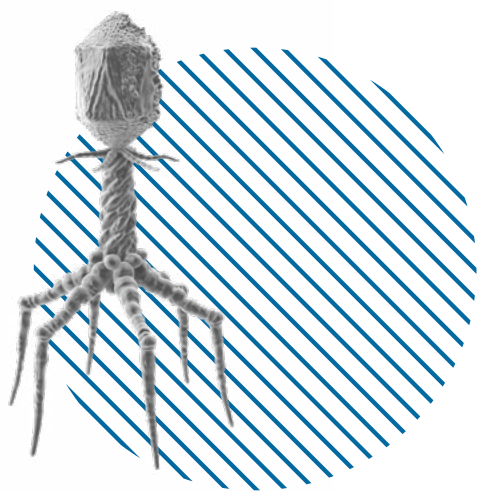


Abstract book





MSS2026, the next-gen bioManufacturing & delivery Science Symposium, is a forward-looking, high-impact powerhouse dedicated to cutting-edge technologies in the biopharmaceutical field.

The symposium covers the entire workflow from upstream to downstream processing in a hybrid format that supports both onsite and online participation. The program focuses on production solutions across the full journey – from development to manufacturing – together with advanced analytics for gene therapies, vaccines, and complex biological products such as plasma, proteins, and enzymes.

Driven by these objectives, the event encompasses innovative production technologies, advanced delivery systems, and the analytical methods essential to support them. These presentation topics will deepen our understanding of how delivery systems behave, both during manufacturing and within complex biological environments like human fluids and cells.

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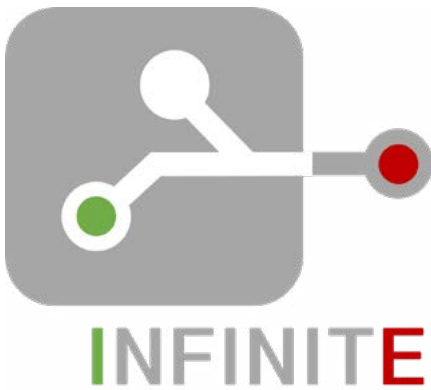


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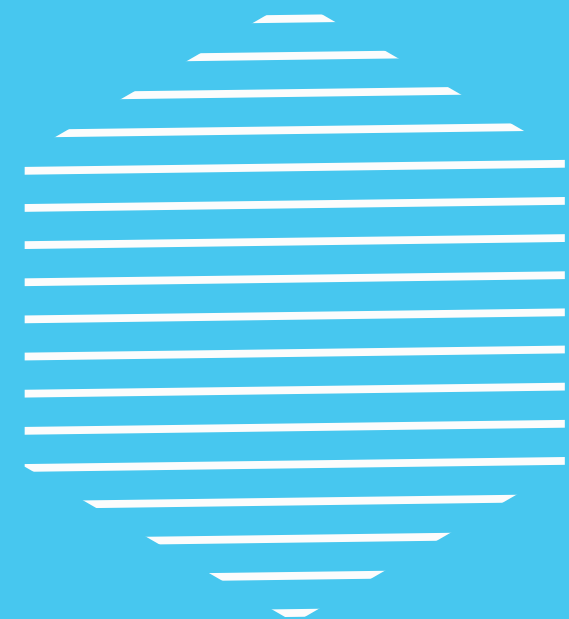
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Advancing Biomanufacturing Education: Adapting Workforce Development for the Next Generation of Biologics

Gary Gilleskie

Biomanufacturing Training and Education Center

The rapid diversification of the biopharmaceutical landscape—driven by new modalities like viral vectors, mRNA, and antibody-drug conjugates—presents a significant challenge for workforce education. Even for established leaders in this field, like the Golden LEAF Biomanufacturing Training and Education Center (BTEC), adapting to these new demands is critical to our mission of developing a skilled biopharma workforce.

This presentation will detail how BTEC has adapted its educational programs to meet the evolving needs of the industry. We will discuss the strategic changes made to our curriculum, facility, and equipment to address the unique manufacturing, analytical, and regulatory challenges presented by these new modalities. A key focus will be on how our programs integrate fundamental scientific and engineering principles with hands-on application, enabling new hires to “hit the ground running” with a deep understanding of the “why” behind the “how.”

We will share the specific challenges we have faced in developing and implementing these new programs, including resource constraints and the need for rapid curriculum development. The presentation will also cover our assessment of student response and provide a forward-looking perspective on BTEC’s future strategies to remain at the forefront of biomanufacturing education. This includes a discussion on how we plan to integrate new techniques and technologies to ensure the workforce is prepared for what’s next in the field.

Beyond the sequence: how intended use shapes the regulatory pathway

Florence Salmon

Roche

The regulatory landscape for nucleic acids is uniquely complex because the regulations that apply to them are determined by how the nucleic acid is manufactured and its specific role in the final pharmaceutical product, rather than just its chemical structure. Global regulatory bodies categorise nucleic acids into distinct legal frameworks according to their use, and different requirements with regards to their quality ensue. Synthetic oligonucleotides are considered a specific class of chemicals by EMA and FDA and there are specific guidelines for oligonucleotide therapeutics. But immune stimulatory oligonucleotides (such as CpG motifs activating Toll-like receptors), DNA and RNA vaccines, virally delivered oligonucleotides, mRNA, and RNA used specifically for gene editing are excluded from these guidelines and have to follow other standards. This presentation will breakdown some of these complexities and discuss requirements with some specific examples.

Digital twins of disease evolution to understand disease and its treatment ahead of time

Janez Štrancar

Infinite Biotech; Jozef Stefan Institute

One of the main problems with chronic diseases is their slow evolution that need months or even years to evolve imposing serious resource challenges to understand this disease, their related determinants and develop the required therapeutics. A digital twin can provide a powerful platform to explore the impact of the therapeutics on the disease evolution ahead of time and particularly ahead of lengthy and expensive preclinical and clinical testing. I will present a subclass – InFinite™ in-vitro-learned digital twin, the way how it is built from response monitoring of exposed advanced cellular platforms and the types of result it delivers (from early Mode-of-Action of both the disease triggers and therapeutics as disease modulators to dose- and time-dependence of selected events far beyond the time of observations that can help to understand the off-target effects of therapeutics and to optimize dosing and timing of the desired on-target therapeutic effect).

Gene Editing and Delivery Breakthroughs: Overcoming therapeutic barriers for unmet needs

Thomas J. Cradick

Gene Editing Frontiers

The therapeutic promise of genome editing has rapidly transitioned from an exciting possibility to clinical reality. Driven by the landmark approval of Casgevy and a growing number of clinical trials, the field has established viable regulatory frameworks and demonstrated tangible clinical success. Possible therapeutic targets now span the spectrum from ultra-rare conditions to widespread global diseases. However, translating these therapies in vivo requires overcoming critical hurdles in activity, delivery precision, off-target specificity, and the scalability of CMC (Chemistry, Manufacturing, and Controls) processes.

This talk highlights how expanding the gene editing toolbox with novel DNA- and RNA-editing nucleases and advanced gene writing systems allow targeting a vastly broader range of diseases. Similarly, pivotal advancements across the genome editing landscape are expanding therapeutic applications by enabling tissue-specific targeting and accelerating the capabilities of both viral and non-viral delivery platforms. Finally, we will cover evolving strategies for navigating modern regulatory frameworks and the roadmap to address previously intractable diseases and fulfill critical, unmet clinical needs.

Don't trust the AI - audit it: Why regulated science is uniquely ready for AI

Anže Videnič

BioSistemika

AI can now read from and act on laboratory systems, and it is tempting to treat its output the way we treat an instrument reading: as fact. It isn't. A language model is built to produce answers that look right, not answers that are right, and for scientists, trained to trust what appears rigorous, that is a subtle and serious hazard. Fluent, confident, and wrong is the most dangerous output a lab can receive. But "don't trust it" has never been how science works. Science trusts nothing at face value, it demands provenance, review, and reproducibility. Regulated biopharma has spent decades building and perfecting exactly this infrastructure: attributable records, audit trails, validation and human sign-off. While other industries are trying to invent trust mechanisms for AI from scratch, regulated science already has them. Drawing on 16 years of experience building software for regulated laboratories and pharmaceutical companies, and recent work integrating regulated lab systems to AI agents in production, we will show how to build software for two users at once: the AI agent that acts, and the human who remains accountable. That means AI operating within existing quality and compliance processes, never as an exception to them. Therefore, every action is traceable, reviewable, and reversible, with the reasoning and uncertainty made visible so that human oversight is meaningful rather than a rubber stamp. Through a case study of a lab data platform built for a global pharma company, we will demonstrate the design decisions that made AI integration possible, and the decisions that would have made it nearly impossible to introduce later. You will leave with a different perspective understanding why the compliance discipline you may have seen as friction is, in the age of AI, your single biggest advantage. The session will conclude with practical principles for evaluating and designing software that allows AI to be useful in regulated laboratories without requiring blind trust.

AI-Driven Digital Twins for Optimizing Chromatographic Purification and Analysis of mRNA Lipid Nanoparticles

Rob Rodick

Ayagence

mRNA-loaded lipid nanoparticles (LNPs) offer an exceptional opportunity for the delivery of novel therapeutics. However, their production and purification pose distinctive process and characterization challenges. These challenges constrain yield, increase cost, and lengthen time to market while complicating the control of off-target toxicity, ultimately limiting the clinical and commercial viability of otherwise promising therapeutics. In this work, we present a platform that mirrors chromatographic process development for mRNA LNPs using AI-driven digital twins. We develop in-silico representations of the manufacturing and analytical steps in the mRNA-LNP workflow, each continuously updated with real-time measurements of critical process parameters (CPPs). An AI framework uses this state to recommend adjustments to in-process controls that steer the process toward target critical quality attributes (CQAs), specifically encapsulation efficiency, purity, and yield. The platform is deployed at research scale in partnership with human lab operators, forming a closed loop between analyst, instrument, and model. We demonstrate the platform on the mRNA loading of LNPs and the subsequent chromatographic purification and analysis of the loaded particles. The result is a human-machine collaboration that increases yield, reduces impurities, and shortens development timelines for mRNA LNPs, opening a path to accelerating the delivery, regulatory approval, and scale-up of novel mRNA-LNP therapeutics.

How can commercially promising scientific results be safeguarded?

Hans-Wilhelm Meyers

Dompatent

Commercial exploitation of new technologies, products, processes, and the like is difficult for inventions that were not developed within commercially oriented institutions. What must inventors absolutely consider prior to planned commercial exploitation, particularly when investors need to be brought on board?

From the Bench to Investor-Ready Intellectual Property: Why Strong Science Is Not Enough

Olga A. Partington

Sterne, Kessler, Goldstein & Fox P.L.L.C.

Turning research into a valuable invention is hard-won work. Turning that invention into IP that holds up when investors and partners come looking is a different challenge, and it often turns on early choices: what's disclosed, when, and how the invention is protected.

This is the second of two linked talks on an invention's IP. Hans-Wilhelm Meyers covers the front end, creating and protecting an invention; this talk covers the back end, whether that IP holds up when a company raises capital or closes a deal.

When an investor or acquirer gets serious, a patent portfolio faces scrutiny it rarely saw earlier. Do the claims cover the product or just the discovery? Can a competitor design around them? Above all, would the patents survive a validity challenge? These are judgments about how the IP was built, usually tested for the first time in diligence, when the answers are hard to change.

Informed by experience in the forums where patents are challenged, and illustrated with public life-sciences examples, the session shows why strong science doesn't automatically become investable IP, and what researchers and technology transfer offices can do early to make sure it holds up later.

Key takeaways:

- How investors and acquirers scrutinize IP in diligence
- The difference between obtaining a patent and building IP that survives scrutiny
- Why validity, claim scope, and freedom to operate decide a portfolio's value
- Common IP problems that surface late, in fundraising or a deal
- Practical steps to take early, while problems can still be mitigated

Fundamental growth milestones and positioning for a high value strategic exit

[Evan Yellin, Raffaele Bonavitacola, Cory Kenny](#)

EC M&A

Building a biotechnology company for a successful financing or strategic exit requires more than strong science. This presentation explores the key milestones that drive value creation, from technology validation and IP development to clinical progress, commercial positioning, and organizational readiness. We will discuss how founders can align their growth strategy with investor and acquirer priorities, create strategic relevance, and maximize valuation by building an exit-ready business long before a transaction process begins.

Drawing on extensive transaction experience across the biotechnology sector, EC M&A has advised founders and entrepreneurs on numerous strategic financings and exits, including transactions that have achieved some of the highest valuation multiples in the industry.

Oligonucleotide Aptamers; Past and Future

Chizuko Koseki

TAGCyx Biotechnologies

Aptamer is short single-stranded DNA or RNA molecules that bind specific targets like antibodies—evolved from the 1990 invention of SELEX (Systematic Evolution of Ligands by Exponential Enrichment).

The aptamer molecules exhibit unique physicochemical properties such as;

- high conformational adaptability
- specific molecular recognition driven by non-covalent forces
- thermal reversibility
- Manufactured simply by chemical synthesis without any biological process involved

Due to those unique and advantageous properties, we can think of various applications in Life Science areas.

Although it has quite long history, we recognize there are not many successful launches of any products, except only a couple of successes in the therapeutic area so far.

Pros & Cons of the technology will be analyzed and its future potential and progress will be presented.

Take home messages: its various potential applications in the future, such as targeted therapy (DDS), Diagnostics, Apheresis, Affinity purification in addition to therapeutic development will be indicated.

Rational design of lipid nanoparticles using impingement jets mixing (IJM) technology

Nadia Elghobashi-Meinhardt

Knauer

Lipid nanoparticle (LNP) formation relies on the rapid mixing of an ethanolic lipid solution with an aqueous acidic buffer containing nucleic acid cargo. Because particle formation occurs on millisecond timescales, small changes in mixing conditions strongly influence critical quality attributes such as particle size, morphology, and encapsulation efficiency. During process development, these particle attributes are often coupled, making optimization resource-intensive.

In this talk, we present a rational design strategy for LNP production that relies on impingement jets mixers (IJMs). IJMs are passive, high-throughput chambers that enable the head-on collision of the liquid streams at high pressures, leading to self-assembly of the particles. This mixing technology has become the field's gold standard for the robust, reproducible manufacturing of LNPs, particularly as therapeutics for drug delivery applications.

Here, we discuss how individual formulation parameters can be controlled and tuned to engineer particle size and morphology, independent of other particle attributes. This approach thereby circumvents traditional empirical trial-and-error LNP process development and provides a basis for efficient automation of LNP manufacturing.

Early stage preclinical development of new biological pan-antiviral

[Uroš Andjelković](#)

SavantiVir

SavAntiVir develop pan-antiviral for immediate protection against respiratory enveloped viruses Influenza A/B/avian strains and SARS-CoV-2. With proprietary IP protected technology SavAntiVir could fill a critical prophylactic niche reducing morbidity, transmission, and pandemic risk, especially among high-risk populations (elderly, persons with underlying respiratory or cardiac disease, diabetes, hospitalized patients, immunocompromised persons (e.g., HIV-infected, transplant recipients, chemotherapy patients), and front-line workers. The clear gap left by vaccine and antivirals, those critical first 90-270 days from outbreak of new strain till vaccines become available, SavAntiVir cover with intranasal/inhaling biologic capable to outperform mutations, designed to provide rapid, local, broad-spectrum prophylaxis. Small protein, virus entry inhibitor, specifically binds to glycosylated spike proteins of enveloped viruses and blocks spike-receptor interaction. Presented will be technology with in vitro preclinical data supporting pan-antiviral activity and option for scalable green manufacture.

Gene transfer with polymeric nanoparticles for ocular disorders

[Niren Shah](#)

Cove Therapeutics

The abstract is not available.

GlycanAge - a tool for personalized health tracking

Dora Lalić

GlycanAge

Advances in molecular biomarkers are expanding the possibilities for personalized health monitoring and the assessment of biological aging, a field increasingly shaped by novel technologies and a growing set of longevity biomarkers. IgG N-glycosylation is a well-established biomarker of immune system function and chronic inflammation, capturing the balance between pro- and anti-inflammatory immune activity and reflecting biological processes associated with aging, health, and age-related disease.

GlycanAge is a blood-based test that assesses biological aging through analysis of the IgG glycome, offering a direct molecular readout of inflammaging. Scientific evidence links IgG glycosylation to chronic disease risk, biological aging, and mortality, while its responsiveness to lifestyle changes, diet, exercise, and pharmacological intervention underscores its value for tracking individual response over time. Such tools are being integrated into preventive and longevity-focused clinical practice, complementing traditional health assessments and supporting a more personalized, longitudinal approach to health management.

ADAscape™: High-Resolution Epitope Profiling for Anti-Drug and Anti-Vector Antibodies

Oskar Smrzka, Kristyna Yatsyk, Christoph Doppler, Melanie Kogler, Katrin Fischer, Gerhard Stadlmayr, Patrice Douillard, and Christof Paparella

Ablevia biotech

Anti-drug and anti-vector antibodies are increasingly recognized as critical determinants of the performance of modern biotherapeutics and delivery systems, including viral vectors and nanocarriers for gene and RNA therapies. Beyond ADA incidence, FDA and EMA expectations increasingly call for deeper immunogenicity characterization: developers need to understand which epitopes are targeted, whether antibody binding is neutralizing or clinically relevant, and how immune profiles differ between patients, products, and development stages.

