-

THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212

Popular Article

February, 2026 Vol.6(2), 434-439

Transition from In Vivo to In Vitro and In Silico: A New Paradigm in Vaccinology

Arundhati Sharma[1]†, Nitish Gaitri[2*]†, Vibha Singh[3], Varun Jasta[4]

[1] Department of Livestock Production Management, Abhilashi University, Mandi-175045, Himachal Pradesh, India

[2] Division of Animal Genetics and Breeding, ICAR- Indian Veterinary Research Institute, Izzatnagar, Bareilly-243122, Uttar Pradesh, India

[3] Division of Veterinary Public Health, ICAR- Indian Veterinary Research Institute, Izzatnagar, Bareilly-243122, Uttar Pradesh, India

[4] Division of Livestock Products Technology, ICAR- Indian Veterinary Research Institute, Izzatnagar, Bareilly-243122, Uttar Pradesh, India

**Corresponding author-* niti.nitish.10@gmail.com

† These authors contributed equally to this work

DOI:10.5281/ScienceWorld.18761722

Abstract

For over a century, laboratory animals have been central to vaccine development, providing models to evaluate safety and efficacy before clinical use. Despite major public health successes, this approach has limitations because animal immune systems do not fully replicate human biology, leading to translational failures alongside growing ethical and economic concerns. Advances in preclinical science are now reshaping this landscape. Organoid systems, derived from stem cells, recreate key structural and functional features of organs, enabling physiologically relevant studies of infection and immune response in controlled laboratory settings. In silico immunology uses artificial intelligence and machine learning to predict antigen behaviour, simulate immune interactions, and prioritize vaccine candidates before experimental testing, accelerating early-stage development. Synthetic biology further enhances predictability by engineering precise cellular assays and highly defined vaccine platforms such as mRNA constructs, reducing reliance on exploratory animal studies. However, complete replacement of animal models remains challenging because vaccines act within complex, systemic biological networks where integrated immune responses and rare adverse effects are difficult to replicate in vitro or computationally. Consequently, regulatory frameworks continue to require rigorous validation. A hybrid paradigm is emerging in which AI guides discovery, organoids provide biologically relevant validation, and animals are used selectively for targeted safety assessment, making vaccine development increasingly predictive, efficient, and ethically aligned.

Keywords: In Silico Immunology, Organoid Models, Synthetic Biology, Translational Vaccinology, Vaccine Development

Introduction

For more than a century, laboratory animals have stood at the frontier of vaccine development. Before any injection reaches a human arm or the body of a calf, pig, dog, or cat it has usually passed through rows of mice, rabbits, or occasionally primates. These animals have helped scientists answer two essential questions that define vaccine science: Is it safe? and will it work? From early rabies vaccines to modern mRNA platforms, animal experimentation has played a critical role in protecting global health.

Yet this long-standing model is being quietly reconsidered. Animal immune systems do not perfectly replicate human immunity. Differences in cytokine networks, antigen presentation mechanisms, microbiome diversity, and genetic variability can lead to outcomes that fail to translate into human success. Many vaccine candidates that perform well in rodents do not survive clinical trials. Beyond biological discrepancies, animal testing is costly, time-consuming, and ethically sensitive. Regulatory frameworks increasingly emphasize the principles of Replacement, Reduction, and Refinement the 3Rs encouraging researchers to minimize animal use wherever scientifically feasible.

At the same time, scientific innovation has accelerated. Advances in stem-cell biology, computational modelling, and synthetic engineering are reshaping how researchers study infection and immunity. Human-derived organoids replicate tissue architecture in vitro. Artificial intelligence predicts antigen behaviour before laboratory testing begins. Engineered cellular systems provide measurable immune readouts without relying solely on live animals. Together, these tools raise an increasingly urgent question: can lab animals be replaced in vaccine development, or are they still indispensable?

The answer lies somewhere between technological optimism and biological realism.

