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VACCINE INSIGHTS

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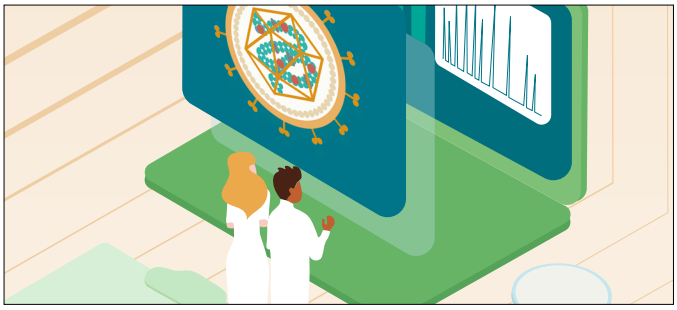

VACCINE INSIGHTS

ANALYTICAL INNOVATION

SPOTLIGHT

EXPERT ROUNDTABLE

Patient-centric approaches to vaccine development

Q&A

Rajat Desikan, Cristiana Campa, Marc Fourneau, Ricardo Palacios, Martine Douha, Frederic Mathot and **Carlo Pergola**

Vaccine Insights has brought together R&D experts from GSK to discuss patient-focused approaches to vaccine development. This approach represents a paradigm shift in chemistry, manufacturing and controls (CMC) processes for vaccine development, by emphasizing the understanding of a vaccine's critical quality attributes (CQAs) and their impact on patient safety and efficacy. Implementing this requires cross-functional expertise. Beyond traditional *in vitro* and *in vivo*/clinical studies, patient-centricity allows for model-based approaches to analyze data and perform predictive simulations. This leverages prior knowledge and new insights to enhance decision-making, flexibility, and robustness from design to market launch, while reducing the need for animal and human data.

Ultimately, patient-centricity aligns vaccine attributes with patient needs, efficacy, and safety, thus ensuring robust and effective vaccine development. In this expert roundtable, the panel explored the foundational aspects of implementing a patient-centric approach from a vaccine developer's perspective.

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Q What is the overarching goal of the patient-centric approach to vaccine CMC development?

CP The overarching goal of the patient-centric approach **[1,2]** is to prioritize patient safety and product efficacy when designing a product and related

CMC characteristics and associated quality expectations. This can be achieved by leveraging product characterization and prior knowledge, and generating nonclinical and clinical evidence. A thorough understanding of the product is crucial for developing a control strategy ensuring that the required quality is consistently achieved at production and maintained throughout the entire shelf-life of the product. According to ICH Q8 (R2), in a 'minimal' approach, product specifications are a primary means of control and are based on batch data available at the time of registration; an enhanced patient-centric approach integrates specifications into the overall quality control strategy, basing them on desired product performance supported by relevant data.

Q What are critical quality attributes (CQAs) and why are they important?

CC CQAs are physical, chemical, biological, or microbiological properties of the vaccine that must be maintained within specific limits to ensure the desired quality of the product. They are crucial because they directly impact the safety and efficacy of the vaccine, guiding the development process to ensure consistent control and monitoring.

Take 'integrity' of an mRNA vaccine as an example. Ensuring the integrity of the mRNA is vital for vaccine efficacy, as degraded mRNA may lead to the production of non-functional antigens, potentially failing to provide protection. Advanced analytical methods, such as high-performance liquid chromatography, are used to monitor mRNA integrity during manufacturing and storage. Throughout the vaccine's lifecycle, mRNA integrity levels may vary without adversely impacting efficacy, if values are within appropriate specification limits. Therefore, degradation kinetics of mRNA integrity is among the CQAs determining vaccine shelf-life.

Q Can you explain the main strategies within the patient-centric approach and their significance?

CP The patient-centric approach comprises both proactive and reactive strategies. The proactive strategy focuses on generating data to establish relationships between patient effects and product characteristics through controlled experimentation via both non-clinical and clinical studies and integrating this information via model-based approaches. The reactive strategy monitors clinical development signals and real-world product usage, assessing observations at the population level. Both strategies ensure continuous evaluation and adjustment of CQAs to align vaccine characteristics with patient outcomes.

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"They are crucial because they directly impact the safety and efficacy of the vaccine, guiding the development process to ensure consistent control and monitoring."
Cristiana Campa

Q What role does model-informed vaccine development (MIVD) play in enhancing the patient-centric approach to vaccine development?

RD MIVD [3] utilizes quantitative *in silico* approaches integrated with data from preclinical and clinical studies. This methodology supports decision-making and regulatory considerations, optimizes development processes, minimizes uncertainty, and improves the probability of clinical trial success by refining doses, dosing regimens, formulations and precisely targeting patient sub-populations. The MIVD toolbox includes classical statistical and translational models, mechanistic quantitative systems pharmacology models that combine systems biology and vaccine pharmacology models, scientific machine learning, and model-based meta-analysis, among other methodologies.

Q How can the challenge of limited data from animal and human studies in vaccine development be addressed?

RD At the heart of patient-centricity is an iterative evidence-based process. This process accumulates data and insights from *in vitro*, *in vivo*, and *in silico* studies to validate or refine hypotheses. Comprehensive data collection—including analytical information, research observations, clinical trials, and real-world evidence—and using *in silico* models to evaluate, connect, validate, and interpret data ensures alignment of vaccine specifications with patient needs and safety standards. A key highlight to emphasize is that *in silico* models support the iterative process of data accumulation, enable predictive simulations, bridge gaps in data, reduce uncertainty, and enhance decision-making throughout the vaccine development lifecycle.

Q What is the purpose of triaging quality attributes in the patient-centric development framework?

FM Triaging involves listing all quality attributes of interest based on the quality target product profile (QTPP) for the purpose of identifying potential CQAs. This process confirms the criticality of these attributes, ensuring that those with a significant impact on safety and efficacy are considered in the decision-making process, thereby streamlining the development and regulatory approval of the vaccine.

"The overarching goal of the patient-centric approach is to prioritize patient safety and product efficacy when designing a product and related CMC characteristics and associated quality expectations."
Carlo Pergola

Q How can evidence-based data for confirmed CQAs be generated?

FM For confirmed CQAs, a comprehensive plan incorporating both direct measures (impact on disease) and indirect measures (immune markers) of safety and efficacy should be developed. This involves conducting *in vitro* and *in vivo* studies focusing on essential properties such as purity, identity, potency, safety signals, and immune biomarkers. The iterative process refines CQA ranges through data from bespoke non-clinical and clinical studies, supported by statistical and modeling analyses.

RD An important related aspect of MIVD in this context is the learn–confirm–predict cycle, which is an iterative process that enhances decision-making and reduces uncertainty throughout vaccine development. This process involves learning from existing data, confirming findings through additional studies, and predicting outcomes using *in silico* models. By leveraging prior knowledge, validating hypotheses, and forecasting outcomes, this process helps to optimize clinical trial designs and refine doses. The iterative nature allows for continuous improvement and adaptation to new information. Overall, it lowers uncertainty and improves the success rates of clinical trials, thus accelerating the development of safe and effective vaccines.

Q What is the significance of the QTPP in the patient-centric development framework?

CC The QTPP serves as the foundational framework for drug and vaccine design, providing a forward-looking summary of quality characteristics critical for ensuring safety and efficacy. It guides the shaping of product attributes and the development of processes and analytical methods, evolving through the development stages from initial drafts to a complete version by launch, ensuring alignment with patient needs.

Q How can the challenge of setting specifications with limited manufacturing experience be addressed?

CP A shift towards a patient-centric development framework that prioritizes patient safety and efficacy over traditional process benchmarks can address this challenge. By leveraging existing knowledge and insights and generating new evidence, vaccine specifications can be reoriented to focus on patient outcomes rather than solely on manufacturing experience and stability data from limited lots, thereby ensuring robust product quality.

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Q How can changes in product attributes throughout the vaccine's lifecycle be handled?

FM An iterative approach should be adopted to consistently review and reassess CQAs, enhancing knowledge through additional *in vitro*, *in vivo*, *in silico*, and clinical studies. This process ensures that any changes in product attributes, such as vaccine thermostability and degradation under various storage conditions, are evaluated for their impact on safety and efficacy, maintaining alignment with patient needs and regulatory requirements.

Q What is the importance of immune biomarkers in the context of a patient-centric vaccine development?

RP Immune biomarkers are crucial for predicting vaccine efficacy, assessing safety, and guiding the development of safe and effective vaccines. They serve as surrogate endpoints that provide insights into the immune response elicited by the vaccine, helping to establish correlations between immune markers and clinical outcomes, such as protection against disease, thereby supporting evidence-based decision-making.

Q Which kind of models or approaches can inform patient-centric vaccine development?

RP There are many such approaches. As an example, controlled human infection models (CHIMs) can provide valuable input on key immune parameters and serve as proof-of-concept to assess potential vaccine candidates. CHIM studies can be used to validate biomarkers associated with protection, support dose selection, and provide early evidence of vaccine efficacy, thereby de-risking later-stage clinical trials. However, not all diseases have CHIMs available, therefore, analysis of samples from patients at early infection stages and exposed uninfected individuals can support biomarker discovery and validation.

MF Preclinical-to-clinical translation involves using data from animal studies to predict human responses [3]. This process helps bridge the gap between preclinical findings and clinical outcomes, ensuring that the vaccines are accurately assessed before human trials, thereby reducing the risk of adverse events and improving the likelihood of clinical success. Based on early clinical data readout and using the learn-confirm-predict paradigm, MIVD approaches can contribute to dose selection by using quantitative models to predict the optimal dose that balances immunogenicity and reactogenicity. This approach allows for the identification of dosing regimens that maximize efficacy while minimizing adverse effects, ensuring that the vaccine is both safe and effective for the target population.

"The right choice of vaccine dose can be the difference between clinical success or failure for a vaccine."
Rajat Desikan

Q Along similar lines, what is the role of dose–response modeling in patient-centric vaccine development?

RD The right choice of vaccine dose can be the difference between clinical success or failure for a vaccine. Dose–response modeling plays a critical role in understanding the relationship between vaccine dose and the resulting immune response. By analyzing dose-response curves, researchers can determine the optimum dose and dosing regimens to achieve the desired immunogenicity with minimal side effects, thereby enhancing patient safety and efficacy. Vaccine developers are embracing this approach for enhancing probability of clinical success. A published example is using model-based approaches to guide the pediatric dose selection of a SARS-CoV-2 vaccine [4].

MF Two key points to highlight here. First, vaccine development teams typically consider the appropriate dose for a new vaccine from the beginning by leveraging prior knowledge on similar products or platforms. This stage, often referred to as 'Phase 0', provides an opportunity to apply model-based approaches, gain quantitative insights, guide experimental design, and increase the chances of clinical success. Second, vaccine dose-responses often differ between animal models and humans, necessitating translational frameworks to bridge the two. Therefore, for both these reasons, it is crucial to embed MIVD approaches into vaccine development from the outset.

Q How do correlates of protection (CoP) to predict vaccine efficacy in new clinical trials fit with MIVD approaches?

MD Correlates of protection are immune markers that are associated with protection against disease [5]. Identifying these markers is important because they can serve as surrogate endpoints in clinical trials, allowing for the prediction of vaccine efficacy without the need for large-scale efficacy studies. CoP can be used to predict vaccine efficacy by quantitatively correlating the immune responses elicited by the vaccine to protection from disease. By analyzing immune responses across vaccinated individuals, researchers can estimate the vaccine's efficacy in new clinical trials, thereby accelerating the development process and ensuring that the vaccine meets patient needs. CoP within the context of MIVD also helps to elevate dose-immunogenicity response modelling to dose-efficacy modelling to enable precision dosing strategies across patient sub-populations such as elderly, pediatric, and immunocompromised, thus enabling patient-centric vaccine deployment.

