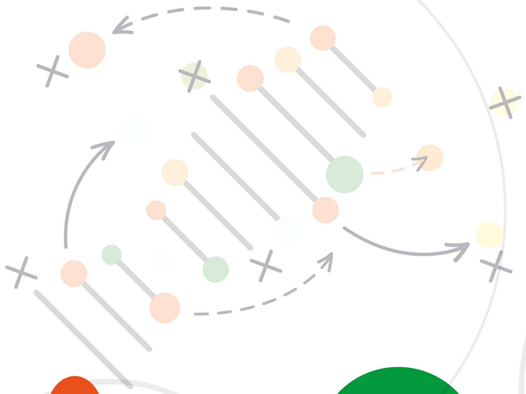
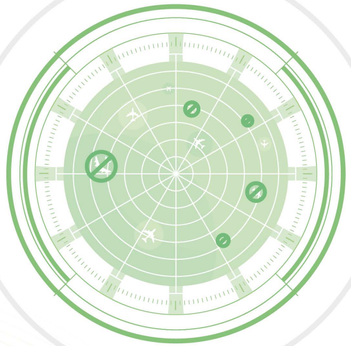
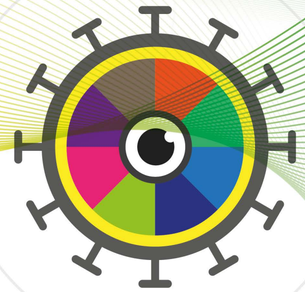
Biopharma Visionaries

Vaccines, mRNA, ADCs, and beyond. We speak with experts about the trends and challenges in biopharma drug development.







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The Speed of Science

From the GSK boardroom to the White House, and now the board of Abzena, the career path of Moncef Slaoui has resulted in billions of doses of lifesaving vaccines. Here he shares his story.

What inspired your interest in science, and how did you come to focus on biologics and vaccines?
My interest in science began early in life. I have always been fascinated by the complexity of the human body and living organisms, and I was eager to understand their mechanisms beyond the religious explanations provided in my early education. By the age of ten, I had developed a strong passion for biology, which ultimately drove me to pursue a career in science. While my initial ambition was to become a physician, I eventually pursued a PhD in immunology, which led me to the study of the immune system.

My transition into vaccines was somewhat serendipitous. During my postdoctoral research in the US, my future wife, an HIV expert, was recruited by a vaccine company, which was a division of GlaxoSmithKline (GSK) in Belgium. As an immunologist, I began advising the company, and through that engagement, I developed a deep appreciation for vaccines.

A personal factor also played a role in my commitment to vaccines; my parents lost a child to whooping cough before I was born. This tragedy instilled in my family a strong awareness of the importance of immunization. Over time, this awareness evolved into a lifelong professional passion.

You have been involved in numerous vaccine projects. What do you consider the biggest challenges in the field?
Vaccine development has evolved significantly over the years. Historically, vaccines were produced by growing entire pathogens — bacteria or viruses — and then either killing or attenuating them for use in immunization. However, advances in immunology and molecular biology in the 1960s revolutionized the field. These breakthroughs enabled us to identify and utilize specific proteins from pathogens, allowing for more targeted and rational vaccine design.

Despite these advances, several challenges remain. The first major challenge is overcoming pathogens that have evolved sophisticated mechanisms to evade the immune system. Viruses such as HIV and herpes, as well as bacteria such as chlamydia, have developed ways to subvert immune responses, making vaccine development for these diseases extraordinarily difficult.

The second challenge lies in the complexities of large-scale vaccine manufacturing. Producing vaccines requires a high level of precision to ensure consistency across billions of doses. This demands advanced infrastructure, significant investment, and highly skilled personnel.

A third and growing challenge is public trust. Vaccines are only effective if people accept and receive them. Unfortunately, misinformation has contributed to a decline in vaccine confidence, which is deeply concerning. Recent policy changes in the US may further exacerbate this issue, making it even more critical to engage in transparent and effective communication about the safety and necessity of vaccines.

How did it feel to be involved in major vaccine projects like Shingrix and the malaria vaccine?
I feel incredibly fortunate to have played a role in these projects.

The Speed of Science (cont...)

"While political controversies and misinformation have been frustrating, I remain confident in the vaccines' effectiveness and safety."

My early involvement in vaccines happened largely by chance, but it became a deeply fulfilling career. Some vaccines, such as the malaria vaccine, took over 25 years to develop from initial concept to regulatory approval. The moment we receive key data demonstrating efficacy is profoundly emotional. I have often found myself overwhelmed with joy, sometimes even in tears, knowing that our work will save millions of lives.

This impact is particularly meaningful in low-income countries, where access to life-saving vaccines can determine survival for large populations. When I was an executive at GSK, I ensured the company remained committed to developing vaccines and medicines that were not necessarily lucrative but were crucial for global health. The malaria vaccine, for example, was never designed to generate profit – it was designed to save hundreds of thousands of children's lives each year in sub-Saharan Africa.

How did you become involved in Operation Warp Speed, and what was the experience like?

My involvement stemmed from prior collaborations with the US government during previous health crises, including the H1N1 flu pandemic in 2008, the Ebola outbreak, and the Zika virus outbreak. During those events, I strongly advocated for better pandemic preparedness. Unfortunately, little action was taken at the time.

When COVID-19 emerged, former congressman Jim Greenwood reached out to me, and after a 45-minute discussion on how to accelerate vaccine development, he informed me that the White House would likely call. Within days, I was in discussions with senior government officials, including Jared Kushner and Alex Azar. I agreed to lead the scientific efforts of what was initially called the "Manhattan Project 2," later known as "Operation Warp Speed".

