



FEATURED ARTICLE

Sweep and Destroy:

Engineering Antibodies for FcRn Engagement

Karen Silence, Vice President, ArgenX

ACADEMIC STEERING GROUP

We proudly introduce our new Academic Steering Group - leading experts stewarding our NextGen Biomed LifeScienceXchange platform and community.

United by our mission to drive innovation in biologics and immunotherapy, they present their curated **Top 25 of '25** R&D leaders in our exclusive ebook, highlighting breakthroughs that accelerate the delivery of life-saving medicines to patients.

The next-generation biomed landscape has advanced dramatically over the past 12 months, driven by technical advances, fundamental scientific breakthroughs, sustainable practises, and advances in manufacturing, analytical and AI capability. Such progress is rapidly reshaping how biomedical interventions and therapies are discovered, developed, and delivered.

Here, we highlight 25 articles that reflect cutting-edge examples of innovation, influence, and impact within the field, shaping best practice, and driving meaningful progress spanning a range of topics. For example, they highlight how recent advances in cell culture technologies are improving scalability, reproducibility and sustainability, enabling more efficient biomanufacturing and accelerating the path from discovery to clinical application.

Articles demonstrate how new and improved synthetic pathways are expanding therapeutic potential, supporting more precise and personalised approaches to disease. They also explore the potential of AI in identifying new biological pathways, new platforms, adjuvants, and manufacturing strategies of cell therapies, biologics and vaccines and how this has the potential to strengthen global preparedness and improving access, efficacy, and speed of response.

These contributions highlight the depth and diversity of expertise within our community and some of the new technologies moving from concept to market. This eBook celebrates contributions while serving as a reference point for future advancement and collaboration.

ALINE MILLER,
Academic Steering Group Member
for NextGen Biomed



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PROTEINS, ANTIBODIES & ADCS

HIGH-THROUGHPUT NEXT GENERATION BIOLOGICS PRODUCTION PLATFORM

Matthew Burrell, Associate Director, AstraZeneca

AstraZeneca have a bold vision to deliver 20 new medicines, become an \$80 billion company, and become carbon negative by the year 2030. A key part of doing this is being able to identify the right molecules through investing in next generation drug discovery platforms.

Matthew Burrell, Associate Director at AstraZeneca, leads a team working on their biologic generation platforms called BETXpress (Biologics Expression Team Express). The goal of the BETXpress team is to drive innovative solutions for the rapid generation of biologics. It started around five years ago in Cambridge, UK, and has since significantly evolved and expanded across the globe with sites in the US.

To be able to identify the right molecules, AstraZeneca have developed two next-generation discovery platforms: First is their machine learning-driven antibody and biologics deep screening platform; Second is B cell miner, AstraZeneca's next generation in vivo platform. Both of these platforms deliver large panels of potential hits.

From there, the BETXpress team work on generating biologics for these hits in the appropriate format. They receive panels of

hundreds of antibody sequences, take them through sequence design, followed by high throughput cloning, expression, purification, and QC. These then get transferred to the downstream team for high-throughput profiling. Key considerations at this stage include developability, accelerated stability, and non-specific binding.

To further increase the throughput, the team have developed an integrated automation platform which integrates liquid handlers with a robotic arm and advanced scheduling software. This platform increased their cloning capacity, reduced turnaround time, and improved robustness.

Once the cloning process is complete, the sequence verified plasmids go into their automated transfection process using their in-house G22 cell line before a ten-day incubation. The biologics are then harvested and purified using an automated PhyTip-based method. Finally, the team measure the concentration of the purified molecules and run a UP-SEC for quality control ■

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PROTEINS, ANTIBODIES & ADCS

THE ALLOSTERIC WAY: SAFER & MORE EFFECTIVE NEXT-GEN SMALL MOLECULES

David Pejowski, Co-Founder & Chief Executive Officer, Adoram Therapeutics

David Pejowski, Co-Founder and Chief Executive Officer of Adoram Therapeutics, explained that pharmaceutical companies do not have a specific way to find allosteric modulators. Therefore, Adoram Therapeutics has developed a platform for screening allosteric modulators that target cryptic sites on GPCRs rather than usual orthosteric sites. This approach is effective in both negative (NAM) and positive (PAM) allosteric modulators.

Pejowski elaborated that allosteric modulators offer several benefits, including lower doses, better safety profiles, and more powerful modulation of receptor signalling. Furthermore, they do not compete with natural ligands and can induce signalling beyond natural levels.

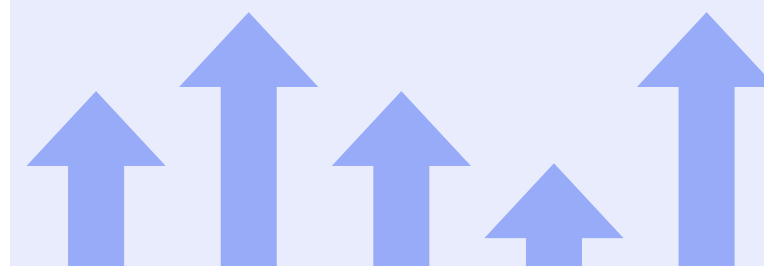
Adoram's current pipeline focuses on finding drugs that target an adenosine A2A receptor (A2AR) with applications in anti-inflammatory treatments and immunotherapy for solid tumours. Regarding the pathway, adenosine can act on 4 different receptors. However, A2AR is the most prominent on immune cells, reducing immune response by decreasing NF Kappa B. Allosteric drugs are more active in disease tissues with high adenosine, inducing very powerful signalling.

“

Allosteric drugs are more active in disease tissues with high adenosine, inducing very powerful signalling.”

In his talk, Pejowski focused on the anti-inflammatory drug discovery program. The first step involves identifying initial hits for the A2AR receptor. Then, additional chemistry campaigns enhanced the potency of the hits. The preclinical translational experiments worked with human PBMCs and mouse models.

The data from human donor PBMCs showed a reduction of TNF alpha by 50% with allosteric modulators, with optimised leads reducing it even further. The molecules are tractable, lasting for 12 to 24 hours in the plasma of mice, and are now being tested in animal models to determine their relevance in different diseases. The company is now seeking to file a patent application and find chronic disease models to test the optimised leads ■



SWEEP AND DESTROY: ENGINEERING ANTIBODIES FOR FCRN ENGAGEMENT

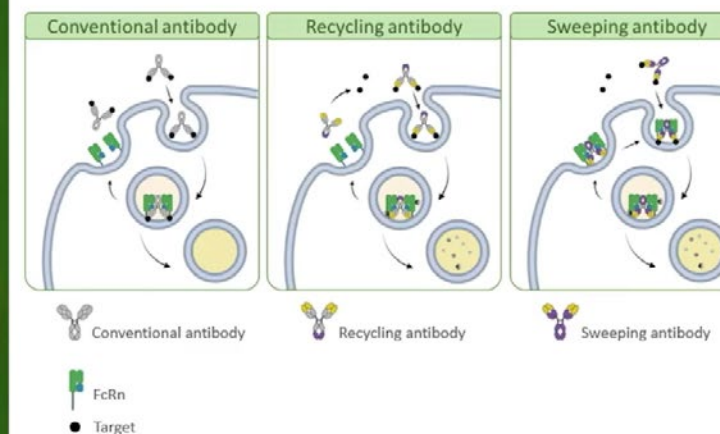
Karen Silence, Vice President, ArgenX

KEY PRESENTATION POINTS:

- FcRn and the Development of Efgartigimod
- Sweeping Antibodies
- Testing of IgA
- One-Armed Antibody Development



Leveraging Efgartigimod backbone to build new class of highly potent target sweeping molecules



- 1 Conventional antibodies:**
 - Cell entrance via nonspecific pinocytosis
 - Remains bound to its target in the endosome
 - Ab:Ag complex either degraded in the lysosome or recycled back to the circulation (buildup)
- 2 Recycling antibodies:**
 - Cell entrance via nonspecific pinocytosis
 - pH dependent target binding to release target in the endosome
 - Target degraded in lysosome and FcRn-mediated recycling of Ab
- 3 Sweeping antibodies:**
 - Cell entrance via receptor-mediated endocytosis (active uptake)
 - pH dependent target binding to release target in the endosome
 - Target degraded in the lysosome and Ab recycles back and remains bound to FcRn

argenx

Image adapted from Qi T, et al. Int J Mol Sci. 2021;22:1-29

During pinocytosis, proteins, antibodies, and other large molecules are taken up into the cells. When they enter the acidic endosome, antibodies and albumin are unique in binding to FcRn so that they can be recycled. This gives these molecules a longer half-life compared to other proteins.

Since binding to FcRn, or neonatal Fc receptor, results in extended half-life, Argenx investigated mutations that enhance binding to FcRn to increase the longevity of antibodies. "AbDeg" mutations, including MST-HN, play this role of enhancing FcRn binding at both acidic and neutral pH levels. This led to the development of Efgartigimod, an Fc fragment with MST-HN mutations. The therapy binds to and blocks FcRn to reduce the half-life of pathogenic IgGs in conditions like myasthenia gravis and ITP.

One of the problems that antibody therapeutics often face in the clinic is that after binding to their target, both target

and antibody enter the endosome and are recycled. This can prolong the half-life of the target and can cause build up.

Recycling antibodies are one proposed solution to this problem; they initially bind to the target but release it once they enter the endosome due to the higher acidity. Here, the antibody gets recycled but not the target which gets pushed into the lysosome and degraded.

Sweeping antibodies are another solution. Rather than relying on pinocytosis, these molecules use active uptake of the complex. Using MST-HN mutations, the antibody-target complex binds to FcRn at a neutral pH and is actively taken up by the endosome. When this is combined with pH dependant binding to the target, the target is released into the endosome while the antibody remains bound to FcRn. This allows the bound antibody to continue grabbing the target in a repeating cycle – binding to the target and releasing it into the endosome to be degraded.

The presentation then outlines a test of this hypothesis using IgA, an abundant target, where antibodies bind to and internalise IgA, facilitating its degradation while recycling the antibody. Despite initial successes, immunogenicity posed challenges, affecting the stability and efficacy of antibody treatments in various levels of IgA.

