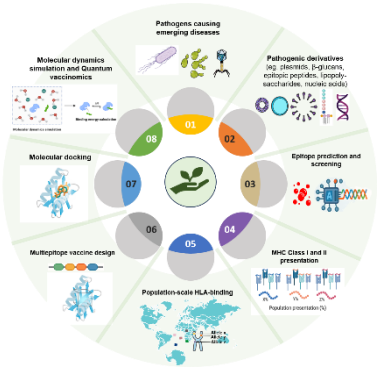
Innovation of Chemistry & Materials for Sustainability
Volume 2, Issue 2, July- Dec. **2025**
ISSN (Print): 3049 – 2548
ISSN (Online): 3049 – 0146
REVIEW ARTICLE

Eco-Friendly Sustainable Vaccine Designing Technology Aiding Personalised Immunotherapy

Pinkan Sadhukhan, Aishwarya Mallick, Bidisha Pal, and Nibedita Mahata*

Department of Biotechnology, National Institute of Technology Durgapur, 713209, India
*Correspondence: nmahata.bt@nitdgp.ac.in (Nibedita Mahata)

Abstract: With the rise of pandemic and endemic cases in recent years, vaccination has been prioritised along with prophylactic therapies. The development of a vaccine candidate sometimes requires lengthy timelines of research and resources. Apart from the unpredictable side effects experienced by individuals, most of the vaccination efforts suffer from population coverage and serotype specificity. Also, lots of euthanised mammals are required for evaluating lethal doses and pharmacokinetic parameters. Worldwide genetic diversity for various human leukocyte antigens (HLAs) or alleles is one of the reasons for zone-specific clinical trials. In these cases, rigorous studies with healthy subjects are required to report statistically reasonable data. In the era of reverse vaccinology, it is now possible to predict immunoproteasomal cleavages of an antigen (upon cellular uptake) and possible nonamers produced from it. These nonamers can be identified for their allergenic, pro-inflammatory characteristics utilising machine learning (ML) and deep learning (DL) algorithms, integrating AI (Artificial Neural Network) driven epitope prediction with HLA-specific binding analyses. These computational tools reduce reliance on animal trials by simulating epitope interactions *in-silico*, addressing sustainable goals in peptide vaccine development for global populations. This review aims to summarise a computational workflow that can lead to an antigenic peptide as a protective immunogen in individuals.



Keywords: *Sustainable vaccine development, quantum vaccinology, personalised vaccine*

Contents

1. Introduction

Enormous shifts in the pathogenic genomes have suppressed the idea of conventional vaccine therapeutics, especially inactivated whole-cell candidates.[1-3] While mRNA platform,[4-5] viral vectors and recombinant protein vaccines are intended to address some technological drawbacks.[6-7] Also, conventional vaccines are mostly targeted at infants for long-lasting immunity.[8-9] Since clinicians would mainly refuse to add more events for infants with hectic immunisation schedules, a recently discovered vaccine candidate for an unresolved health issue may not receive the required recognition.[10-12] Recent studies have hypothesised that childhood cancers and rare leukaemia cases are related to vaccination.[13-15] To agree with these consequences, a new branch of study termed "Adversomics" has surfaced, where the side effects of vaccinations are discussed. International Network of Special Immunisation Services (INSIS) is a global network established to record rare adverse events of special interest (AESIs) upon COVID-19 vaccination based on the adversomics approach.[16] AE-GPT is another surveillance tool built with large language models (LLMs) to identify influenza vaccine adverse effects.[17]

Pinkan Sadhukhan is an Institute Research Scholar at NIT Durgapur, working under Dr. Nibedita Mahata with a Master of Pharmacy degree, his research focuses on high-performance computing-based vaccine design against bacillary dysentery. His interdisciplinary work spans pharmaceutical sciences, immunology, and computational biology to develop innovative solutions in disease prevention.

Aishwarya Mallick is an Institute Research Scholar at NIT Durgapur under Dr. Nibedita Mahata's supervision. She holds an M.Sc. degree (zoology) and conducts research in cell biology, molecular biology, and immunology. Her work focuses on understanding immune mechanisms at the cellular level, contributing to biomedical advancements and therapeutic strategies for disease prevention and treatment.

Bidisha Pal is a DST-Inspire fellow at NIT Durgapur, under the guidance of Dr. Nibedita Mahata. Her research involves developing a vaccine candidate against bacillary dysentery. Focusing on immunological approaches, her work aims to combat bacterial infections and improve infectious disease prevention.

Nibedita Mahata is an Assistant Professor at NIT Durgapur. Her research includes microbial pathophysiology, vaccine design using computational tools, and nanoparticle-based drug delivery. She is widely cited for her contributions to Shigella vaccine development and mentors scholars in immunology, cancer therapy, and environmental biotechnology, promoting interdisciplinary innovation. She did her Ph.D. from Jadavpur University, India.

http://doi.org/10.63654/icms.2025.02093 *Innov. Chem. Mater. Sustain.* **2025**, *2*(2), 093-106
Received: 22 May 2025; Revised: 14 July 2025; Accepted: 15 July 2025; Published (online): 30 July 2025

As a sustainable goal towards more reasonable vaccine development, immunogenic,[18-19] non-allergic,[20-22] and non-toxic[23-24] epitopes can be screened from targeted antigens utilising an ML/DL approach.[25-26] Sometimes these epitopes (mainly 9-mer) are profoundly screened targeting a population based on area, country or ethnicity.[27-33] For investigating immunotherapeutic purposes, these peptides can be synthesised by a solid-phase approach.[34-36]

However, poor antigen presentation and peripheral metabolism of a peptide immediately clear it from the bloodstream, limiting its goal of long-lasting immunity.[5,37] Though these methods primitively solve personalised immunisation purposes, the derived peptides (protease-resistant) can be linked with one another (by linkers) to obtain a small protein or peptide encoding a multi-epitope vaccine with a better half-life.[38-39] Proper selection of the linker residues aids in proteasomal and immunoproteasome cleavage of the designed antigenic macromolecule and targeted antibody generation.[40-44] Peptide vaccine against HIV-HPV cross-protection (COVENANT) is in Phase 3 clinical trial [NCT03284866], currently being investigated in South Africa. Approximately 227 peptide vaccines against cancer, TB, HIV, HBV, HCV, HPV, CMV, multiple sclerosis, COVID-19, malaria, influenza, diabetes, Myasthenia gravis, Streptococcal infection, and Alzheimer's disease are in Phase 2 clinical trial.[45] A proposed multi-epitope vaccine, GroEL, is another example that shows efficient cross-protection against *S. Typhimurium*, *S. flexneri*, and *S. dysenteriae.*[46] Around 16 such multi-epitope peptide vaccines are reported to be in clinical-trial.[47] This approach can be further modified to target a worldwide population with multi-serotype, even multi-disease protection at one single shot, but long-term immunity may require multiple doses.[48-49] While resolving the infectious disease, neo-antigenic epitopes are predicted in quite similar ways to fight against the deadliest cancer from earlier stages and have shown a clear horizon for producing personalised cancer vaccines.[50-52] Thus, a new peptide sequence with appropriate atomic coordination can be identified as an epitope, targeting newly diagnosed diseases and enhancing neutralising antibody generation.[32,53] As a limitation of the vaccine research, antibody-dependent enhancement (ADE) of the disease may be observed in a few cases.[54-55] Researchers have correlated the appearance of aflucosylated IgG antibodies and ADE events as major players limiting dengue vaccination.[54,56-57] As a part of an eco-friendly, sustainable approach, before synthesising these candidates and directly targeting them to a living system, *in-vitro* quantification of protective immunogenicity is important.[58-60] Before targeting peptides to animals for antibody generation, *in-silico* evaluation of peptide-MHC-TCR binding affinity seems essential for tailoring a vaccine model as a personalised immunotherapy.[45,61-63] Here, a sequence-based multi-omics approach, along with structural biology, pave our path.[59, 64] For proper generation of immunity, integration of a modelled antigen is important through PRRs (Pattern recognition receptors), as they are known for bridging between innate and humoral immune responses.[65] Here, the structural generation of an agonist adjuvanted vaccine model, followed by molecular docking with a retrieved structure of any targeted PRRs (TLR,[66-67] CLR,[68] RLR,[69-70] NLR[71]), can help in deciphering probable binding mechanisms and immunological pathways expected after vaccination.[47,72] Evaluating their binding energy can screen down these complexes for molecular dynamics analysis.[73] This is sometimes an expensive computational approach with the requirements of high-performance supercomputers.[74] Upgradation of quantum algorithms and software may improve the idea of "Quantum vaccinomics" study.[75-76] To fulfil the sustainable goal, firstly, normal mode analysis (NMA) can be performed as a coarse-graining (CG) approach evaluating complex stability in a routine manner,[77] complexes can then be evaluated for all-atom molecular dynamics with better resolutions.[78-80] This approach not only emerges quantum vaccinomics profiling of a vaccine candidate but also reduces the use of animals for antibody generation, primarily identifying and calibrating personalised vaccine targets *in-silico.*[80-84]