The first major decision was selecting which vaccines to support. Over 100 candidates were submitted, but I narrowed them down to six based on my experience and intuition. Fortunately, all six turned out to be highly effective. The program involved thousands of professionals across pharmaceutical companies, the US Army, and various agencies. It was an intense, high-pressure experience, but ultimately, we achieved our goal of delivering vaccines in record time.

Given the current political climate, do you feel your efforts were in vain?

Not at all. Our work was never just for the US, it was for the world. Approximately six billion people have been vaccinated, saving tens of millions of lives. While political controversies and misinformation have been frustrating, I remain confident in the vaccines' effectiveness and safety. The rapid development process was rigorous, and after billions of doses, we know these vaccines are both safe and critical in preventing disease. Science enabled us to reclaim normalcy, and that is something to be proud of.

How did you become involved with Abzena, and what excites you about the company?

Since retiring from GSK, I have been active in venture capital, supporting biotech companies. Abzena caught my attention because it operates at the intersection of discovery and manufacturing, offering expertise in designing complex biologics and bioconjugates, with the capability to produce them at scale. Their ability to bridge these two critical areas is invaluable, particularly in the era of advanced biopharmaceuticals such as bispecific and trispecific antibodies, antibody-drug conjugates (ADCs), antibody-oligonucleotide conjugates (AOCs), and radiopharmaceuticals.

What trends in biopharma particularly interest you?

I am especially excited about engineered antibodies, which are revolutionizing oncology and immunoinflammatory diseases. Additionally, cell therapies hold immense potential, though manufacturing remains a significant hurdle. Vaccines remain a core passion, and I continue to monitor new technologies in that space.

Biopharmaceuticals: Simplifying Complexity With mRNA

Here's how an mRNA-based approach can overcome the development challenges of designing protein therapeutics

By Gunasekaran Kannan, Senior Vice President, Protein Engineering, at Nutcracker Therapeutics

The deeper we explore human physiology, the more complexity we uncover. To overcome diseases, such as cancer, our approaches have also become more complex, moving far beyond small molecules, chemotherapies, and radiation into protein-based therapeutics.

The infinite variation allowed by peptide architectures almost always ensures that there is a protein-based therapeutic approach for any disease we choose to address. For example, immune checkpoint modulators orchestrate and help restore cell-mediated immune responses, while immunoconjugates help traffic radioisotopes or toxins to specific tumor cell receptors; monoclonal antibodies bind and inhibit TNF-α to treat various autoimmune diseases or IL-2 on activated T cells to prevent kidney transplant rejection.

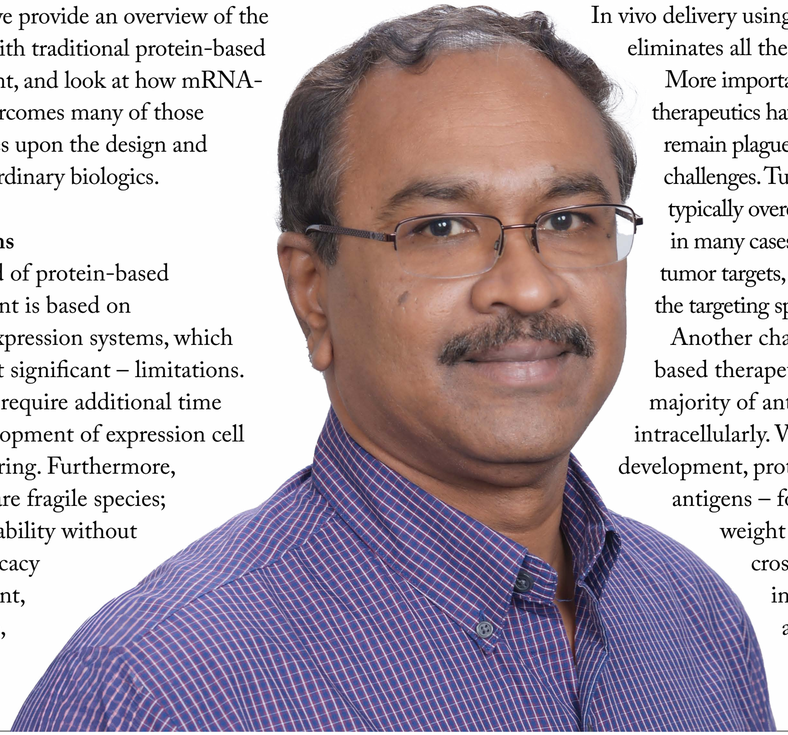
Beyond these examples are cytokine therapies, fusion proteins, peptide hormones, hemolytic factors, and many more. The variations, applications and complexity of protein-based therapeutics are virtually endless. But they come at a price: complex protein-based therapeutics are difficult to develop. Since the first FDA approval of a mAb (muromonab-CD3) in 1986, there have only been around 350 approved protein-based therapeutics out of a total of nearly 4,500 FDA approved drugs, and only a dozen or so bispecific antibodies, which are a little more complex than the conventional mAbs.

That situation is beginning to change thanks to the advent of mRNA-encoded protein therapeutics. An mRNA-based approach – delivering mRNA molecules that have been engineered to express a therapeutic protein in vivo — overcomes many of the limitations and challenges associated with the traditional recombinant approach to protein design and delivery.

mRNA-encoded protein therapeutics also offer further advantages beyond design, in terms of dosing, manufacturing quality, native post translational modifications (for example, glycosylation), and therapeutic applicability across a variety of indications and tissues. In this article, we provide an overview of the challenges associated with traditional protein-based therapeutic development, and look at how mRNA-based development overcomes many of those challenges and improves upon the design and delivery of these extraordinary biologics.

