1)
- **BioprocessWatch: USP and DSP for Viral vectors** (Mid-S2)

mabdesign
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