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BIOGRAPHIES

Rajat Desikan

Rajat Desikan is a Scientific Director within Clinical Pharmacology Modelling & Simulation in R&D at GSK, based in the United Kingdom. He leads the integration of advanced modelling approaches, including quantitative systems pharmacology, into clinical-stage drug and vaccine development, with a focus on infectious diseases such as HIV, Hepatitis B and respiratory vaccine portfolios. His work supports internal and regulatory decision-making, including Go/No-Go assessments, dose selection, and clinical trial design. Prior to this role, Rajat has experience in molecular modelling within the discovery space and disease-area modelling across preclinical and clinical stages, working on therapeutic areas such as immune-oncology, autoimmune diseases, and vaccines. His expertise spans diverse drug and vaccine modalities, including small molecules, monoclonal and bispecific antibodies, siRNA, antisense oligonucleotides, mRNA vaccines, and liposome-encapsulated drugs. In addition to his work at GSK, Rajat serves as an associate editor for *CPT: Pharmacometrics & Systems Pharmacology*, a journal of the American Society for Clinical Pharmacology & Therapeutics (ASCPT).

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Cristiana Campa

Cristiana Campa is the External CMC Intelligence Lead in Global Technical R&D at GSK, based in Italy. She has been instrumental in advancing innovative CMC development strategies and integrating QbD principles across GSK Vaccines. Prior to joining GSK, she served as Head of Analytical Development at Novartis Vaccines and has over two decades of experience as a researcher and team leader in academia and industry. She actively contributes to global regulatory and industry groups, including the Expert Working Group for ICH Q6 Guideline revision (specifications), pandemic preparedness initiatives in Vaccines

Europe/IFPMA, and CEPI. In addition, she is deeply involved in scientific committees and technical conferences, and she serves on the Board of Directors at the Parenteral Drug Association (PDA). Her leadership and advocacy continue to drive innovation and collaboration across the biopharmaceutical sector.

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Marc Fourneau

Marc Fourneau is a Senior Director of Translational Statistics and Modelling in Research at GSK Vaccines, based in Belgium. With a BSc in Biology, he joined GSK in 1988 and has since held various roles of increasing responsibility and leadership within the statistical organization, contributing to pre-clinical, clinical, and epidemiological research for the development of numerous vaccines, including Hepatitis A, B, AB, and E; DTPw and DTPa combination vaccines; Hib, HSV, strep, typhoid, flu, dengue, MMRV, and shingles. In his current role, which he has held since 2021, Marc leads efforts to integrate advanced statistical methodologies and modelling approaches to support translational research and vaccine innovation. His extensive experience and long-standing commitment to vaccine development have been instrumental in advancing GSK's portfolio and addressing global health challenges.

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Ricardo Palacios is the Clinical Project Lead (Senior Director) for Early Bacterial Projects at GSK's Vaccine & Infectious Diseases Research Unit in Siena, Italy. He provides clinical leadership and strategic direction for the development of vaccines and monoclonal antibodies targeting bacterial infections, guiding projects from conception to early clinical stages. Prior to joining GSK, Ricardo led vaccine development for arboviruses and respiratory viruses at the Instituto Butantan in São Paulo, Brazil, where his contributions to the phase III dengue vaccine trial was recognized by the New England Journal of Medicine as one of the Notable Articles of 2024. During the COVID-19 pandemic, he represented the Developing Countries Vaccine Manufacturing Network (DCVMN) on the COVAX Clinical SWAT team, designing a pivotal trial that supported the WHO's Emergency Use Listing for Sinovac's COVID-19 vaccine, CoronaVac, while also supporting clinical sites and trials funded by WHO across Asia, Africa and Latin America. A physician with a PhD in Infectious Diseases, Ricardo also holds a BSc in Social Sciences and a specialization in bioethics.

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Martine Douha

Martine Douha is a Lead Statistician for CMC projects at GSK, based in Belgium. She has been instrumental in integrating statistical methodologies into product, process, and analytical development, supporting successful vaccine development and regulatory approvals, particularly for LVV vaccines. Previously, she served as a clinical project statistician at GSK Biologicals from 2003–2018, where she oversaw vaccine development trial designs,

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Frédéric Mathot is a Scientific and Technical Lead (Associate Director) for drug product development at GSK's Vaccine Research & Development Centre in Rixensart, Belgium. He provides strategic leadership on drug product development and associated processes for new vaccine candidates, collaborating with key internal and external stakeholders. Over the past decade, he has focused on advancing drug product development for nucleic acid-based platforms, including adenoviral/ MVA vectors and mRNA/LNP modalities, working with partners such as BARDA, WuXi Biologics, and CureVac. A pharmacist with a PhD in Pharmaceutical Sciences from UCLouvain, Frédéric also leads initiatives to onboard novel technologies, such as AI/ML platforms, alternative devices, and innovative drying technologies, while contributing to academia through PhD supervision and lecturing at UCLouvain.

Frédéric Mathot, Vaccines Technical R&D, GSK, Belgium

Carlo Pergola

Carlo Pergola is a Senior Director of Global Product Development at GSK, based in Italy and Belgium. He leads cross-functional teams in advancing vaccine drug product technical development through clinical phases and achieving product approvals, with expertise in CMC development and QbD. Prior to joining GSK, Carlo served as Laboratory Head of Vaccine Chemistry and Formulation at Novartis Vaccines and held senior roles at Merck KGaA, where he directed formulation and analytical strategies for biotech therapeutics. Holding a PhD in Pharmaceutical Sciences, Carlo has also contributed to academic research at the University of Naples, Tübingen, and Jena. His work integrates advanced methodologies to accelerate drug development and ensure alignment with global regulatory standards.

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ANALYTICAL INNOVATION

SPOTLIGHT

Leveraging *in silico* tools to accelerate vaccine manufacturing: the promise of computational fluid dynamics and hybrid process models

Irina Meln, Xiyan Li, Antonio Gaetano Cardillo, and Krist V Gernaey

VIEWPOINT

"By integrating computational fluid dynamics, compartment and kinetic models into upstream process design, we are enabling faster development, more efficient small-scale production, and robust control of vaccine manufacturing."

The biomanufacturing landscape is evolving. As the demand grows for vaccines to be delivered faster, more reliably, and with greater efficiency, digital innovation becomes essential. At the core of this evolution is the integration of computational fluid dynamics (CFD), compartment and kinetic modeling into upstream vaccine process development. These tools are helping to intensify processes, improve productivity at smaller scales, and enable more robust and flexible manufacturing strategies.

Within the Inno4Vac project, we are combining CFD with statistical-mechanistic models of microbial cell growth to build a comprehensive hybrid model of the upstream process.

This hybrid model offers predictive power to streamline bioreactor design, optimize productivity, and troubleshoot scale-up challenges.

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FROM COMPLEXITY TO CLARITY

At a glance, modern vaccine production appears straightforward. But inside a bioreactor, fluid dynamics, nutrient gradients, and oxygen transfer interact in ways that are difficult to visualize or predict. CFD models allow us to simulate these internal conditions with high spatial resolution and insight. In Inno4Vac, we used data from Ambr250 and 20 L bioreactors to construct detailed CFD simulations, capturing reactor-specific flow regimes and mixing patterns.

To reduce the computational cost of running full CFD models, we translate these into compartment models. These represent bioreactors as networks of interconnected zones, each with distinct environmental parameters. This compartmentalization enables much faster simulation while maintaining results within an acceptable error range. When linked with kinetic models of microbial growth and antigen expression, these simulations form a hybrid tool that predicts how process changes impact performance.

A MODEL FOR EVERY STAGE

Hybrid models are already proving useful across the vaccine development life cycle:

- Early process development: by calibrating against small-scale experiments, the models help define critical process parameters and identify optimal feeding strategies;
- Process scale-up: CFD-derived models allow virtual testing of scale-up scenarios, highlighting potential issues such as oxygen gradients or mixing inefficiencies before they arise;
- Technology transfer and troubleshooting: the bioreactor model supports consistent process performance across sites and equipment, while also enabling soft-sensing of hard-to-measure variables.

REDUCING RISK, ACCELERATING TIMELINES

Inno4Vac's upstream modeling platform helps reduce reliance on time-consuming physical experiments. By predicting cell growth, product titers, and optimal bioreactor conditions, these models streamline the Design of Experiments (DoE) approach and reduce the need for scale-down models. They are particularly valuable in scenarios where rapid development is critical.

The hybrid model is also designed to comply with Quality by Design (QbD) principles and fits within regulatory expectations as a low-impact mechanistic model. It can be used to inform development decisions, support process validation, and guide real-time process control strategies.

OUTLOOK AND IMPACT

As vaccine platforms evolve, the demand for flexible, scalable, and robust processes will only increase. The integration of CFD, compartment and kinetic models into upstream process development, as demonstrated in Inno4Vac, represents a major step forward. Not only do these tools enable faster and more informed decision-making, but they also support long-term process robustness and regulatory confidence.

To fully realize this potential, continued collaboration between industry, academia, and regulators is essential. By validating these models through shared case studies and open dialogue, we can ensure they become trusted components of the modern vaccine manufacturing toolbox.

BIOGRAPHIES

Irina Meln is Head of Innovation at European Vaccine Initiative (EVI), where she leads strategic initiatives focused on accelerating vaccine development through public-private partnerships and innovative technologies.

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VACCINE INSIGHTS

VACCINE CLINICAL UPDATE

REVIEW

Personalized neoantigen cancer vaccines in the spotlight

Jian Yan, Renzo Perales-Linares, Neil Cooch, and Niranjan Y Sardesai

Neoantigens—mutated peptides arising from somatic changes specific to tumor cells—represent a unique class of immunogenic targets. These non-self-antigens can stimulate potent anti-tumor responses due to their high affinity for T cells and absence of central tolerance, unlike tumor-associated antigens. In this review, we discuss potential of neoantigens as vaccine targets, the advantages of a vaccine approach targeting personalized neoantigens, and the challenges of neoantigen identification and selection. Updates on current neoantigen-based vaccine platforms and clinical trial outcomes are summarized. The emerging synergy between personalized neoantigen vaccines and immune checkpoint inhibitors is highlighted. Future directions and challenges in neoantigen vaccine development are also discussed.

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INTRODUCTION

Immunotherapy has taken center stage in the fight against cancer in recent years. Specifically, immune checkpoint inhibitor (ICI) therapy has revolutionized the immunotherapy field and led to unprecedented clinical outcomes in many cancers. However, the percentage of cancer patients who are eligible for ICI therapy is only about 40%, and only 13% of these patients will respond to it [1]. Cancer remains a major global health, economic, and societal challenge, with an estimated 20 million new cases and 9.7 million cancer-related deaths worldwide in 2022 [2]. By blocking inhibitory signals of T cell induction, activation, or proliferation, ICIs release the brakes of the immune system and promote antitumor T cell activity [3]. However, many patients with immunologically 'cold' tumors exhibit resistance to ICIs mainly due to the lack of pre-existing T cells and T cell tumor infiltration. Developing novel immunotherapies, including therapeutic cancer vaccines, to address this issue has gained increasing interest. Cancer vaccines targeting tumor-specific neoantigens that can elicit robust *de novo* tumor-specific T cell responses or boost endogenous T cells are crucial to improve ICI efficacy and represent a promising approach for treating patients with T-cell excluded 'cold' tumors.

NEOANTIGENS AS VACCINE TARGETS

Cancer vaccines targeting tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs) as a method of driving anti-tumor immunity have been an active area of investigation. TAAs are self-antigens characterized by their low expression in normal cells and overexpression in tumor cells. Historically, many studies have been conducted to develop cancer vaccines targeting TAAs, such as PAP, PSA, hTERT, WT1, MAGE, NY-ESO01, and gp100. TAA-based vaccines often face challenges in generating potent immune responses due to immune tolerance. T cells with high affinity for TAAs are frequently deleted from the immune repertoire through central and peripheral tolerance; thus, developing a TAA-based vaccine that is capable of breaking tolerance and inducing anti-tumor responses remains a challenge [4]. Additionally, vaccines targeting TAAs may lead to autoimmune toxicity due to the presence of these antigens in normal tissues.