2. Computational screening of B cell and HLA-specific T cell epitopes

Lymphocytes, such as B cells and T cells, are integral parts of the adaptive immune system and are responsible for humoral and cell-mediated immunity.[85] B cells utilise B-cell receptors (BCRs) or surface-bound immunoglobulins to recognise solvent-exposed antigens, whereas T cells respond to peptide antigens presented on MHC class I and II molecules.[86] Immune cells do not recognise whole pathogens themselves but rather certain antigenic fragments known as epitopes.[87-88] The epitopes are essential to trigger immune reactions.[89] Conventional experimental techniques to map epitopes, including ELISA, peptide libraries, and X-ray crystallography, are reagent-intensive, time-consuming and usually involve animal models and toxic reagents, posing ethical and environmental concerns.[90-91] To overcome these constraints, the discipline has moved toward computational epitope prediction through tools. Computational screening of HLA-specific T cell and B cell epitopes is a cornerstone in the design

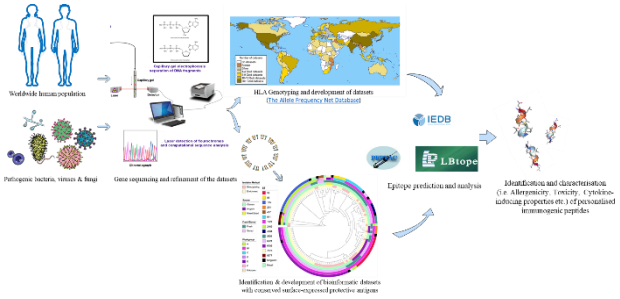


Figure 1: *Population-specific screening of pathogenic patterns as epitopes can screen down personalised immunogenic peptides for neutralising antibody generation.*

Table 1. List of tools for B cell and both T cell epitope prediction.

Method	Tool	Algorithm/Method	Reference
Liner B cell epitope prediction	BepiPred	Hidden Markov Model + propensity scale	104
	ABCPred	Artificial Neural Network (ANN)	105
	LBtope	Support Vector Machine (SVM)-based model	106
	EpiDope	Deep Neural Network	107
	BCPREDS	SVM based classifiers	108
	DiscoTope	Structural features + surface accessibility	109
	ElliPro	Geometric ellipsoid protrusion + residue clustering	110
Conformational B cell epitope	BEpro	Surface exposure + neighbouring residue info	111
	CEP	Spatial distance and accessible surface area	112
	SEPPA	Clustering of spatial neighbours + surface propensities	113
	IEDB	Consensus method combining SMM, ANN, and NetMHCpan	26
	EpiDOCK	Molecular docking with HLA molecules	114
T cell epitope prediction tools	PEPVAC	Matrix-based binding prediction	115
	EpiTOP	QSAR modelling + PLS regression	116
	MHCPred	Partial least squares (PLS), QSPR	117

of sustainable and personalized vaccines.[92] The Human Leukocyte Antigen (HLA) complexes present protein targets of T cells as short linear epitopes on the cell surface (Figure 1 & 2). HLA class I molecules provide the epitopes of killer T cells, whereas HLA class II molecules present the epitopes of helper T cells.[93] Recently, IEDB (Immuno Epitope Database) is one of the well-cited platforms used for online epitope prediction.[94-103] Lists of web servers useful for epitope predictions are mentioned in Table 1.

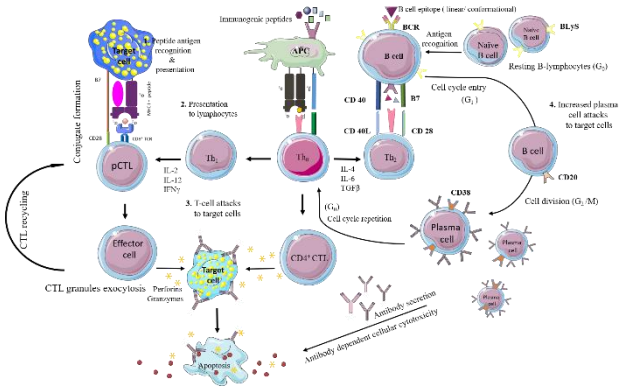


Figure 2: *A diagrammatic representation of peptide antigen processing leads to the activation of adaptive immunity against targeted cells (Abbreviations on immune cells: pCTL: Precursor cytotoxic T lymphocyte, APC: Antigen-presenting cell, Th_0: Naïve T Helper Cell, Th_1: T Helper 1 cell, Th_2: T Helper 2 cell, $CD4^+$ CTL: CD4 positive Cytotoxic T Cell). Portions of this figure were also produced using Servier Medical Art (https://smart.servier.com). Servier Medical Art by Servier is licensed under a CC BY 4.0 Licence (https://creativecommons.org/licenses/by/4.0/).*

2.1. Antigenicity, allergenicity and toxicity profiling

Initially, the protective immunogenicity of a protein or peptide sequence can be predicted through ANTIGENpro[19] and VaxiJen 2.0[118] web servers using machine learning (ML) and Autocross covariations (ACC), respectively.[119] Safety profiling of these protective immunogenic sequences is also important.[120-121] Predictors of allergenicity like AllerTOP,[122] AllerCatPro 2.0,[123] AlgPred,[124] and AllergenFP[125] predict whether peptides are allergenic or non-allergenic by applying machine learning and sequence descriptors.[126-128] AllerTOP v2.0 utilises ACC transformation and k-nearest neighbours classifiers, and AlgPred uses support vector machine (SVM) methods.[129] Toxicity predictor tools such as ToxinPred[130-131] and ToxDL[132] predict toxicity potential based on deep learning models, composition, and physicochemical properties. ToxinPred identifies sequence-based toxicity features with SVMs, while ToxDL identifies toxicity with deep neural networks. These predictive calculations reduce experimental expenses and ethical concerns while maximizing translational success rates.

3. Structural biology aiding sustainable approach for vaccine design

Structural biology enables sustainable vaccine design by precisely targeting conserved epitopes, enhancing thermostability, and streamlining development via computational modelling, reducing resource use and improving global health access.[133-135]