Therefore, the team decided to switch their strategy by developing a one-armed antibody. This improved binding to FcRn and reduced the formation of immune complexes that lead to degradation. The presentation concluded with potential applications of the one-armed antibody platform in treating diseases related to pathogenic IgA, such as IgA nephropathy, and emphasises the need for further research in this area ■



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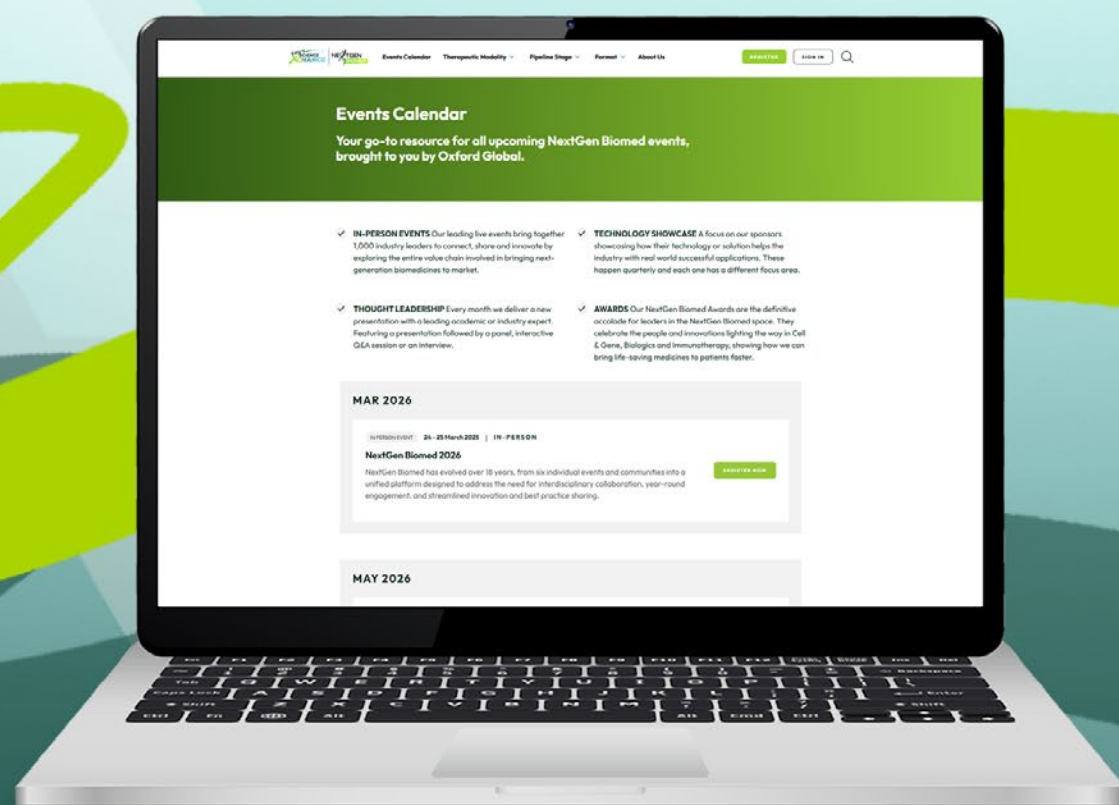
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PROTEINS, ANTIBODIES & ADCS

ALPHAMERS: A NOVEL IMMUNOTHERAPY PLATFORM

Helen Bright, Chief Scientific Officer, Centauri Therapeutics

This presentation outlines Centauri Therapeutics' Alphamer platform, which takes advantage of natural anti-sugar antibodies present in all humans and primates. Anti-sugar antibodies are pre-existing, ubiquitous, high titre and perfused in all individuals. Alphamers use this part of the immune system recruiting these antibodies to the target cell. They are designed for high specificity and can leverage the immune system to effectively kill through complement, antibody dependant cytotoxicity, and opsono phagocytosis.

One end of the Alphamer features the targeting moiety which selectively binds to the target of interest and on the other end is the effector domain which presents the sugar to be recognised by anti-sugar antibodies. The two sides are connected by a stable, non-cleavable proprietary linker which optimises the presence of the sugar to the host immune system.

Centauri's lead candidate is called ABX-01 which aims to treat serious infections caused by Gram-negative pathogens. The molecule is selected to work against clinically prevalent and multi-drug resistant bacterial strains. The sugar-end of the molecule uses Rhamnose as its effector moiety which drives its immune-mediated killing. ABX-01 also has a dual mechanism of action due to the fact that its binding moiety is simultaneously an antimicrobial peptide. This gives the

molecule a broad spectrum and intrinsic antibacterial activity.

Bright then presented the molecule's proof of concept study which used an immune competent mouse lung infection model. Mice were infected with *Klebsiella pneumoniae* and treated either in the presence or absence of anti-rhamnose antibodies (this could be controlled due to the fact that mice possess very few anti-rhamnose IgGs naturally). The mice were treated with the Alphamer for three days and followed up with for a further six days.

Alphamers showed promising results, with a survival rate of 70% when combined with anti-Rhamnose antibodies, outperforming the standard treatment Meropenem. When the mice received the Alphamer on its own, the survival dropped to 20%, suggesting some antimicrobial peptide activity.

The company is also exploring Alphamer technology for oncology, using mAbs and Fabs as binding moieties to enhance antibody-dependent cellular cytotoxicity. Studies show that Alphamers increase complement deposition on target cells, correlating with enhanced cytotoxic effects compared to standard antibodies. The Alphamer technology represents a novel approach in immunotherapy, with ongoing development and a differentiated pipeline addressing both infectious diseases and cancer ■

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PROTEINS, ANTIBODIES & ADCs

PRE-CLINICAL CONSIDERATIONS FOR DEVELOPMENT OF ADCs

Nathan Alves, Research Director & Associate Professor, Indiana University

In his presentation, Nathan Alves provided a comprehensive overview of pre-clinical considerations in the development of antibody-drug conjugates (ADCs). Alves began by outlining his extensive background in chemical and biomolecular engineering, with appointments at Indiana University School of Medicine and Purdue alongside his experience in nanoparticle drug delivery and selective antibody modification.

The presentation first established the significance of antibodies in medicine, noting their specificity and high binding affinity, which underpin their use in both therapeutic and diagnostic contexts. Alves pointed out that, as of 2023, there were around 170 FDA and EU-approved antibodies, with ADCs representing a rapidly evolving subset, primarily for cancer indications. He emphasised the potential for future ADCs to address non-oncological diseases, reflecting a broader trend in the field.

Alves then systematically addressed the critical components of ADCs: payload, linker, and antibody characteristics. He discussed the importance of payload selection, including considerations of hydrophobicity, drug-antibody ratio (DAR), and the mechanism of action. The choice of linker, whether cleavable or non-cleavable, was shown to influence both the stability and release profile of the drug, with entire

pharmaceutical divisions dedicated to linker design.

Antibody characteristics were explored in depth, with Alves cautioning that higher affinity does not always equate to better targeting, especially in the context of solid tumours or off-target effects. He also discussed the relevance of internalisation mechanisms and the impact of antibody isotype on pharmacokinetics.

The presentation moved on to production mechanisms, highlighting the complexities of expression systems, post-translational modifications, and the challenges of conjugation strategies. Alves explained the evolution from heterogeneous lysine conjugation to more homogeneous, site-specific approaches, underscoring the trade-offs between ease of development and product uniformity.

Finally, Alves stressed the importance of formulation, stability, and aggregation concerns, advising that ADCs should be tested as early and as closely to their final form as possible. He concluded by encouraging innovation beyond cytotoxic payloads, suggesting that the future of ADCs lies in expanding their therapeutic scope and delivery methods ■

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CELL & GENE

NANO-ENGINEERING STEM CELLS FOR REGENERATIVE SUCCESS

Darius Widera, Professor of Stem Cell Biology, University of Reading

Darius Widera, Professor of Stem Cell Biology at the University of Reading investigated how to optimise cell culture to increase the regenerative potential of stem cells.

Unlike adult stem cells, pluripotent stem cells can be expanded forever. However, it is vital that all the cells are differentiated, and that any remaining pluripotent stem cells are not transplanted in the process. Regarding clinical translation, there are various challenges including cost, ethical acceptance, and safety.

Neural Crest Derived Stem Cells are unique due to their ability to differentiate into both mesodermal and ectodermal cell types such as bone, cartilage, muscle, and peripheral nervous stem cells. Widera added: "What's even more interesting, you can apply fairly simple protocols and trans differentiate those peripheral neural cells into central nervous system phenotype."

This remarkable discovery led Widera to conduct a clinical study where the neural crest derived stem cells were injected into Parkinson's models. The NCSCs provided

statistically significant functional recovery. No human cells were detected in the brain, Widera attributed the therapeutic benefit to paracrine effects such as the release of supportive growth factors.

Widera also explored the potential of Mesenchymal Stromal Cells (MSCs). The MSCs were derived from various tissues like bone marrow and fat and were optimised for faster proliferation and differentiation. MSCs cultured in 3D nanofibrillar cellulose underwent osteogenic differentiation. The differentiation was marked by increased expression of bone-specific markers like osteocalcin and osteopontin.

To conclude, this case study illustrates a paradigm shift in stem cell research, where physical and environmental cues replace chemical inducers to drive regeneration. This approach increases efficiency but also ensures safety and scalability for clinical applications. By focusing on both NCSCs and MSCs, the research offers a versatile toolkit for addressing diverse medical challenges, from neurodegenerative diseases to bone injuries ■

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CELL & GENE

CRISPR AND AUTOMATION: THE FUTURE OF CELL MODEL DEVELOPMENT

Abdalla Mohamed, Senior Scientist, AstraZeneca

KEY PRESENTATION POINTS:

Applications of CRISPR-Cas9

Off Target Effects of CRISPR

Automation to Accelerate Cell Line Generation

“You can use high fidelity Cas variance in order to reduce off-target cuttings and to increase the on-target efficiency.”

Abdalla Mohamed, a Research Scientist at AstraZeneca, gave an overview of how scientists can use CRISPR to generate high-quality cell models for drug discovery projects. CRISPR is widely celebrated across the life sciences field due to its capabilities in gene editing, as well as its aptitude for identifying unique biomarkers for therapies and uncovering resistance pathways.

Mohamed explained that CRISPR Cas offers unparalleled flexibility regarding target identification. Unlike previous tools which could only identify a specific target, CRISPR can be used to identify multiple targets using guide RNA.

Mohamed reiterated the versatility of CRISPR: “So the CRISPR did not only expedite identification and the validation of therapeutic targets, but it also has helped uncover biomarkers, unique therapies and even understand mechanisms.”

However, CRISPR still presents challenges to the scientific community. The key concern is off-target effects. Mohamed outlined how off-target effects can be addressed: “You can use high fidelity Cas variance in order to reduce off-target cuttings and to increase the

on-target efficiency.” Furthermore, efforts to refine guide RNA designs have mitigated this issue.

Delivering Cas into cells in primary or complex cell lines can also be complicated. Still, ribonucleotide proteins such as Cas9 or mRNA in plasmid form can be used to facilitate the delivery. Lastly, model complexity adds further obstacles to this process. For example, creating a large number of copies for the target gene is difficult: “If you have a huge number of copies through your gene of interest inside the cells, this might have a detrimental effect on the cell and it can be challenging.”

To enhance efficiency, the integration of automation and high-throughput technologies has proven invaluable. Automation accelerates processes such as clonal isolation and validation, while tools like next-generation sequencing enable large-scale analysis of editing events.

Mohamed also suggested that small molecule enhancers play an important role, he stated: “They (AstraZeneca) have shown that using combining the use of DNA protein kinase inhibitor and molecule inhibitors in

combination, you can improve the efficiency of the knock-in and you get precise genome editing,” he continued, “And they have validated the results across different genes and they have used different cell lines like HEK293T or even primary cell lines like iPSCs.”