Unlike TAAs, TSAs are antigens exclusively expressed by tumor cells, making them highly immunogenic and less prone to immune tolerance [4,5]. Neoantigens are an important subgroup of TSAs arising from somatic mutations within the tumor genome, including non-synonymous single nucleotide variants, insertions and deletions, frameshifts, rearrangements, and gene fusions. To expand neoantigen target options, recent studies have explored cancer-specific events in RNA splicing, translation, and post-translational modification [6]. Non-canonical or 'cryptic' alterations in transcription and translation can lead to the expression of cryptic neoantigens [7,8]. For instance, Kwok *et al*. found neojunctions originated from RNA splicing aberrations generated public neoantigens that were expressed across multiple intratumoral samples and tumor types [9]. Presented on the tumor cell surface by MHC molecules, neoantigens can be recognized by T cells, promoting T cell activation and expansion. Neoantigen-based vaccine approaches have recently gained the spotlight due to advances in next-generation sequencing and bioinformatics. Preclinical studies have shown that vaccines targeting neoantigens generate neoantigen-specific anti-tumor immunity and confer tumor control in tumor challenge models [10–13]. Carreno *et al*. demonstrated for the first time that vaccination with neoantigen-loaded dendritic cells increased the breadth and diversity of neoantigen-specific T cells in melanoma patients [14]. Early clinical trials have confirmed that personalized neoantigen-based therapeutic cancer vaccines can successfully induce both CD4 and CD8 T cell responses in patients [15–17]. Additionally, the safety data from these trials indicate that neoantigen-based vaccines are well-tolerated without serious treatment-related adverse events (TRAEs). Together, neoantigens represent highly advantageous and ideal targets for therapeutic cancer vaccines, offering specificity and immunogenicity, as they can bypass central tolerance mechanisms that limit responses against self-antigens like TAAs, and stimulate strong tumor-specific T cell responses, while avoiding risks of induction of autoimmune diseases.

SHARED VERSUS PERSONALIZED NEOANTIGENS

Cancer genomic studies reveal extensive tumor heterogeneity, both across patients within the same tumor type and within individual tumors. This heterogeneity results from tumor evolution, shaped by somatic mutations, clonal adaptation to the tumor microenvironment, and natural selection. Due to genomic instability and high mutation rates, cancer cells accumulate numerous somatic mutations over time. While most of these mutations occur at random and do not contribute

to cancer progression, a small number of mutations, known as driver mutations, are found not to occur at random and play a crucial role in altering protein function, thus conferring a growth advantage to cancer cells and promoting cancer progression [18]. Driver mutations such as mutations in TP53 in non-small-cell lung cancer and ovarian cancers are typically more conserved clonal mutations occurring early in tumor evolution. Additionally, later subclonal 'actionable' mutations—such as BRAF(V600E), IDH1(R132H), PIK3CA(E545K), EGFR(L858R), and KRAS(G12D)—are also identified as driver mutations [19–21]. Since driver mutations are biologically important for cancer progression and present across patients, and across all or a subset of tumor cells within a given tumor, targeting neoantigens derived from driver mutations (known as shared neoantigens) appears to be an attractive therapeutic strategy (Figure 1). These shared neoantigens are often immunogenic and potentially recognizable by the immune system across different patients, provided they share similar HLA types. This commonality enables the development of 'off-the-shelf' vaccines, allowing groups of patients with the same mutations to benefit from immunotherapy tailored to targeting shared driver mutation-derived neoantigens [22]. Recently, an off-the-shelf vaccine targeting 20 shared neoantigens identified from TP53 and KRAS was evaluated in combination with nivolumab and ipilimumab clinically and the data indicated that vaccination provided effective tumor growth control in a subset of treated patients [23]. In a Phase 1 study, Haldar *et al.* demonstrated a synthetic mutant KRAS (mKRAS) long peptide vaccine induced mKRAS-specific T cell response in patients at high risk of developing pancreatic cancer, supporting the potential utility of mKRAS peptide-based vaccine for immune-based early interception [24]. Rindopepimut, a vaccine targeting the in-frame deletion driver mutation EGFRvIII that is shared by approximately one third of glioblastoma (GBM) patients, was studied in a randomized double-blind Phase 3 trial (ACT IV). The study was terminated after a preplanned interim analysis indicated that rindopepimut did not increase survival in patients with newly diagnosed EGFRvIII-expressing GBM [25]. At recurrence, loss of EGFRvIII expression (immunologic escape) has been reported in most patients given rindopepimut. Thus, despite its convenience and advantages for drug development, the shared neoantigen approach has several limitations, including susceptibility to tumor immune escape, challenges in identifying appropriate driver mutations, and HLA restrictions associated with shared mutated epitopes. These limitations may reduce its efficacy in the broader patient population.

FIGURE 1

Classification of neoantigen-based vaccines.

	Neo antigen-based vaccines	
	Personalized neoantigen-based vaccines	Shared neoantigen-based vaccines
Vaccine targets	Private mutations	Driver mutations
Vaccine target prevalence	Patient-specific	Prevalence in multiple patients
Vaccine type	Personalized	Off-the-shelf
Cost	High	Low
HLA restriction	No	Yes
Susceptibility to tumor escape	Low	High

In contrast, a large fraction of mutations is not commonly shared among patients at meaningful frequencies and are considered patient specific. These mutations do not contribute to the development of cancer and are called passenger mutations or private mutations. With advances in deep-sequencing technologies in the past decade, identifying passenger mutations unique to an individual tumor has become feasible, enabling the prediction and identification of potential personalized neoantigens (Figure 1). The vast majority of identified neoantigens, especially clinically relevant neoantigens, appear to be personalized neoantigens derived from private passenger mutations and are thus unique to each patient [26,27]. Van Allen *et al.* found that only about 0.04% (28/77,803) of unique neoantigens identified in a cohort of metastatic melanoma patients were present in more than one patient having a clinical benefit, underscoring the importance of targeting personalized neoantigens to circumvent tumor heterogeneity [27]. Personalized neoantigen vaccines tailor immune responses specifically against an individual's tumor, minimizing the likelihood of tumor escape. Numerous clinical trials evaluating personalized neoantigen vaccines have shown encouraging results, with preliminary data supporting the further development of personalized neoantigen-based immunotherapy [15–17]. Despite the promise of personalized neoantigen vaccine approaches, more research in the field is needed to overcome challenges such as tumor sampling bias and inaccurate neoantigen prediction. Additionally, manufacturing cost and turnaround time may limit the scalability of personalized neoantigen vaccines for widespread clinical use.

NEOANTIGEN IDENTIFICATION AND SELECTION

Tumor heterogeneity poses a challenge to personalized cancer vaccine development. Research has suggested that the majority of mutations do not lead to the formation of neoantigens that are recognized by T cells, making neoantigen prediction critical for clinical success [28]. Many efforts have been made to develop a robust neoantigen prediction and prioritization pipeline and enhance clinical relevance of selected neoantigens. First, neoantigen prediction requires acquisition of samples with high tumor content. If possible, multiple-region tumor samples should be collected to avoid sampling bias. Secondly, high-quality whole-exome sequencing using matched tumor and normal samples followed by variant calling and annotation are required. HLA typing is also performed to determine a patient's HLA alleles. Subsequently, RNA sequencing is performed to quantify variant expression. Finally, the integration of computational tools to predict the epitope processing, transport and presentation, HLA binding, and T cell recognition potentials of a given neoantigen is utilized to identify, select, and prioritize neoantigens that may induce a tumor-specific immune response. Several important criteria are considered in the neoantigen identification and selection process [29]:

- **Epitope expression**, which refers to how abundantly the neoantigen is expressed in the tumor.
- **MHC class I and II binding affinity**, which determines how effectively neoantigen peptides bind to MHC molecules, a vital step for recognition by T cells.
- **Immunogenicity**, reflecting the neoantigen's ability to trigger a robust and effective immune response.
- **Diversity**, involving the inclusion of a wide range of neoantigens to ensure a comprehensive immune attack against the tumor.

- **Mutational burden**, which correlates the number of mutations present in the tumor with the potential availability of neoantigens for targeting.

Among all these factors considered for effective neoantigen identification, one key criterion is that a peptide must bind to the HLA molecules and then be presented to and recognized by T cells. To date, most of the work has been largely focused on predicting neoepitope-MHC binding. As a result, multiple algorithms and tools based on machine learning have been developed to predict peptide-HLA binding affinity with considerable accuracy. However, there is only limited prediction of recognition by T cells since the mechanisms of immunogenic recognition are not fully understood yet [30]. Another challenge in the field is the availability of epitope datasets with adequate quality and quantity that can be used to train prediction algorithms [31]. Recently, the Tumor Neoantigen Selection Alliance (TESLA), a global community-based consortium, brought together 28 unique teams to compare their neoantigen prediction approaches [32]. The result indicated substantial neoantigen prediction diversity on shared whole exome and transcriptome sequencing data, even for highly performing teams. Overall, the average prediction success rate was only 6% (37 immunogenic peptides out of 608 top-ranked peptides selected from all groups). Moreover, only limited overlap was observed for top ranked neoantigens between teams. The overlap between teams was less than 20% in most cases and the median overlap of the top 100 ranked predicted neoantigens was only 13%. However, the median overlap increased to 32% when the overlap between the top 100 ranked neoantigens from one team was investigated with the entire list (ranked and unranked) from another team, indicating each algorithm has different epitope selection and ranking criteria and the accuracy of all these algorithms needs to be improved. While more knowledge and larger datasets are needed to develop better prediction tools, a personalized vaccine including more targetable neoantigens identified from each patient would be critical for effective vaccine development.

In this context, vaccination platforms utilized for delivering the neoantigens to patients play a crucial role – both in terms of the number of neoantigens delivered and in the immune phenotype of T cell responses engendered (elaborated further below). Most mRNA-based personalized vaccines include 10–20 neoantigens encoded by two synthetic mRNAs [16,33]. Similarly, up to 20 neoantigens are included in peptide-based personalized vaccines [15,17,34]. A recent publication by Weber *et al.* indicated that an mRNA-based individualized neoantigen vaccine encoding up to 34 selected neoantigens, in combination with pembrolizumab, prolonged recurrence-free survival (RFS) in high-risk melanoma patients [35]. Due to molecular flexibility, DNA-based neoantigen vaccines can substantially increase neoantigen payloads by combining multiple plasmids (each encoding 40 neoantigens) into a single formulation, thus preventing tumor escape and providing broad anti-tumor immunity [11,12]. In a Phase 1/2 trial evaluating personalized DNA-based neoantigen vaccine in advanced hepatocellular carcinoma (HCC) patients, patients received their personalized DNA vaccine encoding up to 40 targetable neoantigens (the median number of encoded neoantigens/per plasmid was 30) [36]. The data from this study showed a positive correlation between the total number of neoantigens included in the vaccine and the number of positive neoantigen T cell responses. The immune responses were observed not only against neoepitopes with predicted HLA class I high binding affinity (kd<500 nM) but also predicted medium and low binding affinity (kd 500–2000 nM). The number of

TABLE 1

Selected clinical trials of neoantigen vaccines.