Ablevia's epitope profiling platform, ADAscape™, addresses this need through high-resolution, target-specific deep epitope profiling. The platform uses customizable and ready-to-use bacterial display libraries presenting overlapping target peptides, converting antibody binding into quantitative epitope maps. From limited clinical or preclinical sample volumes, ADAscape™ generates patient-specific epitope fingerprints and immunodominant-region maps to support patient stratification, drug monitoring, companion diagnostic development, and safety- or function-related development decisions.

Compared with conventional peptide microarrays, ELISA/domain mapping, phage display and structural approaches, Ablevia's serological epitope-profiling workflow is designed to combine rapid turnaround, high sensitivity, robust signal-to-noise performance, cost-efficient library customization, and scalable cohort analysis. Applications of ADAscape™ include immunogenicity risk assessment, ADA root-cause analysis, biosimilar comparability, AAV and broader anti-vector immunity profiling, longitudinal clinical monitoring, companion diagnostic development, and epitope-guided therapeutic ADA management.

ADAscape™ is offered through flexible commercial models for drug developers, clinicians, CROs, and CDMOs, including customized library development and supply, platform licensing, project-based profiling, strategic technology integration, and controlled platform access. The resulting data packages support FDA/EMA-aligned immunogenicity characterization and companion diagnostic development from preclinical and IND-enabling studies through clinical development.

Advancing Formulation Development with ZetaView® Evolution NTA: High-Resolution Analysis of Lipid Nanoparticles and Viral Vectors

Christina Klasen

Particle Metrix

The development of lipid nanoparticles (LNPs) and viral vectors requires analytical methods capable of providing reliable and reproducible characterization throughout formulation development and process optimization. Accurate determination of particle size, concentration, sample heterogeneity and stability is essential for understanding critical quality attributes and supporting informed development decisions.

This presentation highlights the capabilities of the ZetaView® Evolution nanoparticle tracking analysis (NTA) platform for comprehensive single-particle characterization of complex nanoparticle formulations. In a single analytical workflow, the system provides particle size distribution, concentration and zeta potential measurements, enabling efficient assessment of multiple critical quality attributes from the same sample. High-resolution fluorescence NTA further expands these capabilities by enabling the selective detection of fluorescently labelled particles, for example through nucleic acid dyes, lipid membrane stains or fluorescent ligands and antibodies. This enables targeted characterization of specific particle populations and complements label-free analysis with additional compositional information. By combining multiple orthogonal parameters on a single measurement platform, ZetaView® Evolution delivers comprehensive characterization while minimizing sample consumption, analysis time and experimental complexity.

Scaling the future: the evolution of ATMP facility design from Boutique labs to Flexible Manufacturing Platforms

Matej Štupar

Over the past decade, the design and build of Advanced Therapy Medicinal Product (ATMP) facilities has undergone a fundamental transformation. Using examples from completed GMP facility projects, the presentation illustrates how engineering solutions have evolved alongside the industry's changing needs and the trends that are shaping its future.

It began with small, academic spin-outs operating from boutique facilities with limited budgets, where the challenge was to translate established pharmaceutical principles into practical, cost-effective solutions for organizations with little manufacturing experience.

The COVID-19 pandemic marked a period of unprecedented growth, with large-scale investment driving an urgent need for rapid facility delivery. During this phase, speed often had to be balanced against quality, while a shortage of experienced process architects, engineers, and end users created additional complexity.

Today, the sector is entering a more mature phase. Investment decisions are increasingly driven by robust business cases, and major pharmaceutical companies are becoming key players. Automation of manual processes, compliance with Annex 1 requirements, and navigating an uncertain global funding landscape are defining today's facility design challenges. At the same time, demand for GMP facilities supporting clinical development remains strong as large pharmaceutical companies continue to invest in the search for the next generation of blockbuster therapies.

Looking ahead, artificial intelligence is expected to reshape both manufacturing and drug development. AI-enabled robotics and contained manufacturing platforms have the potential to reduce background cleanroom grades, improve energy efficiency, and create more flexible manufacturing facilities, while AI-driven therapeutic discovery will continue to expand the pipeline of innovative ATMPs. Together, these developments are redefining what the next generation of facilities will look like.

NeoVac: Building the Next Generation of RNA Delivery

Denis Bešić

NeoVac

NeoVac is a clinical-stage biotechnology company developing a next-generation lipid nanoparticle (LNP) platform for precision RNA delivery. Co-founded by Prof. Dan Peer (Tel Aviv University) and Prof. Sir Adrian Hill (University of Oxford, co-inventor of the AstraZeneca COVID-19 vaccine), NeoVac's proprietary and IP protected LNP platform technology addresses the core limitations of first-generation LNPs — safety, immunogenicity, and manufacturing complexity. The lipid architecture is built on a modular library of molecular structures including tunable, cleavable linkers. Superior safety of a NeoVac mRNA LNP vaccine candidate was demonstrated in a Phase 1/2 clinical trial, showing numerically fewer and less severe adverse events compared to published data from marketed mRNA vaccines. NeoVac LNPs are as well promising for therapeutic application of mRNA, fostered by tunable immunogenicity, compliance with repetitive, high dose i.v. injections and, capacity for organ- and cell-specific targeting through both intrinsic tropism and ligand-functionalized nanoparticles. This presentation introduces NeoVac's technology, its underlying lipid science, and the clinical and preclinical data supporting its broad applicability.

Purity and Composition: How Reference Standard Quality Impacts dsRNA Quantitation in mRNA Drug Products

Jamison Grailer

Promega

Accurate quantitation of double-stranded RNA (dsRNA) is an essential quality control requirement for mRNA therapeutic manufacturing. As a byproduct of in vitro transcription (IVT), dsRNA is a potent innate immune activator that can drive inflammation, translational inhibition, and cell death, making its quantitation important for both product safety and potency. However, accurate and precise dsRNA quantitation remains elusive with existing assay technologies and poorly characterized reference standards. Herein, we first describe the Lumit® dsRNA Detection Assay, a novel bioluminescent assay that replaces dsRNA-binding antibodies with a NanoBiT® split luciferase-based dsRNA sensors. Two dsRNA-binding domains are each fused to a complementary NanoBiT® subunit. dsRNA-driven co-localization reconstitutes functional luciferase, generating a signal directly proportional to dsRNA concentration. The assay detects dsRNA fragments ≥ 30 base pairs in a sequence-independent manner, with a limit of quantitation of 1 pg/ml, no cross-reactivity with ssRNA or DNA, and a 75-minute add-mix-read workflow. Second, we demonstrate that reference standard impurity and composition can be critical source of quantitation error. Commercially available dsRNA standards may be uncharacterized, unpure, and unreliable. We show how standard size and purity can impact accurate quantitation. We further demonstrate that base composition matters: standards containing modified nucleotides (e.g., pseudouridine) are required for accurate quantitation, regardless of the assay technology used. Taken together, these findings establish that high-purity, compositionally matched reference standards are a prerequisite for accurate dsRNA quality testing in mRNA drug development.

The RNA Revolution: from Vaccines to Therapeutic Genome Editing

Dan Peer

Laboratory of Precision Nanomedicine, Tel Aviv University

Objectives: Modulating gene expression that can lead to cell death in the case of tumors or to change of expression of desired proteins for protein replacement therapy, or for manipulation leukocytes function or for vaccines or editing of cells for knockout or knockin of genes - are major challenges and unmet medical needs.

Methods: We have developed several strategies to target unique cell surface receptors, as well as a very large library of ionizable lipids with two special features: highly immunogenic or less immunogenic (that can be used for repeated doses). In addition, we developed novel mRNA sequences with more potent immunogenicity that can be utilized against bacterial infection.

Results: In this talk, I will share several examples ranging the first bacterial mRNA vaccine and will also share some data on gene editing for cancer therapeutics.

Conclusions: Cell specific delivery of RNA payloads is feasible and represent the next generation milestone in personalized medicine.

Purification Strategies of Circular RNA

Linpeng Wu

RiboX

Circular RNAs (circRNAs) hold significant therapeutic value in protein replacement therapy, regenerative medicine and autoimmune diseases etc.. The circRNAs are covalently closed single-stranded RNAs without a 5' cap structure and a 3' poly(A) tail. Compared with linear mRNA, circRNA shows higher stability and resistance to nuclease degradation, therefore enable more sustained protein expression. In the In-Vivo CAR therapy application, T/NK cells engineered by circRNAs can lead to rapid and transient CAR expression. Both linear mRNA and circular RNA contain specific impurities that need to be removed via downstream purification. In addition to process related impurities such as residual NTPs, residual plasmid and residual protein, the purification of circular RNA specific product related impurities (including linearized precursors, nicked RNA and introns) is a major challenge for the manufacturing scaled up and is also a key concern of regulatory authorities. Monolithic columns exhibit advantages in circRNA purification. RiboX is the first company to lead circular RNA therapeutics to clinical stage with well-established circRNA manufacturing technology platform. We will share our purification strategies for different types of circular RNAs based on monolithic columns manufactured by BIA.

mRNA gene electrotransfer of IL-12 in melanoma and colorectal carcinoma: From in vitro characterization to in vivo antitumor efficacy

Urban Bezeljak, Ajda Medved, Urša Lampreht Tratar, Martina Durcik, Nastja Štemberger, Tjaša Marušič, Matjaž Peterka, Maja Čemažar

COBIK; Sferogen

Interleukin-12 (IL-12) is a potent immunostimulatory cytokine that counteracts tumor-induced immunosuppression, making it a compelling candidate for cancer immunotherapy. Systemic IL-12 administration is associated with significant toxicity, necessitating local delivery strategies such as gene electrotransfer (GET). Compared to established plasmid DNA GET, mRNA-based GET eliminates the need for nuclear entry, reduces the risk of insertional mutagenesis, and enhances translational efficiency.

We developed a fully in-house mRNA production and purification pipeline. Therapeutic IL-12 mRNA was produced by in vitro transcription using a custom vector incorporating the HBA1 5'UTR, IL-12 fusion gene, HBB 3'UTR, and a stabilized 119-nt poly(A) tail. Two cap variants were prepared: Cap0 and Cap1. mRNA was purified by sequential oligo-dT affinity chromatography and SDVB-based dsRNA removal, with quality confirmed by anti-dsRNA J2 dot-blot and agarose gel electrophoresis. Furthermore, poly(A) tail length and distribution were evaluated with IP-RP-HPLC, capping efficiency was determined using a two-step enzymatic degradation reaction followed by HPLC quantification, while RNA integrity was evaluated by capillary gel electrophoresis (CGE).

In vitro mRNA GET evaluation in murine B16F10 melanoma and CT26 colorectal carcinoma cell lines revealed that Cap1-modified mRNA achieved significantly higher IL-12 protein expression than Cap0 in B16F10 cells, peaking at 24 hours post-GET, consistent with improved cytosolic stability. In vivo studies showed that Cap1 mRNA combined with electroporation produced complete responses in the CT26 model and prolonged survival in the B16F10 model. Tumor re-challenge in complete responders confirmed development of protective immunological memory, underscoring the therapeutic promise of optimized mRNA GET for cancer immunotherapy.

Continuous in-situ Bioprocessing for Scalable mRNA Production: Advancing Manufacturing for Vaccines and Genetic Medicines

Mark Stoops

Biomanufacturing Training and Education Center

Moving away from standard IVT batch production of mRNA is the next step in mRNA biomanufacturing. Here we will showcase our in situ fed batch mRNA production and purification method and discuss how an extended IVT production can save reagents such as enzyme and plasmid, as well as some of the limitations we have encountered. Additionally, we will discuss the development of linear plasmid purification leading up to the mRNA production.

Messenger RNA (mRNA) is increasingly used in vaccines and to treat genetic diseases. However, current manufacturing methods like batch IVT and standard purification are too expensive and inefficient to support the frequent, specialized dosing required for chronic conditions. In this work, we develop an intensified in-situ IVT–capture platform that continuously produces and purifies polyadenylated mRNA in small, well-mixed reactors directly coupled to oligo-dT chromatography, with recycling of unreacted components. This process achieves >90% overall recovery, >99% purity, while efficiently reusing the ARCA cap analog, template plasmid, enzyme, and nucleotides. mRNA from the continuous process retained full translational competence in CHO-K1 and HT1080 cells. The recycled plasmid recovered from the loop remained intact and was utilized in a subsequent IVT reaction. These results show that small-volume, in-situ IVT–capture can decouple productivity from reactor scale, intensify reagent and resin utilization, and deliver clinically relevant mRNA quality attributes, providing a flexible platform for manufacturing mRNA therapeutics for genetic diseases.

Enzymatically Synthesized DNA Templates Enable Scalable mRNA manufacture and Robust PolyA Tail Integrity

Stella Kounadi

4basebio

The growing demand for RNA-based therapeutics and vaccines has placed significant strain on traditional plasmid DNA (pDNA) manufacturing platforms. Fermentation-based production of pDNA is limited by global capacity, long lead times, and challenges associated with handling unstable or repetitive sequences. One critical issue is the instability of long polyA tails (>100 nucleotides), which are essential for mRNA stability and translational efficiency but prone to recombination during bacterial propagation, causing heterogeneity of polyA tails and increasing the risk of batch failure.

Here a fully synthetic, enzymatically produced linear DNA template, opDNA®, has been developed for in vitro transcription (IVT) to address these challenges. This template features a 3' open end, allowing direct use in IVT without additional enzymatic linearization steps. Proprietary enzymes amplify DNA with high fidelity (3.75×10^{-9}) and can handle complex elements such as long polyA tails (>120 bases) encoded directly into the template. Unlike pDNA that relies on large bioreactors, the enzymatic process facilitates production to be scaled according to project needs, minimizing waste and cost. This is especially valuable in personalized medicine and mRNA-based therapies, where relatively small amounts of DNA may be required. Importantly, opDNA® production is fully compatible with GMP-grade manufacturing, supporting clinical and commercial translation of mRNA therapeutics.

A comprehensive analytical framework was established to evaluate the integrity of polyA sequences in opDNA® templates. A capillary electrophoresis method (Fragment Analyzer) enabled sizing of polyA fragments with $\pm 5\%$ accuracy, confirming that constructs with polyA tails of 80, 105, and 120 adenosines exhibited single, homogeneous size distributions. To investigate strand-specific composition, ion-pair reverse-phase liquid chromatography (IP-RP-LC) was employed, resolving sense (polyA) and antisense (polyT) strands as single, distinct peaks with no evidence of heterogeneity or secondary populations. Finally, liquid chromatography-mass spectrometry (LC-MS)

detected a dominant species of the expected mass for 80 nucleotides (± 1 nt) in both polyA and T strands, further validating the robustness of the enzymatic synthesis method.

The performance of opDNA® in IVT reactions was evaluated compared to pDNA across constructs ranging from 1.5 to 12 kb. opDNA® templates produced significantly higher mRNA yields than linearised plasmid, with faster reaction kinetics and lower DNA input requirements due to the absence of bacterial backbone sequences in the opDNA® template. Capping efficiency, RNA integrity, and dsRNA levels were equivalent across both template types.

Functional assessment was performed using 4basebio's Hermes® nanoparticle platform, which combines a 5th cationic component and traditional lipids to drive payload condensation and formulation stability. Encapsulated mRNA was delivered to HEK293T cells and administered intramuscularly in mice. In both systems, opDNA® demonstrated protein expression levels comparable to pDNA when assessed using eGFP and luciferase reporter genes.

In summary, opDNA® provides a flexible alternative to pDNA, addressing critical manufacturing constraints while enabling stable inclusion of long polyA tails. The comprehensive analytics platform ensures polyA integrity and, IVT yields consistently surpass that of plasmids without impacting efficacy.

iCAP: Integrated Continuous and Automated Platform for Plasmid Production

Juergen Mairhofer, Markus C. Berg, Florian Weiss, Ramón Korn, Benedikt Haslinger, Maximilian Krippel, Mark Duerkop, Felix Schelberger, Wolfgang Sommeregger

enGenes Biotech

Plasmid DNA (pDNA) underpins viral vectors, mRNA vaccines, and DNA therapeutics, yet production is limited by costly, low-yield batch processes. iCAP transforms this with a continuous, automated microbial platform integrating bioprocess intensification and digital intelligence. Using genetically stabilized *E. coli* and a growth-decoupled replication system, iCAP enables stable, long-term plasmid production in bioreactor cascades. Continuous alkaline lysis, chromatographic purification, and real-time digital-twin-based control ensure high-throughput, low-variability recovery. Modular and scalable, iCAP reduces costs and environmental impact while supporting decentralized vaccine manufacturing and integrated therapeutic supply, setting a new benchmark for sustainable, next-generation plasmid DNA biomanufacturing.

The use of Mustang Q membrane chromatography as the capture step in a 2-step plasmid DNA purification strategy

Aydin Kavaraa, Kurt Boenninga, Mark Schofielda

Cytiva

Plasmid DNA (pDNA) is a fundamental starting material for the production of viral vectors, mRNA therapies and recombinant proteins. The recent success in these therapeutic spaces has led to a significant increase in the need of high quality pDNA. As of 2022 the global plasmid market was 1.3 billion and is expected to grow at a compound annual growth rate (CAGR) of 17 percent through 2030.