Protein-based problems

The traditional method of protein-based therapeutic development is based on recombinant protein expression systems, which have several basic – but significant – limitations. Recombinant proteins require additional time and resources for development of expression cell lines for biomanufacturing. Furthermore, recombinant proteins are fragile species; maintaining protein stability without impinging on drug efficacy throughout development, manufacturing, storage, and delivery to healthcare centers and patients is both labor and resource intensive.



Drug formulations must be developed and tailored to the protein, as well as to individual patient populations, delivery methods, and (in some cases) to differing disease indications. All these factors add to the development timeline – on average 18 months or more for full molecule development, from the transfection of the production cell line to drug product – delaying clinical studies and the eventual delivery of these much-needed therapies to patients.

In vivo delivery using an mRNA-based approach eliminates all these manufacturing bottlenecks.

More importantly, while protein-based therapeutics have shown great promise, they remain plagued with several critical physiological challenges. Tumor-specific drug targets are typically overexpressed on cancer cells. However, in many cases, healthy cells also express the tumor targets, albeit at a lower level, complicating the targeting specificity of protein therapies.

Another challenge in designing protein-based therapeutics is the fact that the majority of antigens in cancers are expressed intracellularly. With a recombinant approach to development, proteins necessary to target those antigens – for example high-molecular weight antibodies – are unable to cross the cell membrane. As such, intracellularly expressed antigens are still a largely untapped source of therapeutic targets.

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Biopharmaceuticals: Simplifying Complexity With mRNA (cont...)

It is well known that differential tumor cell antigen expression and tumor heterogeneity often result in poor therapeutic response in patients. Engineering multi-target, antigen-binding capabilities within a single protein is necessary to overcome this challenge. However, multi-target design is difficult to accomplish with a recombinant approach, creating complex challenges for biomanufacturing, purification, and retaining drug stability.

mRNA-based advantages

CD47, a cell surface protein expressed on multiple cell types, including overexpression in cancer cells, offers an excellent case study in the advantages of an mRNA-based approach to the development of protein-based therapeutics. CD47-expressing cancer cells can evade immune clearance and proliferate when they bind the signal regulatory protein alpha (SIRPα) on myeloid cells, creating a "don't eat me" signal that causes phagocytic immune cells to mistake the cancer cells for "self" and pass them by. Disrupting this interaction has become an important goal and target in cancer immunotherapeutic development.

However, as a target, the CD47-SIRPα interaction is fraught with barriers. CD47 is broadly expressed at low levels on many healthy cell types. For instance, CD47 is well expressed on red blood cells, which can create off-tumor, on-target activity leading to hematological toxicities in patients. This can dramatically reduce the therapeutic window of drugs that target the CD47-SIRPα interaction. Further, the off-tumor and on-target binding of the anti-CD47 drug can act as a sink, reducing the effective therapeutic concentration.

A promising avenue of development to overcome these barriers is a multivalent approach to complex protein design. For example, engineering an octavalent SIRPα-Fc fusion protein increases CD47 binding (apparent) affinity because of increased avidity (i.e., tighter binding as the target density is increased). This multivalent approach enables the protein to differentiate low versus high target expressing cells with dramatically improved specificity. It achieves a high signal (on-target tumor cell binding) to noise (on-target off-tumor effects) ratio, increasing the therapeutic window and driving potent tumor killing without enhancing binding to low target expressing healthy cells (Figure 1).

mRNA-based engineering of complex proteins can also be used to increase target specificity and circumvent tumor heterogeneity by taking a multi-target approach to protein design. For example, in B cell-mediated diseases, Fc effector function can be enhanced through macrophage checkpoint inhibition via SIRPα. However, off-target binding is still a concern because of the wide expression of CD47 across the immune cell population. A multi-target approach using a trispecific protein – for example, targeting aCD19-aCD20-SIRPα – engages CD47 only when other targets, CD19 and CD20, are present, ensuring that only B cells are targeted out of the total immune cell population. Engaging multiple tumor-associated antigens overcome the tumor heterogeneity, hence results in broader tumor coverage, and enhance cellular specificity, thereby increasing the therapeutic window (Figure 2). In this way, SIRPα-CD47 binding is tuned to avoid off-tumor binding to improve safety (Figure 3).

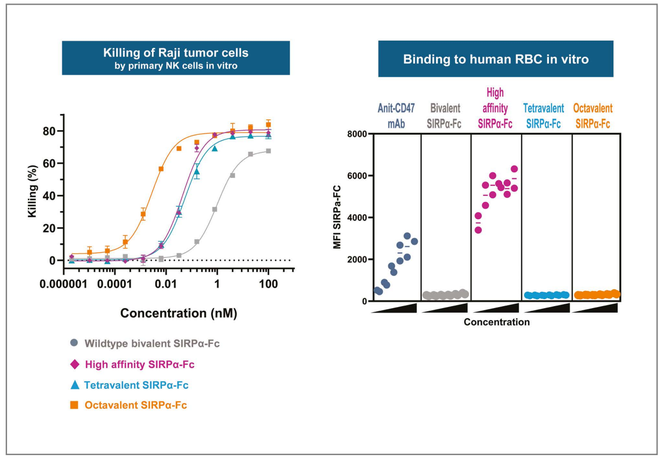

Figure 1. Multivalent SIRPα-Fc molecules enhance potency with minimal impact to healthy cells

Other advantages

Multi-valent and multi-target approaches to engineering protein-based therapeutics address the physiological challenges well,

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Biopharmaceuticals: Simplifying Complexity With mRNA (cont...)

but, in theory, a recombinant approach could produce constructs able to manufacture the same types of molecules. So why would one feel compelled to take an mRNA-based approach over recombinant design?