Tumor types	Combination therapy	Primary endpoint	Secondary endpoint	Phase	Enrolment	NCT number
mRNA-based neoantigen vaccines						
Pancreatic	Atezolizumab	Toxicity	N/A	Phase 1	29	NCT04161755 [31,36]
Advanced solid tumors	N/A	DLTs	ORR	Phase 1	30	NCT05198752
Solid tumor	Toripalimab	DLTs	Immunogenicity	Phase 1	24	NCT05579275
Pancreatic	Pembrolizumab	DLTs; MTD; ORR; DCR; immunogenicity	AEs; PFS; OS	Phase 1	54	NCT05916261
Advanced solid tumors	Pembrolizumab	DLTs; MTD; ORR; DCR; immunogenicity	AEs; PFS; OS	Phase 1	60	NCT05916248
Melanoma	Pembrolizumab	RFS	DMFS; AEs	Phase 2	267	NCT03897881 [33]
DNA-based neoantigen vaccines						
Prostate	Nivolumab/ipilimumab; PROSTVAC	AEs; immunogenicity	FFS; Survival; PSA responses	Phase 1	19	NCT03532217
SCLC	Durvalumab	AEs; feasibility	PFS; DOR; OS	Phase 2	20	NCT04397003
GBM	Retifanlimab	DLTs	PFS; OS; ORR; immunogenicity	Phase 1	12	NCT05743595
GBM	N/A	DLTs	Immunogenicity; PFS; OS	Phase 1	9	NCT04015700
HCC	Pembrolizumab	AEs; immunogenicity	ORR; DOR; DCR; PFS; OS	Phase 1/2	36	NCT04251117 [34]
Advanced solid tumors	Atezolizumab	AEs	ORR; DOR; PFS; OS; immunogenicity	Phase 1	26	NCT05018273 [43]
Peptide-based neoantigen vaccines						
Pancreatic/CRC	Pembrolizumab	AEs	PFS; OS; immunogenicity; ctDNA	Phase 1	150	NCT02600949
Advanced solid tumors	N/A	AEs; ORR	OS; PFS	Phase 1	30	NCT03662815
Pancreatic	N/A	AEs	RFS; OS; serum CA19-9 or CA72-4 levels	Phase 1	30	NCT03558945
Pancreatic/MMR-pCRC	Nivolumab/ipilimumab	Toxicity; immunogenicity	DFS; ORR; PFS; OS	Phase 1	30	NCT04117087
Melanoma	Toripalimab	AEs; ORR	Immunogenicity	Phase 1	30	NCT04072900
NSCLC	EGFR-TKI	AEs	PFS; OS; DCR	Phase 1	20	NCT04487093
Pancreatic	N/A	AEs; RFS	OS	Phase 1	20	NCT04810910
TNBC	Durvalumab/tremelimumab	PFS	AEs; ORR; CBR; OS	Phase 2	70	NCT03606967
CLL	Pembrolizumab	DLTs; feasibility	N/A	Phase 1	15	NCT03219450
Esophageal	N/A	AEs; RFS	RFS; OS	Phase 1	40	NCT05307835
Advanced solid tumors	Pembrolizumab	AEs	Feasibility; immunogenicity	Phase 1	36	NCT05269381
Pancreatic	N/A	DLTs; mmunogenicity	Immunogenicity	Phase 1	37	NCT05013216
Melanoma/breast	Nivolumab	AEs	Feasibility; BOR; PFS	Phase 1	20	NCT05098210
Pancreatic	N/A	AEs	Immunogenicity	Phase 1	35	NCT05111353
Melanoma/lung/bladder	Nivolumab	AEs	ORR; DOR; CBR; RCR; PFS; OS	Phase 1	34	NCT02897765
Lung	Pembrolizumab	AEs	ORR; CBR; DOR; PFS; OS	Phase 1	38	NCT03380871
Melanoma	Nivolumab/ipilimumab	AEs	ORR; CBR; DOR; PFS; OS	Phase 1	22	NCT03597282
GBM	Nivolumab/ipilimumab	DLTs; easibility	Immunogenicity; PFS; OS	Phase 1	3	NCT03422094 [48]
RCC	Ipilimumab	DLTs	Immunogenicity; OS	Phase 1	19	NCT02950766 [49]
Ovarian	Nivolumab	AEs	ORR; DOR; PFS; OS	Phase 1	22	NCT04024878
Melanoma	CDX301; nivolumab/pembrolizumab	DLTs; MTD	Immunogenicity; disease recurrence	Phase 1	30	NCT04930783
Follicular lymphoma	Pembrolizumab	Feasibility	Immunogenicity; BOR; ORR; AEs	Phase 1	20	NCT03361852
Viral vector-based neoantigen vaccines						
Advanced solid tumors	Nivolumab/ipilimumab	AEs; DLTs; ORR; RP2D	Immunogenicity; DOR; CBR; PFS; OS	Phase 1/2	29	NCT03639714 [53]
Advanced solid tumors	Nivolumab/ipilimumab	AEs; DLTs; ORR; RP2D	Immunogenicity; DOR; CBR; PFS; OS	Phase 1/2	39	NCT03953235 [21]
CRC	Atezolizumab/ipilimumab/bevacizumab	ctDNA; PFS	AEs; PFS; OS; DOR; CBR	Phase 2/3	700	NCT05141721
Lynch syndrome	N/A	AEs; immunogenicity	Immunogenicity; cfDNA	Phase 1/2	60	NCT05078866

neoantigens included in the vaccine was also associated with the clinical response achieved. Together, these data suggest targeting more neoantigens leads to better clinical outcomes.

NEOANTIGEN-BASED VACCINE PLATFORMS

To date, more than 100 ongoing or completed neoantigen-based vaccine clinical trials are listed in ClinicalTrials.gov over the past 10 years. Current representative trials and programs focused on personalized neoantigen vaccines are listed in Table 1. Once neoantigens are identified, these neoantigens can be incorporated into personalized vaccines through various platforms, such as DNA, RNA, peptide, and viral vector-based platforms (Table 2). The targeted tumor types include liquid and solid tumor types, including but not limited to brain, breast, colon, lung, lymphoma, melanoma, and pancreatic cancers. Almost half of the vaccine trials have incorporated checkpoint inhibition drugs in combination with vaccine in an effort to obtain an improvement in clinical outcome.

mRNA-based neoantigen vaccines

mRNA vaccines, which gained widespread validation during the COVID-19 pandemic, are well-suited for quick personalized cancer vaccine development due to their safety, flexibility, and ability to induce adaptive immunity. Following tumor sampling and sequencing, neoantigens are identified and then encoded in a patient-specific mRNA sequence via *in vitro* transcription. Technical challenges for mRNA vaccine development are centered on their molecular design and *in vivo* delivery efficiency. To increase mRNA stability and translation efficiency, mRNA sequences need to be modified to have high codon adaptation indices and optimized secondary structure with high minimum free energies [37]. Multiple mRNA delivery strategies, such as encapsulation of mRNA in lipid or polymer-based nanoparticles, have also been developed to reduce the extracellular degradation of naked mRNA by RNA enzymes. Encapsulation in liposomes or polymers enables efficient delivery of mRNA into patient cells, where the mRNA is translated to produce neoantigens *in vivo*, triggering a neoantigen-specific immune response.

To date, many clinical studies have been conducted to evaluate the anti-tumor efficacy of mRNA neoantigen cancer vaccines. Of note, KEYNOTE-942, an open-label, randomized, Phase 2b, adjuvant study of mRNA-4157 in combination with pembrolizumab versus pembrolizumab monotherapy (NCT03897881) [35] is the first neoantigen vaccine study to have achieved statistical significance in a randomized controlled setting. The study included 107 patients receiving the mRNA-LNP vaccine, containing up to 34 personalized neoantigens, plus pembrolizumab, compared with 50 patients receiving pembrolizumab monotherapy alone. RFS was longer with combination versus monotherapy with the hazard ratio of 0.56 (95% CI 0.31–1.02; p=0.053). The 18-month RFS rate was 79% (95% CI 69.0–85.6) in the combination group versus 62% (46.9–74.3) in the monotherapy group. Grade ≥3 TRAEs were observed in 25% patients in the combination group and 18% of patients in the monotherapy group. These data suggested that an mRNA-based individualized neoantigen vaccine may provide clinical benefit in the adjuvant setting. In another Phase 1 clinical trial study (NCT04161755) led by Memorial Sloan Kettering in collaboration with BioNTech, researchers treated 16 post-surgery pancreatic ductal adenocarcinoma (PDAC) patients using atezoluzumab and autogene cevumeran (an individualized uridine mRNA-lipoplex nanoparticle vaccine encoding up to 20 neoantigens) [33]. The treatment was tolerable and induced neoantigen-specific

TABLE 2

Advantages and disadvantages of common neoantigen vaccine platforms.

Platform	Advantages	Disadvantages
RNA	Rapid development Easy to modify, flexible Intrinsic adjuvant effect	Poor stability
DNA	High stability, does not require cold chain Ease of production, quick turnaround time, cost effective Large neo antigen payload Induction of both CD4 and CD8, predominantly CD8 T cells Excellent safety profile	Usually needs electroporation to increase plasmid uptake and immunogenicity
Peptide	Ease of production and scale up Minimal toxicity No risk of biological contamination	Predominantly induce CD4 T cells Poor long-term stability Each peptide needs to be synthesized individually; solubility can be limiting for certain sequences HLA restriction
Viral vector	Direct transfection of professional APC, highly immunogenic Large neoantigen payload Long lasting immune response	Anti-vector immunity

T cells in 8 out of 16 patients. Importantly, patients with vaccine-expanded T cells (responders) had a longer median RFS compared to non-responders (not reached vs 13.4 months) at 18-month median follow up, suggesting that vaccine-induced T cell activity may correlate with delayed PDAC recurrence. In an extended follow up study, the authors confirmed responders with vaccine-induced T cells have prolonged PFS compared to non-responders without vaccine-induced T cells [38]. Vaccination with autogene cevumeran induced *de novo* long-lived CD8 T cells, which may contribute to delayed PDAC recurrence. Furthermore, autogene cevumeran as monotherapy and in combination with atezolizumab was also evaluated in a Phase 1 clinical trial in advanced solid tumors [39]. The results indicated that vaccination with autogene cevumeran was capable of eliciting neoantigen-specific cellular responses across all tested tumor types including microsatellite stable colorectal cancer, triple-negative breast cancer, melanoma, urothelial carcinoma, non-small cell lung cancer and renal cell carcinoma.

Collectively, clinical trials have demonstrated that mRNA vaccines can effectively stimulate neoantigen-specific immune responses with safety profiles that can still be improved. The data from recent mRNA clinical trials highlight their potential, particularly when combined with ICIs. Ongoing advancements in neoantigen selection and mRNA delivery are key to expanding their impact across diverse cancer types.

DNA-based neoantigen vaccines

DNA vaccines offer multiple advantages in the context of immunotherapy. Their stability, safety, lack of immune interference for boosting, ease of production, quick turnaround time, cost efficiency, and large payloads makes them attractive for personalized cancer vaccine development. To improve immune potency of DNA vaccines, several optimization strategies, such as codon and RNA optimization, and the addition of highly efficient immunoglobin leader sequences, have been utilized in DNA vaccine design with

the goal of increasing anti-tumor immunity [40]. Additionally, co-delivery of plasmid-encoded molecular adjuvants, such as IL-12, can significantly improve DNA vaccine-induced immune response [41]. Improvements in delivery are also crucial to enhance the immune responses induced by DNA vaccines. Delivery of DNA plasmids using *in vivo* electroporation increases plasmid uptake, thus enhancing vaccine-induced immune response [42]. Collectively, DNA vaccines co-formulated with plasmid-encoded IL12 delivered by electroporation maximize immunogenicity of DNA vaccines to drive induction of CD4 and CD8 T cells faster and in a higher percent of recipients [43]. Antigen-presenting cell (APC)-targeted technology is another promising strategy to direct and enhance vaccine-induced immune responses [44]. Utilizing this technology, a DNA plasmid is designed to encode not only an antigenic unit but also a targeting unit to attract and bind APCs. APC-targeted DNA vaccine increases antigen uptake through receptors on APC, leading to a broader and stronger vaccine-induced T cell response.

To date, multiple clinical studies have been conducted to evaluate immune response and efficacy induced by DNA vaccine. Krauss *et al.* reported that the individualized APC-targeted DNA neoantigen vaccine (VB10.NEO) was well tolerated in patients with advanced solid tumors [45]. The interim results from this Phase I/2a trial indicated that VB10.NEO induced broad and long-lasting neoantigen-specific CD8 T cells. Moreover, vaccine-induced neoantigen-specific T cells in the periphery were able to migrate to tumor sites. In a recent neoantigen vaccine trial, a personalized therapeutic DNA cancer vaccine encoding up to 40 patient neoantigens was developed and used to treat patients with advanced HCC in combination with plasmid IL-12 and pembrolizumab. Treatment was safe and tolerated. No dose-limiting toxicities or grade ≥3 TRAEs were observed. The objective response rate (modified intention-to-treat) was 30.6% (11 of 36 patients) with three patients (8.3%) achieving complete response. Neoantigen-based DNA vaccine can induce broad and robust T cells that are activated, proliferative, and cytolytic. Expanded T cell clones detected in the peripheral blood were trafficked into the tumor. The authors also noted that clinical responses were associated with the number of neoantigens encoded in the vaccine. Moving forward, randomized controlled trials are needed to show the clinical benefit of personalized therapeutic DNA cancer vaccines relative to standard of care.