Here we present the use of Mustang® Q anion exchange membrane chromatography capsule for the capture of pDNA. This purification step is part of an intensified 2 step purification process, consisting of an initial capture step, followed by a polishing step. In this process, the capture step must effectively remove impurities such RNA and genomic DNA while achieving high pDNA recovery. Here we will showcase a comprehensive process development approach aiming to achieve high recovery and high purity of pDNA directly from the crude lysate. The results presented demonstrate the impact of factors such as buffer excipients and pause time during elution, have on pDNA recovery. The selected operating conditions are then used to show the reproducibility and rapid cycling capabilities of Mustang Q. The data presented outline the benefits of the fast flow rates used with Mustang Q, while also achieving the low shear conditions needed to purify large molecules such as plasmid DNA.

Applied chromatography technologies and analytical applications for preparations of ultra-pure mini-circle plasmid DNAs

Kevin Ainger, Eva Zaletel, Gregor Cerar, Mateja Krapež, Tjaša Goršek, Gordana Uzelac, Rosana Hudej, Brigita Valentinčič, Nastja Štemberger, Petra Virant, Anna Frolova, Nadja Jurinčič, Tjaša Prevc, Mojca Potočnik, Matevž Korenč

GaletaBio

The mini-circle technology is the state-of-the-art for DNA active pharmaceutical ingredients (APIs). The removal of almost all of the sequences necessary for bacterial functions, like the origin of replication and antibiotic resistance, reduces the DNA to be introduced into the patient to the bare minimum necessary to encode the gene of therapeutic interest. While the in vivo function of the minicircle DNA is the hallmark of a useful API, the testing of a new API is complicated by the need to discern possible side effects of the API from the side effects of the API purification and production process contaminants, in addition to stability and formulation issues. The goal is therefore to attain a purity of all materials and the characterization of the nucleic acids that will significantly exceed current industry standards, thereby mitigating risks in data interpretation and permitting a definitive assessment of the underlying scientific hypotheses of the therapy. The demonstration of the validity of these process methods will be highlighted. In particular, the application of this approach to the manufacturing of DNA for In Vitro Transcription DNA templates for the production of mRNA represents a logical and practical extension for this approach.

Simultaneous development of chromatographic monoliths and purification methods to overcome bottlenecks in downstream processing of large nucleic acids

Urh Černigoj, Rok Miklavčič, Tadej Sever, Polona Skrt, Tina Vodopivec Seravalli, Sara Žagar, Sara Rotar, Aleš Štrancar, Shady Hamed, Zoltan Kis, Rok Sekirnik

Sartorius BIA Separations

The biopharmaceutical industry is rapidly expanding the use of large nucleic acid therapeutics, particularly diverse RNA modalities such as messenger RNA (mRNA), for vaccines, gene therapies, and genome editing. Plasmid DNA (pDNA) serves as the template for mRNA transcription and is therefore a critical raw material in mRNA production. This growing use of nucleic acids places increasing demands on downstream processing (DSP), which must deliver products with high purity, high recovery, and robust scalability, while minimizing process complexity. Many current efforts focus on intensifying DSP through more efficient chromatographic separations. These goals can be achieved in several ways, including: (1) introducing innovative chromatographic stationary phases and ligands that improve selectivity, speed, or binding capacity; (2) combining multiple sequential process steps; and (3) developing and optimizing chromatographic methods. Our work addresses all these aspects, and we will present two independent case studies. The first case focuses on a preparative single step purification of pDNA directly from clarified bacterial lysate, combined with desalting. This integration of purification and desalting is enabled by an innovative ligand coupled to a Convective Interaction Media (CIM)[®] chromatographic monolith, CIM Swiper, allowing elution at neutral pH using a low conductivity buffer. The second case study concerns mRNA purification by CIM Oligo dT18 affinity chromatography. By elucidating the mechanism of mRNA binding to the immobilized ligand, we optimized the chromatographic process to achieve binding capacities of up to 8 mg of mRNA per mL of chromatographic monolith.

Evolution of Vaccine Technologies: From Recombinant Vaccines to pDNA and mRNA Platforms

Mukesh Chauhan

BioNet Asia

Vaccine development has undergone remarkable technological advancements over the past several decades, evolving from traditional live-attenuated and inactivated vaccines to highly sophisticated recombinant and nucleic acid-based platforms. Recombinant vaccines revolutionized vaccine development by enabling the production of specific antigens through genetic engineering, improving safety, scalability, and manufacturing consistency. Their success has laid the foundation for the emergence of next-generation vaccine technologies.

This presentation explores the scientific and technological pathway from recombinant protein vaccines to plasmid DNA (pDNA) and messenger RNA (mRNA) vaccines. It highlights the key innovations in molecular biology, genetic engineering, and bioprocess development that have enabled this transition. The presentation will summarize the mechanisms of action, manufacturing processes, advantages, and challenges associated with each platform, including antigen expression, production timelines, and regulatory considerations.

Special emphasis will be placed on the rapid development and global deployment of mRNA vaccines during the COVID-19 pandemic, which demonstrated the potential of nucleic acid technologies to accelerate vaccine development and respond effectively to emerging infectious diseases. Furthermore, the discussion will address current advancements in pDNA and mRNA technologies, including improvements in delivery systems, thermostability, manufacturing scalability, and applications beyond infectious diseases, such as cancer immunotherapy and personalized medicine.

By examining the evolution from recombinant vaccines to pDNA and mRNA platforms, this presentation provides insight into the changing landscape of vaccine innovation and the opportunities these technologies present for addressing future public health challenges.

A Comprehensive Manufacturing and Characterization Approach to Passive or Active Targeted LNP-Based Biopharmaceuticals

Tristan Kovačič

Sartorius BIA Separations

Lipid nanoparticle (LNP)-based therapeutics, from mRNA vaccines to CAR-T and CRISPR gene editing, depend on nano-delivery systems capable of targeted, controlled delivery, yet most formulations still struggle to clear clinical trials because their structure and heterogeneity is poorly understood during scale-up. Active targeting compounds challenge this by adding surface-conjugated ligands whose density and conjugation efficiency are rarely monitored quantitatively, while passive, endogenously targeted formulations depend instead on the biomolecular corona that forms in blood plasma, a phenomenon the field still lacks robust analytical tools to characterize. Convective interaction media (CIM)[®] monoliths, with their low backpressure, laminar flow, and micron-scale pores, are uniquely suited to chromatography of these large, complex bioparticles but remain underexploited. We developed methods that resolve LNP subpopulations by surface properties, enabling separations of tLNP subpopulations with high recovery, scalable to both kinetic monitoring of conjugation reactions and final-product polishing. A complementary hydrophobic interaction method quantifies residual free ligand and combined with reversed-phase separation forms a 2D workflow capable of fully characterizing complex tLNP formulations, the PATfix LNP Switcher. LNP-protein corona complexes require better methods for improving recovery for downstream study of how LNP surface properties shape corona composition and, in turn, biodistribution. Together, these monolith-based platforms address a critical analytical gap in ligand conjugation quality control and corona characterization, offering both quantitative insight and a scalable purification route for active targeted and endogenously targeted LNP biopharmaceuticals.

Monolith liquid chromatography for recovery and purification of intact lipid nanoparticles shows full in vivo compatibility

Sven Even Borgos, Thanh-Huong Bui, Sjoerd Hak, Geir Klinkenberg, Alicja Molska, Jérémie Parot, Frida Petterson, Francesca Roda, Ane Marit Wåggbø, Andreas Åslund

SINTEF Industry

The unprecedented safety, efficacy and development speed of the mRNA-based Covid-19 vaccines demonstrated the potential of mRNA encapsulated into lipid nanoparticles (mRNA-LNPs) as medicines. Currently, a wide range of mRNA-LNP-based vaccines and therapeutics are in preclinical development and clinical testing, with indications ranging from infections, to autoimmune diseases and cancer. But mRNA-LNPs are highly complex, nanosized particulate drugs with unique analytical and preparative requirements. Formulation of the mRNA in the LNPs is done in a microfluidics-based co-precipitation process of the nucleic acids with lipids. Post-formulation processing, including purification, is done today by dialysis in lab scale and by tangential flow filtration (TFF). But dialysis is not applicable at preparative scale, and TFF has important limitations and shortcomings, including poor scalability, high loss of the drug product at late process stages, shear stress impacting colloidal stability, and limited transferability of methods between projects. The recent publication of monolithic liquid chromatography (mLC) as a method to analyse intact LNPs based on their surface chemistry is groundbreaking and has important implications also for preparative use. SINTEF has worked on the use of preparative mLC as an attractive alternative to TFF. We show here the successful use of preparative mLC for purification of mRNA-LNPs, verified by extensive physicochemical analytics, in vitro cell assays and finally in vivo mRNA expression in animals and safety analysis. Firefly luciferase mRNA expression and safety was not significantly different between different purification methods, indicating mLC as a highly attractive method for improving the clinical translation of mRNA-LNPs.

Advanced quality control strategies for mRNA nanoparticles

Heinrich Haas

NeoVac

The success of messenger RNA (mRNA) lipid nanoparticles (LNPs) used in the COVID-19 vaccines has demonstrated the significance of pharmaceutical products utilizing nanoparticle-based drug delivery systems in global healthcare. Nanoparticle formulations comprising mRNA are applicable not only as vaccines but also for a scope of therapeutic purposes. Despite of several initiatives to align on standard panels for quality assessment of such mRNA products, discussions for identifying best and appropriate control strategies are still ongoing. For assessment of the safety, efficacy, and quality of these complex, multicomponent systems, it is important to consider not only the properties of the individual components, but also their colloidal organization. There is a need for standardized methods to fulfill requirements for application in regular quality control providing information on these properties in pharmaceutical products. In this presentation, biophysical approaches to get better insight into such chemical-physical properties with relevance for quality of the mRNA LNPs are presented.

Enabling Scalable Chromatography from Analytical to Preparative Purification for LNPs

John McHale

Arcturus

Lipid nanoparticles (LNPs) are the leading delivery platform for nucleic acid therapeutics and vaccines; however, purification remains a critical bottleneck for scalable manufacturing. This poster describes an integrated analytical and preparative chromatography strategy designed to enable robust, process-relevant purification of intact LNPs while maintaining critical quality attributes.

Analytical chromatography was applied to evaluate method repeatability, impurity resolution, and real-time purity assessment across multiple LNP formulations. Formulations containing either ionizable or permanently charged lipids were studied, with un-encapsulated mRNA and empty LNPs identified as key process-related impurities. The optimized analytical method enabled quantitative measurement of free mRNA and visualization of non-full-length un-encapsulated RNA species, providing actionable feedback for downstream process development. Selection of operating conditions, informed by the Hofmeister series, enabled effective separation of free mRNA from encapsulated LNPs at preparative scale. The resulting purification process demonstrated robust performance and produced intermediate drug product with equivalent or improved particle size, purity, and potency relative to prior approaches.

Chromatographic LNP Purification for Enhanced Purity and Activity in CRISPR, CAR-T, and Vaccine Manufacturing

Mojca Tajnik Sbaizero

Sartorius BIA Separations

Lipid nanoparticles (LNPs) are essential carriers for nucleic acid delivery in CRISPR gene editing, CAR-T cell engineering, and mRNA vaccines, but their purification and characterization remain challenging, particularly with respect to maintaining structural integrity, achieving high recovery and functionality, and attaining clinical-grade purity. We developed a scalable hydrophobic interaction chromatography platform using CIM (Convective Interaction Media)® monolithic columns to address these challenges across LNP-based modalities. In vitro-transcribed RNA payloads relevant for CRISPR, CAR T, and vaccine candidates were first purified on CIM monoliths, then formulated into LNPs and further purified using CIM OH monolithic formats, ranging from high-throughput CIM 96-well plates and CIMmic® discs to lab-scale spin columns and CIMmultus® columns for larger scale. Process conditions were optimized to ensure high LNP recovery and final product stability. Encapsulation efficiency and recovery were quantified with the PATfix® LNP Switcher, particle size and distribution by nanoparticle tracking analysis, and functional activity in a cell-based assay. The CIM-based process consistently delivered high recoveries, narrow and uniform particle size distributions, high encapsulation efficiency, and efficient removal of free nucleic acids and ethanol, without inducing aggregation or structural damage. Performance at high-throughput and lab scale translated well to CIMmultus columns, demonstrating robust scalability from screening to larger-scale manufacturing. CIM monolith-based hydrophobic interaction chromatography thus provides a robust, scalable, and platform solution for LNP purification, enabling higher product purity, more predictable performance, smoother translation from discovery to clinical and commercial production, and selective separation of distinct LNP particle populations.

tLNP as a Novel Gene Therapy Vector to Deliver DNA

Jacek Lubelski

NanoCell

Following the widespread clinical success of lipid nanoparticles (LNPs) as vaccines, non viral gene transfer has gained significant momentum as a promising therapeutic modality. LNPs have demonstrated the ability to deliver both RNA and DNA in a range of preclinical models, and their advantages position them as strong competitors to conventional viral vector systems in various applications.

First, LNPs are relatively straightforward to manufacture, relying on a formulation-based process rather than complex biological production. This enables rapid, scalable manufacturing with clear benefits in terms of cost, flexibility, and speed. In addition, LNPs are highly versatile platforms capable of encapsulating a broad spectrum of genetic cargo, ranging from transient RNA to integrating DNA. This versatility makes them well-suited for emerging genetic engineering technologies and positions them as adaptable vehicles for diverse gene therapy applications.

In this talk, I will review emerging non viral gene delivery systems and highlight their key applications. I will then focus specifically on targeted lipid nanoparticle (tLNP) platforms for permanent gene transfer in T cells aimed at generating CAR T therapies.

Our innovative cell targeted lipid nanoparticle (tLNP) platform is designed to deliver both DNA and RNA directly to T cells, enabling in situ CAR T cell generation. I will present data demonstrating successful CAR T generation in an NSG mouse model engrafted with a human B cell leukemia cell line. A single administration of tLNPs carrying DNA and RNA resulted in durable CAR T cell formation, effective tumor control, and prolonged survival. In addition, we will discuss biodistribution data of the vector and its individual components in preclinical models.

End to End Lipid Nanoparticle Workflow; From Formulation to Large Scale Manufacturing

Dehghani Aslan (Mehdi), Yuji Takeda, Fujun Wang, Xin Gu, Parsa Molaei, Behnam Partopour, Ryan Norton, Laura Maugeri, Sabrina Apel, Shayan Shafiee, Haoyi Hou, Yuan Liu

Sartorius

Advances in lipid nanoparticle (LNP) technology have broadened applications beyond mRNA vaccines, creating demand for rapid, low volume formulation screening. In this study, we aimed to develop an end-to-end LNP manufacturing workflow, from a capex-free and single use microfluidic pipette mixer to a high throughput screening (HTS) instrument and scaled up GMP compliant system. We evaluated four different microfluidic mixer designs as well manual pipetting with a fixed flow rate ratio (FRR) of 3, delivering low volume, monodisperse LNPs with high RNA encapsulation and compatibility with automation. Computational fluid dynamics (CFD) study indicated that spiral channels generate more homogeneous concentration fields via secondary flows; however, low-shear spiral channel produces large particles due to slower mixing. We evaluated and compared the mixer designs using orthogonal analytics, such as Field Flow Fractionation, Single Particle Raman Analysis, PATfix Switcher, Cylindrical Illumination Confocal Spectroscopy. Relative to manual mixing, the high-shear spiral mixer consistently produces LNPs with diameters more than 20 nm smaller, larger particle concentration, higher RNA encapsulation, lower shape factors, less impurities and improved homogeneity. The resulting LNPs achieve robust vitro transfection, advanced cell models and animal models confirming functional delivery. We then integrated our pipette mixers in a liquid handler for automation which resulted in uniform size distribution of LNPs for 48 samples with standard deviation less than 5 nm. Lastly, we designed and developed a large scale and GMP compliant system and showed scalability in LNP formulation.

A Long-Term Perspective on AAV Gene Therapy

Robert Kotin

Massachusetts Institute of Technology

Adeno-associated virus (AAV) has emerged as the leading platform for in vivo gene therapy, yet many of its most therapeutically relevant properties were not engineered — they were discovered through basic research. This presentation reflects on four decades of work aimed at understanding AAV biology and translating those insights into clinical tools. Early studies identified AAVS1, a locus on human chromosome 19 where AAV integrates in a site-specific manner, unique among animal DNA viruses. Biochemical characterization of the Rep non-structural proteins revealed the molecular machinery underlying this behavior: sequence-specific DNA binding, endonuclease and ligase activities, helicase function, and interactions with host factors including the protein kinase PKA. These studies established the mechanistic basis of AAV replication and integration and continue to inform vector engineering. Parallel work on capsid biology led to the characterization of AAV serotypes 4 and 5, demonstrating that vector genomes could be transencapsidated into divergent capsid serotypes, expanding the therapeutic repertoire of the platform. To make AAV accessible at clinical scale, a baculovirus/Sf9 insect cell production system was developed that enabled robust, scalable manufacturing — a platform underlying three regulatory-approved gene therapies for hemophilia A, hemophilia B, and familial hyperlipoproteinemia. More recently, paleovirological analysis of endogenous parvoviral elements in vertebrate genomes has illuminated the deep evolutionary history of AAV and its hosts, offering a rational foundation for next-generation vector design and the identification of new genomic safe harbor sites. This body of work illustrates how sustained investment in fundamental virology can yield durable contributions to human medicine.