There are several reasons. First, because there is no need to develop expression cell lines, manufacturing and purification protocols, or specific drug formulations, development times for mRNA-based therapeutics are greatly reduced, down to six months from eighteen, on average. Multispecific and multivalent proteins have structural, chemical, and binding properties that can make their manufacturing and purification difficult, when working from recombinant constructs. Precision manufacturing involved in mRNA-based therapeutics also allows for elimination of many of the manufacturing, purification, storage, and formulation concerns, and results in a very high quality of product produced through the native in vivo process with endogenous post translational modifications.

In vivo expression of proteins from mRNA delivered with high specificity to the cells also creates a beneficial PK profile, avoiding the initial high Cmax observed with intravenous bolus delivery of recombinantly produced therapeutic proteins. The high C_{max} has been clinically linked to safety issues, such as cytokine release syndrome, in T-cell mediated therapies. Since the "manufacture" of the protein is in vivo, this approach also overcomes the challenges associated with membrane-bound and intracellular targets. In vivo expression of membrane-bound proteins uses cellular protein expression processes and produces a stable protein that is properly transported to the target site through the cell's native cell localization systems. This also allows for in vivo targeting of intracellular antigens, providing access to a large, untapped pool of potential therapeutic targets.

For the moment, consistent delivery of mRNA with high tissue and cellular specificity is the limiting factor for mRNA-based protein therapies, but as the delivery vehicle technologies improve, broader applicability for the mRNA-based therapeutics will emerge very quickly.

The future of cancer and disease treatment is one of increasing complexity. Protein-based therapeutics will be key to realizing the treatments of tomorrow. mRNA-based protein design offers the most flexible path forward for designing drugs that overcome the barriers and challenges associated with durable treatments. It also offers advantages from a business perspective by driving down development times, moving therapies to the clinic at greater speed, and forging a path toward simplifying the emerging complexity in our understanding of human biology.

The author wishes to thank Shruti Lal, Adrienne Sallets, Srinivasa Bandi, Gowrisudha Adusumilli, Ray Low, and the rest of the NTX-471/2 project team members for their contributions to the data shown in this article.

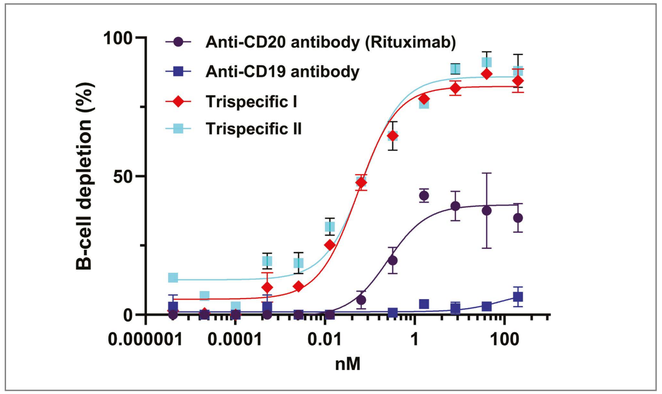

Figure 2. Superior ex vivo B cell depletion in cynomolgus monkey with tri-specific protein designs

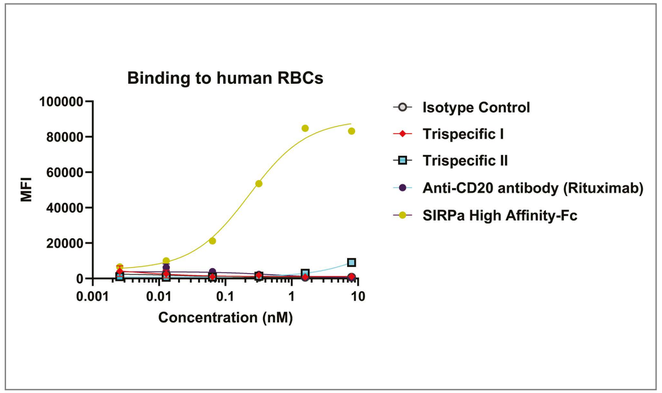

Figure 3. Tri-specific molecules do not bind significantly to human red blood cells

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Accelerating Cell Line Development

The essential roles of optimized cell lines and vectors in accelerating bioprocessing

By Brett Verstak, Director of Cell Line Development at Abzena

In today's rapidly evolving biopharmaceutical landscape, speed and efficiency in cell line development are more critical than ever. While gene integration methods such as transposase technologies have garnered significant attention, it is essential to not overlook the fundamental aspects of gene expression. Regardless of the method used to drive stable integration of the recombinant gene into the host chromosome, it is the quality of the gene expression cassette that truly drives high cellular productivity (Qp). This needs to be combined with a compatible host cell line that can support high levels of gene expression and a process that supports high cell density, cell viability and productivity. All three of these need to be in place to develop a robust process for bioproduction.

By focusing on refining vector components – such as promoters, signal peptides, and untranslated regions (UTRs) – and combining these with a fast-growing, robust cell line and a process for rapid screening and selection of high-quality, stable clones, we can derisk and accelerate cell line development activities to help bring innovative medicines to patients sooner.

Understanding the vector

One of the key factors affecting the productivity of a cell line is the expression vector. The vector carries multiple genetic elements that control the expression of the transgene(s) and allows for efficient selection of transfected cells. Developing a productive vector needs systematic consideration of each of these genetic elements, their role in gene expression and how they may interact with one another.