Peptide-based neoantigen vaccines

Peptide vaccines typically consist of epitopes derived from tumor antigens that are selected for their immunogenicity and compatibility with HLA allies. The length of peptides is critical for the induction of robust immune responses. Short peptides are typically 8–11 amino acids in length. They do not require processing by APCs and can bind directly to MHC class I molecules expressed on the surface of all nucleated cells, most of which are non-professional APCs. Since non-professional APCs do not provide proper co-stimulation, binding to and presentation by these cells results in suboptimal CD8 T cell activation and may lead to immune tolerance [46,47]. Short peptides have several disadvantages such as inherent short half-life and weak immunogenicity. As a result, many studies have focused on designing and evaluating long peptides. Compared to short peptides, synthetic long peptides (SLPs) have enhanced stability and delivery efficiency. Multivalent SLPs with 15–35 amino acids in length, designed to include both CD8 and CD4 epitopes, can induce more diverse and balanced immune responses. Moreover, SLPs are preferentially taken up and processed by professional APCs, leading to

more efficient T cell priming and induction of robust immune response [48].

Peptide-based vaccines have many advantages, including their specificity, lack of biological contamination, ease of production and scale up, and minimal toxicity [49]. Several strategies, such as addition of immunomodulatory and immune-stimulatory adjuvants, have been applied to enhance the immunogenicity and efficacy of peptide-based vaccines. Over the past few decades, peptide vaccines targeting neoantigens have been evaluated in many clinical trials. Ott *et al*. demonstrated that SLPs that target up to 20 neoantigens per patient induced neoantigen-specific CD4 and CD8 T cells in melanoma patients [15]. Similarly, Keskin *et al.* showed vaccination with multi-epitope personalized peptide vaccines generated polyfunctional neoantigen-specific CD4 and CD8 T cells that could migrate into an intracranial GBM tumor [17]. To address intratumoral heterogeneity in GBM patients, Johanns and his team designed a personalized long peptide vaccine including neoantigens identified from multi-region samples (NeoVAX) [50]. The result indicated that NeoVAX stimulated neoantigen-specific, infiltrating, and clonally expanded T cells. Recently, a Phase 1 trial was reported testing a neoantigen-targeting peptide vaccine in patients with high-risk, fully resected stage III or IV clear cell renal cell carcinoma [51]. A median of 15 neoantigen-containing peptides were successfully synthesized for each patient. The immunological analysis revealed that vaccination led to durable expansion of vaccine-specific T cells and recognition of the patient's own tumor. Moreover, none of nine patients enrolled in the study had a recurrence of renal cell carcinoma at a median follow-up of 40.2 months post-surgery.

Taken together, many neoantigen-based peptide vaccine clinical trials have been conducted with demonstration of vaccine-induced immune response and some clinical benefits. Further progress is needed to overcome the limitations of peptide vaccines, such as low immunogenicity, long-term stability, complex manufacture and preparation, lack of solubility of some peptides, and HLA-restrictions. Despite these limitations, with ongoing studies and technological advancements in design and formulation, peptide-based platforms continuously provide valuable insights into neoantigen-based vaccine development.

Viral vector-based neoantigen vaccines

Most viruses are naturally immunogenic and can be engineered to deliver substantial quantities of tumor antigens, including neoantigens, allowing for their application as therapeutic cancer vaccines inducing anti-tumor immune responses. Many types of recombinant viruses can infect professional APCs directly and express tumor antigens, which lead to enhanced antigen presentation and induction of higher-avidity cytotoxic T lymphocytes [52]. A distinguishing feature of viral vector-based vaccines is that tumor antigens expressed by a viral vector are generally more immunogenic, due to the pro-inflammatory environment produced by the expression of viral proteins [53]. Additionally, viral platforms have the unique ability of accommodating large gene inserts. For example, the adenoviral vector platform can encode long antigens (up to 2,000 amino acids) to target many neoantigens [54]. The most used viral vaccine vectors are derived from mammalian poxviruses such as vaccina virus and modified virus Ankara; avian poxviruses such as fowlpox and canarypox (ALVAC); adenoviruses such aschimpanzee adenovirus (ChAd) and great ape adenovirus; alphaviruses, herpes simplex virus (HSV) and vesicular stomatitis virus (VSV). Each viral vector has its own advantages and disadvantages. The most common disadvantages for viral vectors are host pre-existing neutralizing antibodies and

the development of neutralizing antibodies to the vector itself, thus limiting repeat vaccination. To address this, a heterologous prime-boost strategy is often used where a tumor antigen is delivered with one virus vector first, followed by a boost with the same tumor antigen delivered by a different viral vector or vector type (e.g., DNA or RNA vaccine).

As an example, a heterologous prime and boost strategy has been developed by Palmer *et al*. to administer individualized neoantigen vaccines [55]. Patients with advanced metastatic solid tumors were first vaccinated with a neoantigen-encoding chimpanzee adenovirus (ChAd68) vaccine, followed by vaccination with self-amplifying mRNA (samRNA) vaccine encoding the same set of neoantigens. Heterologous ChAd68 and samRNA-based neoantigen vaccine was safe and well tolerated, with TRAEs in less than 10% of the treated population. The vaccination induced long-lasting neoantigen-specific CD8 T cell responses as measured by interferon gamma ELISpot. Using the same ChAd68 prime samRNA boost vaccine strategy, Rappaport *et al*. reported vaccination with shared neoantigens was safe and induced T cell response to dominant TP53 antigens [23]. Another prime/boost strategy for delivering a personalized neoantigen vaccine (NOUS-PEV) has also been employed in a recent Phase 1b study by D'Alise *et al.* [56]. NOUS-PEV is a personalized viral prime-boost cancer vaccine encoding 60 patient-specific neoantigens. Administered intramuscularly with a priming great ape adenoviral vaccination, followed by modified vaccine Ankara boosts, NOUS-PEV induced long-lasting tumor-infiltrating memory T cells. Vaccination led to T cell clonal expansion and broadened the tumor-reactive T cell repertoire. Going forward, more research is needed to address anti-vector immunity. In addition, selecting viral vector platforms to achieve a balance between safety and immunogenicity is also crucial.

SYNERGY OF NEOANTIGEN VACCINES AND IMMUNE CHECKPOINT INHIBITORS

The limited success of past cancer vaccines is largely due to several critical challenges, including targeting poorly immunogenic self-antigens, relying on suboptimal vaccine platforms, and contending with the immunosuppressive environment of advanced cancers. Tumors deploy numerous immune evasion tactics, generally falling into three categories: 'camouflage', whereby cancer cells evade immune recognition; 'coercion', which involves impairment of immune cell function; and 'cytoprotection', where cancer cells shield themselves from cytotoxic responses [57]. A key manifestation of these strategies is the overexpression of immune checkpoints, such as PD-L1, which inhibits T cell activation by engaging PD-1 on T cells, disrupting critical co-stimulatory signals through CD28 and dampening T-cell receptor signaling. PD-L1 expression is routinely measured in biopsies to guide ICI treatment decisions, making it the most validated biomarker in ICI therapy [58].

Over the last decade, ICI therapies have seen expanded indications for solid tumors with MSI-H, dMMR, or high tumor mutational burden (TMB), following stringent clinical evaluation. As of early 2024, the FDA has approved 11 ICIs targeting CTLA-4, PD-1, PD-L1, and LAG-3 in 43 indications [59], revolutionizing treatment for various malignancies, including melanoma and certain solid tumors with specific genetic profiles. Yet, many patients remain non-responsive, often due to 'cold' tumors lacking T cell infiltration, which limits ICI efficacy. This has driven great interest in combining personalized neoantigen vaccines with ICIs, aiming to prime patients for treatments with ICIs by generating neoantigen-specific tumor-infiltrating T cells for a more effective anti-tumor response [60,61].

Many preclinical and clinical studies have been conducted to investigate the synergistic potential of these combinations. Neoantigen vaccines enhance tumor-infiltrating T cells, while ICIs prevent immune suppression, bolstering the durability of these responses. As noted above, a Phase 1 trial evaluating an individualized, heterologous ChAd68 and samRNA-based neoantigen vaccine in combination with nivolumab and ipilimumab showed treatment-OSelicited durable CD8+ T cell responses across multiple neoantigens, expanding effector memory T cells critical for lasting tumor control in advanced metastatic solid tumors [55]. Several patients with microsatellite-stable colorectal cancer (MSS-CRC) had improved overall survival. Likewise, Rojas *et al*. demonstrated that a mRNA-based neoantigen vaccine targeting PDAC, administered with atezolizumab, induced vaccine neoantigen-specific, functional, and durable CD8+ T cell responses [33]. Notably, Weber *et al*. reported promising results from a randomized Phase 2b adjuvant study designed to assess whether mRNA-4157 (V940), a mRNA-based neoantigen therapy in combination with pembrolizumab, improved RFS vs pembrolizumab monotherapy alone [35]. The data showed RFS was longer with a neoantigen vaccine-pembrolizumab combination versus pembrolizumab monotherapy in resected melanoma. Lower recurrence or death event rate was also observed with combination (24 of 107 patients, 22%) vs monotherapy (20 of 50 patients, 40%). To determine whether treatment with personalized cancer vaccines in combination with anti-PD-1 therapy could provide additional clinical benefit in less immunotherapy-responsive tumor types, a personalized DNA-based neoantigen vaccine was evaluated in a Phase 1b study in combination with pembrolizumab in advanced HCC patients [36]. Overall response rate (mITT) per RECIST1.1 was 30.6% with three patients (8.3%) achieving complete response. In contrast, multiple second-line Phase 2 and 3 studies enrolling over 1400 HCC patients have consistently shown that ICIs targeting PD-1 have response rates of 11–18% as monotherapy [62–64]. The increased overall response rate observed with the vaccine and ICI combination warrants further exploration in larger randomized controlled trials.

Collectively, these studies underscore the potential of neoantigen vaccines, especially in combination with ICIs, to generate broad, polyfunctional, and durable T cell responses leading to increased clinical benefits. This approach holds a particular promise for turning 'cold' tumors 'hot' and overcoming the immunosuppressive hurdles in cancers that are refractory to ICIs alone. Personalized vaccine-based immunotherapy has potential to overcome the resistance of low TMB tumors to ICIs, while ICIs may enhance the efficacy of the vaccine therapies. Combining personalized neoantigen vaccines with ICIs represents an exciting frontier in immunotherapy, addressing key limitations of current cancer treatments and offering potential for substantial improvements in patient outcomes.

CLINICAL OUTLOOK AND FUTURE DIRECTIONS

Neoantigen vaccines are emerging as a potent and personalized approach in immune-oncology, yet optimizing their clinical utility demands ongoing research. Key priorities include improving patient selection through advanced biomarker identification. Biomarkers such as TMB, microsatellite instability, unique gene expression profiles, and circulating tumor DNA show promise in refining patient stratification, allowing for more targeted and responsive vaccine therapies. Further, refining neoantigen prediction algorithms, incorporating machine learning to enhance accuracy, and developing algorithms that account for T-cell recognition can

significantly improve neoantigen selection. Additionally, expanding neoantigen payload capacity in platforms like DNA and mRNA could lead to better outcomes, particularly in heterogeneous tumors with diverse mutational landscapes. Quick turnaround time from biopsy to the first dose is also crucial, especially for treatment in advanced cancer patients. Neoantigen vaccines that harness ICIs have shown great potential to overcome immune resistance by making tumors more immunogenic or 'hot'. Further clinical trials exploring this synergy could establish neoantigen vaccines as a mainstay for difficult-to-treat cancers and contribute to novel immunotherapy combinations that address unmet needs in resistant cancers.