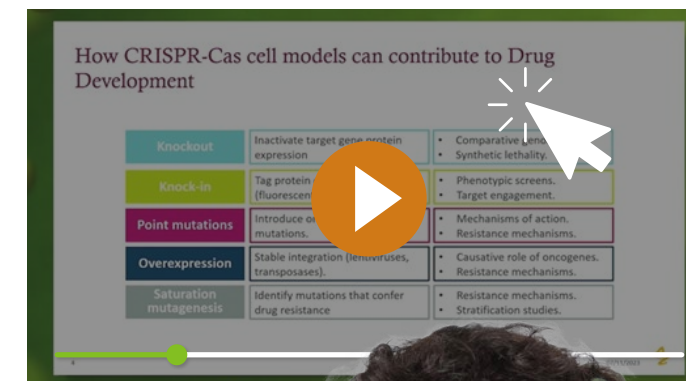
To wrap up, Mohamed demonstrated how combining CRISPR with automation can increase the efficiency of cell model generation. Despite numerous challenges, CRISPR-Cas9 has become an indispensable technology for generating robust cell models, with applications spanning the drug discovery pipeline ■

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CELL & GENE

OVERCOMING AAV DOWNSTREAM CHALLENGES FOR SAFER GENE THERAPY

Richard Liu, Senior Scientist, UCB

Yu-Tsan (Richard) Liu, Senior Scientist at UCB discussed the challenges linked to adeno-associated viruses (AAV) downstream processing. He explained the main complexity associated with AAV downstream processing; often the capsid and gene of interest will have different serotypes leading to variations in viral capsid proteins. Liu continued: "So that means our product is very complicated and during capsid packaging, we'll get different species like a full and empty impurity like the picture shows here. So it's not as though we just got the only one product."

Separating full and empty capsids is challenging because they share a similar isoelectric point. During downstream processing, obtaining a product with high purity is the goal, however obtaining purity requires removing impurities which has a knock-on effect on total volume and yield. Liu stressed that during upstream processing the balance of product quality and yield must be considered.

The downstream purification process involves steps like clarification, chromatography, virus removal filtration, and ultrafiltration/diafiltration (UF/DF). At various points in the process, there are bottlenecks including step material loss, material demand during development, balance of product quality

and yield and process, and product-related impurities and contaminants.

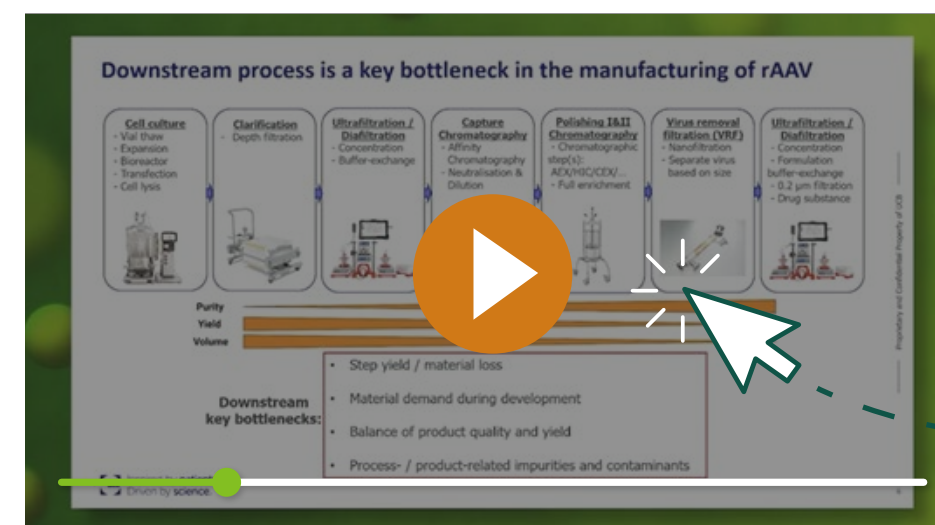
The majority of biopharma players apply a two-step chromatography purification process but minimising the number of steps downstream is one way to combat bottlenecks. Liu stated: "For example, maybe we can just directly load the harvest from clarification on to the next chromatography step directly, so we can save at least one step." Therefore, using a one-step chromatography approach could reduce yield loss and shorten the process time.

Viral clearance is particularly complex, as AAVs themselves are viral particles. Unlike traditional protein biology processes, low pH inactivation and robust filtration are less effective for AAVs due to particle sensitivity and size limitations. Detergent treatments and carefully designed chromatography steps are critical to addressing these issues. Early-stage viral clearance studies, though not mandatory, are often performed to gather data for late-stage regulatory compliance.

To finalise, it is crucial to strike a balance between quality, yield, and safety in the downstream process. To achieve this, it is essential to adapt and tweak methodologies from protein purification where possible ■



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CELL & GENE

FROM LAB TO INDUSTRY: NIBRT'S VISION FOR ADVANCING CELL THERAPY

Sakis Mantalaris, Professor, Trinity College Dublin

KEY PRESENTATION POINTS:

Training Achievements

Importance of Biopharma in Ireland

Research and Facilities

CONCEPT Facility

The National Institute for Bioprocessing Research and Training (NIBRT) is focused on supporting the biopharma industry to develop cell therapeutics. The organisation is based in Ireland which is the third largest exporter of pharmaceuticals in the world. The NIBRT offers training programs in the CGT field, from cell engineering to advanced analytics, bioinformatics, and downstream processing.

Sakis Mantalaris, Don Panoz Chair of Pharmaceutical Biology & Principal Investigator, Trinity College Dublin & NIBRT explained that the NIBRT is a purpose-built facility that has recently completed an advanced therapies extension. A recent 2 million fill finish suite has enhanced the facility's capabilities.

Although the facility itself is very useful and adaptable to a variety of different needs, Mantalaris also emphasised the training programs on offer: "We do the traditional academic programs, MSCs, diploma certificates, but we offer short courses. Again, the link between academia and industry is one to five days in duration on key specialist topics. And finally, we can actually customise

training programs based on the client's needs."

Regarding research on cell and gene therapies, the NIBRT recently received funding from the Science Foundation Ireland for their CONCEPT facility. Mantalaris outlined the goal of CONCEPT: "The aim is to provide an infrastructure ecosystem and a one-stop shop and hopefully you will see why that's the case in the thinking behind that and what CONCEPT is the example part excellence is being able to support development of advanced therapeutics. So, once you have completed your research, you can take your ideas into CONCEPT and be able to work out everything for the production and manufacturing states."

CONCEPT assists with sequence optimisation and is then used to synthesise the molecule or transfect the cell line. CONCEPT performs synthesis using a Codex BioXP and the Maxcyte ExPERT system performs electroporation of any cell with any vector, this demonstrates its broad adaptable nature.

Mantalaris introduced other technologies used by NIBRT: "We have the Precision Nano Systems Ignite system that allows you to

"The aim is to provide an infrastructure ecosystem and a one-stop shop and hopefully you will see why that's the case in the thinking behind that and what CONCEPT is the example part excellence is being able to support development of advanced therapeutics."

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generate nanoparticles, the liposomes that you will use in your research or process development." Furthermore, Nova Biomedical's FLEX2 Bioanalyzer is a fully robotic high throughput cell culture system that can select the ideal clone and optimise process parameters within CONCEPT'S facilities.

In a nutshell, CONCEPT can give end users a real product; what may start as an idea becomes reality. Mantalaris reiterated that both academia and industry can access NIBRT's training programs. He closed with the following statement: "We focus on personalisation as opposed to precision." ■





EXPLORING THE MHRA'S ADVANCEMENTS FOR ATMP DEVELOPMENT AND REGULATION

Jon Beaman, Deputy Director Innovative Medicines, MHRA

KEY PRESENTATION POINTS:

- **MHRA's Evolving Role and Guidance**
- **Addressing Backlogs and Expanding Assessment Capacity**
- **Parallel Process with NICE and Innovative Licensing**
- **Modular Manufacturing and Localised Production**
- **Rare Diseases Consortium and Regulatory Options**

In his presentation, Jon Beaman provided an insightful overview of the recent advancements and ongoing initiatives at the Medicines and Healthcare products Regulatory Agency (MHRA). Beaman began by acknowledging his background in the licensing area, and that the agency is well supported by a team of technical assessors. He outlined the MHRA's evolving role, particularly since the UK's departure from the European Medicines Agency (EMA), emphasising the agency's commitment to developing flexible and progressive regulatory pathways.

Beaman highlighted the agency's recent efforts to address assessment backlogs by expanding its capacity. The MHRA has established new assessment teams and recruited additional assessors, enabling a more efficient review process. Notably, the agency now offers a 150-day assessment pathway for innovative medicines, provided dossiers are of high quality and free from major objections. Early engagement with the MHRA, through scientific advice and pre-

submission meetings, is strongly encouraged to facilitate this accelerated process.

A significant development discussed was the piloting of a parallel process with the National Institute for Health and Care Excellence (NICE), allowing companies to undergo MHRA and NICE assessments simultaneously. This initiative, set to become mainstream, aims to streamline access to innovative medicines. The Innovative Licensing and Access Pathway (ILAP) has also been relaunched to further support rapid access.

Beaman addressed the introduction of new guidance on modular manufacturing and point-of-care regulations, which supports the decentralised production of advanced therapies. This approach allows for localised manufacturing, moving away from traditional centralised models and providing greater flexibility for novel therapies.

A major focus of the presentation was the Rare Diseases Consortium, a collaborative effort involving the MHRA, NICE, NHS, academia, and trade associations. This

consortium seeks to address the unique challenges of bringing therapies for rare diseases to market, where clinical trials may be impractical and patient populations are small. Beaman outlined the various authorisation and access options available, including conditional marketing authorisations and early access schemes, and stressed the importance of patient-centred approaches, transparency, and real-world evidence in regulatory decision-making.

In summary, Beaman's presentation underscored the MHRA's proactive stance in adapting regulatory frameworks to foster innovation, improve efficiency, and ultimately deliver better outcomes for patients ■

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“
The Rare Diseases Consortium seeks to address the unique challenges of bringing therapies for rare diseases to market, where clinical trials may be impractical and patient populations are small.”



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OLIGONUCLEOTIDES

CHALLENGES AND SOLUTIONS IN THE PURIFICATION OF OLIGONUCLEOTIDES

Yiping Wu, Senior Scientist, AstraZeneca

This presentation noted the diverse range of purification techniques and strategies AstraZeneca employ for peptides, oligonucleotides, and oligonucleotide conjugates. AstraZeneca's portfolio of peptides encompasses linear, cyclic, and bicyclic types. Most of these are produced by solid phase synthesis and in most cases are purified by reverse phase liquid chromatography (RP-LC). In vitro samples use TFA as an additive for their purification while in vivo samples are TFA-free, instead using acidified ammonium acetates or acetonitrile in the mobile phase.

Oligonucleotides are similarly purified on solid supports and can be released with their five prime protecting group on or off. This would be left on because the DMT or MMT provides extra hydrophobicity to the oligo. If the protecting group is left off, the oligo needs to be purified using ion pairing RP-LC. In the mobile phase, they use either ammonium bicarbonate buffers or alkylamine acetates.

Oligonucleotides which are conjugated to other molecules like dyes, GalNAcs, lipids, or peptides, can either be synthesised in solution or directly on solid supports since the conjugated part will usually offer the extra hydrophobicity. The oligos are purified by the reverse phase HPLC. The

mobile phase uses ammonium bicarbonate, ammonium acetate or acetonitrile buffers.