Characterization and release testing of AAV-based products for clinical use – where are we?

Jaap Twisk

UniQure

Testing for characterization and release of AAV-based products has evolved over the years: using examples from various AAV5-based programs, testing of product quality and safety will be discussed, as well as the extended characterization performed to better understand these products and to help refine the analytical panel.

Regarding safety, the 3-pillar approach is used for viral safety: the testing of starting materials used in manufacturing, defining the viral clearance capacity of the downstream process, as well as lot-to-lot monitoring at appropriate sampling points in the process to address viral (and non-viral) contamination.

Product quality attributes (safety, general physico-chemical quality, identity, content/strength, potency, and purity) are monitored routinely using methods that are largely platform. Exceptions include product-specific methods: identity (vector genome identity) and potency. Potency assurance from one product lot to the next, or in stability, may be defined by the potency matrix: genome copy content, infectivity, and potency (transgene expression, functional activity).

Extended characterization is performed for each product, investigating the characteristics that define the AAV capsid protein content, the vector genome content, and the AAV particle population characteristics, as well as the overall impurity profile.

Examples of analytical methods that are key for release testing and characterization will be high-lighted. Opportunities to leverage between programs will be discussed, used to streamline product development and refine the testing performed, from one AAV-based product to the next.

Impact of Genome Fragmentation and Empty Capsids on rAAV Functional Potency in Liver Cells

David Dobnik, Mojca Janc, Alja Štern, Katja Kološa, Maja Štokelj, Rok Žigon, Maja Leskovec, Tina Zavodnik, Ana Dolinar Česarek

National Institute of Biology

Gene therapy manufacturing aims to produce pure, safe, and effective products, yet the presence of incomplete viral genomes and empty capsids remains a critical quality concern. Our study evaluated how these impurities affect functional potency using rAAV2 vectors containing GFP as a reporter gene. We analyzed 13 fractions from anion exchange chromatography (AEX) purification, spanning empty, full, and tail portions of the elution gradient. Each fraction was characterized using digital PCR assays to quantify complete genomes versus genome fragments, and mass photometry to measure full, partial, and empty capsid concentrations. Viral titers ranged from $4\text{E}+07$ to $2\text{E}+12$ viral genomes per milliliter (vg/mL), with complete genome titers between $1\text{E}+07$ and $1\text{E}+12$ vg/mL. The highest proportion of complete genomes in one of the fractions was only 46% of total detected fragments. When normalized to equal numbers of complete genomes and tested in HepG2 liver cells, fractions from the "full" AEX peak produced varying GFP expression levels, while "empty" fractions showed minimal fluorescence. Flow cytometry analysis revealed a direct correlation between reduced fluorescence intensity and higher numbers of empty capsids and fragmented genomes. These findings demonstrate that both genome integrity and capsid content significantly impact therapeutic efficacy, emphasizing the necessity for comprehensive quality control methods beyond standard genome titer measurements to ensure optimal gene therapy product development and patient outcomes.

Universal AAV Standard: Advancing Standardization in AAV Genome Quantification and Quality Assessment

Andrzej Noyszewski, Alex Deiulio, James Brown

VerumGen Labs

Adeno-associated virus (AAV) has become a leading platform for gene therapy; however, analytical standardization remains a challenge. Differences in primer/probe sets, analytical targets, reference materials, and laboratory workflows can lead to variability in reported AAV vector genome titers and assessments of genome integrity. The diversity of AAV constructs further limits the utility of product-specific reference materials, creating a need for broadly applicable standards that support harmonization across laboratories and vector platforms. To address this need, we developed the Universal AAV Standard (UAS), an engineered multi-target DNA reference material designed to support harmonization of AAV genome quantification and genomic integrity assessment. UAS incorporates analytically relevant target regions commonly used throughout the gene therapy field, providing a common framework for assay development, method comparison, and inter-laboratory studies. By enabling evaluation of multiple analytical targets within a single reference material, UAS facilitates more meaningful comparisons of vector genome titers and genome integrity measurements across studies, laboratories, and analytical platforms. This presentation will describe the design and development of the Universal AAV Standard and present data demonstrating its application for vector genome titer determination and genomic integrity assessment. Particular emphasis will be placed on assay benchmarking, method comparison, and inter-laboratory evaluation, highlighting the impact of analytical target selection on reported results. The Universal AAV Standard represents a practical step toward greater harmonization of AAV analytics and may support improved consistency, reproducibility, and comparability of AAV measurements across research, process development, manufacturing, and quality control environments.

Interferon-inducing viral vector immunotherapy reprograms tumor immunity and eliminates persistent HPV infection

Thomas Muster

BlueSky Immunotherapies

Tumor immune suppression remains a major barrier to effective cancer immunotherapy and therapeutic vaccination. Here we describe a dual-functional viral vector platform, delNS, designed to simultaneously induce innate interferon signaling and deliver tumor antigens to promote antigen-specific immunity. In preclinical studies, delNS vaccination triggered robust type I, type II and type III interferon responses, promoted CD4+ and CD8+ T-cell infiltration without expansion of regulatory T cells, and induced antigen-specific immune responses detectable by ELISpot assays. In a Phase I clinical study in women with persistent human papillomavirus type 16 (HPV16) infection and cervical intraepithelial neoplasia, treatment with a delNS vector expressing HPV16 E6/E7 was well tolerated and associated with clearance of persistent HPV16 infection in the majority of treated participants and regression of cervical lesions in evaluable subjects. Analysis of tumor biopsies from patients with HPV-positive oropharyngeal squamous cell carcinoma treated with the vector demonstrated marked infiltration of T cells and macrophages and induction of PD-L1 expression within the tumor microenvironment. Together, these findings suggest that interferon-inducing viral vectors can reprogram tumor immune environments while promoting antigen-specific immunity and support further development of the delNS platform for treatment of HPV-associated malignancies.

Ex tempore Oncolytic Virus Manufacturing: A Feasibility Assessment

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The clinical translation of oncolytic viruses (OVs) is constrained by regulatory and manufacturing paradigms largely inherited from gene therapy and conventional biologics. While essential for large-scale production, these frameworks may limit flexibility and accessibility in innovative therapeutic settings. As an alternative—supported by prior clinical experience with experimental self-administration¹—we propose ex tempore OV manufacturing directly at the point of care.

To assess feasibility, we established a comprehensive analytical framework to ensure reproducibility, batch consistency, and defined quality attributes of freshly prepared oncolytic virus candidates. Viral potency, purity, and genomic integrity were evaluated across multiple batches. Infectious titre was determined by CCID₅₀ assay; particle concentration and size distribution by NTA; host cell DNA and proteins by qPCR and ELISA, respectively; genomic stability by next-generation sequencing.

Mumps virus (MuV) preparations demonstrated consistent infectivity (CCID₅₀/mL), particle concentration (particles/mL), and a median particle size of 208 nm. Vesicular stomatitis virus (VSV) preparations showed higher infectivity (CCID₅₀/mL) and particle concentration (particles/mL), while smaller median particle size (140 nm). VSV contained lower levels of host cell-derived impurities (24 µg/mL HCP; 25 ng/mL HCDNA) than MuV (51 µg/mL HCP; 450 ng/mL HCDNA). Genomic stability was confirmed for both viruses. Short-term storage at +4 °C without stabilizers caused ~30% loss of infectivity. Benzonase treatment followed by diafiltration significantly reduced impurities without compromising infectivity. Overall, these data define critical quality attributes for ex tempore OV preparations and support their consideration as a distinct medicinal product format.

Curative Gene Therapy for Hypophosphatasia and Thrombotic Thrombocytopenic Purpura

Wolfgang Schönfeld

A-SpecTar

A-SpecTar GmbH, located at Korneuburg near Vienna, Austria, is a preclinical stage company with a unique delivery platform based on VLPs (see presentation Vera Schoft et al.). To strengthen its gene therapy business A-SpecTar licenced in two developmental candidates for gene therapy of rare diseases, hypophosphatasia (HPP) and thrombotic thrombocytopenic purpura (TTP). These two developmental candidates would cure the respective disease by a single injection.

HPP is characterized by a gene mutation in the tissue-nonspecific alkaline phosphatase (TNAP); the lack of functional TNAP leads to an accumulation of substrates such as inorganic pyrophosphate (PPi), which inhibits mineralization leaving the organism without ability to form bone and teeth; severe forms have a fatal disease course if not treated by replacement enzyme therapy, requiring frequent costly injections. Milder forms of hypophosphatasia show loss of teeth, deformed extremities, lower mineralisation and pain.

Our gene therapy approach is based on AAV8 vector delivering the transgene to the cells, however restricting the expression mainly to the liver while avoiding expression in other tissues which may lead otherwise to ectopic calcification. In relevant preclinical models (knock out mice, wt mice) we demonstrated expression of TNAP comparable to normal levels and higher than repeated enzyme replacement. The safety profile confirmed the liver specific expression in vitro and in vivo. A-SpecTar is now entering preclinical development stage.

Our second project is aiming for gene therapy of TTP, a rare disease with a severe, repeated episodes of thrombotic events together with bleeding due to exhaustion of platelets counts. The disease is based on a mutated ADAMTS13 enzyme, a metalloprotease necessary for cleavage of the von-Willebrand-factor. The disease is treated currently by repeated plasma transfusion and/or enzyme replacement therapy. Our transgene construct for TTP cure delivered by AAV8 vector shows sustained expression of the ADAMTS13 enzyme in vivo after single injection curing the clinical symptoms of TTP in relevant mouse models. The potency of gene therapy is comparable to sustained enzyme replacement therapy. Thus, a safe, single injection can cure the disease and avoid sustained life long treatment.

Based on these two projects A-SpecTar is further developing its VLP platform for application in gene therapy overcoming current limitations such as immunogenicity of the vector, high manufacturing costs and limited payload size.

From viral complexity to clinical manufacturing: a platform approach for cancer immunotherapies

Binod Prasad

Abalos Therapeutics

Virus-based cancer immunotherapies are emerging as a promising class of advanced therapy medicinal products. However, scalable manufacturing remains a major challenge due to stringent safety, regulatory, and process requirements. Enveloped live-replicating viruses require highly specialized chemistry, manufacturing, and control (CMC) approaches to ensure product safety, efficacy, scalability, and regulatory compliance. The presentation discusses the development of scalable manufacturing platforms for arenavirus-based cancer immunotherapies using the lymphocytic choriomeningitis virus (LCMV)-based candidate ABX-001 as a case study. Key regulatory considerations for virus-based immunotherapies are outlined alongside critical manufacturing parameters, including infectious titer, particle integrity, host-cell DNA (hcDNA) clearance, and process-related impurities.

The presentation discusses how platform-based manufacturing concepts analogous to those used in monoclonal antibody and viral vector production may enable scalable, multi-product manufacturing of next-generation arenavirus therapeutics. A major focus is placed on downstream process design and the impact of hcDNA removal strategies on product recovery, safety profile, and manufacturing economics. A comparative evaluation of clarification technologies and chromatographic purification approaches demonstrated that conventional process designs led to substantial co-concentration of residual hcDNA and significant losses in infectious virus recovery. By implementing optimized nuclease digestion and redesigned two-step chromatographic purification workflows, infectious virus recovery increased from ~20% to >60%, while maintaining hcDNA levels below regulatory thresholds. In addition, the relationship between process performance and manufacturing cost per dose was assessed, demonstrating how enhancements in upstream titers and downstream recoveries transform early-phase manufacturing from economically non-viable to commercially feasible.

Overall, these findings demonstrate that strategic CMC development and platform-oriented process design are critical for the safe, effective, and economically sustainable manufacturing of next-generation virus-based cancer immunotherapies.

Affinity and mixed-mode convective adsorbents for the purification and enrichment of vectors for cell and gene therapies

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The convergence of molecular biology and medicine has made viral vectors indispensable tools for treating genetic disease, cancer, and neurological disorders. Yet the manufacturing infrastructure needed to deliver these therapies to patients at scale remains profoundly inadequate. Downstream purification, in particular, is a field-wide bottleneck: existing packed-bed chromatographic platforms were designed for proteins, not for particles an order of magnitude larger. This talk presents a fundamentally different approach, hinged on convective affinity and mixed-mode membrane adsorbents built on hyperbranched polymer architectures, that aligns the physics of mass transport with the biology of viral vectors. Across adenovirus, lentivirus, and adeno-associated virus, these platforms achieve excellent dynamic binding capacities at low residence time, together with high recoveries (> 85%) and robust host cell protein clearance (>300-fold) at residence times as little as 2 seconds. The broader implication is a manufacturing paradigm in which purification is no longer the limiting step in bringing gene therapies to patients.

Evaluation of PrimaS and PrimaT Monolithic Chromatography Columns for Purification of Therapeutic Bacteriophages Targeting ESKAPE Pathogens

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Antibiotic-resistant infections pose a major global health threat, with urgent need for new therapeutics against the World Health Organization (WHO) priority bacterial pathogens. Bacteriophages offer a promising targeted approach, particularly against multidrug-resistant ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.). However, scalable GMP-compliant manufacturing remains challenging.

Current phage production typically involves batch or fed-batch infection of host bacteria using stirred-tank bioreactors, followed by harvest and multi-step purification: depth filtration for clarification, ultrafiltration/diafiltration for phage concentration and buffer exchange, and polishing to remove host cell proteins, DNA, and for Gram-negative hosts removal of endotoxins.

This study aimed to assess the purification performance of two multimodal monolithic chromatography columns (CIMmultus PrimaS and PrimaT from Sartorius BIA Separations) as a polishing step for therapeutic phages.

Five distinct phages targeting Pseudomonas aeruginosa, Staphylococcus aureus, and Acinetobacter baumannii were evaluated. Phage lysates after the UF/DF purification step underwent gradient elution on both columns. Fractions were analyzed for phage titer (recovery), total protein, residual DNA, and endotoxin levels. Sample quality was further characterized using cryo-TEM and mass photometry to evaluate empty/filled capsid ratios.

Results showed both columns effectively reduced host-related impurities, with PrimaT consistently demonstrating superior performance (notably better host cell protein and DNA removal). Phage recovery remained high across both columns, and eluted fractions exhibited no significant shift in empty-to-filled capsid ratios, indicating gradient elution does not preferentially enrich filled capsids.

These findings highlight PrimaT (and to a lesser extent PrimaS) as promising polishing tools for enhancing the purity and quality of GMP phage drug substances, supporting their advancement toward scalable clinical manufacturing.

AE1-BHK: A Novel E1-Complementing BHK Platform for Recombinant AAV Production

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VerumGen Labs; Agathos Biologics

Recombinant adeno-associated virus (rAAV) vectors have emerged as a leading platform for gene therapy, with most current manufacturing processes relying on HEK293-derived production systems. AE1-BHK is a genetically engineered baby hamster kidney (BHK) cell line developed as an alternative E1-complementing host for rAAV production using the standard triple-transfection method. The performance of the AE1-BHK platform was evaluated across multiple AAV serotypes using transient transfection and vector genome quantification of crude lysates. The cell line successfully supported production of AAV2, AAV5, AAV6, and AAV8, achieving average yields of approximately 4.4e9, 1.1e10, 9.1e9, and 1.2e10 vector genomes per cm², respectively. Vector production was observed for all serotypes evaluated, with AAV8 and AAV5 demonstrating the highest yields. These results establish AE1-BHK as a promising alternative mammalian host for rAAV production while maintaining compatibility with established plasmid-based manufacturing workflows. The platform combines the simplicity of conventional triple-transfection processes with a non-HEK293 production system, providing an additional option for vector development and manufacturing. Future studies will focus on process optimization, adaptation to chemically defined media and suspension culture, and evaluation of the platform for scalable biomanufacturing.

Programmable Virus-Like Particles for Targeted Drug Delivery

Vera Schoft

A-SpecTar

A-SpecTar GmbH is a biotechnology company based in Korneuburg near Vienna, Austria. The company focuses on the research and development of a novel, unique, patent protected approach using virus like particles (VLPs) for targeted delivery of active pharmaceutical ingredients. VLPs are empty virus particles that can no longer replicate (VLPs contain no genetic material). A-SpecTar's VLPs are derived from a virus that does not infect humans and is non-immunogenic. It consists of identical protein subunits assembled to form the capsid of the VLP while exposing specific binding sites at the surface that show high binding specificity comparable to antibody binding sites. These can be quickly modified so that they specifically recognize target cells or tissues. The VLPs can be stably loaded with various active substances, such as small molecules (e.g. cancer-killing agents), RNA, DNA or peptides/proteins, and display a high payload capacity with hundreds of small molecules packaged into each capsid. These VLPs can safely and efficiently be produced in high yields and at low cost in a microbial expression system. We envision a broad application, e.g. for oncology, gene therapy, vaccines, and inflammation. Tumor-targeted VLPs have already been shown to selectively and efficiently kill tumor cells in vitro. Furthermore, in a relevant in- vivo model, VLPs with a payload of a chemotherapeutic reduced tumor size/number and metastases without toxicity. VLPs were also successfully loaded with DNA and RNA and efficiently delivered to cells in vitro paving the way for a novel, safe targeted gene therapy overcoming current limitations.