CONCLUSION

Neoantigen-based cancer vaccines represent a shift toward highly personalized cancer treatment, targeting unique mutational profiles with precision. These vaccines harness immune recognition of tumor-specific mutations, bypassing tolerance and reducing off-target effects seen with conventional antigens. When combined with ICIs, neoantigen vaccines have demonstrated the potential to improve immune infiltration and persistence, particularly in 'cold' tumors that traditionally evade immune detection.

Advances in sequencing and bioinformatics have catalyzed this approach, but further optimization in predictive modeling, dosing strategies, and patient selection will be key to broadening the clinical applicability of neoantigen vaccines. As our understanding of tumor immunology deepens, neoantigen-based approaches may transform immunotherapy's role in oncology, offering a customizable and highly targeted option for cancers resistant to existing treatments. If successful, neoantigen vaccines will represent a cornerstone in personalized cancer therapy, marking a new era in how we approach tumor immunogenicity and patient-specific treatment strategies.

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VACCINE CLINICAL UPDATE

Building trust in vaccines: why emotions are as important as facts

INTERVIEW

"I think some of the biggest recurring challenges we face in science communication...all have significant roots in people's feelings about science and technology."

Jokūbas Leikauskas (Editor, BioInsights) speaks to **Stephen Hughes** (Lecturer, Department of Science and Technology Studies, University College London) about how fear, mistrust, and frustration drive vaccine hesitancy, and why science communication must go beyond simply providing information and speak directly to people's emotions.

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Q Can you tell us about your current work in the Science and Technology Studies (STS) department at UCL?

SH Primarily, I am a social scientist, meaning I am interested in the relationships between people and scientific knowledge, as well as emerging technologies. I am particularly curious about the instances where those relationships break down—such as vaccine hesitancy or conspiracy theories. That puts me in the field of science communication, because I think a lot about these relationships, and especially about what kinds of emotions are involved when they start to break down.

Beyond trust, there are other feelings too, such as anxiety, frustration, or anger. Like in any relationship, these feelings can get in the way of a harmonious connection, one that brings value to both parties.

I am particularly focused on emerging technologies because these seem to spark a lot of uncertainty and anxiety, including innovations such as brain-computer interfaces, AI applications, and even quantum sensors in biomedicine. Oftentimes, people find these areas very difficult to understand, which may lead to challenges in achieving public legitimacy or buy-in.

The STS department at UCL explores science and technology from the perspective of history (looking at what has worked or gone wrong in the past), philosophy (deep thinking about ethics and morality, questions of expertise and causality), and social science.

Q What are the key differences between vaccine hesitancy and being anti-vax?

SH A lot of these distinctions change depending on who you are talking to. Largely, the term vaccine hesitancy is used by organizations such as the WHO to cover both reluctance and refusal to vaccinate, despite the availability of vaccines.

Being anti-vax also falls under this definition—but implies people who are very vocal in their refusal and actively trying to convince others not to get vaccinated. They often join communities in which being against vaccines is a part of their identity. Being anti-vax is usually connected to a broader mistrust of healthcare, government, and a mistrust of pharmaceutical companies, or science and technology in general.

When we are defining vaccine hesitancy, it is important to think about the causes. The WHO identifies three key causes: complacency, convenience, and confidence. Complacency relates to not treating vaccination as an urgent priority. Convenience is related to logistical barriers—for example, difficulties booking a vaccination appointment with a healthcare provider. Confidence is linked with people who may not fully trust the vaccines or institutions providing them.

Q How do emotions, such as fear and mistrust, shape decisions about vaccination?

SH Emotions are fundamental in the relationships between people and institutions such as pharmaceutical companies, health services, or politicians. Trust is a deeply complex emotional investment. It involves feeling secure enough to be vulnerable—to expose yourself to someone, sometimes quite invasively, like allowing something to be injected into your body. If you do not have that sense of security, you are naturally going to feel uncertain and anxious.

On an individual level, the emotions can range from anxiety and fear to frustration that arises from the conflict between knowing you should get vaccinated and feeling a certain amount of social or family pressure to do it.

Importantly, emotions do not just exist within a single person. They are also shared through the media, conversations, and wider cultural representations in movies, YouTube

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"One of the aspects I have been working on is how certain groups in the UK feel emotionally let down by science on a very deep emotional level..."

videos, documentaries, or websites. Here, we start to see a more interesting social or cultural layer of emotion. These emotions are tied by a shared sense of mistrust toward pharmaceutical companies, shaped by media representations—including mainstream news stories or content from conspiracy theory websites. There is a whole range of sources where people can absorb what are almost emotional instructions.

There are many interesting theories about why people feel these shared emotions. One of the aspects I have been working on is how certain groups in the UK feel emotionally let down by science on a very deep emotional level, because of what they see as a failure to predict, warn about, or protect them from COVID-19. The pandemic created a huge amount of public uncertainty and anxiety.

Ultimately, I think a lot of these emotions come down to trust, and to deep emotional needs like certainty, dependence, and security, and how people respond when they feel those needs have not been met. Often, in popular media or even academic literature, trust gets described as a simple quantity that we need to "increase," as if it is an essence inside people that can be raised or lowered. However, trust is a very complex, dynamic interaction—a set of relationships between people.

Q What should vaccine scientists and advocates keep in mind when speaking to people who are vaccine-hesitant or anti-vax?

SH I think many scientists do fantastic work in presenting the reality of the situation, which is that vaccines are an incredibly effective and valuable healthcare intervention. That knowledge, information, and education are all very important, and we need to continue doing that, especially in the context of misinformation, conspiracy theories, and other narratives that can drive people away from the important reality of the positive benefits of vaccines.

However, when it comes to communicating trust, we need to consider that trust is a two-way street. Why would someone who is vaccine-hesitant trust doctors or scientists if they feel those professionals do not trust them or see them as stupid, or have some kind of pathological thinking or trust deficit? It is crucial to acknowledge that building a relationship between scientists and the public is like building any relationship.

It involves emotions from both parties, and scientists need to acknowledge the emotions they feel, perhaps frustration or even anger with people who are anti-vax. I have seen some interesting perspectives from scientists who express deep hurt. They feel like the public has let them down—scientists have poured all this effort into a lifesaving technology, and then people have ignored or dismissed that work.

You cannot have a genuine conversation or proper dialogue if only one party in that exchange is allowed to be seen as emotional. Everyone involved must acknowledge their emotional investment in the conversation and recognize that both sides are dependent on each other. Trust cannot exist if only one side is dependent, because that is not trust, that is just dependence.

> "People are often less concerned with the science and more with the institutions behind the science..."

Trust exists when there is mutual interdependence, where scientists recognize that the reason they are doing this work in the first place is for the public, and they rely on public uptake of vaccines. And in turn, the public relies on the expertise and insight of scientists to develop healthcare innovations.

Practically, I believe it is important to avoid being judgmental and second-guessing why someone might be hesitant. Instead, we need to be as open as possible in the conversation, to try and create a shared space where there is the possibility of mutual vulnerability. At a very human level, that is what is needed to develop trust.

Q Some people feel overwhelmed or fatigued by constant public health messaging, especially after the COVID-19 global pandemic. How does 'information fatigue' influence vaccine uptake?

SH Information massively influences vaccine uptake, but it is only part of the story. Going back to that analogy of any relationship, if you are attracted to someone and you are trying to convince them of your value as a potential partner, you are not going to send them fact sheets or lists of your reliability, dependability, and worth. You are going to try to develop an actual relationship with that person.

Regarding the relationship between scientists and society, it is not just about saying, "the scientific method is reliable," or presenting the statistical evidence for the effectiveness of the vaccine. While all those things are important, and we should have that information at hand, I think people are often more interested in other questions. These include questions of purpose (why is it happening?) and ownership (who owns the vaccines and profits from them?).

People are often less concerned with the science and more with the institutions behind the science; for example, pharmaceutical companies, health services, politicians, and the government. People who take an anti-vax position or end up refusing vaccines often do so not because they believe the information on conspiracy theory websites is more scientifically valid. It is because they feel that those sources have their interests at heart. They feel that the people on those conspiracy theory sites are speaking to them and care about them.

Unfortunately, this level of trust is currently missing in the relationship between scientists and the public. It is almost entirely factual, and people do not feel cared for. It is not just about scientists—it is also about the institutions and systems behind them. Healthcare systems like the NHS are under-resourced, and politicians are struggling with an underperforming economy, meaning people are not able to get the care they need.

Therefore, when scientists say, "We care about you, here is a potentially lifesaving vaccine," people do not always trust them. People do not feel that those scientists or institutions have their interests at heart. I think that is where the real work needs to happen.

Information is very important—we absolutely need the knowledge, the facts, the education. But just as important, or maybe even more important, is establishing those emotional aspects of the relationship so that people can feel, "This is someone who cares about me, and I can trust them."

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Q What are the biggest mistakes that policymakers and science communicators make when addressing vaccine hesitancy?

SH The first issue is the simplification of trust, treating it as a simple substance that can be raised or lowered. As I mentioned earlier, we often hear, "We just need to increase public trust," but trust is not a quantity that lives inside people. It is a relationship—something that needs to be developed and strengthened.

Another issue is that scientists often underestimate the public's ambivalence. People often hold multiple perspectives at once. Very few people are completely and utterly anti-vax. They might tell themselves they are, and they might express themselves very vocally as if they are, but most people are actually unsure, uncertain, or confused.

Sometimes, the way they express themselves is a way of managing their emotions. It is more comfortable to be certain, or at least to act certain. But beneath that, there is often a very deeply felt ambivalence or split feeling. Trust is not absolute; it is not blind faith. Doubt and scepticism can be healthy.

I would describe myself as someone who fully trusts in science and the robustness of vaccine science. But when I developed heart palpitations after receiving the COVID-19, part of me wondered whether it was caused by the vaccine.

Q What are your goals and priorities over the next 1–2 years, both for yourself and for the UCL STS department as a whole?

SH I am excited about my forthcoming book *Affect, Emotion, and Feeling in Science Communication*. It primarily addresses the massive silence in the science communication literature regarding the role that emotions play.

Emotions are everywhere. I think some of the biggest recurring challenges we face in science communication, like vaccine hesitancy, misinformation, mistrust, conspiracy theories, climate denial, and even the rise of populism and anti-intellectualism around the world, all have significant roots in people's feelings about science and technology.

The book explores several different case studies, such as vaccine hesitancy, technology-related conspiracy theories, and anxiety about climate change, and examines their emotional dimensions. It also considers what these insights can teach us, as science communicators, about how we might build better relationships with the public and confront some of the problems.

One of the core insights in the book is that we often try to bypass difficult conversations or avoid topics that bring up strong emotions. Any psychotherapist would say that the only way to move past an emotion is to go through it. We need to engage with some difficult and uncomfortable topics if we want to build stronger, more reliable, and more trusting relationships between scientists, clinicians, and society.

Beyond publishing the book, I am also contributing to the development of a new center for science communication at UCL alongside my colleagues Melanie Smallman, Simon Lock, and Emily Dawson.

BIOGRAPHY

Stephen Hughes is a Lecturer in Science, Technology and Society at University College London. His research seeks to understand how emotions shape relationships between people and emerging technologies like neural interfaces, digital touch, and AI. He is particularly interested in cases where these relationships break down, such as conspiracy theories, misinformation, and technology hype. His first book, *Affect, Emotion, and Feeling in Science Communication* will be published by Bristol University Press in 2026.

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VACCINE CLINICAL UPDATE

EXPERT ROUNDTABLE

Controlled human infection models in vaccine development: what's new in 2025?

Matthew Laurens, Anna Durbin, Marco Cavaleri, and Robbert van der Most

PANEL

"The use of genetic modification of some pathogens will help to develop a controlled human infection model that can then be used along the de-risking pathway."

Controlled human infection models (CHIMs) can be a powerful tool for generating dosing, safety, and efficacy data throughout the vaccine development process, from early development to licensure. CHIMs can speed up development by rapidly eliminating unsuccessful candidates and de-risking later clinical trials. They are also invaluable when opportunities for field trials are limited.