3.1. Three-dimensional (3D) structure prediction of protein and peptide

Structure prediction has been challenging in bioinformatics and structural biology (Figure 3). However, Deep learning (DL) models have proven to suggest nearly accurate protein structures. Recently, AlphaFold2[136] and ColabFold[137] have highlighted atomic-level accuracy more than conventional modelling techniques in CASP competitions.[138] Various DL models discuss the significance of strategies in model generalization.[139-140] Evaluation metrics include model quality assessment, like 3D-equivariant graph neural networks to help improve model quality.[141] Context-specific alignment motifs like ProALIGN enhance alignment accuracy, which is crucial for predicted structures.[142] Key parameters in 3D structure prediction depend heavily on specific input parameters and intermediate representations that guide computational models. First, multiple sequence alignments (MSAs) remain foundational.[143] Like, AlphaFold2's ability to refer to residue-residue contacts related to deep MSAs.[138] Similarly, the quality and depth of MSAs are directly correlated with the accuracy of predicted distance maps.[140] Structural templates are another factor; here, models incorporate high-confidence templates (taken from databases like PDB or preprocessed alignments) from solved structures to produce more reliable predictions in conserved protein families.[139,141] Neural network topologies usually contain physical limitations like bond angles, torsion angles, and steric hindrances.[144] According to Leman and Künze (2023), these characteristics are especially crucial for NMR-driven modelling with ROSETTA, where precise sampling of the local and global conformation is required.[145] ROSETTA fold integrates NMR data with computational modelling, improving its predictive confidence score.[146] Model quality assessment (MQA) parameters, including predicted local distance difference test (pLDDT) and predicted aligned error (PAE), are crucial for model confidence as these parameters allow users to discriminate between high- and low-certainty regions in the final predicted structures.[147] Finally, geometric deep learning models rely on graph representations of molecular structures with node and edge features such as residue identity, bond distance, and orientation of 3D-equivariant neural networks, making the model's stability.[141] PEPFOLD 4 is another tool solely dedicated to peptide structure prediction. It uses the *de-novo* structure prediction method and additionally considers the debuy-huckel ionic contribution if needed. Making the prediction more realistic than the previous versions.[148-149]

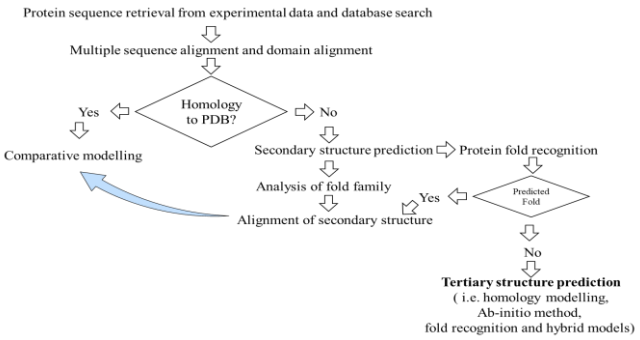


Figure 3: *Critical assessment of structure prediction of protein.*

3.2. Molecular docking

Molecular docking is a computational method that predicts an optimal peptide orientation in the MHC binding groove (Figure 4).[150] Computational methods like Rosetta FlexPepDock, and AutoDock tools provide nearly realistic modelling strategies for flexible peptide–MHC interactions.[151-154] Rosetta's scoring function evaluates peptide backbends and side-chain positions, providing low-energy binding poses as probable candidates.[151] Recent docking research shows a high correlation between experimentally measured peptide–MHC affinities and those calculated by docking procedures.[155] Application of flexible docking to peptides, such as

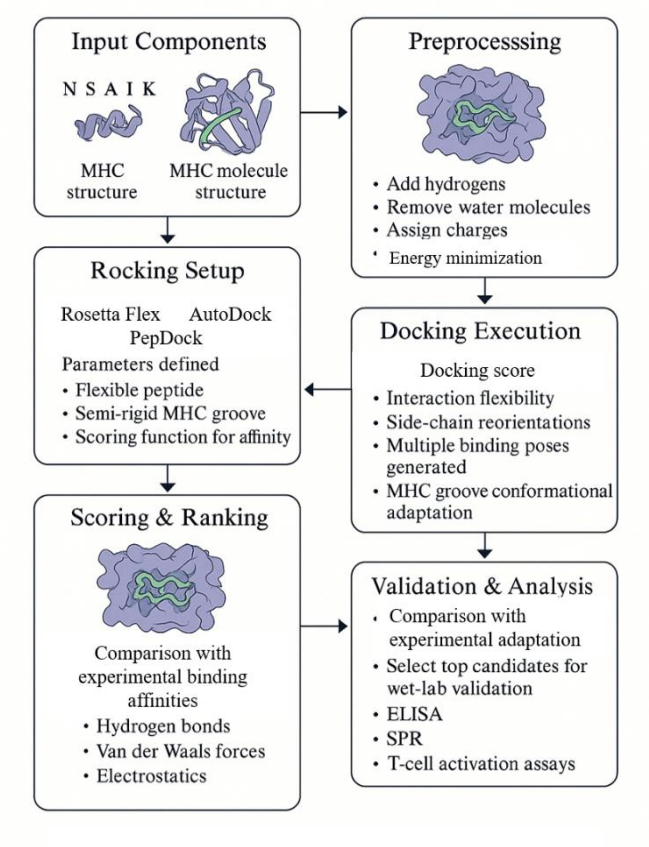


Figure 4: *Molecular docking workflow.*

in Rosetta FlexPepDock, is particularly relevant in view of the MHC groove plasticity.[156] Successful docking predictions enable candidates among peptides to be ranked for subsequent experimental validation, thereby optimising resource utilisation (Table 2).

3.3. Molecular dynamics simulation

3.3.1. Normal Mode Analysis

Normal Mode Analysis (NMA) is a powerful computational tool for studying protein flexibility (Figure 5).[77] This helps researchers uncover slow, large-scale motions that are often crucial for a protein's biological function. There are different ways to perform NMA, ranging from highly detailed (all-atom) models to simpler, more efficient methods like the Gaussian Network Model (GNM) and Anisotropic Network Model (ANM).[172] Among these, the Cα-based coarse-grained approach is particularly popular because it strikes a balance between accuracy and speed.[173] Focusing only on the alpha carbon atoms (the backbone's key points) simplifies the calculations while still capturing the most important large-scale movements of the protein (Table 3). This makes it a practical choice for studying big proteins or large molecular complexes without sacrificing essential insights.[174-178]

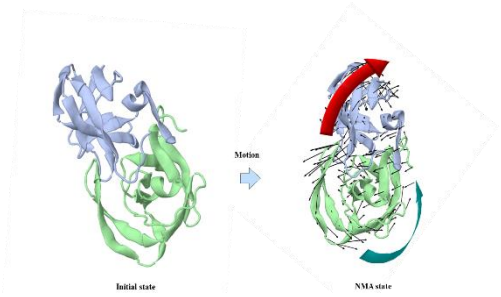


Figure 5: *NMA display of HIV-1 Protease" ID ProteaseHIV on C-alpha based coarse-graining (CG) as the example provided by the Imods webserver (https://imods.iqf.csic.es)*

Table 2. Molecular docking tools for performing protein-peptide docking.

Category	Tool	Input	Applications	References
Template based Docking	GalaxyPepDock	Protein structure + Peptide sequence	Best when TM-score >0.7; tested on PepBind dataset	157
	PepComposer	Binding site information	Suitable for small peptides (tested on LEADS-PEP)	158
	InterPep2-Refined	Protein structure + Peptide sequence	Slightly better than GalaxyPepDock	159
Local Docking	HADDOCK	Protein structure + Peptide ensemble + Ambiguous site info	Suitable for ambiguous binding site info	160
	HPEPDOCK-local	Protein structure + Peptide ensemble + Binding site info	Higher success if the binding site known	161
	AutoDock Vina	Protein structure + Peptide sequence + Binding site coordinates	Best for short peptides (<5 residues)	153
	DINC 2.0	Protein structure + Peptide conformation + Binding site info	Suitable for peptides up to 8 residues	162
	PepCrawler	Initial coarse structure of complex	Refinement tool for peptides <15 residues	163
	Rosetta FlexPepDock	Coarse peptide-protein complex	Refinement tool; best when initial RMSD <5 Å	164
	MDockPeP	Protein structure + Peptide sequence	Suitable for peptides <15 residues	165
	MDockPeP2	Protein structure + Peptide sequence	Peptides up to 29 residues	166
	pepATTRACT	Protein structure + Peptide sequence	Small and large peptides	167
Global Docking	CABS-dock	Peptide sequence + protein structure	Best when peptide secondary structure known	168
	PIPER-FlexPepDock	Protein structure + Peptide sequence	Suitable for large peptides (>15 residues)	169
	AutoDock CrankPep	Protein structure + Peptide sequence	Suitable for large peptides (>15 residues)	170
	patchMAN	Protein structure + Peptide sequence	Outperforms AlphaFold in some datasets	171