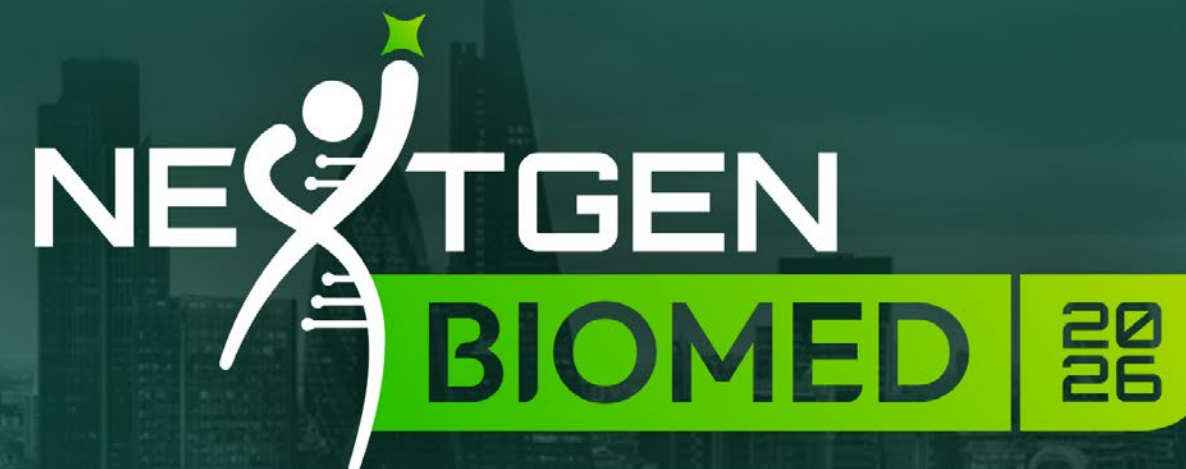
Wu then discussed the challenge of purifying guanine (G)-rich oligonucleotides. These particular oligos have a tendency to form heterogeneous aggregates which lead to poor chromatographic behaviour and low solubility. This can make the purification process time-consuming and challenging.

The team investigated how this aggregation is stabilised. It was shown that the aggregate structure is stabilised by the presence of a cation that sits in a central channel between each pair of tetrads. Guanine tetrads often feature Hoogsteen-style hydrogen bonding and are more stable when stacked because the intermolecular forces between each layer help stabilise them. Therefore, by reducing cations during synthesis and adjusting mobile phase conditions, the team successfully mitigated aggregation issues, improving chromatography outcomes ■

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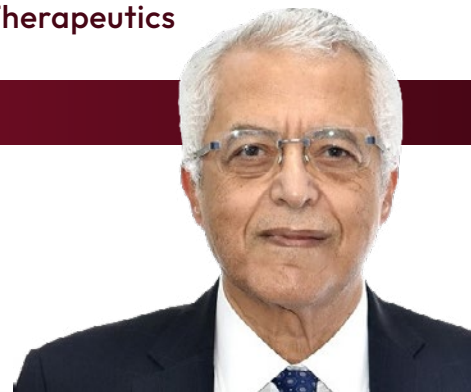
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OLIGONUCLEOTIDES

RNA ACTIVATION IN ACTION

Nagy Habib, Founder & Chair of Scientific Advisory Board, MiNA Therapeutics



KEY PRESENTATION POINTS:

- Mechanism of RNA Activation
- Clinical Trials and Results
- Applications in Neurodegenerative Diseases
- Future Prospects in Rare Genetic Diseases

Nagy Habib, Founder & Chair of the Scientific Advisory Board at MiNA Therapeutics discussed RNA activation and RNA delivery across a range of therapeutic areas including NASH, rare genetic diseases, and cancer. Habib began by explaining the key differences between siRNA and saRNA: “So saRNA and siRNA can be used really in most genes, but the saRNA are for diseases where there is low expression of the gene of protein. siRNA is a reverse of this, it’s when you have a high expression of a toxic gene and you want to bring it down.”

In several autoimmune diseases, the IL-10 gene is repressed but saRNA can upregulate up to 20-fold. In fact, saRNA can upregulate other interleukin genes in autoimmune diseases including IL-19, IL-20, and IL-24 by targeting the enhancer that controls the promoters. Habib outlined how his team spent 20 months producing their first clinical saRNA called MTL-CEBPA which was used in three clinical trials. The main purpose of CEBPA alpha is to prevent immunosuppression by tumour-associated macrophages. Habib explained CEBPA’s role as a master regulator: “It regulates more

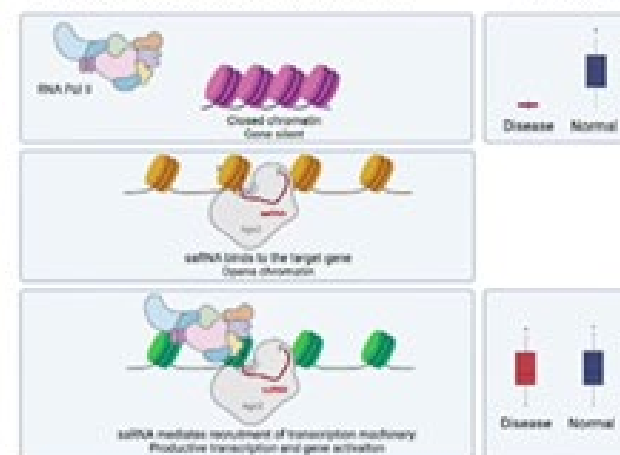
than 500 genes that’s why it’s called master regulator and it leads to the differentiation of the cell, the normal monocyte macrophage and dendritic cell.” However, in cancer and chronic inflammation, there is very little CEBPA leading to malformation of myeloid cells.

140 patients were injected with empty CEBPA, the first study was on liver cancer, and it was with thyroid kinase inhibitor while the second study was conducted on solid cancers. One example highlighted a patient with lung cancer, initially presenting with six metastases in the right lung and ten in the left lung, who achieved complete clearance following treatment with MTL-CEBPA and Sorafenib. Four years later, the patient remains recurrence-free. These promising results showed the ability of MTL-CEBPA to modulate immune responses by reprogramming macrophages to anti-tumoral states.

Habib also discussed the use of saRNA in other conditions, including brain inflammation, neurodegenerative diseases, and rare genetic disorders such as Hurler’s disease. saRNA was shown to downregulate

saRNAs enhances the natural mechanism of transcriptional activation (Chromatin opening)

A) Summary of saRNA mechanism when a gene is silenced



Manuscript in preparation

Detailed mechanism

- saRNA opens up chromatin on target locus and enhances transcriptional activation
- saRNA upregulates target locus pre-mRNA and mature mRNA
- saRNA can upregulate repressed / poorly expressed genes

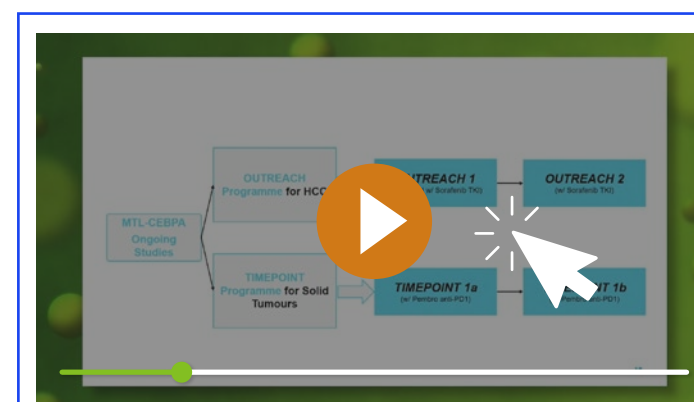
3 mechanisms of transcriptional repression / silencing

- DNA methylation
- Histone de-acetylation
- Repressive histone marks
- This will vary for each target

inflammatory markers in the brain, promote weight loss, and improve liver function in mouse models of fatty liver disease (NASH). He argued that while most scientists would suggest that GalNAc technology is the optimal way of delivering siRNA to the liver, one should note that the FDA has approved 6 drugs for the liver based on GalNAc but none for NASH. He urged the audience to consider alternative options to GalNAc. In Hurler’s disease, saRNA increased enzyme production in donor cells, potentially improving outcomes for affected children.

RNA activation is highly versatile and its ability to precisely upregulate gene expression without long-term genetic alterations is particularly noteworthy. Habib aims to further investigate future applications of saRNA in rare genetic diseases and other unmet medical needs through collaboration. He concluded: “As people say, it takes a village. 140 patients, 20 hospitals, 7 countries, the MiNA therapeutic

team that developed the RNA activation and so many people contributed, City of Hope with John Rossi and his team, especially their collaborations and another company called APTERNA.” ■



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OLIGONUCLEOTIDES

ASSESSING OLIGONUCLEOTIDE IMPURITY: GUIDELINES, TECHNIQUES, AND ANALYSIS

Ulrike Rieder, Scientific Lead, Novartis



KEY PRESENTATION POINTS:

- Complexity of Oligo Impurity
- Quality Guidelines and Regulatory Updates
- Analytical Techniques
- siRNA Analytics

The synthesis of oligonucleotides comes with a complex impurity profile which creates challenges in their analytical separation with product impurities being similar to the parental sequence. In addition, the oligo backbones can be highly modified via thiolation which creates diastereoisomers.

Many of the available ICH quality guidelines are applicable for oligos, with a few exceptions. For example, the guideline for method validation applies for oligos but with some adjustments. Focusing on guidelines for impurity of drug substance and drug product ICH Q3 A and B but explicitly do not cover oligonucleotides but the principles can be applied to process and product related impurities.

However, this field is developing, and researchers are awaiting updates regarding quality guidelines. The EMA recently drafted guidelines relating to development and manufacture of oligos, and the Chinese Center for Drug Evaluation (CDE) is preparing guidelines for their chemical synthesis.

Furthermore, the upcoming ICH Q6 update also promises to cover oligonucleotides.

This talk focused on the product related impurities of oligonucleotides, of which the toxicological qualification is vital. This typically involves a combination of analytical techniques to identify and quantify the various impurities that can be present in chemically synthesised oligonucleotides. Your choice of method can depend on type of impurities, required sensitivity of detection, and available equipment.

Liquid Chromatography with UV detection (LC-UV) Methods

Evaluating the need for orthogonal methods is essential in LC-UV analysis. One must also assess the peak purity of the main UV peak and the impurity UV peaks, which helps in controlling co-eluting impurities, such as those identified by HR-MS. Using MS-compatible buffer and solvent systems can facilitate the eventual hyphenation for better process control and impurity

“Focusing on guidelines for impurity of drug substance and drug product ICH Q3 A and B but explicitly do not cover oligonucleotides but the principles can be applied to process and product related impurities.”

identification. Employing 2D-LC technologies, such as salt swapping and additional characterisation, can be beneficial. Attention must be paid to retention time shifts, and peak alignment strategies should be employed accordingly.

Liquid Chromatography with UV detection and Mass Spectrometry (LC-UV-MS) Methods

For LC-UV-MS methods, low-resolution analysis enables the quantitation and identification of impurities within a single method, while controlling co-eluting impurities and avoiding false positive detection. It is crucial to aim for low noise and adduct levels in MS, as leaching of metal

ions from buffer instrument components can affect results. Implementing such methods in a QC environment can be challenging, necessitating evaluations of long-term strategies either in-house or externally.