Native Elution Immunoaffinity Chromatography for Efficient Purification of Vesicular Stomatitis Virus

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Vesicular stomatitis virus (VSV) is an enveloped, negative-strand RNA virus with growing potential as an oncolytic agent and vaccine vector. Efficient purification of infectious VSV is critical for therapeutic development but remains challenging, as conventional multistep methods are often labor-intensive, difficult to scale, and can compromise viral infectivity.

This study demonstrates that our patented "native elution" immunoaffinity chromatography, originally developed for mumps virus, can be adapted for VSV purification. Results show that immunoaffinity chromatography using hydrazide-activated monolithic columns functionalized with polyclonal anti-VSV IgG antibodies allowed high-capacity capture of VSV. Bound virus was eluted with high-molarity amino acid solutions at neutral pH, preserving viral integrity. Purification efficiency was evaluated by the recovery of infectious virus (CCID50) total particle concentration (nanoparticle tracking analysis), alongside the removal of host cell proteins (ELISA) and DNA (RT-PCR). Elution efficiency of VSV strongly depended on the amino acid used, with arginine clearly showing superior performance compared to all other tested conditions. It successfully recovered infectious VSV while minimizing co-elution of host contaminants. Its effectiveness was concentration-dependent, highlighting the importance of optimizing elution conditions. Other amino acids were less effective, with lysine showing moderate recovery, glycine limited effectiveness, and serine largely ineffective. These findings indicate that native amino acid-based elution provides a gentle and effective strategy for recovering infectious VSV from immunoaffinity monolith columns, providing a promising downstream solution for producing high-quality VSV preparations suitable for therapeutic applications and scalable manufacturing.

Non-viral, polymeric nanoparticle gene therapy for ocular disorders

Jordan Green

Cove Therapeutics

Current ocular gene therapies face challenges including incomplete retinal penetration and biodistribution, limited DNA cargo capacity, complex and costly manufacturing, and potential safety risks. To address these limitations, we developed a scalable, nonviral gene-delivery platform combining hydrolytically degradable, end-group-modified poly(beta-amino ester) (PBAE) nanoparticles with suprachoroidal administration for plasmid delivery to retinal photoreceptors. Cationic PBAEs were synthesized through Michael addition reactions and self-assembled with anionic plasmid DNA in acidic buffer to form nanoparticles that could be lyophilized and stored until use. Nanoparticles were administered by injection into the suprachoroidal space. Gene expression, retinal distribution, and safety were evaluated using immunohistochemistry and ELISA in Brown Norway rats, Yucatan minipigs, and Göttingen minipigs. PBAE nanoparticles encapsulated 100% of the plasmid DNA during self-assembly and carried an average of 250 ± 20 kbp per particle, demonstrating substantial nucleic acid cargo capacity. Following administration, no evidence of treatment-associated toxicity or retinal degeneration was observed in the evaluated animals. In the human-sized eyes of minipigs, the nanoparticles penetrated the retina, transfected photoreceptors, and achieved broad circumferential biodistribution and gene expression extending from the anterior to posterior eye. Although the polymeric nanoparticles degraded rapidly under aqueous physiological conditions, the delivered plasmids persisted and supported durable transgene expression, which was detected for at least eight months following a single suprachoroidal injection in rats. These findings demonstrate that biodegradable PBAE nanoparticles can safely deliver large plasmid cargos to the retina while avoiding the manufacturing constraints associated with viral vectors. Combined with a suprachoroidal administration strategy that is compatible with an outpatient procedure, this platform offers a scalable approach to broad and durable nonviral ocular gene transfer and has potential applications in inherited retinal degeneration and other causes of blindness.

nanoSFERIC™: A Novel Flexible Nanoparticle Vaccine Platform for Infectious Disease and Cancer

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Sferogen; COBIK

Rapidly emerging infectious diseases and the growing need for personalized cancer immunotherapy highlight the limitations of current vaccine development timelines. Existing platforms often lack the speed, flexibility, or immunogenicity required for pandemic preparedness and individualized treatment strategies.

nanoSFERIC™ is a modular vaccine platform based on engineered protein scaffolds that self-assemble into oligomeric nanoparticle rings with planar antigen display. This architecture enables rapid antigen exchange and optimization within weeks. The platform supports scalable production in bioreactors, yielding stable nanoparticles particles with defined composition and structural consistency. The rigid ring geometry promotes enhanced B cell receptor clustering and CD45 exclusion, resulting in improved humoral immune responses following single-dose administration.

The key innovation of nanoSFERIC™ lies in its high-density, planar antigen presentation combined with plug-and-play antigen modularity. In preclinical models, nanoSFERIC™ induced stronger and more durable antibody responses compared to soluble antigens and virus-like particles and was compatible with both intramuscular and mucosal delivery. Potential applications include rapid-response vaccines for emerging pathogens and personalized cancer vaccines targeting neoantigens. Overall, nanoSFERIC™ provides a flexible and scalable platform for next-generation vaccine development.

Long and winding road to scalability and clinical viability of Extracellular Vesicle–based therapies

Natasa Zarovni

RoseBio

Extracellular vesicles (EVs) have demonstrated immense potential as natural carriers for therapeutic molecules along with high biocompatibility and intrinsic ability to cross biological barriers. Despite significant progress in EV biology and manufacturing technologies, the field still lacks scalable, clinical-grade, and commercially viable production platforms. Key limitations include low yields from conventional culture systems, extensive dependence on manual intervention, heterogeneity in EV size and cargo composition, and donor-to-donor variability in EVs derived from stem cells as well as other human, animal, and plant sources, all of which complicate standardization under GxP conditions.

Drawing parallels with the evolution of cell therapies, viral vectors, and lipid nanoparticles (LNPs) may help identify potential pathways toward robust and controllable end-to-end manufacturing processes. Emerging strategies include physical and chemical stimulation to enhance EV secretion, the adoption of scalable bioreactor systems such as hollow-fiber and stirred-tank bioreactors, and advanced purification technologies including tangential flow filtration (TFF) and chromatography. In parallel, genetic engineering approaches and the development of EV-mimetic nanovesicles are proposed as new avenues to improve yield, consistency, and therapeutic functionality.

The wide range of approaches currently being explored suggests that the field has not yet reached full technological maturity. Rather than underscoring regulatory issues, several foundational challenges remain unresolved, including incomplete understanding of EV biology, often speculative mechanisms of action (MOA), and unclear competitive advantages within specific application niches. Addressing these gaps will be essential to accelerate the transition of EVs from laboratory research tools to critical clinical materials and technologies.

From consistent manufacturing to understanding mechanisms of action (MoAs) for extracellular vesicles from MSC

Klaus Graumann

Phoenestra

Cell-free therapies using Extracellular vesicles (EVs) from Mesenchymal Stromal Cells (MSCs) hold great promises for many therapeutic applications. Several roadblocks on the way to successful clinical translation need to be removed. We demonstrate the importance of a consistent and scalable manufacturing system on biological activity and, consequently, pre-clinical testing of EV preparations. Also, orthogonal characterization data will be shown which support proposed mechanisms of action (MoAs) of these multipotent therapeutic modalities.

We are using stable, telomerized MSC (MSC/TERT) lines and a perfusion bioreactor assembly/ system. Serum- and platelet lysate (PL)-free conditioned media is processed using depth filtration, ultra-/diafiltration and selected chromatographic steps. The resulting EV preparations are analyzed with physical, biochemical, -omics and bioanalytical methods. Functional activity was evaluated in relevant in vitro and in vivo disease models.

While the comparison of different manufacturing runs demonstrates a high level of reproducibility and consistency in MSC-EV process performance with our novel manufacturing system, in depth orthogonal characterization reveals excellent biological activities of the resulting EV preps. Based on molecular profiles, we are exploring proposed mechanisms of action (MoAs) by correlating the presence of specific proteins, enzymes and micro-RNAs with functional outcomes.

Comparative analysis of multiple manufacturing runs demonstrates a high degree of reproducibility and process consistency with our novel manufacturing system. In-depth orthogonal characterization further reveals robust biological activity of the resulting EV preparations.

With our holistic approach to MSC-EV manufacturing and orthogonal characterization we overcome current limitations for the clinical and commercial translation of these exciting cell-free treatment options. Besides enabling a consistent and scalable supply of defined EV products, we also enable cost-efficient manufacturing, both enabling broad access of patients in indications with large unmet medical need.

Overall, this integrated manufacturing and characterization strategy addresses key limitations in the clinical and commercial translation of MSC-derived EV therapeutics. The approach enables scalable and cost-efficient production of well-defined EV products, supporting broader patient access in indications with substantial unmet medical need.

Harnessing Nature's Nanoparticle: Process Development of Exosomes for Drug Delivery

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NurExone Biologic

Exosomes, often referred to as nature's nanoparticles, offer immense potential as innovative drug delivery vehicles. At NurExone Biologic, we have focused on the process development and scalable manufacturing of exosomes derived from a proprietary human bone marrow mesenchymal stem cell (hBM-MSC) Master Cell Bank. This platform enables the consistent, cost-effective production of high-quality exosomes for advanced therapeutics. Our lead program, ExoPTEN, exemplifies this approach by utilizing BM-MSC-derived exosomes to deliver a proprietary siRNA targeting PTEN, a critical regulator of neuronal regeneration pathways.

To achieve robust and scalable exosome production, we transitioned from conventional 2D cultures to a 3D bioreactor system, optimizing donor selection and culture conditions for maximal yield and functionality. Comprehensive characterization confirmed exosome identity, purity, and potency, while functional assays demonstrated their biological activity. ExoPTEN-loaded exosomes effectively reduced PTEN expression in vitro and showed significant therapeutic efficacy in preclinical models of spinal cord and optic nerve injury.

Our findings establish a strong technological foundation for the reliable, large-scale manufacture of exosome-based drug delivery systems. This process development not only supports the clinical advancement of ExoPTEN but also paves the way for future exosome therapeutics across a range of central nervous system injuries and diseases.

Plasma fractionation - The past, present and future

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The University of Western Australia

Initial attempts to produce therapeutic preparations of hyperimmune antisera from animal blood led to the first plasma/serum protein therapies. The production of human plasma protein therapies (PPTs) followed Edwin Cohn's meticulous characterisation of human albumin in Harvard University over the 1930s, and resulted in the United States (US) military commissioning his group to develop a stable albumin solution at high yield from human plasma. This was successfully used to treat blood/plasma loss from battlefield injury, and was first produced at pilot scale in Harvard but passed on rapidly on to private industry for industrial manufacture. The fractional nature of Cohn's scheme, while optimised to produce albumin, allowed access to other fractions, which were successfully applied to a number of other medical conditions. While in the USA the burgeoning plasma industry remained a private enterprise, drawing on paid donors for the raw material, by the 1950s a number of governments in social market economies had established their own fractionation plants for the provision of PPTs from plasma collected from voluntary donors organised by their own state blood services. Over the evolution of modern economic management, this state-based sector has shrunk progressively, while the private sector has undergone considerable consolidation.

The industry's initial primary focus on albumin gradually evolved to include other proteins, particularly blood coagulation Factor VIII (FVIII) from the 1960s-70s, and immunoglobulin from the 1980s. With other therapeutically useful, but low usage, protein such as alpha-1 antitrypsin concentrate (AAT) and antithrombin III (ATIII). The allocation of collection and fractionation costs across a range of products established the basis of the economics of the industry for several decades. The development of alternative biopharmaceutical methods of production, coupled with developments in the medical treatments underpinning PPT use, has introduced pressures in this model. The disruption of the PPT product landscape occurred rapidly in the 21st century, as the development of coagulation factors by recombinant technologies and other non-factor based therapies made plasma-derived FVIII (pd FVIII) redundant in the Western economies, where the highest reimbursement occurs. Modern intensive care medicine has obviated much of the use of albumin, making the initial PPT a low-priced commodity rather than an evidence-based therapy. This has shifted the focus of the industry's manufacturing and marketing increasingly on to immunoglobulin products, which are effective in a range of indications.

Disruption is also looming over some of these immunoglobulin indications, with possible future implications. Disruption has also been attempted sporadically, on the original Cohn technology, with the industry showing remarkable adeptness in modifying the fractionation chemistry to adapt to the requirements posed by the current product driver. Overall, plasma fractionation has proven to be a robust and effective industry with a global presence, although the USA and Europe continue to provide the bulk of the raw material and final products. The industry continues to attempt to expand its product portfolio, with varying and modest success, and the pressures posed by disruptive technologies continue. These pressures may absorb even more of the current product range, but core indications will continue to depend on an industry which will, hopefully, manage to celebrate a century of therapeutic provision over the next two decades.

Beyond the Cohn Process: Novel Approaches to Overcome Bottlenecks in Plasma Fractionation

Aleš Štrancar,

BIA Separations Inc

The Cohn plasma fractionation process, developed by Edwin J. Cohn more than 80 years ago, relies on a series of ethanol (EtOH) precipitation steps. It is based on the differential solubility of albumin and other plasma proteins as a function of pH, ethanol concentration, temperature, ionic strength, and protein concentration.

Proteins produced by the Cohn process are well characterized and have a long-established safety record, despite historical challenges from HIV and other potential contaminants that are now effectively controlled by modern methods.

Nevertheless, the process suffers from low yields, high equipment costs, large facility footprints, limited manufacturing flexibility, long processing times, and heavy ethanol use. These drawbacks continue to motivate the development of improved approaches.

This paper examines key bottlenecks of classical Cohn fractionation and presents novel strategies that offer higher recoveries, a smaller facility footprint, greater manufacturing flexibility, reduced ethanol consumption, and more integrated manufacturing. Novel in-process analytics that enable faster process development and tighter in-process control are also described.

Commercial-Scale Evaluation of a CIMmultus® Mixed-Mode Monolith for IgG Production

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National Bioproducts Institute

Subcutaneous immunoglobulin (SCIG) demand is rising globally for the treatment of immune deficiencies and an expanding range of autoimmune and neurological conditions. Regulatory requirements mandate minimal procoagulant activity in IgG products, particularly activated Factor XI (FXIa). National Bioproducts Institute (NBI, South Africa) supplies IgG products to low- and middle-income countries, where affordability is as critical as quality and safety. NBI currently uses Heparin-Sepharose (HS) affinity chromatography for FXIa removal in its 20% SCIG process. While effective, HS resin is costly with a short operational lifespan, adding substantially to production costs and rendering the product unaffordable. We evaluated the CIMmultus® SO4 mixed-mode monolithic column (SO4) from Sartorius BIA Separations as a cost-effective alternative. Laboratory-scale studies identified optimal pH, conductivity and buffer components for maximum FXIa removal and high IgG recovery in a robust, scalable process. A commercial-scale 20% SCIG run was performed using an 8 L SO4 monolith and directly compared to three HS-based batches. At commercial scale, the SO4 process achieved IgG recovery of 98.8% versus 92.8% (HS), with equivalent FXIa clearance (0.4 mIU/mL post-chromatography for both). Upon switching from HS resin to SO4 monolith, chromatographic process lifespan increased 7-fold, process time decreased from ~28.5 to ~6 hours and the process step cost contribution dropped 5-fold, without compromising IgG purity. The CIMmultus® SO4 monolith offers a robust, scalable, more economical alternative to HS chromatography for procoagulant removal in commercial 20% SCIG manufacture, supporting NBI's mission to deliver safe, affordable immunoglobulin products.

Purification of FIX from Cryopoor Plasma using DEAE and SO₄ Monolithic Supports

Lucija Dončević, Tomislav Friganović, Djuro Josić

Genos

Factor IX (FIX) is a vitamin K-dependent coagulation factor required for efficient thrombin generation, and congenital FIX deficiency or dysfunction causes hemophilia B. Plasma-derived FIX concentrates are produced to restore missing or functionally impaired FIX activity. Purification of active FIX from plasma is technically demanding because FIX is present in a dense protein matrix containing highly abundant plasma proteins that may co-elute with FIX and contaminate target fractions. Conventional plasma-derived FIX workflows commonly rely on packed-bed chromatography, multistep intermediate processing, and heparin-based isolation or polishing. These approaches for handling highly viscous plasma matrix can be limited by diffusion-controlled mass transfer, pressure-flow restrictions, feedstock dilution requirements, increased process volumes, and the biological origin and sanitization sensitivity of heparin ligands. This work evaluated a heparin-free monolithic chromatography workflow for direct FIX purification from undiluted cryopoor plasma. The capture step was performed on DEAE monolithic supports, with plasma loads of 10, 25, 50, and 75 column volumes compared to determine loading capacity before FIX breakthrough. FIX recovery in the main eluate was 34–37% at 25–50 column volumes, whereas 75 column volumes caused FIX loss into the flow-through. The optimized workflow used single DEAE capture followed by polishing step using SO₄ monolithic support. The integrated DEAE–SO₄ process achieved high recovery of loaded FIX, while SDS-PAGE and vitronectin immunoblotting supported progressive reduction of plasma-protein complexity and depletion of vitronectin as a major co-purifying contaminant.