3.3.2. All-atom molecular dynamics simulation

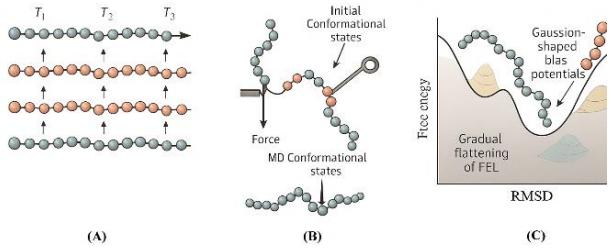


Figure 6: *Different sampling techniques on all-atom molecular dynamics study:* ***(A)*** *Replica exchange MD: parallel simulations at different temperatures (or other thermodynamic parameters) at low conformational sampling to overcome energy barriers. i.e. Periodic exchange of confirmations (T1<T2<T3<T4).* ***(B)*** *Steered MD: a mechanical force is applied to a part of the molecule (e.g. ligand or domain) to induce a conformational change.* ***(C)*** *Metadynamics: a history-dependent biasing potential is aided along selected collective variables to accelerate escape from relatable states.*

While docking provides static complexes, molecular dynamics (MD) simulations facilitate tracking of the temporal dynamics of peptide–MHC complexes.[124,150] Computational packages like GROMACS, AMBER, and CHARMM facilitate an atomic investigation of peptide flexibility, hydrogen bonding interactions, solvent exposure, and conformational stability.[182-184] Root mean square deviation (RMSD), root mean square fluctuation (RMSF), and radius of gyration (Rg) analyses supplement the outcomes of docking studies and identify stable binding conformations.[182] Improved sampling techniques, including replica exchange molecular dynamics (REMD),[185] steered molecular dynamics (SMD)[186] and metadynamics,[187] enable crossing energy barriers and sampling of rare but biologically relevant peptide conformations (Figure 6). Free energy estimation techniques, including MM/PBSA and MM/GBSA, enable estimation of binding affinity and provide thermodynamic validation.[188] Molecular dynamics is therefore a bridge between computational prediction and biological paradigms.

4. Personalized edible vaccines

Edible vaccines are tools of sustainable and eco-friendly advancement in immunisation, utilising genetically modified plants to produce protective antigens that safely stimulate immune responses (Figure 7).[189] Crops like potatoes, bananas, lettuce, corn, soybeans, rice, and legumes contribute to a greener alternative in combating diseases such as cholera, hepatitis, measles, and diarrhoea.[190] This technology is currently being applied to design multi-epitope vaccines against viral disease and gastrointestinal infection.[191-192] The mRNA vaccine delivery platform plays a critical role in the personalisation of edible vaccines, allowing for scalable antigen expression when introduced into plant chloroplasts, such as those of lettuce. Upon ingestion, these vaccines trigger both mucosal and systemic immunity in mice.[193-194] Additionally, microalgae like *Chlamydomonas reinhardtii* are gaining recognition as efficient platforms for edible vaccine development for their fast biomass production and chloroplast-based protein expression capabilities.[195] As part of SARS-CoV-2 vaccine research, the TOMAVAC study demonstrates that tomatoes (genetically engineered) to express the SARS-CoV-2 S1 protein can safely induce systemic and mucosal immune responses in mice and humans.[196] Plant-derived vaccines also expressed reasonable efficacy in hepatocellular and prostate cancer therapeutics.[197-198] As a part of the limitation, the production of edible vaccines faces several challenges, including regulatory uncertainties, scalability issues, dosage control, and potential consumer scepticism. Additionally, integration of biotechnology in food crops raises ethical and environmental concerns, potentially limiting public acceptance and widespread application.[199]

5. Limitations & future directions

Personalised vaccines are a potential breakthrough due to the emergence of precision medicine, which depends on the availability of high-fidelity human genome sequences and objective biological data.[64,200] Impactful genomic changes that drive human evolution, disease, and genetic diversity remain incompletely understood due to technical challenges, especially in repetitive regions.[201] Hyper-personalisation of a vaccine candidate mainly suffers from biased datasets,[202-203] lack of personalisation markers[64,204-205] and high-performance computational resources.[206-208] Targeting Killer cell

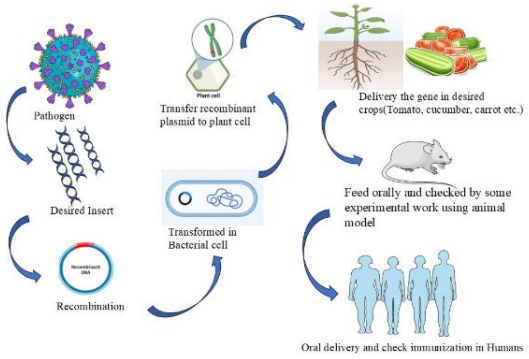


Figure 7: *Diagrammatic representation for the applications of edible vaccines using genetically modified plants and algae.*

immunoglobulin-like receptor (KIR) genes can be developed, which will revisit the allele selection and design of the vaccine peptide.[209-211] However, targeting KIR genes for vaccination purposes would be critical due to the high sequence homology between activating and inhibitory receptors, necessitating

Table 4. Vaccine candidates in clinical trials developed using computational and AI-driven approaches.

Vaccine candidate	Developer	Clinical trial phase	Computational/AI Contribution	Reference
mRNA-1273 (Spikevax)	Moderna	Phase 4 (approved; post-marketing surveillance ongoing)	*In-silico* antigen design using prototype pathogen preparedness model; structure-based spike protein modelling	221
BNT162b2 (Comirnaty)	Pfizer-BioNTech	Phase 4 (approved; surveillance ongoing)	Bioinformatics-based mRNA optimization and epitope prediction; computational immune profiling	222
INO-4800	Inovio Pharmaceuticals	Phase 2/3	Designed using AI-based SynCon® platform for DNA vaccine antigen generation; CELLECTRA® delivery system optimized via computational modelling	223
UB-612	Vaxxinity	Phase 3 (as of 2023)	Epitope-based peptide design using structural modelling and AI-driven multi-epitope optimization	224
EpiVax's epitope-based vaccines (e.g., for influenza, HPV)	EpiVax Inc.	Various stages (preclinical to early Phase 1 for selected candidates)	AI-powered immunoinformatics platforms (EpiMatrix™, JanusMatrix™) used for epitope prediction and immunogenicity filtering	225

careful re-evaluation of sequencing strategies to distinguish their functional outcomes.[212] Nevertheless, correcting HLA allele bias in predictive models is essential to facilitate global equity and studies have established that pan-allele models based on machine learning can perform worse for underrepresented HLA alleles, most of which occur in non-European populations.[213] Implementation of bactoneuron-based multicellular ANN architecture for vaccine design may help in reducing computation cost and computational carbon footprints.[214-215] However, it may be possible to retrain or adapt FDA-recommended models such as Tox-GAN and AnimalGAN (originally developed to predict toxicity from unknown chemical compounds), extended for immunotherapeutic applications. Platforms like C-IMMSIM, a fast-responding web server capable of predicting both T and B cell responses (including danger signals) as well as probable antibody generation from a given protein sequence, have shown promising correlation with *in-vivo* data.[216-217] Future tools can be developed using agent-based modelling (ABM) integrated with cellular automata (CA) frameworks to simulate complex immune interactions at both the cellular and systemic levels.[218-220] Integrating computational biology and artificial intelligence (AI) has transformed vaccine development, enabling faster and more precise immunogen design. These approaches have facilitated antigen selection, epitope prediction, and structural modelling, both approved and in clinical progress, that have employed computational and AI-based workflows (Table 4). Prominent cases include **mRNA-1273 (Moderna)**[221] and **BNT162b2 (Pfizer-BioNTech),**[222] *in-silico* modelling, and bioinformatics-accelerated COVID-19 vaccine development. **INO-4800**[223] leveraged AI-driven platforms like SynCon® and CELLECTRA® for DNA vaccine design, while **UB-612**[224] used AI-assisted epitope modelling. **EpiVax**[225] has applied machine learning-based immunoinformatics tools (EpiMatrix™, JanusMatrix™) across various vaccine pipelines. Collectively, these examples highlight how AI and computational tools reduce development time, improve safety and efficacy predictions, and enable rational, scalable vaccine design, which is especially vital for emerging infectious diseases. Their clinical progression underscores the growing role of in silico methods as a validated and essential component of modern vaccinology.[221-225]

6. Conclusion

The integration of AI-driven computational tools with vaccine design represents a transformative shift toward sustainable, precise, and globally applicable immunisation strategies.[226] By implementing reverse vaccinology and predictive models for immunogenicity, toxicity, and HLA binding affinity, researchers can significantly streamline the vaccine discovery process, minimising both the time and ethical concerns associated with animal testing. The ability to simulate immune responses *in-silico*, identify population-specific epitopes, and predict proteasomal processing and antigen presentation holds immense promise for developing broad-spectrum and personalised edible vaccines. This review underscores the potential of a holistic computational workflow to translate antigenic peptides into viable protective immunogens, accelerating the path from antigen identification to clinical readiness in a more ethical, efficient, and globally inclusive manner.