High-resolution LC-UV-MS methods provide a deeper understanding of the impurity profile through supportive information and isotopically resolved MS spectra. Optimising source settings for the most informative charge states involves balancing signal intensity, adduct presence, and in-source fragmentation. It requires intensive data processing to handle the resultant information effectively ■

Watch the key moments of Ulrike's presentation now, for free on





OLIGONUCLEOTIDES

SUSTAINABLE PRINCIPLES IN PRACTICE

Kuda Muchandibaya, Lecturer for Supply Chain Management & Logistics, Rhine-Waal University of Applied Sciences

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Presenting on how companies can set up their own sustainability strategies, Kuda Muchandibaya, Lecturer for Supply Chain Management & Logistics, Rhine-Waal University of Applied Sciences, outlined how companies can develop a roadmap to position them in the top 5% of companies in terms of eco values.

ESG (Environmental, Social, Governance) is a framework that underpins sustainable practices. Since 2015, the Paris Agreement has been adopted by over 190 parties to limit their climate impact, with the aim of limiting temperature rise and achieving net neutrality by 2050. Legally, companies are required to disclose certain sustainability metrics, as governments and regulatory bodies clamp down on unsustainable activity.

Sustainability has moved beyond a buzzword; it is becoming a financially consequential issue for companies. Within the pharma industry, there is a need for energy efficiency and investing in greener technologies and solvents across drug development lifecycles. While sustainable processes require effort and commitment, in the long run, they can help companies save money.

On the other hand, Muchandibaya described the regulatory complexity as a minefield. Navigating what is legally binding and the different regulations across different countries is complicated. Even within the EU,

certain member countries implement the regulations in various ways.

To make these processes easier, Muchandibaya strongly encouraged the audience to adopt a proactive approach to regulatory compliance, including setting up internal compliance programs and using tools like ChatGPT to stay informed. He also recommended establishing a small team to manage compliance. Next, he mentioned that companies should take advantage of bonds that are given from the government. For instance, the German government gives companies tax rebates if they can prove that the investment they made bore a sustainable gain.

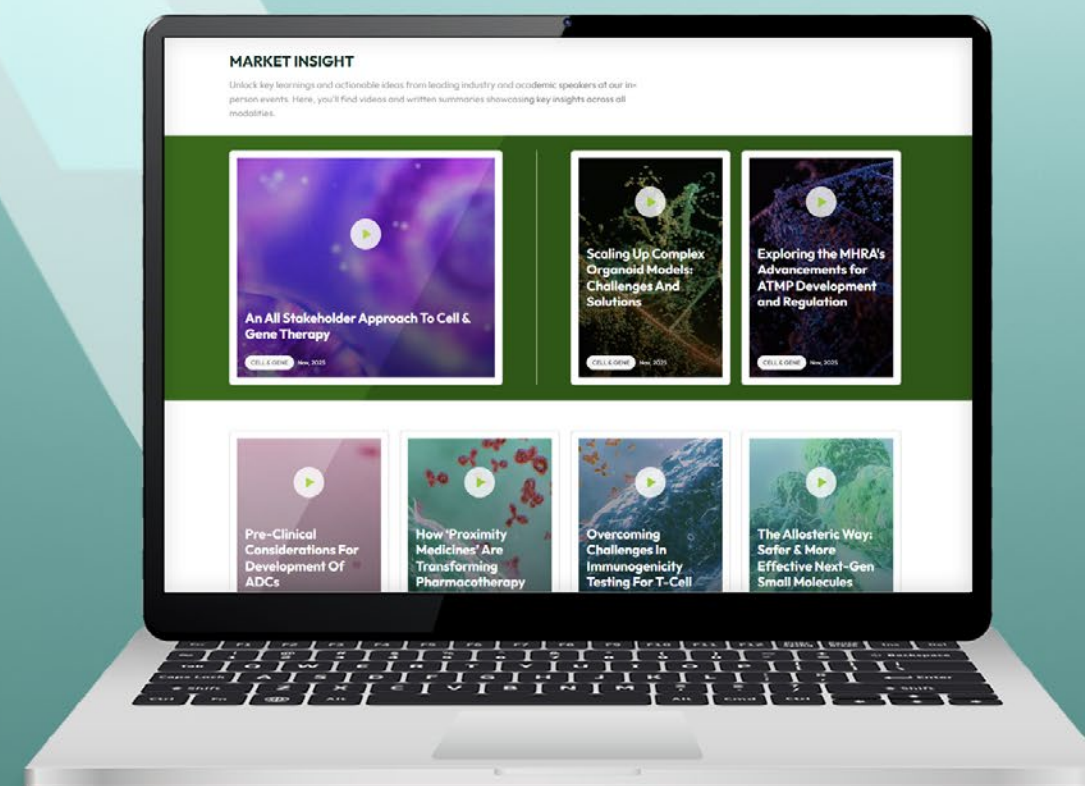
Maintaining transparency with external stakeholders and ensuring everyone is aligned can also be arduous with intellectual property laws to consider. However, having frequent and transparent discussions with suppliers and stakeholders can facilitate this alignment. Furthermore, it is key to incorporate green practices at each stage of the supply chain, from early R&D to manufacturing and transportation.

Muchandibaya concluded by saying that it is vital to start small and slowly build when investing in sustainability. Moreover, he suggested that recognising the value of sustainability beyond the costs is a crucial mindset ■



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OLIGONUCLEOTIDES

SIX TIPS FOR EXTERNAL INNOVATIONS IN BIOLOGICS

Alexandria Cogdill, Head of Strategic Initiatives, Global Business Development, Daiichi Sankyo

In this presentation, Alexandria Cogdill, Head of Strategic Initiatives, Global Business Development, at Daiichi Sankyo outlines the benefits of leveraging external innovation to overcome challenges in biologics manufacturing. Cogdill's talk aimed to outline how partnerships with external innovators can address complex challenges in biologics manufacturing. Furthermore, she discussed how integrating cutting-edge technologies from external sources can streamline manufacturing and lower cost of goods sold (COGS).

01 Understand Your Market

When looking to external partners in biologics manufacturing innovation, it is vital to first understand your market. The ADC market is already large and complex, and it will continue to grow rapidly in the coming years. Innovation of individual manufacturing steps comes from understanding the force factors that drive possible innovation across a specific asset.

02 Shared Challenges Mean Better Partnerships

Challenges that affect biologics companies broadly are often solved by up-and-coming startups. Therefore, shared manufacturing processes in pharmaceuticals allow a company to identify those common challenges, which can then be met by the external market. Herein, Cogdill stressed the importance of paying attention to the external market and where innovation may be solving prevalent problems.

03 Not All Innovations are Created Equally

When innovating manufacturing steps, evaluating technical complexity and research integration at the same time is extremely important. Cogdill said that costly, time-consuming, and difficult projects are not suited to be the first integration a company chases. Instead, integrating easier to handle integrations to reduce COGS are the best first win. From there, a company can continue to improve their processes, tackling harder integrations later.

04 Survey Your External Market from Both Sides

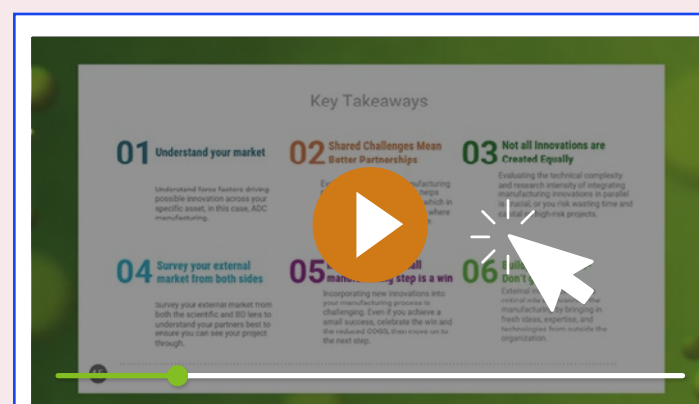
Companies should always survey the external market from both a scientific and a business development lens to ensure their partners can see the project through. Therefore, Cogdill recommended that when presenting to a pharma company, recognising that they consider both of these sides.

05 Innovating in a Small Manufacturing Step is a Win

Although, Cogdill recommends taking the smallest leaps first, the successful implementation of these innovations should still be seen as big wins. When manufacturing at a global scale, even small COGS reductions can lead to billions of dollars saved. So Cogdill said to celebrate small improvements and move on to the next step.

06 Build, Buy, and Partner

Finally, Cogdill added that she was of the opinion that it was best not to undertake complex projects alone. External innovation plays a crucial role in advancing all aspects of internal development, from scientific to R&D and manufacturing. She said that organisations only stand to benefit from bringing in fresh ideas, people, expertise, and technologies from the outside ■



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PEPTIDES

EMPOWERING PEPTIDE SCIENCE WITH OPEN SOURCE TOOLS

Rodrigo Ochoa, Senior Scientist, Novo Nordisk

KEY PRESENTATION POINTS:

BI Line Notation

PyPept Package

PepFun Methodology

Peptide research has boomed recently due to its applications as biomarkers, therapeutic alternatives, or antigenic sub-units in vaccines. Computational tools have assisted with the identification of novel sequences, the prediction of properties, and the modelling of structures. Yet the lack of open-source tools hinders the analysis of this data.

Rodrigo Ochoa, Senior Scientist at Novo Nordisk, an expert and pioneer in open-source peptide technology presents two specific tools that facilitate peptide analysis and design: pyPept and BI Line (BILN).

BILN is a promising alternative to other biologics line notations like HELM. Medicinal chemists reported that BILN was more human-readable, more user-friendly, and more appropriate for annotating complex peptide sequences than its competitors. Ochoa presents multiple examples of non-natural and natural amino acids to illustrate BILN's impressive capabilities and unambiguous nature. "BILN provides an unequivocal translation between the string format and the atomistic description."

pyPept is a tool that analyses the peptide notation and creates a 2D or 3D representation of them. Scientists can use the 3D format to run an MD simulation to relax the molecule or perform any other modification. By connecting sequence-level notations with molecular objects, pyPept allows researchers to streamline peptide design processes and supports library generation for experimental workflows.

PepFun is another methodology that Ochoa advocates for. He outlined PepFun's main purpose: "In this package there are different functionalities for analysing the sequences of the peptides, for example, to run basic alignments including natural and non-natural amino acids." It includes functionalities such as scoring matrices for non-natural amino acids, SAR (structure-activity relationship) analysis, and prediction of peptide properties using machine learning.

Furthermore, Ochoa reiterates the importance of collaboration between academia and industry and democratising these technologies to promote their wider use the field of peptide analysis

"The protocols are fully open-source so they can be embedded in any commercial or non-commercial protocol."