Efficient and Scalable Purification of Plasma derived Therapeutic Proteins

Yow-Pin Lim

ProThera Biologics

Inter-alpha Inhibitor Proteins (IAIP) are critical host defense and immunomodulatory proteins that reduce inflammation and restore immune homeostasis. Because IAIP levels markedly decrease during severe systemic inflammation or sepsis, they hold significant potential as both sensitive prognostic host response biomarkers and as effective therapeutic agents. In preclinical models of systemic inflammation/sepsis and neuroinflammation/ischemic stroke, exogenous IAIP administration has significantly improved outcomes in reducing morbidity and mortality. To advance toward Phase I/IIa clinical trials for infant indications, current efforts are focused on developing scalable, GMP-grade purification processes. We utilized anion exchange chromatographic supports, including monolithic CIMmultus QA media, to optimize capture and elution conditions, yielding highly enriched and biologically active IAIP from human plasma. To further increase process efficiency and productivity, we are currently integrating the continuous Multi-Column Chromatography system (Tosoh Bioscience Octave) to establish a robust, high-throughput manufacturing platform for these therapeutic proteins.

Direct chromatographic capture of therapeutic proteins from undiluted human plasma on large-channel monoliths

Tomislav Friganović, Lucija Dončević, Jasmina Simović Medica, Petra Grbčić, Marko Filipović, Djuro Josić

Genos

Cohn ethanol fractionation remains the industrial standard for plasma protein isolation, yet it requires plasma dilution, low-temperature processing, and sequential precipitation steps that limit throughput and reduce the yield of labile coagulation factors and other plasma proteins. Monolithic supports with large flow-through channels offer an attractive alternative: their open architecture permits direct loading of viscous, nanoparticulate-rich plasma without prior dilution, while mass transport in the channels is predominantly convective rather than diffusive, permitting high flow rates without substantial backpressure increase. We first showed that large volumes of undiluted plasma can pass through an inert hydroxyl (OH) monolith at ~36 °C without clogging or coagulation cascade activation. Building on this, we evaluated monoliths with different chromatographic chemistries for the selective capture of clinically relevant plasma proteins such as immunoglobulin G (IgG) and coagulation factor VIII (FVIII). Protein G affinity monoliths selectively bound IgG from undiluted plasma in a single chromatographic step, with reproducible multi-cycle performance. For FVIII, a strong anion-exchange (quaternary amine) monolith captured the FVIII from undiluted plasma without detectable gross protein degradation. Our results show that large-channel monoliths are particularly suitable for difficult biological feedstocks such as undiluted plasma. Given that monolith technology has been scaled industrially for other biopharmaceuticals, the dilution-free capture at near-physiological temperature demonstrated here offers a viable route to industrial plasma processing.

Chromatography on newly developed monolithic supports for biological nanoparticles and large biomolecules

Djuro Josić, Tomislav Friganović, Lucija Dončević

Juraj Dobrila University of Pula

Chromatography on monolithic supports combines convective flow through interconnected macropores with tunable surface chemistries, enabling high-flow, low-shear purification of large biomolecules and biological nanoparticles [1]. Demonstrated applications include the high-resolution discrimination of adeno-associated virus (AAV) empty and full capsids, the isolation of supercoiled plasmid DNA, and the removal of double-stranded RNA impurities from mRNA therapeutics. Furthermore, efficient purification of extracellular vesicles and the direct recovery of biotherapeutics from cryopoor plasma and even undiluted blood plasma and at physiological temperature was also achieved. Process analytical technologies utilizing monolithic columns now enable rapid and robust at-line monitoring of industrial processes for current good manufacturing practice (cGMP) control. Ongoing progress in multimodal chemistries, continuous and multicolumn operations, and integrated analytics establishes chromatography on monolithic supports as a versatile and robust platform for the rapid, selective purification of large biomolecules and biological nanoparticles.

Technoeconomic and sustainability evaluation of 3D printed monolithic adsorbers for integrated clarification and capture of therapeutic antibodies

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Monoclonal antibodies (mAb) are the dominant class of approved biopharmaceuticals, owing their success to their specificity to bind a virtually infinite variety of antigens. Large scale mAb manufacturing has been enabled by the development of a robust Protein A chromatography platform process. During the past 20 years, traditional protein A chromatography resins have seen only incremental improvements (such as enhanced binding capacity and alkaline stability of protein A) and are now run at maximum capacity to cope with the increase in mAb titres from upstream processing. Alternative convective media like membranes, nanofibres and monoliths have the potential to increase throughput thanks to unaffected performances at high flow rates, but generally suffer from low adsorptive performances and suboptimal fluid distribution.

With 3D printing technologies, the prospect of conceiving radical changes in chromatography adsorbents, such as new geometries and bespoke channels, has finally become a reality. The current 3D printing resolution of around 300 μm enables the fabrication of bespoke structures with flow through channels able to process fluids containing cells and/or cell debris, without risking particles' entrapment as it would occur in the interstitial voids of traditional packed beds or of monoliths. This potential removes the need for costly clarification procedures, usually performed in multiple rounds of filtration and/or centrifugation steps, before sending the harvest to the following chromatographic capture step. Thus, 3D printed monolithic adsorbers (PMA) could find application as integrated clarification and capture columns, combining into a single unit operation the functions currently performed by two distinct unit operations.

This work investigates the economic and sustainability advantages that the implementation of PMA could have in the biomanufacture of monoclonal antibodies (mAbs). A technoeconomic model that includes the PMA unit in the bioprocessing train is developed. After model calibration using experimental data of a prototype Protein A functionalized PMA, the economics and environmental burden arising from the combination of clarification and capture in a single unit operation are

evaluated. The results obtained are compared against established mAb biomanufacturing processes, ultimately demonstrating that PMA have the potential to simplify bioprocess operations while at the same time producing Cost of Goods (CoG) savings, as well as a decrease in the process mass intensity (PMI) and carbon emissions.

Monolith-based Immobilized Enzyme Reactors: Enabling Technologies for Diverse and Evolving Landscapes

Manuela Bartolini

Alma Mater Studiorum University of Bologna

Immobilized enzyme reactors (IMERs) based on monolithic chromatographic supports are emerging as versatile and enabling tools across diverse sectors. Their integration into advanced analytical and preparative workflows aligns with the principles of green chemistry, circular economy, and resource efficiency, which are critical pillars in both European and global innovation agendas.

Thanks to their continuous porous structure, monolithic supports offer high surface area and efficient convective mass transfer, making them ideal matrices for enzyme immobilization and high-throughput biocatalysis under flow conditions. These features facilitate IMER deployment in both production and quality control environments, promoting the shift toward greener, scalable, and more reproducible processes, in full compliance with the European Green Deal and international sustainability frameworks. In particular, owing to their structural and functional advantages, monolith-based IMERs are increasingly recognized as valuable tools in biopharmaceutical quality control, enabling streamlined and reproducible workflows for proteolytic digestion, glycosylation analysis, and stability evaluation of complex therapeutic proteins.

Moreover, IMERs are expanding into the therapeutic space, serving as bioactive components in drug discovery, gene therapy, and diagnostic platforms.

By combining the catalytic versatility of enzymes with the structural advantages of monoliths, next-generation IMERs are driving innovation across different fields, offering scalable, precise, and environmentally conscious solutions for evolving analytical and industrial challenges.

Advanced fluorescence microscopy platforms for imaging of (biological) samples at various spatial and time scales

Boštjan Kokot, Cody Tripp, David Kopitar, Luka Šalamun, Ervin Mustafić, Hana Kokot, Tomaž Ličina, Tomasz Kolodziej, Janez Štrancar, Iztok Urbančič

Jožef Stefan Institute

One of the major challenges in therapeutic development is understanding the interactions between therapeutic(s) and functional units on the molecular, subcellular and cellular level, possibly in an unperturbed way, identifying the targets, their locations and entire response dynamics. To localize the therapeutics with their targets and unravel their response dynamics at “10-100 nm”, below the resolution of the standard confocal microscopy (CFM), we applied super-resolution Stimulated-Emission Depletion (STED) microscopy, here to track DNA particles, packed in the 100 nm-sized lipid/protein capsules. To increase the statistics of the events at high resolution with limited field of view, we employed automated identification of regions that require high-resolution modality while monitoring other regions at standard resolution, here to track sparse protein-RNA condensates in cells [NucleicAcidsRes2026]. To co-localize two molecules/components as part of the same mobile vehicle/supramolecular-system we applied Fluorescence cross-correlation spectroscopy (FCCS), here to confirm membranes wrapping around inorganic nanoparticles, responsible for relocating the membrane receptors/enzymes to unexpected locations [Nanoletters2018]. To track small vesicles during cell-cell communication over large field-of-view, Structure-illumination microscopy (SIM) is used with the best resolution-to-acquisition-speed ratio. While monitoring the cellular response to peroxide exposure, we were able to achieve 3s acquisition time for 3-channel SIM over 360 um field-of-view, which is 90-times faster than standard laser-scanning CFM, that would completely miss such fast dynamics of so small objects. Finally, when biological problem requires tracking of >4 structures, in presented case 8+1, Hyper-channel confocal microscopy rely on merging lifetime information, gated detection and digital spectral decomposition.

Proteinaceous pan-antiviral entry inhibitor for crossing the gap in pandemic preparedness

[Uroš Andjelković](#)

SavAntiVir

Antivirals are compounds that interfere with different stages of the viral replication cycle, thereby limiting viral infectivity. The development of antivirals represents a highly challenging task, given current concepts in small-molecule organics design, the associated costs and mechanisms of viral infectivity & high mutational potential.

Recent pandemic outbreaks have demonstrated that current prevention strategies do not bridge the gap between the initial outbreak of a new viral strain and the moment when vaccines and other antivirals become available. New methods of vaccine development and drug repurposing advanced during the COVID-19 pandemic, and the gap without protection now spans about 90-270 days. Additionally, because vaccines rely on an individual's immune system, they face the challenge of being effective in high-risk populations: the elderly, persons with underlying respiratory or cardiac disease, diabetes, hospitalized patients, and immunocompromised persons. Therefore, pandemic preparedness requires the development of broad-spectrum antiviral drugs or vaccines that can be deployed before a new strain emerges.

A group of small proteins that bind spike glycoproteins specifically interacting with their glyco component offers a biochemical concept that can outpace the virus's mutational capacity. These antivirals bind to the spike protein and block its interaction with the cell-surface receptor, preventing the virus from entering cells. Acting as entry inhibitors, with high pan-antiviral potency and precise binding, a vast population of new and drug-resistant viral strains can be blocked. High blocking activity has been confirmed against enveloped viruses: respiratory Influenza and SARS-CoV-2, body fluid-transmitted HIV and HSV, and others. Pre-exposure prophylaxis can be achieved by applying entry inhibitors to the nasal and respiratory mucosa to block Influenza and emerging flu viruses, providing an effective first line of defense, especially for high-risk populations. Other suitable pharmaceutical forms can be used for application on the genital mucosa against sexually transmitted enveloped viruses. Production of these protein antivirals can be performed with a low carbon footprint using green expression systems. Due to high stability of these proteinaceous pan-antivirals cold chain of distribution can be omitted.

Applications of highly functional Xenoligo ssDNA aptamer technology for medical and bioprocessing

[Miyuki Hori](#)

TAGCyx Biotechnologies

TAGCyx Biotechnologies Inc. based in Tokyo possess its proprietary technology platform to generate specific and highly functional ssDNA aptamers using innovative unnatural base-pair technology. The technology enables us to overcome some weakness of conventional aptamers available and uneasy to develop.

In addition to therapeutic development as drug candidates, aptamers can be applied for various applications, such as DDS, affinity purification, apheresis development as a ligand. Highly specific ssDNA aptamers represent a powerful class of synthetic, customizable affinity ligands for bioprocessing. Compared to other ligand material candidates, such as antibodies, nanobodies, peptides and sugar moieties, aptamers possess various advantages, including rather simple linker conjugation, long stability, chemical synthesis, no batch-to-batch gap, possible sterilization.

Aptamer based affinity technologies are increasingly relevant for next generation biotherapeutics.

Some of useful feasible applications including DDS and apheresis will be presented and discussed.

Finding the Golden Site: how synthetic amino acids and third-generation click-chemistry enable the next generation of protein conjugates

Katarina Belačić

VALANX Biotech

Developers of protein–drug conjugates remain constrained in choosing conjugation sites. Our GoldenSite platform leverages stop-codon suppression to install synthetic amino acids at any position in any protein, enabling highly efficient, catalyst-free third-generation click chemistry to precisely attach diverse payloads. We enable systematic site scanning across antibodies and novel formats, yielding optimized developability and efficacy. Our lead antibody–drug conjugate asset, VLX-ADC-001, for triple-negative breast cancer demonstrates the power of our GoldenSite platform in enabling best-in-class therapeutics.

Precision Management of Anti-Drug and Anti-Vector Antibodies: Deep Epitope Profiling and Adaptable Molecular Decoys for Selective ADA Removal

Oskar Smrzka, Kristyna Yatsyk, Christoph Doppler, Melanie Kogler, Katrin Fischer, Gerhard Stadlmayr, Patrice Douillard, and Christof Paparella

Ablevia biotech

Anti-drug, anti-vector, and anti-PEG antibodies (ADAs) remain a major barrier to the safe administration, repeat dosing, and clinical efficacy of modern biotherapeutics. These antibodies can neutralize therapeutic agents or accelerate their clearance, limiting treatment durability across oncology, gene therapy, and rare disease indications. Current mitigation strategies, including broad immunosuppression and plasma exchange, are non-specific, slow-acting, and often insufficient, highlighting the need for targeted and rapid ADA removal.

Ablevia combines deep antibody epitope profiling with the development of injectable molecular decoys, called Selective Antibody Depletion Compounds (SADCs), to enable pre-treatment of ADA-positive patients for precise ADA removal: The company's proprietary ADAScape™ platform maps antibody-epitope interactions at high resolution, providing the basis for the rational design of peptide-based, antibody-specific SADC decoys. When injected, these multivalent decoys selectively bind circulating ADA and promote their depletion before treatment with the main drug, while avoiding the need for broad immune suppression or extracorporeal plasma treatment approaches.

We demonstrate in a preclinical setting that SADCs achieve rapid, targeted clearance of anti-vector and anti-PEG antibodies in vivo, thereby reopening therapeutic windows for gene therapy vectors, biologics, and PEGylated or LNP-based modalities. Ablevia's integrated platform enables both personalized and indication-specific SADC design and pre-treatment strategies, with the aim of improving therapeutic efficacy.

Our lead candidate, PEG-SADC, selectively removes anti-PEG antibodies and restores the activity of PEGylated therapeutics and LNP-delivered drugs. Together, Ablevia's epitope-guided SADC platform establishes a versatile and scalable approach for preconditioning patients and overcoming humoral immunity barriers in next-generation therapies.

Closing the Target-Validation Gap for Complex Biologics with an Integrated AI Knowledge Platform

Konstantin Glebov

University of Plymouth; Exosome Consulting

Most extracellular vesicle (EV) therapeutics—especially those based on naïve, unengineered vesicles—advance into clinical development and manufacturing without a fully characterized active pharmaceutical ingredient (API) or a clearly defined mechanism of action (MoA). This is not primarily a documentation gap. It is a direct consequence of the multi-component complexity of EV cargo: identifying which constituents actually drive observed effects, then rigorously validating them, has remained slow, fragmented, and difficult to reproduce. Without compelling, mechanism-supported efficacy data, the field lacks the foundation needed for robust process development, consistent manufacturing, and confident regulatory progression. KnowlEx Cloud is an AI-enabled platform built specifically for target identification and validation in EVs and other complex biologics. It consolidates cargo profiling, target prioritization, evidence linking, and hypothesis generation into one traceable, reproducible workflow. The result is a prioritized, evidence-backed target list and a defensible API/MoA hypothesis—complete with full audit trails and export-ready documentation suitable for regulatory submissions, manufacturing process development, analytical method qualification, and partnering or licensing discussions. Its decisive differentiator is data sovereignty. KnowlEx Cloud runs entirely offline—first on the user’s own infrastructure. All data, models, and analytical outputs remain local; nothing leaves the organization unless the team explicitly chooses to share it. This architecture protects proprietary cargo compositions, unpublished efficacy datasets, and IP-sensitive target hypotheses—critical when developing competitive EV or complex biologic therapeutics. The platform transforms an empirical, high-risk development path into a mechanistically grounded, manufacturing-ready program while preserving full control over sensitive information.