Promoters are the engines of gene expression and, typically, a strong constitutive promoter is selected to ensure robust RNA transcription of the gene of interest. The untranslated regions (UTRs) play a critical role in the transcribed RNA stability, processing and transport out of the nucleus, as well as the affinity for ribosomes. These are often overlooked sequences that can play a critical role in translation efficiency. Fine-tuning these regions allows you to capitalize on the choice of a strong promoter and ensure that more of the message transcribed results in a translated polypeptide.

Signal peptides guide the nascent polypeptide through the secretory pathway, and optimizing these sequences can improve protein folding and secretion efficiency, which is critical in maintaining cell health, productivity and product quality.

The selection marker's design and regulation can significantly impact the speed and reliability of post-transfection selection, cloning, expansion, and characterization of clones. The position and orientation of the different gene expression cassettes can also impact expression levels, through both trans- and cis- mechanisms.

By carefully designing the gene cassette, we can also influence epigenetic factors that stabilize gene expression over time. This stability is crucial for maintaining high protein production levels throughout manufacturing and complying with regulatory guidance. Holistic optimization of vector architecture can result in less stress on the cells and eases the initial phases of cell line development, allowing for the more efficient selection of high-producing, stable clones.

Accelerating Cell Line Development (cont...)

Optimized cell lines

The ideal host cell line will have the potential to grow to high cell density and maintain high viability throughout the production process. A host cell that has been selected to achieve high viable cell density and withstand the biological and mechanical stresses of the bioreactor environment puts you in a great starting position. Selecting clones that accumulate low levels of toxic metabolites, such as lactate and ammonium, also provides the best chance of maintaining performance, particularly as you scale-up. This gets you a long way towards a production system that maximizes the integral of viable cell density (IVCD), the effective working time in the bioreactor. Boosting the two sides of the protein expression equation; maximizing Qp (each cell's productivity) and achieving higher IVCD, results in much higher titers.

Critical to maximizing IVCD and maintaining the high Qp for the duration of the culture is having an upstream process built around the cell line and vector combination. With a reliable upstream process that consistently gives high performance across different molecules, we can establish a robust platform that is flexible enough to accommodate a range of protein modalities. This gives the cell line developer the tools and flexibility to rapidly develop clones that perform well under standard conditions, to allow for the rapid development and progression of biopharmaceuticals, including mAbs, mAb fragments, bispecifics, and other more complex biologics.

While optimizing a flexible expression platform is crucial, it is also essential to incorporate this strategy with other technological advancements. For example, employing process intensification strategies such as an N-1 seed train intensification or a fully continuous perfusion process alongside optimized cell lines can increase productivity and reduce production costs. Moreover, integrating real-time monitoring and control systems allows for better bioprocess management, ensuring optimal cell growth, productivity and consistent product quality. This wider approach ensures that improvements in one area are complemented by advance in others.

Benefitting all of us

Traditionally, generating a production-ready cell line can take anywhere from six to 12 months. Using optimized vectors and cell lines with a high expression capacity can reduce this timeline to a matter of weeks. Speeding up these early development stages reduces costs associated with prolonged development times and hastens the delivery of potentially life-saving therapies to patients. In a field where time is of the essence, any reduction in development timelines is invaluable. A more efficient development process also enables companies to respond quickly to emerging medical needs. In pandemic responses or urgent therapeutic demands, the ability to rapidly develop and produce biologics can significantly impact public health.

Another important aspect of advancing vector optimization is collaboration. Sharing knowledge, data, and best practices can accelerate innovation and overcome common obstacles. Partnerships between biopharmaceutical companies, academic institutions, and technology providers can foster an environment where new ideas are tested and implemented more rapidly. Open-source platforms and collaborative networks enable researchers to access information and tools that might otherwise be unavailable. Working together, the industry can develop standardized protocols and methodologies that benefit all of us.

Adopting new strategies requires us to remain aware of regulatory requirements. Ensuring that changes in cell line development and production processes comply with regulatory guidelines is essential. Early engagement with regulatory bodies and thorough documentation of development processes can facilitate smoother transitions through the approval pipeline.

By demonstrating that flexible platforms lead to consistent and stable cell lines, we can build confidence with regulators regarding the safety and efficacy of the resulting therapeutics. The future of biopharmaceuticals lies in our willingness to innovate and adapt. Holistic optimization of vectors, cell lines, and processes can offer a tangible pathway to accelerate cell line development and enhance productivity without the need to burden drug developers with unpalatable license fees or royalty payments. By focusing on the fundamental elements of gene expression and harnessing our collective expertise, we can drive significant advancements in the industry.

It's an exciting time to be part of this field. The challenges are substantial, but so are the opportunities. As we continue to refine our approaches and embrace new strategies, we stand to make a profound impact on global health.

Streamlining Biologics from IND to Commercial Scale with Continuous Manufacturing

Leveraging its data-driven, fully integrated design capability and continuous manufacturing technology platform (J.DESIGN), Just – Evotec Biologics aims to deliver the highest product quality and cost efficiency to its partners.

By Nick Hutchinson, Associate Vice President, Business Development

At Just - Evotec Biologics, our goal is to help customers bring their antibodies and next-generation biologics to market faster, reliably, and with a more efficient process that will reduce production costs. A central component in this mission is our comprehensive J.DESIGN service, which integrates AI/ML-driven antibody selection and optimization, high-expression cell lines, and continuous manufacturing infrastructure to support every phase of biologics development – including design, optimization, and commercial production.

For example, at the earliest stages we can select and optimize antibody variants with favorable manufacturability profiles, which helps to smooth the path to process development. Our manufacturing platform – built on an intensified, continuous process and using our proprietary J.CHO™ High Expression System – is highly robust and allows us to bypass many aspects of traditional process development by confirming product fit rather than building a new process from scratch. Because this platform is highly productive, we can consistently generate more than enough material for first-in-human studies. However, our customers are also welcome to integrate their own cell line.