These benefits have led to increased interest in CHIMs, including expanding their use in endemic and low-resource settings. However, to unlock their full potential, vaccine developers must navigate ethical and safety concerns, regulatory hurdles, and selection and sourcing of appropriate models.

Vaccine Insights assembled a panel of leading experts from academia, pharma, and regulatory bodies to discuss the opportunities and challenges for CHIM studies in 2025 and beyond.

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Q In what scenarios do CHIMs provide the greatest value to vaccine research?

RvdM For me, it would be a combination of a very clear unmet medical need, costly or complex development, no correlates of protection (CoPs), or a history of failure.

A good example is TB, where we know that the development is expensive and there are no CoPs. In that setting, the risk is that further development will be stifled and blocked by the massive expense and the uncertain return of investment. In that setting, a challenge model could potentially de-risk vaccine candidates, identify CoPs, and serve as Phase 2b or 3 studies for vaccine efficacy.

AD I see two major roles for CHIM studies in terms of vaccine development. One Robbert mentioned, which is early de-risking of potential candidates. I think that's very important. We've seen that with malaria vaccine development, and we used it in development of a dengue vaccine. It really gave us confidence in knowing that the candidate we chose was the best candidate.

The second is when we have, for instance, a disease that is sporadic and unpredictable. Here, we won't be able to do our traditional Phase 3 efficacy trials, so a good, reliable CHIM model can play a role in the regulatory pathway. It may not be the be-all and end-all to give full licensure, but it certainly can play a very important role in the regulatory pathway toward licensure.

MC It is not common, but there is already a case in which a CHIM study has played a pivotal role in generating clinical evidence to support the approval. Indeed, there is a cholera vaccine that has been approved in Europe and in the USA, essentially, based on the results of the CHIM study. There are circumstances, as Anna described, where it is very difficult to conduct field efficacy study.

At the same time, if we've got a CHIM that really mimics the actual disease that we're seeing in humans, and you can come to really clinical endpoints that are robust, then you could use those data in order to infer the level of protection of a vaccine, and even approve a vaccine based on such data. I really look forward to seeing more cases. I'm sure there will be more cases in which we could use evidence from CHIM studies to support the approval of a new vaccine.

Maybe what I can add is that CHIMs can be important in understanding CoPs, because you can measure immunity in many different ways, looking both at humoral and cellular-mediated immunity, and you can try to depict what really matters in terms of what is going to be protected with a specific vaccine or other prophylactic intervention. Clearly, there is an opportunity here to learn about CoPs and use this data to regulate and define how to measure protection.

ML One additional point I'd like to make is that the safety of a vaccine can effectively be tested with a CHIM. This was recently demonstrated, particularly looking for vaccine enhancement of disease. When a vaccinated population is

exposed to an infectious agent, they might actually have a poorer response to that infection than the unvaccinated population. This was recently demonstrated with a dengue vaccine that was tested in the CHIM model before it went to a population that was endemic for the same disease. This CHIM study demonstrated enhancement of disease and essentially stopped the development program for this vaccine going forward. It was very informative.

Q What key safety considerations and transparency measures are needed to ensure public trust in CHIM research?

ML The main safety considerations that we take into account when discussing CHIM models are, first and foremost, ethics. The ethics of conducting CHIM studies need to be supported by the possible benefits, such as understanding the burden of disease, evaluating how well a vaccine might work against an infectious pathogen, and informing all potential participants of the possible risks and the individual risks they would incur by participating.

It is essential to outline what mitigation strategies are in place for those potential risks and to have extensive standardization of those strategies so that every participant is protected to the fullest extent. Reviews by groups such as an ethics committee are necessary to ensure that all risks are well defined and well understood by potential participants through informed consent.

It is also important that the communities where these CHIM studies are conducted are able to understand these risks. Oversight of CHIM studies must include a safety committee that meets before a study begins enrollment, throughout enrollment, and after enrollment to ensure that participants remain safe and that their safety is protected at the highest level.

MC I agree—it is very important that we safeguard the participants in a CHIM study and make sure that there is no undue risk for anyone who takes part in this type of research.

We have learned that this research can be conducted safely, and we need to continue down this path, without exposing individuals to unacceptable risks. There is a role for the ethics committee, but also for regulatory authorities, in making sure that appropriate measures are in place and that there are no undue risks.

AD First, it is essential to be able to justify why you are conducting a CHIM in the first place. Why is it needed? Why are we doing it?

In terms of safety considerations, it is important that experienced groups are conducting these CHIMs. CHIMs involving a certain pathogen are generally developed by one or two groups who have strong familiarity with the pathogen and the CHIM, including the development of endpoints and safety profiles. It is important for people to understand that you cannot simply conduct a CHIM study without experience with the pathogen, the vaccine, or the CHIM. It is essential that experienced groups carry out these studies.

RvdM I would like to add two thoughts. One is the importance of radical transparency in the data being generated. For example, in the RTS,S

program, the malaria vaccine-associated challenge studies produced a large amount of data, including transcriptomics data, antibody data, and T cell data. The publication and availability of these data for others to review and analyze is critically important, along with open discussion and disclosure.

The second point is the scientific and clinical rigor within the study, which reflects Anna's point. Communication is also essential. I have found the use of a community advisory board to explain a study to participants to be a very positive experience. That is something that could be extended to CHIM studies, particularly those conducted in endemic areas.

Q What are the regulatory considerations for 1) approving CHIM studies, and 2) applying CHIM data for vaccine approvals?

MC These are both very important points. Regarding the first, regulatory authorities will review the protocols and must agree on them. It is important to keep in mind that legislation varies across countries, which can create hurdles or additional barriers in conducting CHIMs. The regulatory landscape is extremely heterogeneous, but the regulatory community has made efforts to come together to discuss the scientific aspects of CHIM protocol approval and to align on a common approach.

A key point is the challenge material. The level of quality of the challenge material is critical, and the concept of GMP is often referenced. Although challenge material is not a vaccine or a drug, it should be manufactured in a way that closely mimics GMP standards for drugs and biological products. The same spirit of quality and safety should apply, with proportionality in the requirements. Each case must be discussed individually with regulatory agencies to ensure that the quality of the challenge material is sufficient to allow participants to enter the research safely. This is always a crucial point that must be thoroughly addressed with regulators.

Then there is the protocol itself. As discussed earlier, it is essential to safeguard participants in clinical trials. This includes not only safety measures but also containment measures to ensure that the site conducting the research has protocols in place to prevent the spread of the CHIM agent beyond the facility.

The scope of the research must also be clear. CHIMs should not be conducted without a defined purpose. There must be a clear objective in terms of clinical research and the evidence sought to support the development of vaccines or other interventions. All of this is part of the package reviewed to ensure the study design is rigorous and can be approved.

After CHIM approval and execution, the next consideration is how the data will be used for regulatory decisions. There is a wide range of possibilities. CHIMs can support clinical evidence to initiate vaccine development, help determine which candidates to advance, inform dosing decisions, assess the need for adjuvants, or even support approval. For approval, the study must be well designed methodologically, with clearly defined primary analyses and comprehensive data collection.

It is also important to address the external validity of the study. CHIMs have excellent internal validity due to the homogeneity of participants and controlled pathogen exposure. However, the extent to which results can be extrapolated to broader populations must be discussed. This includes considering whether the route of administration mimics natural infection and how a single controlled dose compares to the variability of pathogen

exposure in real-world settings. These are all part of the broader discussion required for regulatory approval.

We believe this model can be used in selected circumstances to support approval and serve as pivotal evidence, potentially replacing larger clinical trials. Lastly, the availability of rescue medication is critical in many settings and must always be addressed in any clinical trial application.

AD I would echo what Marco said. The first very important point is that you must have a clear endpoint for the CHIM. Why are you doing the study? What is the endpoint that you will use as your regulatory criterion for moving the product forward—whether toward licensure, a different dosing regimen, or the need for an adjuvant?

You must pre-specify and be very clear about what those endpoints are and what you will accept or not accept in terms of your product when you evaluate the outcome.

RvdM What I want to add is what I sometimes feel is the elephant in the room—the question of how good the challenge model is. For some, this may be obvious. If we conduct a challenge study for malaria in the Global North with healthy adults, I would ask whether that truly reflects children in Africa. The answer is probably complex.

For me, the opportunity lies in examining the collective data from all malaria CHIM studies to assess the extent to which the findings translate to children in Africa. The RTS,S development was, to some extent, connected to that and provides some opportunity. I do not think this analysis is complete, but in considering how we can use these studies to support or enable approval, including smaller studies, understanding and identifying strong correlates is critically important. It is also essential to determine how well these correlates translate to real-world conditions. That is a field we can explore further.

Q There is increasing discussion around conducting CHIM studies in endemic regions. What are the advantages and challenges of that?

AD One important point, which Robbert alluded to, is that when you conduct a challenge study in the Global North, the population may be very different from the population in the endemic area. Differences can include prior exposure to other pathogens, diet, nutrition, and many other variables.

We often see that vaccines studied in one region, such as the Global North, behave very differently in terms of efficacy when rolled out in endemic areas. Challenge studies conducted in endemic areas can provide a better perspective on how a vaccine or therapeutic tested in the challenge study will actually perform in those settings. This is of particular interest when targeting products—whether vaccines or therapeutics—that will be used in endemic populations. It is important to get an early indication of how they will behave in that population and whether we can get a preliminary glimpse of effectiveness or efficacy.

However, this is challenging due to the complexities involved in conducting challenge studies, including regulatory, development, and operational aspects. Regulatory authorities in endemic areas (some of which are relatively new to regulating vaccines or therapeutics) must become comfortable with how to evaluate challenge studies, assess their benefits and risks, and communicate this to the population.

There are also cultural and regulatory differences. For example, in the USA, we compensate volunteers for their time and effort. Other countries have different guidelines and regulations. Challenge studies are intensive, often requiring inpatient stays of more than a week and extensive sample collection. Communicating this and helping countries unfamiliar with this level of intensity and regulation understand it can be quite challenging.

We are seeing progress. Challenge studies have been conducted in Africa, including malaria studies, and we are working on Shigella challenge studies there. However, it requires significant education of both regulatory authorities and local populations.

ML The challenges are present, but there are also potential benefits and advantages. One challenge involves the importation of a challenge product. If you are conducting a challenge with an infectious agent, importing that product—whether it is an infectious mosquito under carefully controlled conditions to maintain viability during transport, or an infectious agent that must be cryopreserved in liquid nitrogen—requires ensuring that the product can be imported and maintained properly.

You must explain the process to regulatory authorities and obtain their approval to bring an infectious agent into the country. Additionally, you must maintain the proper conditions for the infectious agent during transport and after arrival at the challenge site.

Another issue arises when conducting CHIM studies in areas where the disease is already circulating. In such cases, you must have a plan to differentiate between infection caused by the challenge agent and natural infection. This is particularly important when rapid diagnosis is needed to determine the source of infection.

There are various mitigation strategies, including reducing the risk of naturally occurring infection among challenge participants and using genomic analysis to distinguish between infections caused by the challenge agent and those from natural sources.

MC I would just like to reiterate the point that the type of immunity in different parts of the world may be different depending on the strains circulating in each area. For example, we are seeing that studies with pneumococcal vaccine conducted in the UK and in Malawi gave very different results. That is because the background immunity and exposure to different serotypes are very different in the two regions.

There is value in conducting these studies in different regions, to understand the potential differences in protection that you can achieve with different types of vaccine in light of the different exposure to wild-type strains and the general immunity in the population.

Q How can trial sponsors work with regulatory authorities, particularly in the Global South, to increase their comfort level with CHIMs?

MC That is a very good point, and we are actively working on it. There have been several opportunities in the past to collaborate, including meetings such as one sponsored by IABS in Kenya. In that meeting, we engaged with regulators from Africa, Southeast Asia, and the Americas. Together, we discussed what is critical when approving a CHIM study, what needs to be evaluated, and the different perspectives involved.

It was striking to learn that in some countries, CHIMs are prohibited by law. In these cases, the goal is to spread understanding of their scientific value and to clarify that

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CHIMs can be extremely informative and significantly advance our approach to infectious diseases and vaccine development. Of course, this must be done with great care, and there was consensus on that point.