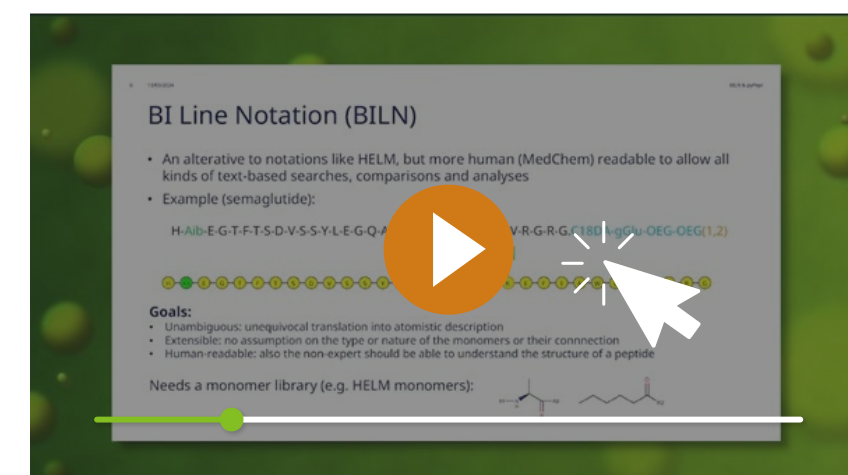


and design. "I think having a community working together on these kinds of methodologies will accelerate the research around these tools."

These tools promote standardisation in peptide research while addressing the complexity of peptide chemical space and

enhancing the design of therapeutics. While they are a good starting point, there are ongoing improvements to expand their functionalities and applications ■

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PEPTIDES

SNAKEBITE MEDICINES: VENOM DERIVED PEPTIDES FOR THERAPEUTIC INDICATIONS

Dorothy Bray, Executive Director, Celtic Bio

Since the time of ancient Greece, the snake has been used as an enduring symbol of medicine and healing. And, although legend says there are no snakes in Ireland, Irish company Celtic Biotech have set about pushing this connection further. Snake venom contains bioactive molecules which can be isolated for potential medicinal purposes in multiple therapeutic areas including cardiovascular disease, cancer, diabetes, pain, and stroke.

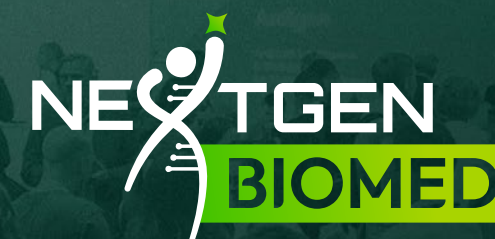
Snake venom-based therapies occupy an important place in the history of medicine. In 1968, John Vane showed that peptides from Brazilian viper venom could inhibit ACE activity in dog lungs. This went on to be the active ingredient in the first angiotensin-converting enzyme (ACE) inhibitor, Captopril. The drug is widely prescribed today for hypertension.

Molecules in snake venom have been developed into the active ingredients in many other drugs, including Tirofiban and Eptifibatide: synthetic fibrinogen antagonists

and heart medications; Batroxobin: purified from lancehead snake venom and used for acute cerebral infraction; and Cobratide: purified from Chinese cobra venom for use in chronic arthralgia, sciatica, and neuropathic headache.

Celtic Biotech sources their venom from cobras and South American rattlesnakes. Bray shares that cobras are easy to breed in captivity, but the rattlesnakes are less so. The snakes live about 12-15 years in captivity and in that time, females can birth 5-12 live young. When the reptiles are around 12 months old, they can be milked for their venom, yielding 70-300mg per snake. Doses for humans' range between 0.1-2mg per day depending on the application.

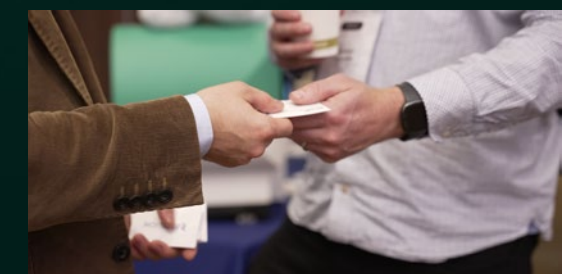
Two promising venom-derived compounds, Crotamine and Cobramine, show potential in cancer treatment and chronic kidney disease, respectively. Bray shares insights on the ongoing clinical studies of CB-24 Crotoxin, a snake venom-derived compound, which has shown selective toxicity to cancer cells and a favourable safety profile ■



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PEPTIDES

ENGINEERING FLUORESCENT PEPTIDES AND PROTEINS AS NOVEL BIOSENSORS

Marc Vendrell, Professor Translational Chemistry, University of Edinburgh

KEY PRESENTATION POINTS:

- Fluorescent Peptides and Proteins
- Cell Penetrating Peptides
- Antibody Drug Conjugates
- Imaging T Cell Activity
- Clinical Applications



Fluorogenic peptides (example 1: cell-penetrating peptides)

- Commercial dyes: bulky and hydrophobic **X**
- HaloTag-based systems: genetic modifications **X**

This work:

unprotected peptide/protein $\xrightarrow[\text{60 min}]{\text{pH 7, 37°C}}$ fluorogenic peptide/protein

Cellular uptake

✓ Late-stage ✓ Non-perturbative ✓ Fluorogenic

Nadal-Buñi et al. ACS Cent. Sci., 2025, 66.

Marc's team builds fluorescent imaging tools that range from very small fluorophores and fluorescent molecules in peptide scaffolds to heavier fluorescent proteins, helping to span diverse product targets. This presentation highlights two examples of fluorescent peptides and one example of a fluorescent protein. All these fluorescent molecules share a common utility as probes in understanding both the innate and adaptive immune systems.

Cell Penetrating Peptides

Vendrell discusses Ferran Nadal-Buñi's work on cell penetrating peptides. Nadal-Buñi wanted to find a way to put the smallest possible tag in a cell penetrating peptide without modifying the peptide's properties. Then, he could use imaging to understand where the peptide travels inside the cell.

The team's strategy uses extra small benzodiazole fluorophores with a palladium activated group which reacts exclusively with cysteine – this results in a cysteine-tagged peptide. This means that the fluorophore has the ability to be introduced in an unprotected peptide or protein. Other benefits include the fluorophore's small, non-perturbative molecular weight of only 200 Daltons, and its fluorogenicity, allowing it to be used in wash-free real-time imaging.

Antibody Drug Conjugates

In the second example in collaboration with AbbVie, the team engineered a fluorophore that can monitor the location of antibody-drug conjugates within cells and determine when the drug payload is released. This fluorophore was based on the chemical naphthylamide with three legs attached. One leg was used for antibody conjugation using lysine residues. Another was used for monitoring the subcellular location of the

fluorophore due to its pH sensitivity. And the final leg used a 'caging group' which could quench the fluorescence until the payload was released

Imaging T Cell Activity

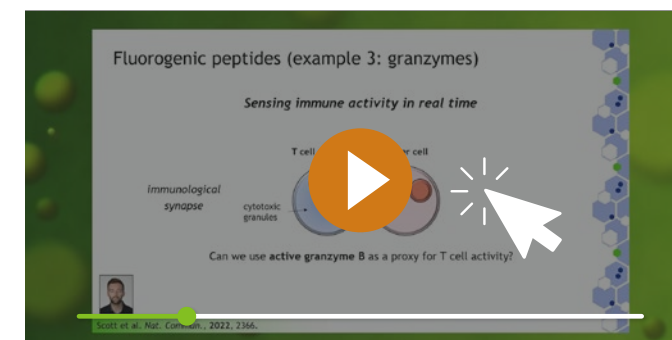
The final example that Vendrell discusses involves creating a fluorogenic peptide to visualise T cell activity in real time, specifically their interaction with cancer cells. To do this, the team set about creating a fluorogenic peptide that could monitor the release of the cytotoxic enzyme granzyme B by T cells. An approach using highly

optimised FRET-based peptides allowed researchers to monitor when T cells release granzyme B to kill cancer cells, providing valuable insights into immune responses

Clinical Applications

The team's work on fluorescent peptides and proteins has significant potential for clinical applications, with some peptides already tested in human subjects. This represents a major advancement in using fluorescent reagents for imaging in clinical settings ■

Watch the key moments of Marc's presentation now, for free on





PEPTIDES

BENCHMARKING SYNTHETIC PEPTIDE SUSTAINABILITY

Paul Richardson, Director of Analytical Synthesis Technologies, Pfizer

KEY PRESENTATION POINTS:

Peptide Synthesis Overview

Solvent Usage and Sustainability

Hybrid Approaches to Peptide Synthesis

Process Mass Intensity (PMI) and Future Assessments

There is an exponential growth in the number of peptide drugs reaching the market which has led the biopharma industry to examine the environmental burden of peptide production. Paul Richardson, Director of Analytical Synthesis Technologies at Pfizer highlights the importance of benchmarking synthetic peptide sustainability.

Richardson explains that peptide synthesis has not changed much over the last 50 years. With the solid phase synthesis, there is no continuous purification at separate stages, so purification is conducted at the end which is complicated and involves chromatography and an isolation step. At an industrial scale, polystyrene linkers are used but the process is not 'atom economical'. The atom economy refers to the number of atoms at the start of a product versus at the end.

In solid-phase synthesis, scientists may use a huge excess of reagent to push their reactions to completion, generating a high volume of waste but improving yield. The solvents used for peptide synthesis are particularly harmful; DMF

(dimethylformamide) is a substance of high concern and is restricted in the EU under the REACH guidelines. However, DMF's high degree of solubility for amino acid synthons and other reagents makes it a valuable solvent that is hard to replace.

Richardson adds: "It (DMF) is ideal for the chemistry in terms of its polarity and viscosity. You can do couplings in less than an hour, and deprotections in less than 30 minutes. You want the chemistry to go as quickly as possible, and you see negligible racemisation of the peptide amino acids or the amino acid synthons."

The mixed/combined solvents approach has been suggested as an alternative option to DMF with many industry leaders working in this space. Yet combining solvents also presents supply chain challenges because it requires changing processes that are already in place. Piperidine is most commonly used for the deprotection of Fmoc groups but researchers are searching for alternatives since piperidine is a controlled substance. Richardson also discusses the transition to liquid-phase or hybrid peptide synthesis, methods and

"We've promoted a sustainable vision for pharmaceutical chemistry, collected metrics for various modalities, and identified new technologies for synthetic peptide manufacture."

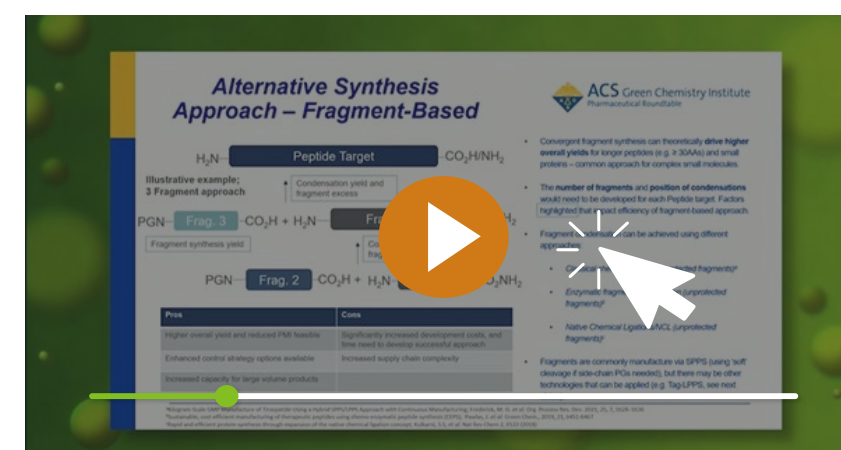


advancements in purification techniques such as supercritical fluid chromatography.