Supporting greater efficiencies

Integrating cell line development and process development has a huge impact on minimizing inefficiencies. By integrating development activities, we can initiate process development, formulation and analytical work even before cell line development is complete, shaving weeks – even months – off development timelines.

Another powerful advantage of our manufacturing platform is that scale-up is unnecessary. Unlike fed-batch processes that often require facility and equipment changes in late-phase or commercial production, our approach relies on running the same process for longer, or at slightly higher volumes. We typically move from a 500 L to a 1,000 L perfusion bioreactor and extend the production duration – without changing facilities, equipment, or operating teams. This continuity also streamlines the path to filing because data collected during early clinical manufacturing can support commercial submissions.

Perfusion technology supports higher product quality by minimizing residence time in the bioreactor, reducing the risk of enzymatic or chemical degradation. The continuous process maintains cell health and product stability throughout, making it particularly advantageous for complex or fragile molecules, such as bispecific antibodies. Downstream, material flows continuously through purification steps with minimal hold times, further preserving product integrity.

Continuous product collection through perfusion enables highly efficient downstream processing. Our multi-column protein A capture systems run a high number of cycles per campaign, significantly reducing resin consumption compared to the 5 or 10 cycles typical in fed-batch. This level of intensity applies across

Streamlining Biologics from IND to Commercial Scale with Continuous Manufacturing (cont...)

the downstream process, supporting both cost-efficiency and facility compactness.

Integrated and de-risked approach

Our regulatory affairs team will engage from day one to align development work with each client's investigational new drug (IND). We've filed our own INDs, including Modules 1 through 5, so we understand the full scope of regulatory expectations. Clients can lean on us for as much – or as little – support as they need. Some prefer a hands-on approach; others want us to act as their de facto regulatory department. The choice is yours.

Our J.POD® facilities were purpose-built for continuous biomanufacturing, and can support first-in-human and early phase clinical, late phase clinical, and commercial production. By controlling cell line development, process development, and manufacturing under one roof, we can detect and mitigate issues earlier. This tight integration minimizes risk and supports faster, more reliable development, with fewer handoffs, faster timelines, and a more seamless experience for partners. Competitors with less integrated approaches may only catch problems later, which can delay timelines and increase costs.

We have J.POD® facilities in both the US and Europe, allowing us to manufacture close to key markets and patient populations. However, we can also work with clients to integrate our platform into their own infrastructure. We provide design, intellectual property, and technical expertise to help clients achieve the same operational efficiency we see in our sites.

The future of biologics manufacturing isn't just faster; it's smarter, more connected, and built for agility at every stage.

Credit: Benjamin Benschneider

Vial Wars

Study investigates why vial choices matter for frozen biopharmaceutical storage

Researchers from Ludwig-Maximilians-Universität and Boehringer Ingelheim have published an open-access study that explores the effect of vial quality on biopharmaceuticals stored at low temperatures. The team analyzed the suitability of various vial types for the storage of frozen drug products, considering factors such as mechanical stress during freeze-thaw cycles, vial surface characteristics, particle formation, and gas permeability.

The research comes in response to growing demand for biopharmaceutical products that require frozen storage, such as vaccines and oncolytic viruses. These products must maintain their integrity during storage at temperatures as low as –70°C, necessitating reliable container closure systems that preserve quality, efficacy, and sterility. At the same time, there are also many new types of vials being introduced to the market, such as chemically strengthened glass vials made of aluminosilicate instead of borosilicate, and polymer vials. These various vial types may react differently to freezing and thawing.

The study focused on vials made from different materials, including type I borosilicate glass, aluminosilicate glass, and several polymer-based alternatives (including vials from Schott, Corning, and West, among others). Researchers assessed the vials' surface properties (e.g., roughness, hydrophobicity, and free energy), ability to withstand freeze-thaw stress, and potential for particle formation under extreme conditions. The study also examined the integrity of vial coatings and the permeability to gases, particularly oxygen.

One key finding was that the mechanical stresses of freezing and thawing did not significantly alter the surface properties of most vials. Surface roughness and hydrophobicity remained stable even after ten freeze-thaw cycles. This was true for both glass and polymer vials, with no observable damage or particle formation in most samples. However, coated glass and polymer vials did show some instances of particle formation, particularly after drop testing at frozen temperatures. These particles were typically of the same material as the vial (e.g., glass particles from glass vials or silicon from coated polymer vials), but their occurrence was rare and not deemed critical in terms of product safety.

Regarding vial integrity, the study revealed no significant differences in container closure performance before and after freeze-thaw cycles. While polymer vials, especially those without coatings, exhibited slight increases in helium leak rates, these were well within the acceptable range as defined by compendial standards. Notably, polymer vials with multi-layer coatings showed superior oxygen barrier properties compared to uncoated versions, although some increased permeability was observed after freeze-thaw cycles.

The findings suggest that multiple vial types, including both glass and polymer variants, can be suitable for the frozen storage of biopharmaceuticals. The choice of vial should depend on specific product requirements, such as formulation sensitivity to oxygen or the need for improved mechanical resilience during storage and transport. The study emphasizes the importance of careful selection of packaging materials and the consideration of stress factors during the storage lifecycle.

Original image sourced from: Adobestock.com

The Future of Bioprocessing

Automation, conjugation, and collaboration have all contributed to the augmentation of biopharmaceutical manufacturing in the last ten years. But what factors will drive change and propel innovation over the next ten years? We asked a range of experts from the sector.

We asked: What has/have been the key disruptor(s) driving the industry over the past ten years, and how will this change in the next ten years?