Author Contribution Declaration

All authors contributed equally to the conception, design, and execution of the research work. They were collectively involved in planning the experimental strategy, analyzing the results, drafting the manuscript, and approving the final version for submission.

Conflict of interest

The authors declare no competing interests.

Funding sources

The author gratefully acknowledges the scholarship support provided by NIT Durgapur (Ministry of Education, Government of India). We also thank the funding agencies for their support to the Department of Biotechnology, NIT Durgapur, through the DST-FIST program.

Data Availability Declaration

No newly data was generated.

Acknowledgements

The authors thank the Department of Biotechnology, NIT Durgapur, for providing laboratory facilities, network connectivity, and infrastructural support essential for conducting this research and preparing the manuscript.

References

1. A. Bouazzaoui, A. A. H. Abdellatif, F. A. Al-Allaf, N. M. Bogari, S. Al-Dehlawi, S. H. Hari. Strategies for Vaccination: Conventional Vaccine Approaches Versus New-Generation Strategies in Combination with Adjuvants. *Pharmaceutics*, **2021**, *13*, 140. https://doi.org/10.3390/pharmaceutics13020140
2. S. Pattanayak. LIMITATIONS OF THE CONTEMPORARY VACCINES: HOW TO OVERCOME? *Explor. Anim. Med. Res*., **2023**, *13*, 140.
3. A. Detmer, J. Glenting. Live bacterial vaccines a review and identification of potential hazards. *Microb. Cell Fact*., **2006**, *5,* 23. https://doi.org/10.1186/1475-2859-5-23
4. R. Verbeke, M. H. Y. Cheng, P. R. Cullis. A Historical Overview on mRNA Vaccine Development. *In: Trends in mRNA Vaccine Research*, **2025**, *1*. https://doi.org/10.1002/9783527838394.ch1
5. F. Zahedipour, K. Jamialahmadi, P. Zamani, M. R. Jaafari. Improving the efficacy of peptide vaccines in cancer immunotherapy. *Int. Immunopharmacol.,* **2023**, *123*. https://doi.org/10.1016/j.intimp.2023.110721
6. P. Sadhukhan, I. Sutnga, B. Bingari, A. Choudhury. A Retrospective Assessment of the Initial Phase of Covid-19 and Its Implemented Treatment Strategies. *J. Drug Deliv. Ther.,* **2021**, *11*, 81. https://doi.org/10.22270/jddt.v11i3-S.4868
7. A. Patel, R. Patel. Next-Generation Vaccine Development: mRNA, Viral Vector, and Protein-Based Approaches for Pandemic Preparedness. *Int. J. Innov. Res. Sci. Eng. Technol.,* **2024**, *13*, 15577. https://doi.org/10.15680/IJIRSET.2024.1308180
8. N. Z. Miller, G. S. Goldman. Neonatal, Infant, and Under Age Five Vaccine Doses Routinely Given in Developed Nations and Their Association With Mortality Rates. *Cureus,* **2023**, *15*, e42194. https://doi.org/10.7759/cureus.42194
9. DISEASES COI, Y. A. Maldonado, S. T. O'Leary, R. Banerjee, J. D. Campbell, M. T. Caserta, J. S. Gerber, A. P. Kourtis, R. Lynfield, F. M. Munoz, D. Nolt, A. Ratner, S. S. Shah, W. J. Steinbach, K. M. Zangwill, T. E. Zaoutis. Recommended Childhood and Adolescent Immunization Schedule: United States, 2021. *Pediatrics,* **2021**, *147*, e2020049775. https://doi.org/10.1542/peds.2020-049775
10. R. Hutubessy, J. A. Lauer, B. Giersing, S. Y. Sim, M. Jit, D. Kaslow & S. Botwright. The Full Value of Vaccine Assessments (FVVA): a framework for assessing and communicating the value of vaccines for investment and introduction decision-making. *BMC medicine*, **2023**, *21*. https://doi.org/10.1186/s12916-023-02929-0