A general, biologically-interpretable image analysis pipeline for microscopy of pharmaceutical agents in biological systems

Hana Kokot, Boštjan Kokot, Tomaž Ličina, Tomasz Kolodziej, Tilen Koklič, Iztok Urbančič, Janez Štrancar

Jožef Stefan Institute

Microscopy represents a cornerstone technique for exploring the intricate effects of pharmaceutical agents on biological systems and observing their efficacy, toxicity, and pharmacokinetics at the cellular and subcellular levels. The key to obtaining reliable and interpretable microscopy data is to gather large datasets and quantify the images in a mechanistically meaningful way. To avoid laborious and slow manual image analysis, specialised automated scripts are used, which are typically developed on a case-by-case basis. Moreover, the connection between quantified image properties and biologically-relevant processes are often unclear, e.g., in cell painting, which precludes mechanistic interpretation of the analysed data. Motivated by the lack of general, biologically-interpretable image analysis approaches, we are tapping into our 20+ years of experience in image analysis to develop a pipeline that can automatically extract a multitude of biologically-relevant observables from images of fluorescently labelled cellular structures. Examples of these observables range from binucleation and chemotaxis to neurite (de)arborisation, plaque degradation, and changes in the cell’s lipid production. Importantly, we confirmed that the changes of cellular structures and behaviour that we observed reflect known modes-of-action of external agents. Our analysis pipeline can be applied to different cell structures and cell types (tissue models), and can determine the sub-cellular location of agents that scatter or fluoresce. Even in cases when the agents cannot be tracked, their local effects can still be detected and quantified, together with cell’s response. Our image analysis pipeline thus offers a local mechanistic view of the complex processes in living cells.

High-Throughput IgG Glycosylation Analysis Using Protein G Monoliths

Irena Trbojević Akmačić

Genos

Immunoglobulin G (IgG) is the most abundant glycoprotein in human blood plasma and one of the most extensively studied proteins in terms of glycosylation, owing to its relatively straightforward purification through specific binding to protein G. Glycosylation, the process of attaching sugar molecules (glycans) to proteins during and after synthesis, influences not only protein structure but also biological function. Large-scale population studies, genome-wide association studies, and clinical cohort analyses have demonstrated strong associations between IgG glycosylation patterns and factors such as age, sex, and disease state. These studies have relied on the development of high-throughput methods for efficient IgG purification and sensitive glycosylation analysis. Chromatographic monoliths with immobilized protein G have emerged as valuable tools for IgG purification from blood plasma, enabling high-throughput sample preparation due to their favorable chromatographic properties. Monolithic supports in a 96-well plate format have been successfully applied in large-scale glycomics studies, primarily using adult human samples of sufficient volume. We will discuss methodological adaptations enabling reliable high-throughput IgG glycosylation analysis from low-volume and low-concentration samples, expanding the applicability of monolithic platforms to challenging biological materials.



Young Researcher's Corner

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From Hours to Minutes: Development of an Oriented PNGase F IMER for Automated Glycoprofiling

Wendy A. Mensah, University of Bologna

Development of scalable purification strategy for minicircle DNA vaccines in different monoliths

Rafaela Gaspar, Rok Miklavčič, Ângela Sousa, Urh Černigoj

University of Beira Interior

Cervical cancer (CC) is among the top five most common and leading cause of cancer related deaths among women worldwide. It is estimated that between 79% and 100% of all cases are related to Human Papillomavirus (HPV) infection, representing a public health issue. Nucleic acid vaccines have emerged as a new approach to immunization, being more versatile and adaptable to pandemics, such as coronavirus disease 19. Minicircle DNA (mcDNA) has emerged as an alternative to conventional plasmid DNA, due to its innovative processing, overcoming limitations related to bacterial host backbone presence. mcDNA is obtained through induced in vivo recombination of Parental Plasmid (PP), resulting in two different small plasmids: mcDNA containing the eukaryotic sequences and miniplasmid (mP) containing the prokaryotic sequences. Transfer of mcDNA in industrial processes remains a challenge due to the lack of suitable strategies capable to differentiate and isolate mcDNA from a complex sample containing impurities with similar structures and chemical properties (unrecombined PP, mP and host impurities, such as RNA and genomic DNA fragments).

This study explored new approaches to separate and purify multigenic mcDNA vaccine encoding mutant HPV16 E6/E7 (E6/E7 mut) antigens, in order to establish fast, efficient and profitable solutions for the biopharmaceutical industry. Resorting to two orthogonal chromatographic techniques (weak anion exchanging (DEAE) and reverse-phase (SDVB) monoliths) and tangential flow filtration (TFF), it was possible to establish three different purification strategies. In two of the established strategies, the sample was captured in a DEAE monolith with increasing NaCl gradient, and two different polishing approaches were developed. One polishing approach was performed in a DEAE monolith with an increasing guanidine hydrochloride (GndHCl) gradient, successfully achieving isolation of supercoiled mcDNA with a purity of 90%, whereas other polishing approach was performed in a SDVB monolith with an acetonitrile increasing gradient, successfully achieving isolation of supercoiled mcDNA with a slightly lower purity of 81%. The third purification strategy was performed using a TFF membrane for a capture step followed by a polishing step in a DEAE monolith with increasing GndHCl gradient, successfully achieving isolation of mcDNA with a 78% purity. Finally, delivery systems based on mcDNA/PEI were prepared to protect and deliver the purified samples of the mcDNA vaccine into APCs.

Scalable purification of a DNA-launched RNA replicon-based vaccine candidate against Trypanosoma cruzi infection using monolithic chromatography technology

María Alicia Delfino, Jimena Borgo, Sofia Rodríguez Zuzek, Rocío Cenizo, Natacha Cerny, Augusto Ernesto Bivona and Andrés Sánchez Alberti

LITAN, CONICET – University of Buenos Aires

Trypanosoma cruzi infection causes a life-threatening illness known as Chagas disease, which affects more than 6 million people worldwide. Currently, no vaccine is available, and existing treatments have limited efficacy. To address this, we designed a DNA vaccine candidate that encodes a self-replicating RNA (DREP) platform capable of expressing a chimeric T. cruzi antigen. Our DREP vaccine platform, based on the SFV alphavirus genome, was constructed using Gibson Assembly. The chimeric antigen sequence was incorporated into the DREP vector via in vivo cloning to obtain DREP-Tc. Scalable production of the 13 kbp DREP-Tc was implemented using a 1ml CIMmultus® DEAE 2 µm monolith column on a Knauer FPLC system. The purification process began with a conventional alkaline lysis and neutralization of the bacterial cell pellet, followed by a 1 M calcium chloride precipitation step to reduce host genomic DNA and RNA contamination. The step-chromatography procedure utilized three buffers with distinct NaCl concentrations: 0.6 M for equilibration, 0.85 M for elution, and 1 M for stripping. The purity of the obtained DREP-Tc was verified by spectrophotometric analysis, yielding a 260/280 nm ratio greater than 1.8. The absence of contaminating bacterial RNA was confirmed via agarose gel electrophoresis (AGE). Furthermore, AGE allowed for identity confirmation through restriction mapping and showed a supercoiled plasmid abundance greater than 80%. Finally, the functionality of the purified DREP-Tc was validated through in vitro transfection studies alongside in vivo immunogenicity and efficacy assays in mice.

Engineered recombinant baculoviruses for efficient production of enveloped virus-like particles

[Martina Lokar Kosmač](#), [Urban Bezeljak](#), [Matjaž Peterka](#)

[COBIK](#)

Efficient removal of baculovirus vectors remains a major downstream bottleneck in the baculovirus expression vector system (BEVS), limiting the safety, stability, and overall quality of enveloped virus-like particle (VLP) vaccines and hindering their broader biopharmaceutical application. Here, we introduce a rationally engineered baculovirus designed for selective affinity capture and removal during purification. We engineered baculovirus envelope glycoproteins for efficient immobilized metal affinity chromatography (IMAC) capture using structure-based protein design. Specifically, histidine residues were inserted into exposed, flexible protein loops of selected surface proteins, enabling specific interactions with column matrices. These modifications did not influence baculovirus propagation, while enabling selective binding to Cu^{2+} -charged monolithic iminodiacetic acid (IDA) columns. This design enabled single-step baculovirus depletion of three orders of magnitude, substantially outperforming conventional clearance strategies. The engineered baculoviruses were applied to the scalable production of SARS-CoV-2 VLPs that are a promising multivalent vaccine platform. More broadly, this work establishes surface engineering of viral vectors as a generalizable strategy for integrating upstream design with downstream purification, improving the manufacturability and quality of BEVS-derived biologics and enabling a new generation of advanced cost-efficient therapeutics.

A combined 3D printing–phase inversion process as a new platform for monolith production

Gabriele Malagoli

University of Bologna

Monoliths are used in bioprocessing for a variety of applications. 3D printing is a crucial resource for fabricating monolith, since it enables to produce structures with well-defined, tailored geometries and great accuracy. However, additive manufacturing suffers from limitations related to the resolution of current 3D printers and the limited range of processable polymers. Immersion precipitation 3D printing (IP3DP) is a recently developed technique that combines extrusion-based 3D printing with non-solvent-induced phase separation (NIPS), enabling the production of complex 3D structures using a wide range of polymers.

This work was developed within the framework of BiomembrOS, aiming to develop a new generation of biomimetic extracorporeal membrane oxygenators (ECMO). Using thermoplastic polyurethane (TPU) as a model polymer, this study investigates how adjusting IP3DP parameters influences the morphology of the printed filament. This can range from solid, dense or porous filaments to microporous hollow fibers. The printing conditions were optimized to produce TPU monoliths suitable for ECMO applications, with mechanically stable, microporous, and internally void filaments that have an external diameter of less than 200 μm and a wall thickness lower than 30 μm . Optimized complex monolith structures were 3D printed. Finally, monoliths were coated with PDMS to create a dense skin layer, which is essential for ECMO applications. This study demonstrates IP3DP as a viable technique to produce monoliths with variable morphologies, tailored to the target application.

Acknowledgement: This work is part of BioMembrOS, a project funded by the European Union's Horizon Europe research and innovation program under Grant Agreement No. 101130006.

From Hours to Minutes: Development of an Oriented PNGase F IMER for Automated Glycoprofiling

Wendy A. Mensah

University of Bologna

The increasing demand for high-throughput, cost-efficient analytical methods in protein biochemistry has driven innovation in enzyme-based technologies. Immobilized enzyme reactors (IMERs) represent a transformative solution streamlining workflows and lowering costs through enzyme reusability. Integrating IMERs into high-performance liquid chromatography (HPLC) systems combines both technologies' advantages, creating a powerful platform for automated biochemical analyses. To address this challenge, recombinant PNGase F was covalently immobilized onto epoxy-activated CIMmic® monolithic discs using either non-oriented or oriented strategies. While the non-oriented approach relied on a single-step enzyme immobilization, oriented immobilization required surface functionalization for site-specific enzyme positioning. This translated into IMERs with more than tenfold higher activity, a key feature for efficient N-glycan release and subsequent glycan profiling. Surface modifications and reactor performance were characterized to establish a robust and reproducible immobilization protocol. The optimized PNGase F-IMER was subsequently integrated into a biocompatible two-dimensional LC platform for online glycoprofiling. The system couples the IMER with trapping and analytical columns, enabling online deglycosylation, retention of the protein fraction, and direct chromatographic profiling of released glycans within a single automated workflow. This IMER-LC platform reduces digestion time from hours to minutes, simplifies workflows, and enables enzyme reusability, thereby advancing automated and cost-effective protein glycoprofiling for both research and clinical applications.



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AAV production - Polishing step optimization and scale up – from resin to monolith

Lea Arnaud

Aavantgarde Bio

This poster describes how changing the matrix and optimizing the conditions in the polishing step led to an improvement in downstream performance. The optimization was carried out in several stages. The first stage involved screening different available matrices. The second part was to optimize the conditions of the best matrix selected. The optimization focused on buffer composition as well as chromatographic parameters such as gradient versus step elution. This optimized polishing step resulted in an increase in full capsid percentage and overall recovery. In addition, the selected matrix improved process performance by reducing the duration of the polishing step process and facilitating its scalability. Importantly, this final optimized step met the pre-set critical quality attributes on final drug product. Finally, this abstract presents development and GMP scale up bioreactor data. These findings support the use of monoliths to enhance AAV production performance at scale.

Vitamins' B6 and C enhance HuIFN- α 3 induction by NDV ZG1999HDS or Sendai virus

Bratko Filipič, Lidija Gradišnik, Adriana Pereyra, Hrvoje Mazija

University of Ljubljana

Interferon's (IFNs) are glycoproteins/proteins made and released by cells in response to different pathogens like viruses, bacteria or tumor cells. There are two Types of IFNs: Type I including IFNs α and β , Type II including IFN γ . HuIFN- α 3 inducing capability of NDV (strain ZG1999HDS) can be enhanced with vitamin B6 to the 3.286 ± 34 pg/mL versus 4.557 ± 34 pg/mL in the case of SV. To test vitamins B6 and C enhancing effects on HuIFN- α 3 inducing capacity, of NDV ZG1999HDS or SV, the combinations were used: (1) Priming with 50 IU/mL of HuIFN- α 3 +50 mg/mL of Vitamin C + 50 HAU of Sendai virus or NDV ZG1999HDS = 23.700 IU/mL of HuIFN- α 3. (2) Priming with 50 IU/mL of HuIFN- α 3 +50 IU/mL of Vitamin B6 +50 HAU of Sendai virus or NDV ZG1999HDS = 37.321 IU of HuIFN- α 3 (3) Priming with 50 IU/mL of HuIFN- α 3+100mg/mL of Vitamin B6 + 50 HAU of Sendai virus or NDV ZG1999HDS = 29.390 IU/mL of HuIFN- α 3 (4) Priming with 50 IU/mL of HuIFN- α 3 +(20mg/mL of Vitamin C +50mg/mL of Vitamin B6) +50 HAU of Sendai virus or NDV ZG1999HDS = 60.628 IU/ mL of HuIFN- α 3; (5) Priming with 50 IU/mL of HuIFN- α 3 + (50mg/mL of Vitamin C +100mg/mL of Vitamin B6) +50 HAU of Sendai virus NDVZG1999HDS = 73.784 IU/mL of HuIFN- α 3. It can be concluded that the additive activity of the vitamins' combination of: Vitamin C (50mg/mL) + Vitamin B6 (100 mg/mL) on the HuIFN- α 3 induction with NDV ZG199HDS or SV can be found.

From isolation and in vivo evaluation to clinical application of phages in a compassionate use setting

Martina Durcik, Vida Štilec, Monika Marušić, Klara Gregorič, Nika Janež, Lucija Rebula, Simon Horvat, Matjaž Peterka

COBIK

Phage therapy is not yet approved as a standard medicinal product in Europe and is primarily accessed through compassionate use or specialized frameworks (1). We report the isolation and characterization of bacteriophage COP-80B, its safety and efficacy evaluation in an animal model, production, and clinical application in a patient with Staphylococcus epidermidis periprosthetic joint infection (PJI). COP-80B was isolated from wastewater and characterized in vitro for antibacterial and antibiofilm activity and genetic safety (2). Its efficacy, alone and in combination with vancomycin, was assessed in a murine PJI model (3). To support efficacy evaluations and subsequent compassionate use cases, the phage was produced in an animal component-free medium, clarified by filtration, purified on CIMmultus OH and QA columns, and concentrated via diafiltration. The final formulation was prepared in 0.9% NaCl and tested for endotoxin levels and sterility. In the mouse PJI model, COP-80B demonstrated significant antibacterial activity, with the combination treatment showing the greatest reduction in bacterial burden. COP-80B was subsequently selected for compassionate use in a patient with recalcitrant S. epidermidis PJI, effectively lysing all five patient isolates. The patient received local phage therapy during surgery in combination with systemic antibiotics, experienced no adverse effects, and remained infection-free six months after treatment (4). These findings support the potential of phage therapy as an adjunctive approach for managing complex infections.

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A platform approach for full capsid enrichment polishing using CIMmultus PrimaT monolith on different serotypes and transgenes

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Genethon

Gene therapies are expanding and represent a highly promising approach for rare diseases, especially at Genethon for muscular dystrophies and metabolic disorders. During the production of AAV vectors, a significant proportion of empty and partial capsids is generated alongside full capsids. This proportion strongly depends on the serotype–transgene combination. The clinical effect of these undesired capsids remains unclear. Empty capsids are not the intended therapeutic product, while partial capsids can lead to the expression of nonfunctional or undesired proteins. For this reason, process development teams must consider empty and partial capsids as impurities and aim to reduce their presence. This objective can be achieved by optimizing upstream production or by implementing a dedicated polishing step in the downstream purification process. The latter approach was evaluated using the CIMmultus® PrimaT monolithic column. This mixed-mode monolith, combining three interaction types, provides an opportunity to increase the proportion of full capsids across multiple AAV-based gene therapy products. Its use as a platform polishing tool can enable faster method development with strong transposability. Based on the generated data, particularly full capsid enrichment and viral genome recovery, PrimaT enhances full capsid enrichment while removing undesired capsids and product-related impurities such as host cell proteins or viral potential contaminants, with robust repeatability and scalability up to 200L without performance loss. The results demonstrate the efficacy of the PrimaT monolithic column on AAV2, AAV8, AAV9 and chimeric capsids across at least five transgenes. This platform approach achieves equivalent performance compared to specific development using other polishing columns.