Organoids: Miniature Organs in a Dish

One of the most transformative advances in modern biomedical science is organoid technology. To understand its significance, it helps to revisit where laboratory models began. Traditional cell culture relied on two-dimensional monolayers, where cells grow flat on plastic surfaces. These systems are inexpensive, scalable, and easy to manipulate, but they fail to reproduce the three-dimensional microenvironment found inside living organisms. In the body, cells exist within a dynamic network of extracellular matrix, nutrient gradients, mechanical forces, and cell-to-cell communication. When grown in flat layers, cells lose much of this complexity, altering gene expression and function. Three-dimensional culture systems emerged to address these shortcomings, allowing cells to form spheroids or grow within biomaterial scaffolds. Organoids represent the next evolutionary leap. Derived from adult

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com

Published 24/02/2026

stem cells, embryonic stem cells, or induced pluripotent stem cells, organoids self-organize into three-dimensional microtissues that resemble miniature versions of real organs. They exhibit polarity, contain multiple differentiated cell types, and reproduce aspects of physiological function.

In vaccine research, organoids offer remarkable possibilities. Human intestinal organoids can mimic epithelial barriers and immune signalling pathways relevant to oral vaccines. Lung organoids can model respiratory infection dynamics. Brain organoids allow investigation of neurotropic viral behaviour. Importantly, organoids are not limited to human medicine. Veterinary research has successfully established organoid models from cattle, pigs, dogs, and cats. Bovine intestinal organoids reproduce crypt-villus architecture and express markers characteristic of stem cells and differentiated epithelial cells. Porcine intestinal organoids closely resemble human gut physiology, making them particularly valuable in studying zoonotic infections. Canine intestinal organoids derived from biopsy samples maintain stem cell markers and can be passaged long term, offering disease-specific models for inflammatory bowel conditions.

These species-specific models are transformative for vaccine evaluation. Instead of infecting live animals to observe immune responses, researchers can expose organoids to pathogens and measure epithelial integrity, cytokine production, and antigen processing in controlled laboratory conditions. Organoids provide improved physiological relevance compared to 2D systems, reduced experimental timelines, and decreased ethical burden. However, they are not complete organisms. Most organoids lack vascularization, full immune cell diversity, and systemic interactions. They simulate parts of biology but not the whole.

In Silico Immunology: Vaccines Designed in Code

While organoids recreate biology in laboratory dishes, artificial intelligence recreates it in silicon. In silico immunology uses computational modelling and machine learning to predict immune responses before biological testing begins. Modern algorithms integrate genomic sequences, protein structures, transcriptomic data, and known immune interactions to identify promising vaccine candidates. Deep learning tools can scan entire pathogen genomes and predict antigenic regions likely to stimulate T-cell or B-cell responses. Platforms that model peptide–MHC binding interactions narrow candidate lists dramatically, reducing the need for exploratory animal studies. Protein structure prediction systems, such as those developed through advanced neural networks, allow researchers to visualize antigen conformations with unprecedented accuracy. Structural vaccinology, once reliant on years of crystallography experiments, now benefits from rapid computational modelling.

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com
Published 24/02/2026

The promise of in silico immunology extends beyond candidate screening. Researchers are developing "digital immune twins" computational systems capable of simulating immune responses at the level of individuals or populations. By integrating multi-omics data and experimental readouts from organoids, these models can forecast immunogenicity, estimate durability of protection, and predict potential adverse events. During global health emergencies, such computational pipelines have the potential to compress vaccine design timelines from years to months. Yet computational power does not eliminate uncertainty. AI systems rely on high-quality training data. Bias, overfitting, and limited interpretability remain concerns. Biological systems are inherently complex and sometimes behave unpredictably. Therefore, computational predictions still require experimental validation.

Synthetic Biology: Engineering Predictability

Synthetic biology occupies a fascinating middle ground between digital modelling and living organisms. Instead of merely observing biological systems, scientists design and engineer them to behave in predictable ways. In vaccine development, synthetic biology enables the construction of engineered cell lines that produce measurable signals when specific immune pathways are activated. Reporter systems can fluoresce or generate quantifiable markers, allowing researchers to assess immune stimulation without immediately resorting to animal testing.