11. W. P. Hausdorff, J. D. Anderson IV, A. L. Bourgeois, A. Clifford, J. A. Fleming, F. Muhib, C. Pecenka, C. Puett, M. S. Riddle, S. Scheelea & K. H. Bagamian. Reassessing potential economic value and health impact of effective Shigella vaccines. *Bull. World Health Organ.*, **2024**, *102,* 65. https://doi.org/10.2471/blt.23.290163
12. B. Giersing, A. X. Mo, A. Hwang, S. Baqar, K. Earle, A. Ford, C. Deal, P. Dull, M. Friede, B. Fenton Hall. Meeting summary: Global vaccine and immunization research forum, 2023. *Vaccine,* **2025**, *46.* https://doi.org/10.1016/j.vaccine.2024.126686
13. A. Alberts, S. K. Kjaer, S. H. Søegaard, J. F. Winther, K. Schmiegelow, L. Sopina, F. Erdmann, M. Hargreave. Childhood vaccinations and the risk of leukemia: A nationwide cohort study. *Int. J. Cancer.,* **2025**, *157*, 55. https://doi.org/10.1002/ijc.35338
14. A. C. MacArthur, M. L. McBride, J. J. Spinelli, S. Tamaro, R. P. Gallagher, G. P. Theriault. Risk of Childhood Leukemia Associated with Vaccination, Infection, and Medication Use in Childhood: The Cross-Canada Childhood Leukemia Study. *Am. J. Epidemiol.,* **2007**, *167,* 598. https://doi.org/10.1093/aje/kwm339
15. M. Marron, L. K. Brackmann, P. Kuhse, L. Christianson, I. Langner, U. Haug, W. Ahrens. Vaccination and the Risk of Childhood Cancer-A Systematic Review and Meta-Analysis. *Front. Oncol.*, **2020**, *10.* https://doi.org/10.3389/fonc.2020.610843
16. D. Amodio, A. Angelidou, N. Cotugno, A. C. Sherman, O. Levy, P. Palma. Biomarkers of vaccine safety and efficacy in vulnerable populations: Lessons from the fourth international precision vaccines conference. *Vaccine,* **2025**, *43*. https://doi.org/10.1016/j.vaccine.2024.126477
17. Y. Li, J. Li, J. He, C Tao. AE-GPT: Using Large Language Models to extract adverse events from surveillance reports-A use case with influenza vaccine adverse events. *PLoS One*, **2024**, *19*. https://doi.org/10.1371/journal.pone.0300919
18. I. A. Doytchinova, D. R. Flower. VaxiJen: a server for prediction of protective antigens, tumour antigens and subunit vaccines. *BMC Bioinformatics*, **2007**, *8*. https://doi.org/10.1186/1471-2105-8-4
19. C. N. Magnan, M. Zeller, M. A. Kayala, A. Vigil, A. Randall, P. L. Felgner, P. Baldi. High-throughput prediction of protein antigenicity using protein microarray data. *Bioinformatics,* **2010**, *26*, 2936. https://doi.org/10.1093/bioinformatics/btq551
20. I. Dimitrov, I. Bangov, D. R. Flower, I. Doytchinova. AllerTOP v.2—a server for in silico prediction of allergens. *J. Mol. Model.,* **2014**, *20*. https://doi.org/10.1007/s00894-014-2278-5
21. S. Saha, G. P. S. Raghava. AlgPred: prediction of allergenic proteins and mapping of IgE epitopes. *Nucleic Acids Res*., **2006**, *34,* W202. https://doi.org/10.1093/nar/gkl343
22. M. N. Nguyen, N. L. Krutz, V. Limviphuvadh, A. L. Lopata, G. F. Gerberick, S. Maurer-Stroh. AllerCatPro 2.0: a web server for predicting protein allergenicity potential. *Nucleic Acids Res*., **2022**, *50,* W36. https://doi.org/10.1093/nar/gkac446
23. A. S. Rathore, S. Choudhury, A. Arora, P. Tijare, G. P.S. Raghava. ToxinPred 3.0: An improved method for predicting the toxicity of peptides. *Comput. Biol. Med*., **2024**, *179.* https://doi.org/10.1016/j.compbiomed.2024.108926
24. Q. Yu, Z. Zhang, G. Liu, W. Li, Y. Tang. ToxGIN: an In silico prediction model for peptide toxicity via graph isomorphism networks integrating peptide sequence and structure information. *Brief. Bioinform.,* **2024**, *25.* https://doi.org/10.1093/bib/bbae583
25. M. Wang, L. Kurgan, M. Li. Comprehensive assessment and comparison of tools for HLA class I peptide-binding prediction. *Brief. Bioinform.*, **2023**, *24.* https://doi.org/10.1093/bib/bbad150
26. R. Vita, N. Blazeska, D. Marrama, IEDB Curation Team Members, S. Duesing, J. Bennett, J. Greenbaum, M. D. A. Mendes, J. Mahita, D. K. Wheeler, J. R. Cantrell, J. A. Overton, D. A. Natale, A. Sette, B. Peters. The Immune Epitope Database (IEDB): 2024 update. *Nucleic Acids Res.,* **2025**, *53,* D436. https://doi.org/10.1093/nar/gkae1092
27. J. B. Nilsson, A. Grifoni, A. Tarke, A. Sette, M. Nielsen. PopCover-2.0. Improved Selection of Peptide Sets With Optimal HLA and Pathogen Diversity Coverage. *Front. Immunol.,* **2021**, *12*. https://doi.org/10.3389/fimmu.2021.728936
28. H. H. Bui, J. Sidney, K. Dinh, S. Southwood, M. J. Newman, A. Sette. Predicting population coverage of T-cell epitope-based diagnostics and vaccines. *BMC Bioinformatics*, **2006**, *7*. https://doi.org/10.1186/1471-2105-7-153
29. M. S. B. Islam, M. Miah, M. E Hossain, K. M. K. Kibria. A conserved multi-epitope-based vaccine designed by targeting hemagglutinin protein of highly pathogenic avian H5 influenza viruses. *3 Biotech.,* **2020**, *10*. https://doi.org/10.1007/s13205-020-02544-3
30. B. E. Haug, K. A. Camilio, L. T. Eliassen, W. Stensen, J. S. Svendsen, K. Berg, B. Mortensen, G. Serin, J. F. Mirjolet, F. Bichat, Ø. Rekdal. Discovery of a 9-mer Cationic Peptide (LTX-315) as a Potential First in Class Oncolytic Peptide. *J. Med. Chem.,* **2016**, *59,* 2918. https://doi.org/10.1021/acs.jmedchem.5b02025
31. H. Zhang, L. Liu, J. Zhang, J. Chen, J. Ye, S. Shukla, J. Qiao, X. Zhan, H. Chen, C. J. Wu, Y. X. Fu, Bo Li. Investigation of Antigen-Specific T-Cell Receptor Clusters in Human Cancers. *Clin. Cancer. Res.,* **2019**, *26*. https://doi.org/10.1158/1078-0432.CCR-19-3249
32. G. S. Antipas, A. E. Germenis. Atomic Coordination Reflects Peptide Immunogenicity. *Front. Mol. Biosci.,* **2015**, *2*. https://doi.org/10.3389/fmolb.2015.00077
33. W. C. Lim, A. M. Khan. Mapping HLA-A2, -A3 and -B7 supertype-restricted T-cell epitopes in the ebolavirus proteome. *BMC Genomics,* **2018**, *19.* https://doi.org/10.1186/s12864-017-4328-8
34. B. Bacsa, K. Horváti, S. Bõsze, F. Andreae, C. O. Kappe. Solid-Phase Synthesis of Difficult Peptide Sequences at Elevated Temperatures: A Critical Comparison of Microwave and Conventional Heating Technologies. *J. Org. Chem*., **2008**, *73,* 7532. https://doi.org/10.1021/jo8013897
35. D. C. Hancock, N. J. O' Reilly, G. I. Evan. Synthesis of Peptides for Use as Immunogens. *In: Pound JD, ed. Immunochem. Protoc., Totowa, NJ: Humana Press,* **1998**, *80*. https://doi.org/10.1007/978-1-59259-257-9_7
36. D. C. Hancock, N. J. O' Reilly, G. I. Evan. Synthesis of Peptides for Use as Immunogens. *In: Pound JD, ed. In: Pound JD, ed. Immunochem. Protoc., Totowa, NJ: Humana Press,* **2005**, 295, *13*. https://doi.org/10.1385/1-59259-873-0:013
37. M. TopuzoĞullari, T. Acar, P. P. Arayici, B. uçar, E. uğurel, E. ş. Abamor, T. arasoğlu, D. balik, S. derman. An insight into the epitope-based peptide vaccine design strategy and studies against COVID-19. *Turk. J. Biol.*, **2020**, *44*, 215. https://doi.org/10.3906/biy-2006-1
38. S. Halder, N. Jaiswal, S. C. Balajee, N. Mahata. Efficient production of a novel recombinant fusion protein of EIEC effector IpaD and EGFP: Biophysical characterization and functional studies. *Biochim. Biophys. Acta Proteins Proteom*., **2025**, *1873,* 141066. https://doi.org/10.1016/j.bbapap.2025.141066
39. S Halder, N Jaiswal, H Koley, N Mahata. Cloning, improved expression and purification of invasion plasmid antigen D