Mass Spectrometry Analysis of Monolith-Derived Plasma Protein Fractions

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Genos

Monolithic supports can be used for separation, enrichment, and/or purification of plasma proteins. Due to the complexity of the plasma protein matrix, collected chromatographic fractions often require verification of the target protein and identification of co-eluting molecules. Mass spectrometry provides a complementary analytical readout for monolith-derived plasma protein fractions by enabling protein identification and comparative evaluation of relative protein abundance. Bottom-up LC-MS/MS combined with database search enables peptide-level identification of target proteins and co-eluting components. Depending on the experimental design and data structure, proteomic data can also support relative abundance comparison between fractions with normalization, scaling, and other statistical procedures. While chromatographic profiles describe elution behavior and peak distribution, LC-MS/MS analysis can indicate whether the separation enriched the expected protein and reveal accompanying plasma proteins present in the same fractions. This is particularly relevant for plasma-derived workflows, where high sample complexity and broad protein concentration ranges may limit interpretation based on chromatographic profiles alone. This analytical strategy can be applied to different plasma protein fractions obtained using monolithic supports, including fractions enriched in abundant plasma proteins and fractions containing clinically relevant targets such as coagulation factors or immunoglobulins. Combining separation on monolithic supports with LC-MS/MS-based data analysis therefore supports protein identification, relative abundance comparison, impurity assessment, and interpretation of plasma protein fractionation outcomes.

Advancing AAV Analytics with a 4-Plex dPCR and Universal AAV Standard for Genome Integrity and Titer Assessment

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Accurate quantification and characterization of adeno-associated viral vectors (AAVs) are critical for gene therapy development and manufacturing. However, variability across analytical methods highlights the need for standardized reference materials for vector genome (vg) titer and genome integrity assessment. To address this challenge, Agathos Biologics developed a Universal AAV Standard (UAS) containing multiple PCR target regions distributed across the AAV genome. The rAAV8-UAS was previously characterized by Agathos Biologics (COA). At NibaLabs, two NibaPlex 4-plex dPCR assays targeting different genomic regions were performed on the QIAcuity Digital PCR System to quantify vg titer and assess genome integrity through multiplex analysis. Total vector genome titers determined by summing all detected fragment combinations were highly comparable between assays, with titers of $1.08\text{E}+13$ vg/mL for assay 4.01 and $1.03\text{E}+13$ vg/mL for assay 4.03. Genome integrity analysis demonstrated that approximately half of detected genomes across the bGHpA-SV40pA region contained all four target regions, with intact genomes measured at 46.85% ($5.07\text{E}+12$ vg/mL) in assay 4.01 and 52.67% ($5.41\text{E}+12$ vg/mL) in assay 4.03, in agreement with previously reported COA values for both vector genome titer and genome integrity. The remaining signal consisted of incomplete genome fragments, demonstrating characterization beyond total vg titer alone. These results demonstrate strong comparability between independently developed workflows and support the combined use of the UAS and NibaPlex multiplex dPCR assays as a practical approach for comprehensive AAV characterization across laboratories.

Rapid process optimization and simultaneous characterization of multiple vector variants using high-throughput small-scale rAAV production platform

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Recombinant adeno associated viruses (rAAVs) are widely used in gene therapy, yet their production is limited by low throughput, high cost, and restricted capacity to systematically study factors that influence vector quality. To address these challenges, we developed a small scale, suspension based rAAV production platform using triple transfection of HEK293T cells, enabling efficient process optimization and production of multiple vector variants to systematically investigate factors that influence genome integrity in the future.

rAAV vectors were produced by triple transfection of HEK293T suspension cells at 50 ml, 30 ml, and 3 ml scales. Cells were harvested 72 hours post-transfection, and clarified lysates were subsequently analysed to determine viral titers. Capsid titers were quantified using ELISA, while vector genome titers and fragmentation profiles were determined using multiplex digital PCR and NibaPlex 4.01 assay targeting four genomic regions within vector genome. A design of experiments (DoE) approach was applied to optimize key transfection conditions to improve the complete genome titer concentration.

Comparable vector genome titers across all tested scales demonstrated that the rAAV production process could be successfully miniaturized without compromising productivity or analytical compatibility. The 3 ml format in 6-well plates enabled high throughput screening of up to 18 conditions simultaneously. DoE guided optimization identified parameter combinations that improved complete genome titers, and increased the proportion of fully packaged genomes, which is crucial for downstream vector potency.

This miniaturized platform provides a robust foundation for further studies planned in our laboratory, focusing on improvement of packaging efficiency and genome integrity.

Surviving the Shear: The Impact of Purification Methods on mcDNA-LNP Integrity

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GaletaBio

Lipid nanoparticles (LNPs) have emerged as a leading non-viral platform for nucleic acid delivery. While messenger RNA (mRNA) is the most widely utilized payload, durable expression can be achieved using minicircle DNA (mcDNA) vectors. However, due to its rigid double-stranded structure and higher charge density, the encapsulation and structural behaviour of mcDNA differs significantly from that of single-stranded mRNA, necessitating specialized analytical methods to evaluate LNP integrity. Following self-assembly, efficient removal of organic solvents and exchanging buffers is crucial to ensure product stability. In this study, LNPs were formulated using mcDNA produced in-house and commercially sourced lipids. mcDNA LNPs were purified using three distinct methods: i) industry-standard tangential flow filtration (TFF), ii) chromatographic purification via a CIM® (Convective Interaction Media) OH monolith column and iii) dialysis. LNP integrity and critical quality attributes were evaluated using an advanced PATfix® Switcher two-dimensional (2D) chromatographic system, Zetasizer - dynamic light scattering (DLS) system and ZetaView® Evolution - nanoparticle tracking analyzer (NTA). Results confirmed successful mcDNA encapsulation with high encapsulation efficiency. While size and polydispersity index (PDI) remained comparable after dialysis and chromatography purification, TFF – purified LNPs exhibited increased size and higher PDI, likely due to shear-induced stress damaging the nanoparticles. For small-scale dialysis, the only feasible method for scale-up is TFF. However, since these methods are not directly translatable, preliminary screenings, as presented in this study, are essential to provide critical information for choosing the right process conditions. These findings highlight the distinct challenges of DNA-LNP formulations, emphasizing the need to combine suitable downstream processes and advanced analytical tools to achieve high-quality LNPs.

Ionizable Lipid-Dependent mRNA Delivery to Human Motor Neurons in 2D and 3D Cultures

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The transfection performance of lipid nanoparticles (LNPs) in hard-to-transfect primary cells depends on both lipid composition and RNA loading. In particular, the ionizable lipid plays a critical role in endosomal escape and subsequent cytosolic release of the RNA cargo. Here, we compare novel LNP formulations for mRNA delivery to human motor neurons in 2D and 3D cultures, supported by single-particle-based LNP characterization.

Methods

LNPs were produced using an ethanol-injection method. Formulations differed exclusively in the ionizable lipid component and included newly developed proprietary ionizable lipids as well as commercially available ionizable lipids. Hydrodynamic diameter and particle concentration were determined by nanoparticle tracking analysis (NTA; ZetaView, Particle Metrix). RNA loading was assessed by single-particle colocalization of fluorescence (FL500) and light-scattering signals (SC488) using the ZetaView system and complemented by flow cytometric analysis. Transfection performance of mCherry mRNA-loaded LNPs was evaluated in human iPSC-derived motor neurons cultured as 2D monolayers and 3D neurospheres using fluorescence microscopy.

Results

The ethanol-injection process generated LNP formulations with comparable particle concentrations. LNPs containing the newly developed ionizable lipids showed higher mRNA transfection activity than formulations containing commercially available ionizable lipids. In 3D neurospheres, widespread mCherry expression throughout the motor neuron population was achieved without apparent impairment of neuronal morphology or neurite formation.

Conclusion

Novel ionizable lipids enable highly efficient and well-tolerated mRNA delivery to human motor neurons, including complex 3D cultures. Single-particle-based LNP characterization provides a valuable analytical approach for the systematic comparison of LNP formulations and their transfection performance.

Application of ssDNA Xenoligo aptamers for plasma protein affinity purification

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Single-stranded DNA (ssDNA) Xenoligo aptamers—developed by TAGCyx Biotechnologies using proprietary artificial base technology (Ds)—represent a highly specific, stable, and cost-effective alternative to antibodies for plasma protein affinity purification and therapeutic apheresis. Process of plasma fractionation has a long history which has been depending on the Cohn fractionation. There are significant unmet needs for new technologies which can avoid Cohn fractionation, EtOH and need to reduce the production facility size. Also, importantly, we need to prepare for next unknown pandemic outbreak. In order to improve the current plasma fractionation issues, we demonstrate affinity purification process using TAGCyx's ssDNA aptamer affinity purification of plasma protein. The ssDNA aptamers have various advantages, such as possible Tag-less isolation of native and functional protein under low temperature, tunable elution and sterilizable with its physico-chemical stability without much batch difference with long shelf life.

Additive Manufacturing Techniques for Immobilisation of T7 RNA Polymerase

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mRNA vaccines have been used as the main technology to fight the recent COVID-19 pandemic, which proved the importance of RNA-based therapeutics (Webb et al. 2022). The sudden growth in mRNA vaccines caused an immediate demand for cost-effective methods for large-scale mRNA production.

Enzymatic processes have been progressively adopted as green and sustainable methods for chemical manufacturing. Enzyme immobilisation is a proven technique that facilitates enzyme handling and their separation from the product (Sheldon and Van Pelt 2013). However, the method has not been extensively applied for the manufacturing of mRNA vaccines.

Additive manufacturing (AM) is a versatile fabrication technique that enables to achieve structures with fully customizable design. In the context of protein synthesis, 3D-printed supports for enzyme immobilisation have shown significant potential to lower production costs, enhance process sustainability, and accelerate manufacturing timelines (Remonatto et al. 2023).

This work is concerned with combining the aforementioned techniques to develop an enzyme-immobilised 3D-printed bioreactor prototype for large-scale mRNA production. Preliminary data showing the effectiveness of purification and immobilisation of T7 RNA Polymerase will be presented.

A versatile platform to achieving graft-functionalised polymer layers on diverse convective chromatographic materials

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The rapid advent of complex, curative biotherapeutics poses unprecedented challenges for bio-separations and downstream processing. To address the growing industry demand for next-generation purification platforms, the downstream processing toolkit must be expanded. Convective chromatographic supports are often preferred to conventional ones for the purification of larger biomolecules due to their higher throughput. While commercial convective media typically take the form of membranes or monoliths, novel formats such as customisable 3D printed structures and compressible foams offer highly promising alternatives.

In this study, we propose a methodology to achieve targeted surface grafting across complementary support materials, including rigid 3D printed geometries and compressible foams. By employing controlled radical polymerisation to graft polymer brushes—such as sulfopropyl methacrylate (SPMA) and poly(glycidyl methacrylate) (GMA)—onto the media surface, we significantly increase the available surface ligand density. This versatile approach facilitates the flexible derivatisation of various surface chemistries, imparting a wide range of functionalities, including ion-exchange and hydrophobic interactions, which result in greatly enhanced binding capacities.

Results demonstrate that grafted polymer layers could be reproducibly achieved with a degree of grafting of 20%. The functionalised materials were extensively characterised, evaluating the mechanical, chemical, and surface properties of the supports as a function of the grafting process parameters. Finally, we successfully validated the practical applicability of these functionalised supports through bind-and-elute studies using model proteins under both static and dynamic conditions, highlighting their potential as highly adaptable stationary phases.

Extracellular vesicles, extracellular particles, liposomes and hybriodosomes: Experience in theoretical, experimental and clinical studies

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Research on intercellular communication points to nano-sized particles as the entities that are most likely exchanged between cells and also between cells and the environment. Furthermore, nano-sized membrane inclusions are being considered as key in designing targeted structural rescue strategies and mapping out the future landscape of molecular medicine. The hypothesis of extracellular vesicles as a common language between organisms of all types as well as between organisms and inorganic entities is very promising in the pursuit of manipulation of different pathologies, food production, and environmental sustainability. Furthermore, it concerns the One Health problem at its origin, supporting microorganisms, plants, and animals. The extracellular particle hypothesis has been extensively elaborated; however, the extracellular particle-based methods have not yet made a breakthrough to common clinical practice. Due to their small size, fragility and integration with other structures, their harvesting, characterization and manipulation present considerable challenges. We present selected results, challenges that have been overcome, and emergent open questions regarding this field.

Monolithic immunoaffinity column functionalized with polyclonal guinea pig IgGs for vesicular stomatitis virus purification

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Vesicular stomatitis virus (VSV) is an enveloped, negative-strand RNA virus with proven potential in oncolytic virotherapy and vaccine development. Efficient immunoaffinity purification of infectious VSV remains challenging due to the strong interactions between viral particles and affinity ligands, as well as the sensitivity of enveloped viruses to elution conditions.

This study investigated the applicability of immunoaffinity chromatography (IAC) using a hydrazide-activated monolithic column immobilized with polyclonal guinea pig anti-VSV IgG antibodies coupled with proprietary native elution for VSV purification. Purification efficiency was evaluated by nanoparticle tracking analysis (NTA) and CCID50 assay.

The prepared immunoaffinity column demonstrated a very high binding capacity for VSV. However, the interaction between VSV and immobilized guinea pig anti-VSV antibodies proved exceptionally strong, resulting in very limited virus recovery. Various elution conditions were tested, including high-molarity amino acid solutions, low- and high-pH buffers, MgCl₂ solutions, and high-salt conditions, but none achieved recovery higher than 3.5% of total particles in the eluate. Column cleaning was performed using Triton X-100 and NaCl.

The study highlights the importance of balancing binding strength and elution efficiency in the development of immunoaffinity purification strategies for enveloped viral therapeutics.

Advancing rAAV Manufacturing with Novel Plasmid Systems and the PLASMITEC® Platform

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WACKER

Recombinant Adeno-Associated Viruses (rAAV) are amongst the most widely used vectors to mediate the delivery of genetic information in Advanced Therapy Medicinal Products (ATMPs), yet their accessibility is constrained by the availability of high-quality plasmid DNA (pDNA). Accordingly, both the development and application of advanced therapies demand optimized pDNA compositions that exhibit high biological activity and can be produced at high titers and quality. The availability and thus affordability of these raw materials in turn demand high-performing manufacturing processes. The PLASMITEC® platform allows scalable production and isolation of plasmid DNA, integrating proprietary high performance producer strains, high-cell-density fermentation processes and state-of-the-art purification techniques. This platform delivers high product titers at superior product quality within shortened turnover times, thereby facilitating the development and translation of advanced medicine applications. In extension of this toolbox, WACKER has developed optimized DNA sequences that improve the productivity of the target plasmids, further reducing manufacturing costs. By combining these sequences with novel plasmid architectures, proprietary systems were developed that facilitate production of functional rAAVs. The enhanced producibility and reduced size of these compositions improve both accessibility and efficiency, thereby addressing a critical bottleneck in the commercialization of gene therapies. With its flexibility and scalability, the PLASMITEC® manufacturing platform provides high-quality and affordable raw materials and is therefore an invaluable facilitator for the development and application of advanced therapies.

Revolutionizing Plasmid DNA Production: A Chromatography-free, High-yield, High-quality Platform Process

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CoJourney Bio

Plasmid DNA (pDNA) is a critical starting material for viral-vector manufacturing, mRNA production, DNA vaccines, gene editing, and other cell and gene therapy applications. Conventional chromatography-dependent downstream processes can present limitations in recovery, resin cost, operational complexity, scalability, and cross-contamination risk associated with resin reuse in multiproduct facilities. In addition, poorly controlled alkaline lysis and flocculation can increase the solids burden during clarification, while prolonged or unsuitable lysate hold conditions can convert supercoiled plasmid DNA into open-circular forms, reducing product quality and process yield. This study describes the development of Zero-Chrom, a closed, single-use, chromatography-free pDNA purification platform designed to address these interconnected manufacturing challenges. The integrated pDNA manufacturing makes the CMC development of vector highly cost efficient.

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mRNA development at NeoVac

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NeoVac

RNA-LNPs are transforming vaccine and therapeutic development. However, successful translation into therapy/vaccine requires coordinated capabilities across design, process development, analytical characterisation, stability and GMP-ready manufacturing of RNA-based drug-substances (DS). NeoVac's RNA development team addresses this need through an integrated platform.

The workflow of the RNA-team at NeoVac spans through "Target → Concept → RNA Engineering → Manufacturing → Analytics". This enables development decisions to be aligned from early target selection and protein design through sequence optimisation, RNA construct engineering, manufacturing strategy, analytical quality assessment, and translational planning.

NeoVac applies expertise across multiple RNA modalities, including mRNA, self-amplifying RNA (saRNA), siRNA, sgRNA, and emerging RNA platforms. Continuous innovation in RNA design, analytical methods, and quality attributes supports improved manufacturability, product characterization, and development efficiency.

NeoVac has established CDMO and CRO partnerships that provide access to GMP manufacturing capacity, analytical development support, and specialised translational infrastructure. This partnership model enables flexible progression of RNA programmes from discovery-stage concepts to clinic-ready materials.

Conclusion: NeoVac has established an integrated RNA development platform to connect every aspect of RNA development process. Our platform combines broad RNA-modality expertise, an innovative mindset, comprehensive development capabilities, as well as strategic external manufacturing and analytical partnerships. NeoVac is uniquely positioned to accelerate clinical translation of RNA-based drugs by combining our strength across mRNA, lipids, LNPs, analytics and biology expertise together to tackle global health challenges.

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