Modern vaccine platforms such as mRNA and virus-like particles are themselves products of synthetic biology. These platforms are highly defined at the molecular level, allowing precise analytical characterization before in vivo experimentation. By engineering antigens and delivery systems with predictable properties, researchers reduce the degree of uncertainty traditionally addressed through extensive animal trials. Gene-editing technologies, including CRISPR-Cas9, further enhance this approach. Organoids can be genetically modified to replicate disease susceptibilities or immune pathway alterations, enabling targeted studies of vaccine response. Synthetic biology thus strengthens the bridge between computational prediction and biological validation.

Why Complete Replacement Remains Difficult

Despite extraordinary technological progress, complete replacement of animal models remains challenging. Vaccines function within integrated biological systems. After administration, they travel through tissues, interact with immune cells in lymph nodes and spleen, and may trigger systemic reactions. Rare adverse events, including inflammatory or autoimmune responses, can arise from interactions that are difficult to simulate fully in isolated systems. Organoids, while physiologically relevant, often represent immature developmental stages and lack vascular networks. Organ-on-chip systems introduce dynamic flow and multi-tissue integration but still approximate rather than replicate whole-organism complexity. Artificial intelligence can predict patterns but cannot yet capture every emergent biological phenomenon.

Regulatory standards also demand caution. Vaccines are administered to healthy populations, often including children and vulnerable individuals. The safety threshold is exceptionally high. Regulatory agencies require rigorous validation of new testing methodologies before replacing established animal models. Hybrid approaches combining AI predictions, organoid validation, and selective animal testing are currently viewed as the most responsible path forward.

A Gradual Transition Already Underway

Although complete replacement may not be imminent, reduction is clearly underway. Computational screening now dominates early antigen discovery. Organoids routinely inform mechanistic studies and candidate prioritization. Engineered assays have replaced certain traditional potency tests. Each innovation narrows the circumstances in which animal use is considered necessary. The emerging paradigm resembles a layered system. Artificial intelligence filters and optimizes vaccine candidates before laboratory testing. Organoids assess tissue-specific responses. Organ-on-chip systems simulate dynamic physiology and pharmacokinetics. Animals are reserved for targeted validation of systemic safety and rare events. In this framework, animals shift from default gatekeepers to specialized validators within a far more sophisticated scientific ecosystem.

Conclusion

The prospect of replacing lab animals in vaccine development captures the imagination, but science rarely advances through abrupt substitution. It evolves through accumulation of better tools, stronger evidence, and increasing confidence. Organoids bring laboratory research closer to human and species-specific biology than many traditional models ever could. In silico immunology compresses months or years of exploratory work into days. Synthetic biology introduces precision and standardization into experimental systems. For now, animals remain part of the safety net, particularly when systemic complexity and rare adverse events must be evaluated. Yet their role is shrinking. The transformation unfolding in vaccine science reflects not a rejection of safety but a refinement of how safety is achieved. The future is unlikely to be entirely animal-free, but it will almost certainly be far less animal-dependent than the past. In that evolving landscape, vaccine development becomes not only more efficient and predictive, but also more ethically aligned with the values of modern

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com
Published 24/02/2026

science. The laboratory mouse may not disappear, but its place in biomedical research is being thoughtfully redefined one technological breakthrough at a time.

References:

Elfatimi, E., Lekbach, Y., Prakash, S., Karan, S., Dorotta, J. C., Garcia, A., ... & BenMohamed, L. (2025). Artificial intelligence-, organoid-, and organ-on-chip-powered models to improve pre-clinical animal testing of vaccines and immunotherapeutics: potential, progress, and challenges. *Frontiers in Artificial Intelligence*, *8*, 1681106.

Hu, X., Xie, Y., Wang, J., Zhang, X., & Wu, R. (2026). Development and Transformation of Veterinary Experimental In Vitro Models: From 2D Culture to 3D Organoids. *Animals*, *16*(3), 469.

Dokumacı, M. T., & Soydam, S. (2025). Advancing Vaccine Development: The Role of In Vitro Models and Progress in Reducing Animal Testing. *Animal Health Production and Hygiene*, *14*(2), 78-85.

Bertorello, S., Cei, F., Fink, D., Niccolai, E., & Amedei, A. (2024). The future exploring of gut microbiome-immunity interactions: From in vivo/vitro models to in silico innovations. *Microorganisms*, *12*(9), 1828.