(IpaD): an effector protein of enteroinvasive Escherichia coli (EIEC). *Biotechnol. Genet. Eng. Rev.,* **2024**, *40,* 409. https://10.1080/02648725.2023.2184027
40. M. Gomez-Perosanz, A. Ras-Carmona, E. M. Lafuente, P. A. Reche. Identification of CD8(+) T cell epitopes through proteasome cleavage site predictions. *BMC Bioinformatics*, **2020**, *21*. https://doi.org/10.1186/s12859-020-03782-1
41. S. S. Ella Mae Joy, C. B. Edward, L. E. Fajardo, N. M. O. Odchimar, A. M. Simbulan, F. L. Orosco. Current strategies, advances, and challenges in multi-epitope subunit vaccine development for African swine fever virus. *Vet. Integr. Sci.,* **2024**, *23,* 1. https://doi.org/10.12982/VIS.2025.011
42. P. Saxová, S. Buus, S. Brunak, C. Keşmir. Predicting proteasomal cleavage sites: a comparison of available methods. *Int. Immunol*., **2003**, *15,* 781. https://doi.org/10.1093/intimm/dxg084
43. O. W. Liew, S. S. M. Ling, S. Lilyanna, J. P. C. Chong, J. Y. Xia Ng, A. M. Richards. One-Shot Generation of Epitope-Directed Monoclonal Antibodies to Multiple Nonoverlapping Targets: Peptide Selection, Antigen Preparation, and Epitope Mapping. *Methods Mol. Biol*., **2023**, *2578*, 121. https://doi.org/10.1007/978-1-0716-2732-7_9
44. H. X. Lim, J. Lim, S. D. Jazayeri, S. Poppema, C. l. Poh. Development of multi-epitope peptide-based vaccines against SARS-CoV-2. *Biomed. J.,* **2021**, *44*, 18. https://doi.org/10.1016/j.bj.2020.09.005
45. P. Kalita, T. Tripathi. Methodological advances in the design of peptide-based vaccines. *Drug. Discov. Today*, **2022**, *27,* 1367. https://doi.org/10.1016/j.drudis.2022.03.004
46. H. Ardestani, S. Nazarian, A. Hajizadeh, D. Sadeghi, E. Kordbacheh. In silico and in vivo approaches to recombinant multi-epitope immunogen of GroEL provides efficient cross protection against S. Typhimurium, S. flexneri, and S. dysenteriae. *Mol. Imm.,* **2022**, *144,* 96. https://doi.org/10.1016/j.molimm.2022.02.013
47. M. Shah, S. Rafiq, H. G. Woo. Challenges and considerations in multi-epitope vaccine design surrounding toll-like receptors. *Trends Pharmacol. Sci*., **2024**, *45,* 1104. https://doi.org/10.1016/j.tips.2024.10.013
48. S. Chowdhury, P. Sadhukhan, N. Mahata. Immunoinformatics investigation on pathogenic Escherichia coli proteome to develop an epitope-based peptide vaccine candidate. *Mol. Divers*., **2024**. https://doi.org/10.1007/s11030-024-11034-0
49. H. Zelba, A. McQueeney, A. Rabsteyn, O. Bartsch, C. Kyzirakos, S. Kayser, J. Harter, P. Latzer, D. Hadaschik, F. Battk, A. D. Hartkopf, S. Biskup.Adjuvant Treatment for Breast Cancer Patients Using Individualized Neoantigen Peptide Vaccination-A Retrospective Observation. *Vaccines*, **2022**, *10*. https://doi.org/10.3390/vaccines10111882
50. P. Patra, M. Bhattacharya, A. R. Sharma, P. Ghosh, G. Sharma, B. C. Patra, B. Mallick, S. S. Lee, C. Chakraborty. Identification and Design of a Next-Generation Multi Epitopes Bases Peptide Vaccine Candidate Against Prostate Cancer: An In Silico Approach. *Cell Biochem. Biophys*., **2020**, *78,* 495. https://doi.org/10.1007/s12013-020-00912-7
51. H. Namdari, F. Rezaei, F. Heidarnejad, M. Y. Maleki, M. Karamigolbaghi. Immunoinformatics Approach to Design a Chimeric CD70-Peptide Vaccine against Renal Cell Carcinoma. *J. Immunol. Res*., **2024**. https://doi.org/10.1155/2024/2875635
52. M. Saxena, T. U. Marron, J. Kodysh, Jr. J. P. Finnigan, S. Onkar, A. Kaminska, K. Tuballes, R. Guo, R. L. Sabado, M. Meseck, T. J. O'Donnell, R. P. Sebra, S. Parekh, M. D. Galsky, A. Blasquez, G. Gimenez, M. Bicak, C. C. Bozkus, D. D. Zagelbaum, D. Rodriguez, A. A. Villaorduna, K. J. Misiukiewicz, M. R. Posner, B. A. Miles, H. Y. Irie, A. Tiersten, D. B. Doroshow, A. Wolf, J. Mandeli, R. Brody, A. M. Salazar, S. Gnjatic, J. Hammerbacher, E. Schadt, P. Fiedlander, A. Rubinsteyn, N. Bhardwaj. PGV001, a Multi-Peptide Personalized Neoantigen Vaccine Platform: Phase I Study in Patients with Solid and Hematologic Malignancies in the Adjuvant Setting. *Cancer Discov*., **2025**, *15,* 930. https://doi.org/10.1158/2159-8290.CD-24-0934
53. R. J. Malonis, J. R. Lai, O. Vergnolle. Peptide-Based Vaccines: Current Progress and Future Challenges. *Chem. Rev.,* **2020**, *120,* 3210. https://doi.org/10.1021/acs.chemrev.9b00472
54. T. J. Wells, T. Esposito, I. R. Henderson, L. I. Labzin. Mechanisms of antibody-dependent enhancement of infectious disease. *Nat. Rev. Immunol*., **2025**, *25,*6. https://doi.org/10.1038/s41577-024-01067-9
55. M. Pang, X. Z. Sun, T. He, H. Yang, J Chen. Clinical Manifestation of Arboviruses in Paediatrics. *Rev. Med. Virol*. **2025**, *35,* e70016. https://doi.org/10.1002/rmv.70016
56. A. Teo, H. D. Tan, T. Loy, P. Y. Chia, C. L. L. Chua. Understanding antibody-dependent enhancement in dengue: Are afucosylated IgG1s a concern? *PLoS pathog.,* **2023**, *19*. https://doi.org/10.1371/journal.ppat.1011223
57. S. J. Thomas. Is new dengue vaccine efficacy data a relief or cause for concern? *NPJ Vaccines,* **2023**, *8,* 55. https://doi.org/10.1038/s41541-023-00658-2
58. T. Šuštić, J. V. Coillie, M. D. Larsen, N. I. L. Derksen, Z. Szittner, J. Nouta, W. Wang, T. Damelang, I. Rebergen, F. Linty, R. Visser, J. Y. Mok, D. M. Geerdes, W. J. E. V. Esch, S. W. de Taeye, M. J. V. Gils, L. V. de Watering, C. E. V. der Schoot, M. Wuhrer, T. Rispens. G. Vidarsson. Immunoassay for quantification of antigen-specific IgG fucosylation. *EBioMedicine*, **2022**, *81,* 104109. https://doi.org/10.1016/j.ebiom.2022.104109
59. R. I. Kitney, J. Bell, J. Philp. Build a Sustainable Vaccines Industry with Synthetic Biology. *Trends Biotechnol*., **2021**, *39,* 866. https://doi.org/10.1016/j.tibtech.2020.12.006
60. O. M. Oyedele. The Cobra Effect: Exploring the Dark Side of Innovation and Environmental Sustainability in Developing Nations. In: Singh R, Joshi A, Filho WL, Khan S, eds. Zero Carbon Industry, Eco-Innovation and Environmental Sustainability. *Cham: Springer Nature Switzerland.,* **2025**, 251. https://doi.org/10.1007/978-3-031-80220-1_15
61. S. Yadav, D. S. Vora, D. Sundar, J. K. Dhanjal. TCR-ESM: Employing protein language embeddings to predict TCR-peptide-MHC binding. *Comput. Struct. Biotechnol. J.,* **2024**, *23*, 165. https://doi.org/10.1016/j.csbj.2023.11.037
62. Y. Zhao, J. J. Yu, Y. Su, E. Ma, J. Wang, S. Jiang, C. Wei, D. Li, Z. Huang, G. Cheng, H. Ren, J. Feng. A unified deep framework for peptide–major histocompatibility complex–T cell receptor binding prediction. *Nat. Mach. Intell.,* **2025**. https://doi.org/10.1038/s42256-025-01002-0
63. Y. Wei, T. Qiu, Y. Ai, Y. Zhang, J. Xie, D. Zhang, X. Luo, X. Sun, X. Wang, J. Qiu. Advances of computational methods enhance the development of multi-epitope vaccines. *Brief. Bioinform*., **2025**, *26*. https://doi.org/10.1093/bib/bbaf055
64. M. Rahman. Editorial: design considerations for future personalized vaccination approaches. *Nanomedicine,* **2025**, *20,* 329. https://doi.org/10.1080/17435889.2024.2419816
65. A. Vasou, N. Sultanoglu, S. Goodbourn, R. E. Randall, L. G. Kostrikis. Targeting Pattern Recognition Receptors (PRR) for Vaccine Adjuvantation: From Synthetic PRR Agonists to the Potential of Defective Interfering Particles of Viruses. *Viruses*, **2017**, *9*. https://doi.org/10.3390/v9070186
66. H. Afzal, A. Murtaza, L. T. Cheng. Structural engineering of flagellin as vaccine adjuvant: quest for the minimal domain of flagellin for TLR5 activation. *Mol. Biol. Rep*., **2025**, *52*. https://doi.org/10.1007/s11033-024-10146-y