Peptide synthesis has a high environmental impact and peptides have a significantly higher process mass intensity (PMI) compared to small molecules and biologics, as a result of DMF and water

usage. However, liquid-phase synthesis shows better PMI trends, resembling small molecule production. Richardson states that despite high PMI, the lower dosage requirements for peptides reduce waste on a per-patient basis ■

Watch the key moments of Paul's presentation now, for free on





PEPTIDES

CRYSTALLISATION OVER CONTINUOUS CHROMATOGRAPHY: BOOSTING SUSTAINABILITY IN PEPTIDE MANUFACTURING

Steve McIntyre, Peptide Process Development Manager, Almac

KEY PRESENTATION POINTS:

Green Chemistry
in Peptide
Manufacturing

Process Mass
Intensity (PMI) in
Peptide Synthesis

Challenges with
DMF Replacement

Optimisation -
Purification
Process

Almac is a CDMO focused on chemical and analytical development for small molecules and peptides. Steven McIntyre, Peptide Process Development at Almac, states that sustainable peptide manufacturing has seen significant progress but there's still a long way to go. Almac has created a toolkit to analyse peptide structures, based on thousands of peptides manufactured in the company's lab. Peptides are typically isolated by lyophilisation after concentration; however, McIntyre is exploring crystallisation and precipitation as alternatives for certain peptides.

Sustainable peptide manufacturing has many challenges. McIntyre identifies developing greener processes for peptide API as a critical unmet need. At Almac, greenness is measured using process mass intensity (PMI), a metric indicating how much raw material is needed to produce one kilogram of product. A high PMI correlates with higher CO₂ emissions and water usage. Replacing toxic solvents like DMF with greener alternatives like binary solvent systems

derived from renewable feedstocks is also a feasible option to promote sustainable chemistry. Unfortunately, no single solvent could fully replace DMF.

McIntyre points out the key issue in solid-phase synthesis: "Solid-phase synthesis uses protected amino acids, resulting in significant waste; roughly 75% of the amino acid building block is waste." The more complex the structure of the peptide, the higher the PMI. Almac's semi-synthetic cyclic peptide has a PMI of 2300, which is manufactured in solution to conduct a solution-step synthesis and then purification. The team identified that the majority of waste was produced from purification. Although continuous chromatography is an effective way to reduce buffers and increase yields, McIntyre adopted a different approach. He scrutinised purification steps, increasing loading and optimising chromatography by minimising dead-time to reduce PMI by about 20%.

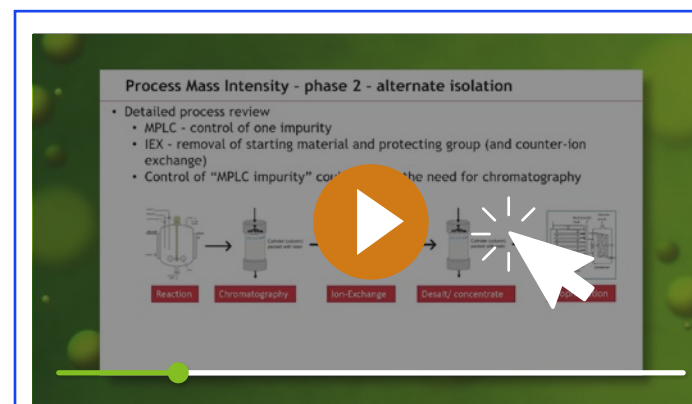
McIntyre expanded on Almac's extraordinary result when crystallising their semi-synthetic cyclic peptide: "We could crystallise this cyclic peptide in amorphous form, and it offered a



"Solid-phase synthesis uses protected amino acids, resulting in significant waste; roughly 75% of the amino acid building block is waste."

key impurity uplift. By switching isolation techniques, we reduced PMI from 2300 to 630." Building on this, the team decided to apply their crystallisation technique to a linear peptide. This research is still in its infancy, but early estimates show significant PMI reductions.

McIntyre illustrates that there's momentum in making peptide chemistry more sustainable. Avoiding chromatography and replacing it with crystallisation had a huge impact on process sustainability. However, fundamental issues in peptide chemistry are still present, specifically amide bond formation, which is a big contributor to waste ■



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VACCINES

TWO AI PLATFORMS FOR TRULY PERSONALISED CANCER VACCINES

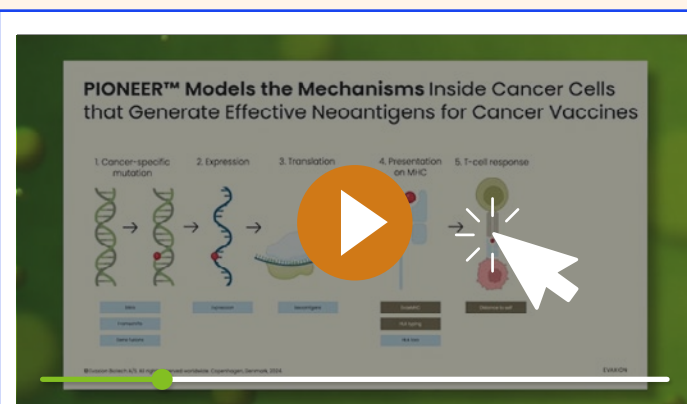
Jens Kringelum, Vice President, Evaxion Biotech

The introduction of immunotherapy has meant that targeted treatments for cancer are slowly becoming available. Jens Kringelum is a bioinformatician at Evaxion Biotech, specialising in immuno-informatics. Kringelum focuses on predicting and investigating immune system reactions to diseases to develop better treatments.

Evaxion Biotech has been working on neoantigen vaccine development, using AI platforms to identify and target specific mutations in cancer cells, aiming for personalised treatments. A major challenge of using neoantigens is the fact that high-quality neoantigens are often unique to each patient, requiring personalised approaches rather than one-size-fits-all treatments.

Kringelum outlines Evaxion's PIONEER and ObsERV AI platforms which are put together using modular bioinformatic building blocks. The PIONEER platform is designed to identify neoantigens. It simulates what's happening in cancer cells and their interaction with the immune system. The platform focuses on identifying specific mutations in cancer cells, ensuring these mutations are expressed and translated into proteins, and presented on the surface of cancer cells. This helps the immune system recognise and target malignant cells while leaving healthy cells alone.

The ObsERV platform offers an alternative source of neoantigens for personalised cancer vaccines. It uses another AI model, designed to identify epitopes from endogenous retroviral elements expressed in cancer cells. These endogenous retroviruses (ERVs) are viral elements integrated into the human genome, which can be expressed in cancer cells serving as targets for vaccines. ObsERV selects these epitopes and validates them through various studies, including animal models, to ensure their effectiveness in controlling tumours ■



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VACCINES

LEVERAGING ONTOLOGY TO DEVELOP A CANCER VACCINE PLATFORM

Oliver (Yongqun) He, Associate Professor, University of Michigan

Yongqun He, Professor at the University of Michigan introduces the CanVaxKB database which aims to standardise, integrate, and support rational vaccine design for cancers. While there are various cancer therapies like chemotherapy, radiology, and immunotherapy, the demand for cancer vaccines is growing following the advancement of mRNA technology for the COVID-19 vaccine.

He notes that identifying antigens is critical for vaccine development. By collecting antigens and performing statistical and informatics analysis, researchers can observe patterns and leverage these for rational vaccine design. The main challenges are translating tools and technology into cancer vaccine design and integrating several data types.

To address this, He's lab has developed the cancer vaccine knowledge base (CanVaxKB) which forms part of the wider VIOLIN vaccine knowledgebase. The data is collected and stored in a MySQL database and ontology is used for analysis. The canvaxgen concept refers to the genes expressing proteins or parts of proteins that can serve as antigens for cancer vaccine development. From over 800 cancer vaccines, approximately 260 canvaxgens have been identified so far as potential targets for vaccine development.

The next step requires analysing the canvaxgens functions in more detail. The gene ontology analysis revealed patterns related to glycoproteins, cytokine activity, and signalling pathways. Ontology was used to classify, annotate, and gain a deeper understanding of the vaccines. Cancer vaccines are classified based on components, target diseases, cell types, and organs.

“We introduced the concept of ‘canvaxgen’, which are genes expressing proteins or parts of proteins that can serve as antigens for cancer vaccine development.”

He advocated combining AI and deep learning methods to deepen our understanding of cancer mechanisms. The CanVaxKB database provides researchers with a standardised and user-friendly database that links data from clinical trials, licensed vaccines, and laboratory studies. Future work will focus on peptide-level analysis and expanding the platform's capabilities ■

WATCH THE KEY MOMENTS of Oliver's presentation now, for free on [Lifesciencexchange.com](https://lifesciencexchange.com)



VACCINES

IMMUNE MODULATORY VACCINES: A NEW MODALITY

Mads Hald Andersen, Director, Professor,
The National Center for Cancer Immune Therapy (CCIT-dk),
Copenhagen University Hospital, Herlev, Denmark



KEY PRESENTATION POINTS:

- IDO/PD-L1 Vaccine
- Clinical Trial and Survival
- Immune Response Mechanisms
- Immune Modulatory Nature
- Clinical Outcomes

Mads Hald Andersen presents on the development and efficacy of immune modulatory vaccines targeting tumour microenvironment antigens in cancer treatment. He begins by providing a historical overview of these vaccines, which have now reached phase three trials and are nearing approval for some cancers.

The primary focus of his talk is on IDO and PD-L1 vaccines, which have shown promising results in clinical trials. Andersen explains that these vaccines work by activating anti-regulatory T cells, which can generate an immune response not only against cancer cells but also against the entire tumour microenvironment.

This approach aims to change the status of the environment from being anti-T cells to more pro-inflammatory. Andersen highlights the distinct roles of CD4 and CD8 T cells in eliciting an antitumour response, with CD4

cells primarily killing target cells and CD8 cells providing support.

Andersen discusses the synergistic effects observed when combining the immune vaccine with PD-1 inhibitors, which demonstrated enhanced antitumour effects. He notes that these vaccines act as immune modulators, affecting myeloid populations in the tumour microenvironment rather than solely targeting cancer cells.

Andersen shares results from a phase one trial of the PD-1 vaccine combined with IDO peptide, which show a response rate of 80%, significantly higher than the expected 40% for PD-1 monotherapy.