Better Vectors – with David Kirn, CEO and Co-Founder, 4DMT

The biopharmaceutical industry has been shaped by several key disruptors, particularly in the field of genetic medicine. While AAV vectors have brought genetic medicines to patients with rare and often fatal diseases, the challenges associated with the in vivo delivery of genetic medicine technologies have left many without safe and effective treatment options. Major challenges of AVVs include the need for high doses, expensive manufacturing, and the potential for adverse side effects – such as liver toxicity. Additionally, pre-existing antibodies to conventional vectors limit the utility of these therapies.

The field needs vectors that are more efficient at transducing specific cell types, and vectors that are more efficiently delivered at low and safe doses by routine routes of administration clinically; simply, we need better vectors. I foresee a shift in the introduction and development of next-generation AAVs using synthetic biology and novel capsids to overcome the limitations of conventional AAVs across the next ten years. One widely recognized approach that could bring superior AAV vectors is directed evolution, which allows humans to create novel bespoke biologics. In the case of AAV, the capsid can be diversified in order to generate billions of potential synthetic AAV capsids. In vivo iterative selection can then be used to identify the synthetic AAV capsid with the best match to the investigator's target vector profile.

Though past successes focused predominantly on rare diseases, the industry's gaze now appears set on larger, more complex conditions. As such, we might also expect to see breakthroughs in delivery systems, as enhancements in vector design, transgenes, and immunomodulatory regimens will likely improve delivery efficiency and gene expression, and reduce immunogenicity.

The Future of Bioprocessing (cont...)

"We're now entering the 'antibody 2.0' era, wherein the field has begun to overcome the initial limitations of antibody-based therapeutics."

Specificity, Strategy, Safety – with Jeng Her, CEO, AP Biosciences

We've witnessed antibody-based therapeutics transform the treatment landscape for patients across autoimmune disease, infectious disease, and especially cancer. Monoclonal antibodies have drastically improved patient outcomes in oncology and become the backbone for a range of therapeutic strategies. Their ability to bind specific targets continues to offer near limitless applications across drug development.

We're now entering the "antibody 2.0" era, wherein the field has begun to overcome the initial limitations of antibody-based therapeutics, such as efficacy and resistance. We've seen the adoption of new strategies in the form of antibody-conjugates, which are quickly becoming the norm, and now bispecific antibodies are emerging as another breakthrough drug class. These drugs can function as a combination treatment in a single molecule, simultaneously reducing toxicities associated with multidrug regimens and decreasing the likelihood of resistance. The high specificity of bispecifics can be combined not only with ADCs, but an array of other treatment modalities to enhance on-target activity and reduce side effects. The incredible flexibility of this approach is already creating new therapeutic strategies and improving on existing approaches.

With the growing number of applications, I foresee a concurrent rise in investment and collaboration aimed at streamlining antibody design and manufacturing, enabling us to treat patients with safer, more potent therapeutics.

In Support of Single-Use – with Tom Fletcher, Director of Process Development, FUJIFILM Irvine Scientific

Bioprocessing has played and continues to play an essential role in the life sciences. By providing the materials needed to fuel the revolution in next-generation therapies, cell and gene therapies and biologics have come to the forefront of disease treatment. Ever increasing demand for these therapies is continuing to push our industry to develop more optimized workflows capable of ensuring consistent and cost effective, large-scale drug substance manufacturing. At the same time, mounting global awareness and necessary pressure to develop environmentally sustainable processes is pushing our sector to innovate faster than ever.

When it comes to sustainability, one of the most crucial areas is single-use technologies (SUTs). Thermoplastic-based SUTs are widely recognized as essential for supporting the evolving bioprocessing sector, and more broadly within healthcare.

Owing to the significant risks that contamination poses in bioprocessing, SUTs have rapidly become the gold standard of mitigating these risks. However, they pose an apparent challenge when considering environmental impact as they, by definition, create a visible wastestream.

As the industry continues to transform, we can see a shift in perspective – companies taking a more holistic approach to integrating sustainability practices to minimize environmental impact wherever possible, whilst maximizing innovation to meet global healthcare demands. For example, SUTs offer

The Future of Bioprocessing (cont...)

"Wherever possible, platform processes and standardized raw materials and consumables should be employed to reduce complexity."

clear benefits over more permanent, reuseable equipment solutions as they reduce the need for on-site cleaning and sterilization that, in an industrial setting, can require huge amounts of water and energy – both of which contribute significant amounts of waste of their own.

Already, it is motivating to see how the industry is responding to these discussions and investing in appropriate solutions. Methods currently being employed include repurposing waste for energy production, or recycling scrap materials into usable products such as plastic lumber. In the coming years, I believe we will continue to see the development of new and exciting strategies to push this further, as well as the emergence of cutting-edge instruments and technologies built with efficiency and environmental impact at their core.

Are Attributes More Important Than the Process? – with Jerry Keybl, Senior Vice President, Biopharma Products and Strategy, Avantor

Regardless of the manufacturing path, one transformative improvement that could dramatically elevate the biopharmaceutical industry is the adoption of modular manufacturing defined by product attributes rather than the manufacturing process. This not only optimizes existing therapies, but paves the way for rapid production of new, emerging therapies.

This approach focuses on critical quality attributes and process parameters that define the product's efficacy, safety, and quality. This method ensures that the final product meets its intended quality and efficacy standards, allowing for more dynamic and adaptable manufacturing processes.

In addition, the manufacturing process can be broken into modular units that can each be validated for specific attributes. These manufacturing modules can be reconfigured or replaced if needed, providing greater flexibility and efficiency. Modular manufacturing allows for rapid adaptation to new therapies and changes in production needs, which is particularly beneficial for personalized medicines and rapidly evolving treatment modalities. This method provides a holistic and integrated approach to validation, with process and product data flows as the foundation.