The intent is to bring the global regulatory community together to agree on shared principles and to support one another in enabling the approval of these studies in regions where they can provide valuable evidence—beyond just sites in the Northern Hemisphere. Clearly, more work remains.

While we cannot change legislation in individual countries, it is very helpful for all regulatory agencies to understand the value of CHIMs and how to evaluate protocols and challenge materials. This understanding will enable them to make informed decisions and allow this type of clinical research to be conducted in many parts of the world.

AD I want to emphasize the importance of education and taking time. You cannot simply move forward at full speed and say, 'We are going to do a challenge study here in Thailand', or elsewhere. It must be a gradual process involving educational opportunities, discussions with regulators, and meetings with the group proposing the challenge study in the endemic area.

It is essential to meet with regulators in that region and educate them on the challenge model, what we have learned from it, and why it is important to conduct the study in their country. This process takes time. You must build a relationship with the regulators to help them understand the intricacies involved and to ensure they feel comfortable and confident that conducting a challenge study in their country is the right decision.

ML The issue I would like to highlight is the standardization of procedures in the form of a working document that can be approved by governing bodies, including the World Health Organization and other leading groups, outlining how a particular CHIM should be conducted.

For example, in the case of malaria, a working group developed clinical guidelines and diagnostics for malaria CHIM. This type of document can be reviewed by regulatory and ethics groups, who can then compare the protocol in front of them with the standardized guideline to determine whether it meets the necessary criteria.

RvdM First, it is essential to clearly communicate the intent of the development. A CHIM study should not be seen as a one-off effort to generate research data, but as part of a broader development program within the country.

Second, it is important to recognize that there are different types of challenge models. For example, I would be very cautious about introducing a mosquito-driven malaria model into sub-Saharan Africa. In contrast, using a well-known existing live attenuated strain, such as BCG or ACAM2000, is a different matter. Taking a step-by-step, purpose-driven approach is essential.

AD The pathogenicity of the agent is also relevant for where you might do a study. Some challenge models come with specific guidance on how you make the agent and what kind of facility is needed, and the region must be able to meet those requirements.

MC Many have asked why regulators don't issue guidance that describe how to conduct CHIM studies. In fact, the WHO have already published such a

document, but if you cover all CHIMs, you end up being very general. It is very difficult to cover everything.

If there are certain types of CHIMs that are quite common, and becoming more widely used in different parts of the world, such as a malaria CHIM, then having some more granular and specific guidance would be helpful.

Q How can CHIMs be standardized to ensure reliability and comparability of findings?

ML Standardization of the CHIM model is highly important, not only for the participants in CHIM studies but also for the communities from which they are drawn. We aim to maintain the safety of both participants and communities, which is the foremost consideration in CHIM design. Standardized guidelines help preserve this safety.

Standardization also ensures comparability between different centers conducting CHIM studies. If the same procedures are followed across centers, results can be directly compared. This comparability increases the potential impact of CHIM models.

When we think about standardization, we consider procedures from participant enrollment through exposure to the challenge agent and follow-up. We also consider laboratory endpoints, including how infection is determined and the procedures required to confirm infection status. These standardizations are essential for participant and community safety, as well as for ensuring comparability across study centers.

RvdM I completely agree on the need for assay standardization, and we must be extremely rigorous—using overlapping or similar endpoints, standard operating procedures (SOPs), and validated assays. At the same time, particularly in immunology, we should allow room for exploratory assays to investigate potential correlates. These may involve advanced techniques such as RNA sequencing and T-cell immunology, which are more difficult to validate and standardize.

That should not prevent us from incorporating these assays. There must be a careful balance between as much standardization as possible (for example, using antibody levels as a secondary endpoint) and exploratory endpoints that provide deeper insights. Once that balance is achieved, we should also standardize how we report and analyze the data.

AD I will comment on what we have done. We have worked to transfer our CHIM model to other groups, including transferring the dengue CHIM to a group in Thailand. This involves transferring our policies, procedures, and SOPs, and providing training on the model itself—what to expect, how to grade different adverse events, and ensuring consistent grading, including for placebo recipients. This helps distinguish background noise from effects that may be representative of the model.

We aim for an in-depth transfer of the model to ensure consistent protocols, assays, and use of the same reagents. Standardization includes ensuring that, when evaluating clinical or laboratory endpoints, the reagents used in those assays are consistent. For example, differences in key reagents, such as target viruses used in neutralization assays, can lead to different results, which may or may not be significant. We strive to standardize everything from reagents to protocols to clinical evaluation so that we achieve consistency

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across sites. This allows us to extrapolate results between sites with confidence that the findings are valid.

MC We all would like to see more standardization to benchmark results and understand how different studies perform with different vaccines. At a minimum, we should start with a consistent approach to protocol design, endpoint data collection, and SOPs. These elements would be extremely valuable.

As Anna mentioned, experienced centers can help new centers grow and conduct studies according to the required standards, ensuring participant safety and proper implementation of CHIM studies. Having the same assays would be ideal, not only in CHIMs, but across the board. However, the reality is more complex, and we must accept that full harmonization is not always possible. Still, any opportunity to align approaches should be pursued.

Challenge material is another important aspect. Using the same material across studies would be ideal, but that is not always feasible. We must accept that different studies may use different challenge materials.

The more data we gather, the more confidence we can have in CHIM outcomes. This will also help regulators become more comfortable using CHIM data in their decision-making. If we can compare CHIM study results with vaccine performance in field efficacy studies and see how well they align, regulators will gain greater confidence in the predictive value of CHIMs.

Q How can we address the need for more or improved challenge agents, especially where the pathogen itself cannot be used?

RvdM That is a great question, and one without an easy answer. I want to respond by giving an example. Consider tuberculosis. There is no challenge model, but there is a clear medical need. That creates an incentive to explore what can be done.

One option is to use an attenuated strain, such as BCG. This keeps us in a safe zone, but it creates a distance from real-world infection that we need to bridge. One step further would be to standardize the route of administration. For example, a study is set to begin in Oxford using aerosolized BCG, which would bring us closer to natural infection.

The most exciting development is recent work on an actual Mycobacterium tuberculosis (Mtb) strain with a triple kill switch. This approach would allow the use of actual Mtb, but with a built-in safety mechanism. TB is interesting in this regard because such kill switches are feasible.

For other pathogens, such as Ebola or Marburg, this approach is not viable. However, for others like influenza, reassortant strains offer possibilities. In some cases, attenuated strains can be used, and the level of attenuation can be optimized.

Ultimately, there is a trade-off between how realistic the model is and how safe it is. In an optimistic view, we can bridge that gap by using the right readouts and immunological markers to connect the model to natural immune responses.

ML I agree with Robbert that the challenge can be addressed by using attenuated strains. This is a novel and effective way to manipulate the challenge

"I wish I had a crystal ball. We are trying to respond day by day to new developments."
Anna Durbin

model while maintaining participant safety. One method of attenuation is through genetic modification. By altering the organism genetically, it is possible to prevent it from establishing a full infection or causing complications in the person being challenged, while still allowing for the measurement of important endpoints.

This approach enables detection of initial infection, followed by termination of the infection before it causes any harmful effects.

AD I want to return to a point I have emphasized before: first ask yourself, what is the purpose of the challenge model? What are you trying to achieve? For some pathogens, it will be difficult to use a challenge model for licensure. As Matt and Robbert noted, using attenuated strains can make it harder to translate findings to real-world pathogens. However, these models can be useful for down-selection of candidates.

Another useful strategy is to focus on the protective antigen of a particular pathogen. Using recombinant DNA technology, you can create vectors that express the protective antigen on their surface. This allows you to evaluate whether a vaccine or therapeutic can prevent or modulate infection.

Vectors may play a role for pathogens that are too dangerous for direct challenge, such as HIV. These approaches may not be suitable for licensure, but they can help determine whether an intervention affects key antigens and may support down-selection or identification of correlates of protection.

MC When it comes to attenuated strains, these studies move away from the reality of natural infection and disease, which makes it more difficult for regulators to accept them as pivotal evidence for approval. Nevertheless, they can provide very useful information about what a vaccine is capable of and the type of immunity it confers. Scientifically, they can still be of great value.

Each case will be different. For example, as Robbert mentioned, in the case of tuberculosis, I personally see more value in attenuated strains of Mtb than in BCG. How far we can go with data from such models is not straightforward to determine.

However, as Robbert said, developing a TB vaccine is a major endeavor involving significant investment and effort. If a model can help determine which vaccine candidates are worth advancing to larger clinical trials, that would be extremely valuable. It is worthwhile investing in this type of study. Even with attenuated strains, if the study is well-designed and scientifically justified, it can be of great value.

Q How could new policies from the US Department of Health and Human Services impact on the future of CHIM studies in the USA?

AD That is a great question, and I wish I had a crystal ball. We are trying to respond day by day to new developments. In my opinion, the new administration will likely not have a major impact on the use of CHIMs for therapeutics or drugs. The

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focus appears to be on changing the regulatory pathway for vaccines. I have no direct insight into the FDA or CDC, but this is my perspective.

I believe it will be more difficult to approve vaccines in the USA over the next 4 years. It is likely that the use of CHIMs for vaccine approval will be viewed with greater caution. If CHIMs are used, post-licensure regulations may be quite stringent. Only time will tell.

Pharmaceutical companies and vaccine manufacturers will likely continue to pursue CHIMs if they can showrten the pathway to licensure. I do not expect major changes in early-phase clinical trials, but the process may become more complicated. For example, using a CHIM in the licensure pathway for a vaccine targeting a sporadic disease such as cholera, may become more difficult. However, it is hard to predict.

CHIMs remain very useful and play an important role in the development of both vaccines and therapeutics, and I hope that continues.

RvdM It is difficult to predict where this is going. From my perspective, the perception of risk appears to be shifting. In that context, I can envision a scenario in which challenge studies become increasingly important. A combination of a challenge study and an existing safety database could provide a quick, small-scale indication of whether a vaccine is viable for the US market.

For example, I could see this approach being used for novel or universal influenza vaccines. It would help minimize the risk of vaccine development under uncertain conditions. Once initial viability is established, the focus could shift to building a safety database sufficient to move the product forward. That is a scenario I could imagine, though the future remains highly uncertain.

MC Regulators are not frequently using CHIMs to approve vaccines. There is only one clear-cut case so far, so it is too early to determine what direction future policy might take. Additionally, CHIMs have always been conducted as placebo-controlled clinical trials, which at least satisfies one important regulatory requirement.

Q What are your predictions for the future development and application of CHIM studies?

RvdM From the perspective of vaccine developers, the current de-risking choices are increasingly difficult. I think anything that can de-risk development will be looked at very favorably.

AD I think we're going to see CHIMs used more and more frequently. I was discussing a vaccine development program just last week, which included non-human primate studies. My question was, 'Why are you doing a non-human primate study when you can do a CHIM?'

I do think that they are going to be utilized more frequently, and I also think we're going to see greater development of CHIMs. The use of genetic modification of some pathogens will help to develop a CHIM that can then be used along the de-risking pathway. I think we will see more and more of that as the technology improves.

MC I completely agree that we will see more CHIM studies. Where they are positioned will depend on the type of pathogen. For example, with enteric pathogens, where a CHIM can include a clear disease endpoint, I see this as a very useful model that could even provide potential clinical efficacy data to support approval.

However, a model is still a model, and we must always consider its limitations. We should be cautious about using CHIMs for new pathogens too quickly. A negative result in a CHIM does not necessarily mean the vaccine is ineffective. We must be prudent when expanding the CHIM portfolio to new pathogens, using them wisely and with the intent of advancing vaccine understanding and streamlining development.

It is also important to reach a point where we validate the predictive value of CHIMs. That will be a key milestone. Once achieved—at least for certain pathogens—we may be able to use CHIMs more frequently than we do now.

ML I agree that the enormous impact of CHIM studies in terms of rapidly determining efficacy is remarkable. I'm optimistic that CHIMs will be widely used and that we will see new products developed, in both vaccines and therapeutics.

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