Andersen also discusses ongoing and future trials conducted by companies such as IO Biotech and Moderna. IO Biotech is running large phase three trials and phase two trials in head and neck cancer and lung cancer. Moderna is conducting a phase two trial using mRNA technology with the same

IDO/PD-L1-peptide vaccine combined with nivolumab in first line melanoma

ARTICLES

A phase 1/2 trial of an immune-modulatory vaccine against IDO/PD-L1 in combination with nivolumab in metastatic melanoma

Julie Westerlin Kjeldsen, Cathrine Lund Lorentzen, Evelina Martinonali, Eva Elbak, Marco Donat, Rikke Bødker Rasmussen, Tobias Wronfeldt Kjaer, Cecilie Oelvang Mathsen, Shamala Munir Ahmed, Stine Emilie Wils-Bæk, Morten Orlow Rasmussen, Helle Westergaard Høndel, Eva Elvén, Mai-Britt Zouca, Ayako Wakatsuki-Pedersen, Mads Hald Andersen and Inge Marie Svane

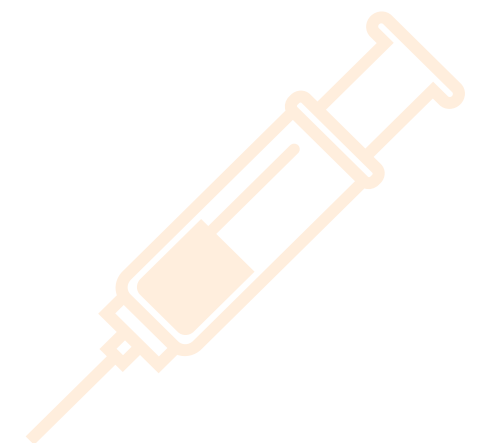
Julie Westerlin Kjeldsen, Cathrine Lund Lorentzen

- The combination of IDO/PD-L1 peptide vaccine and nivolumab was safe with no additional systemic toxicity
- An ORR of 80% was reached with 50 % reaching CR (as recently updated)
- Median PFS reached 26 months and mOS was not reached (as recently updated)
- ORR was significantly higher than a matched control group, who had received anti-PD-1 monotherapy as standard of care.
- Vaccine specific T-cells were demonstrated in PBMCs and at tumor site.
- Vaccine specific T cells recognized both tumor cells and tumor conditioned immune cells
- Treatment-induced pro-inflammatory response at the tumor site

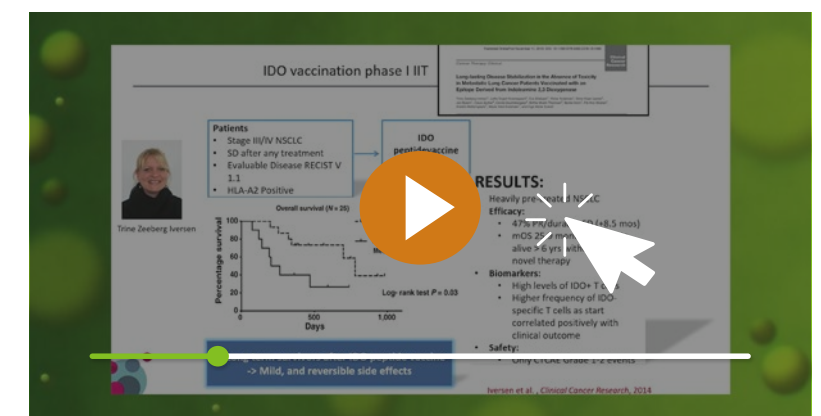
Kjeldsen et al. *Nature Medicine* (2021)
Lorentzen et al. *Journal for Immunotherapy of Cancer* (2023)

epitopes as the IDO and PD-L1 vaccines. Additionally, a trial at Memorial Sloan Kettering is exploring the combination of PD-1 and anti-LAG-3 treatments.

Andersen emphasises the potential of next-generation vaccines targeting other tumour microenvironment antigens, such as TGF-beta and arginase, to induce inflammation in less responsive tumour types. These vaccines could be combined with traditional cancer vaccines and other forms of immunotherapy to enhance their effectiveness ■



Watch the key moments of Mads' presentation now, for free on



VACCINES

CATALYSING VACCINE ACCESS: VACCINE INEQUALITY AND MANUFACTURING IN AFRICA

Christiane Gerke, Program Director, International Vaccine Institute

KEY PRESENTATION POINTS:

- The IVIs role
- COVID19 and Rapid Innovation
- Global Vaccine Inequality
- Inequality in Vaccine Manufacturing: Africa
- Partnership for African Vaccine Manufacturing

The world learned a lot during the global response to the pandemic, and although a triumph in Europe and North America, the roll out of vaccines was slow to catch up in low-income countries. The pandemic highlighted significant disparities in vaccine access between high-income and low-income countries, with slower vaccine rollout particularly in Africa despite global production efforts..

The International Vaccine Institute (IVI) is an international organisation with the goal of developing and delivering safe, effective, and affordable vaccines. Founded in 1997 by the United Nations Development Programme, they focus particularly on expanding vaccine access for low and middle-income countries.

The IVI conducts the entire vaccine development process from discovery in their labs, including in-house projects and partnerships, to implementation and policy recommendations. Their labs are based in their Seoul, South Korea, headquarters, and they also operate regional offices in Europe

(Stockholm and Austria) to improve global coordination and footprint, particularly for activities in Africa.

The COVID-19 pandemic accelerated vaccine development, with the first vaccines being developed in just 11 months, using various technologies such as RNA, DNA, and non-replicating vectors. Furthermore, traditional vaccine development timelines were significantly compressed, with overlapping phases and rolling reviews, which helped speed up the process. In that time, Africa's vaccine production is minimal, with only 1% of vaccines used in Africa being locally produced on the continent. This has prompted the IVI to build on what was learned from the pandemic via initiatives to boost local manufacturing capacity.

Various projects have been launched to strengthen vaccine manufacturing in Africa, including efforts by the MasterCard Foundation, Aspen, and Institute Pasteur Dakar. The Partnership for African Vaccine Manufacturing (PAVM) aims to increase local



“The Partnership for African Vaccine Manufacturing (PAVM) have set a goal to increase the 1% of local production in 2019, to 60% in 2040.”

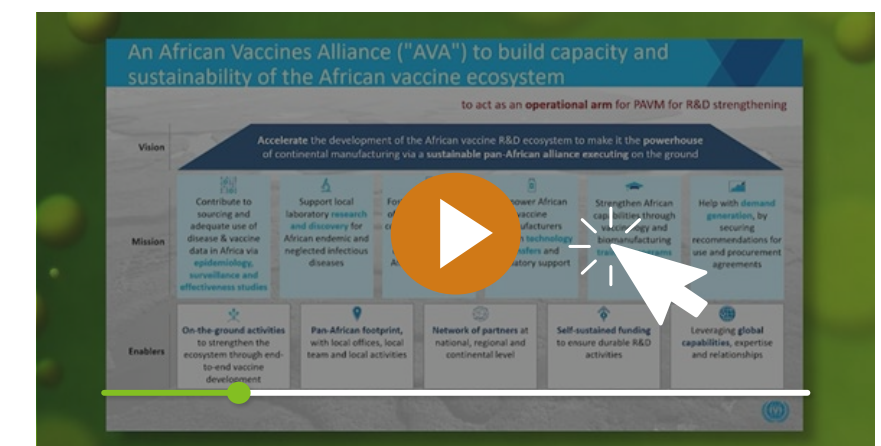
production from 1% in 2019 to 60% by 2040, enhancing pandemic preparedness and addressing endemic diseases.

Rather than instituting changes from the top-down, the IVI instead sees their role to catalyse the scale up of local vaccine development efforts. To do this, the IVI support end-to-end vaccine capacity building in Africa through clinical development and

tech transfer, from discovery to market introduction.

Over time, the IVI plans to retreat from operations ultimately transitioning to local leadership once capacity is sufficiently ramped up. This allows the partnership to truly be an initiative from African countries with African partners ■

Watch the key moments of Christiane's presentation now, for free on





VACCINES

RESHAPING RNA VACCINE PRODUCTION WITH QUALITY BY DIGITAL DESIGN (QBDD)

Mabrouka Maamra, Project Manager, University of Sheffield

KEY PRESENTATION POINTS:

- Challenges and Inequalities in Vaccine Distribution
- Grant for RNA Vaccine Development
- Quality by Digital Design (QbDD)
- Oligo – dt Chromatography for RNA Purification

Mabrouka Maamra, Project Manager at the University of Sheffield, discusses the importance of quality by digital design for developing RNA vaccines and therapeutic manufacturing processes. She describes mRNA vaccines as a lifeline due to their rapid dose production compared to traditional vaccines. While the COVID-19 pandemic highlighted the potential of mRNA vaccines, it also showcased the great inequality and disparity in terms of vaccine distribution and technology access.

To fight any future global pandemics or epidemics, pandemic preparedness is key to ensure that we have worldwide access to vaccines. In late 2022, Maamra's team led by Doctor Zoltán Kis was awarded a grant in the R3 programme RNA Readiness response by Welcome Leap. "The aim of the project was to address the challenges of producing large volumes of RNA-based vaccines and therapeutics rapidly, at high quality, low cost, and in a disease-agnostic manner."

Experts in process development, modelling, and analytical methods combined their expertise to produce an RNA platform that

enabled multi-product production at high-quality secure low-cost manufacturing with high productivity to enable rapid development and mass production of mRNA vaccines. To achieve this, applying quality by digital design (QbDD) is crucial. Within the manufacturing context, a risk management approach is key to ensuring quality control throughout the process. Furthermore, critical quality attributes define efficacy and safety, and process optimisation through real-time monitoring and digital modelling are key to creating a robust QbDD & Manufacturing Framework.

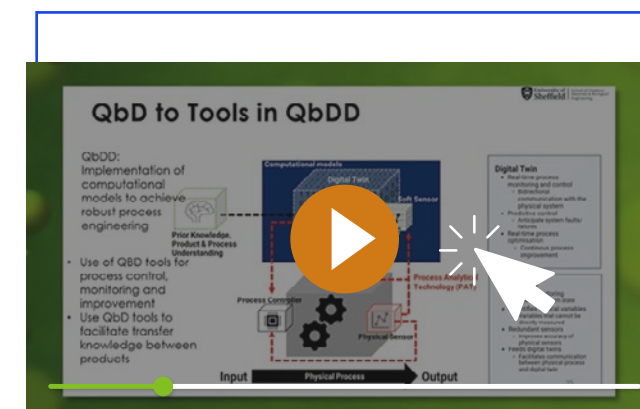
In vitro transcription is an essential process in manufacturing; this method aims to convert the substrates (NTPs) into the desired product (RNA). This stage requires implementing process parameters like time, Ph, reagent type, concentration, and mixing with the hope of achieving all the critical attributes required and key performance indicators. The RNA is produced via enzymatic reactions and chromatography purification which has been optimised using oligo dT chromatography to improve efficacy and reduce costs.

“The RNA box will allow rapid access to RNA technology, rapid development and manufacturing of high-quality mRNA vaccines and therapeutics, and simplified technology transfer.”



Maamra explains that the team has created a web app connected to manufacturing analytical equipment. This gives researchers real-time data analysis and graphical analysis: "We've developed a tool and built it into the dashboard to look at the continuous chromatography peak area, and it takes into account the peak area in real-time. We can quantify the purified mRNA from the continuous chromatography in real-time." The digital model integrates soft sensors and digital twins which allow the predictive modelling to find faults and optimise process parameters in real-time.

Regarding future directions, the team aims to finalise the RNA box to scale up production and further integrate analytical tools for improved process control. Maamra concludes: "This (the RNA box) will allow rapid access to RNA technology, rapid development and manufacturing of high-quality mRNA vaccines and therapeutics, and simplified technology transfer." ■



Watch the key moments of Mabrouka's presentation now, for free on