Transitioning to attribute-based validation and modular manufacturing represents a paradigm shift for the pharmaceutical industry. We can unlock significant manufacturing productivity, enhance flexibility, and drive down costs – making these new treatment options accessible to more patients.

In addition, something else I would like to see in drug development and manufacturing is as much standardization as possible around novel therapies. Wherever possible, platform processes and standardized raw materials and consumables should be employed to reduce complexity, accelerate manufacturing timelines and reduce costs. In addition, I would like to see clear and consistent regulatory standards for new modalities, balancing safety and the unique aspects of these therapies, such as production processes and efficacy definitions.

Together, these changes would improve patient outcomes and advance the industry as a whole.

Read more opinions about the future of the biopharma industry by clicking here.

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A Love for Complexity: ADC Drug Development

Yoonjin Kwon, Lead Scientist, ADC Analytical Method Development, Samsung Biologics, offers her perspective on the future of antibody drug conjugates

How did you first get involved with the field?
I started my journey with ADCs as a junior analytical scientist at a biotechnology company after earning my master's degree. Then in 2014, I moved to Samsung Biologics to lead monoclonal antibody development. With the recent launch of the ADC service, my work has come full circle as I return to working with ADCs. Today, my role focuses on managing ADC development timelines in a way that mitigates risk while providing flexibility. Our ADC plant is under construction, so we have an opportunity to manage the ADC development process correctly – right from the start.

I take pride in contributing to optimal ADC development infrastructure. Soon, I envision working in Samsung Biologics' dedicated ADC facility that would enable me and my colleagues to readily problem-solve any unexpected deviation, and thus execute ADC projects of various scales on time and without compromising quality.

As one can rarely predict when an issue may occur during ADC development, creating and then nurturing a culture of problem-solving readiness is especially important – not only for the safety of scientists, but also for the quality of ADC product delivery. Whenever I have time to spare during my packed lab schedule, I enjoy sharing my know-how on how to keep calm and readily cope in the face of unexpected problems in ADC development!

What makes these therapies so interesting?
The development of an ADC is a fascinating process that requires various complex analytical methods because of the different components involved, including the mAb, linker and the potential cytotoxicity of the payload. To create an ADC, you must optimize the drug-to-antibody ratio, drug load distribution, conjugated antibody, and naked mAb. Separate methods are needed to confirm the identity and purity of the payload, the linker, and the successful attachment. Along with the individual components, the functionality of the ADC needs to be characterized by understanding how to evaluate the conjugation site based on the manufacturing process. Fortunately, analytical techniques have improved alongside ADC candidates. We now have access to approaches, such as liquid chromatography-mass spectrometry (LC-MS), that are incredibly useful for ADC characterization.

None of these tests begins to characterize the potency of the ADC itself. Here, cell-based assays are needed to profile the potency and effectiveness of the ADCs – a crucial step.

Why has ADC drug development faced so many challenges over the past decade?
The previous challenges of ADC development were because of limitations in earlier ADC technologies. The first generation of ADCs suffered from toxicity issues because of the novelty of the linker. However, as ADCs progressed, so too has linker technology, reducing the rates of off-target toxicity and improving patient outcomes. We are now in the third generation of ADC therapies, where site-specific conjugation can improve the safety profile and

A Love for Complexity: ADC Drug Development (cont...)

target specificity. Through experience, we can now better predict site toxicity before a therapeutic enters clinical trials.

What other key trends are you seeing in this space?
Combination therapies – and that reflects a trend we've seen globally within the cancer therapeutic space. Bioconjugates are particularly exciting because of the many combinations available for experimentation: mAb with cytotoxic molecules (maytansinoids, auristatins, camptothecins, calicheamicins, PBDs, duocarmycins), mAb with protein toxins (diphtheria toxin, Pseudomonsas exotoxin), mAb with radionuclides (131I, 177Lu, 90Y, 225Ac), mAb with nucleotides (siRNAs, antisense), mAb with immunomodulators (STING agonists) and mAb with protein degraders . A second trend is the miniaturization of therapeutics. As we understand and optimize ADC therapies, we may be able to deliver effective treatments that do not require a complete antibody. I also see a trend towards bispecific antibodies (which can bind two antigens at the same time).

And what are the biggest challenges?
Intellectual property and the patent landscape remain significant challenges across biopharma. With inter-industry collaboration, we could accelerate the development of complex therapies to help patients, but the red tape of licensing often slows this process down.

Right now, there is a great deal of focus on supply chains in the wider pharma industry. Are there any specific supply issues in the ADC space – and what can be done to minimize disruption?
Reliable supply chains are essential for all therapies. The complex requirements for ADCs often translate to fragmented supply chains. It can be challenging to oversee vendor management to ensure consistent quality controls, synchronized timelines, and efficient communication. The absence of integration exposes developers to potential inconsistencies in product quality and leaves them susceptible to supply chain issues at multiple points. Some companies choose CDMO partners that can help simplify supply chain logistics with a more streamlined approach.

What's next for the ADC field?
ADCs continue to advance rapidly. We understand how to use ADCs to activate the immune system to destroy cancer cells, allowing us to design targeted agents and potent payloads. Alongside ADCs, new companion diagnostics will enable us to match patients with the correct therapeutic for maximum response.

There are also exciting applications for bioconjugates beyond ADCs. With our advanced understanding of linker technology, we can combine two other modalities to create new functionality. For example, new bioconjugates could pair a vaccine with different polysaccharides – or nanoparticles could be combined with small molecules to deliver targeted treatments. These exciting technologies can help us push into the next generation of personalized medicine.