67. T. Lu, S. Das, D. R. Howlader, A. Jain, G. Hu, Z. K. Dietz, Q. Zheng, S. S. K. Ratnakaram, S. K. Whittier, D. J. Varisco, R. K. Ernst, W. D. Picking, W. L. Picking. Impact of the TLR4 agonist BECC438 on a novel vaccine formulation against Shigella spp. *Front. Immunol.,* **2023**, *14*. https://doi.org/10.3389/fimmu.2023.1194912
68. C. G. Park. Vaccine strategies utilizing C-type lectin receptors on dendritic cells in vivo. *Clin. Exp. Vaccine Res.,* **2014**, *3,* 149. https://doi.org/10.7774/cevr.2014.3.2.149
69. H. Y. Yong, D. Luo. RIG-I-Like Receptors as Novel Targets for Pan-Antivirals and Vaccine Adjuvants Against Emerging and Re-Emerging Viral Infections. *Front. Immunol.,* **2018**, *9.* https://doi.org/10.3389/fimmu.2018.01379
70. A. Atalis, M. C. Keenum, B. Pandey, A. Beach, P. Pradhan, C. Vantucci, L. O'Farrell, R. Noel, R. J ain, J. Hosten, C. Smith, L. Kramer, A. Jimenez, M. A. Ochoa, D. Frey, K. Roy. Nanoparticle-delivered TLR4 and RIG-I agonists enhance immune response to SARS-CoV-2 subunit vaccine. *J. Control Release*., **2022**, *347,* 476. https://doi.org/10.1016/j.jconrel.2022.05.023
71. Q. Li, Z. Li, N. Deng, F. Ding, Y. Li, H. Cai. Built-in adjuvants for use in vaccines. *Eur. J. Med. Chem*., **2022**, *227*. https://doi.org/10.1016/j.ejmech.2021.113917
72. P. Bhardwaj, G. P. Biswas, N. Mahata, S. Ghanta, B. Bhunia. Exploration of binding mechanism of triclosan towards cancer markers using molecular docking and molecular dynamics. *Chemosphere*, **2022**, *293,* 133550. https://doi.org/10.1016/j.chemosphere.2022.133550
73. R. López, N. Díaz, E. Francisco, A. Martín-Pendás, D. Suárez. QM/MM Energy Decomposition Using the Interacting Quantum Atoms Approach. *J. Chem. Inf. Model.,* **2022**, *62,* 1510. https://doi.org/10.1021/acs.jcim.1c01372
74. J. R. Perilla, B. C. Goh, C. K. Cassidy, B. Liu, R. C. Bernardi, T. Rudack, H. Yu, Z. Wu, K. Schulten. Molecular dynamics simulations of large macromolecular complexes. *Curr. Opin. Struct. Biol.*, **2015**, *31,* 64. https://doi.org/10.1016/j.sbi.2015.03.007
75. G. A. Poland, J. de la Fuente. Quantum vaccinology: A new science and epistemological abstraction framework for developing new vaccines and understanding the generation of the immune response. *Vaccine,* **2025**, *46*. https://doi.org/10.1016/j.vaccine.2024.126641
76. J. M. Chow. Quantum computing requires high-performance software. *Science,* **2025**, *387*. https://doi.org/10.1126/science.adt0019
77. I. Kolossváry. A Fresh Look at the Normal Mode Analysis of Proteins: Introducing Allosteric Co-Vibrational Modes. *JACS Au*., **2024**, *4,* 1303. https://doi.org/10.1021/jacsau.4c00109
78. A. G. Moulick, R. Patel, A. Onyema, S. M. Loverde. Unveiling nucleosome dynamics: A comparative study using all-atom and coarse-grained simulations enhanced by principal component analysis. *J. Chem. Phys.*, **2025**, *162.* https://doi.org/10.1063/5.0246977
79. M. Wang, A. Ma, H. Wang, X. Lou. Atomic molecular dynamics simulation advances of de novo-designed proteins. *Q. Rev. Biophys.,* **2024**, *57.* https://doi.org/10.1017/S0033583524000131
80. J. Rizo, L. Sari, Y. Qi, W. Im, M. M. Lin. All-atom molecular dynamics simulations of Synaptotagmin-SNARE-complexin complexes bridging a vesicle and a flat lipid bilayer. *eLife,* **2022**, *11.* https://doi.org/10.7554/eLife.76356
81. S. Phogat, J. Yadav, D. Chaudhary, R. Jaiwal, P. K. Jaiwal. Synthesis of an Adjuvant-Free Single Polypeptide-Based Tuberculosis Subunit Vaccine that Elicits In Vivo Immunogenicity in Rats. *Mol. Biotechnol*., **2025**, (online). https://doi.org/10.1007/s12033-025-01431-7
82. W. Z. Huang, W. H. Hu, Y. Wang, J. Chen. Z. Hu, J. Zhou, L. Liu, W. Qiu, F. Tang, S. Zhang, Y. Ouyang, Y. Ye, G. Xu, J. Long, Z. Zeng. A Mathematical Modelling of Initiation of Dendritic Cells-Induced T Cell Immune Response. *Int. J. Biol. Sci.,* **2019**, *15,* 1396. https://doi.org/10.7150/ijbs.33412
83. G. Gasperini, N. Baylor, S. Black, J. Cramer, G. de Lannoy, P. Denoel. M. Feinberg, T. Helleputte, G. Kang, W. R. Schief, L, Stuart, C. Weller, M. Zwierzyna, R. Rappuoli. Vaccinology in the artificial intelligence era. *Sci. Transl. Med.,* **2025**, *17.* https://doi.org/10.1126/scitranslmed.adu3791
84. L. Wu, H. Lin, Y. Huang, Z. Gao, C. tan, Y. Liu, T. Wu, S. Z. Li. Relation-aware equivariant graph networks for epitope-unknown antibody design and specificity optimization. Paper presented at: *Proceedings of the AAAI Conference on Artificial Intelligence,* **2025**. https://doi.org/10.48550/arXiv.2501.00013
85. G. Giusmin. The immune system. *In: The Anatomy and Physiology Textbook for Midwives. Routledge,* **2025**, 197. ISBN-9781032130842.
86. I. Rastogi, D. Jeon, J. E. Moseman, A. Muralidhar. H. K. Potluri, D. G. McNeel. Role of B cells as antigen presenting cells. *Front. Immunol*., **2022**, *13*. https://doi.org/10.3389/fimmu.2022.954936
87. R. J. Ji, M. Y. Wang, Y. Zhang. Precision epitope editing: A path to advanced immunotherapies. *Cell Insight,* **2025**, *4.* https://doi.org/10.1016/j.cellin.2024.100226
88. C. L. P. Eng, T. W. Tan, J. C. Tong. Immunoinformatics Databases. *In: Ranganathan S, Gribskov M, Nakai K, Schönbach C, eds. Encyclopedia of Bioinformatics and Computational Biology. Oxford: Academic Press,* **2019**, 931. https://doi.org/10.1016/B978-0-12-809633-8.20469-X
89. J. Sidney, B. Peters, A. Sette. Epitope prediction and identification- adaptive T cell responses in humans. *Semin. Immunol*., **2020**, *50*. https://doi.org/10.1016/j.smim.2020.101418
90. J. M. Gershoni, A. Roitburd-Berman, D. D. Siman-Tov, N. T. Freund, Y. Weiss. Epitope mapping: the first step in developing epitope-based vaccines. *BioDrugs,* **2007**, *21,* 145. https://doi.org/10.2165/00063030-200721030-00002
91. R. Viswanathan, M. Carroll, A. Roffe, J. E. Fajardo, A. Fiser. Computational prediction of multiple antigen epitopes. *Bioinformatics*, **2024**, *40.* https://doi.org/10.1093/bioinformatics/btae556
92. N. Lalinde-Ruiz, L. C. Martínez-Enriquez, D. A. Gutierrez, H. H. Nieto, L. F. Niño, C. A. Parra-López. Methodological approach to identify immunogenic epitopes candidates for vaccines against emerging pathogens tailored to defined HLA populations. *Comput. Biol. Chem*., **2025**, *116*. https://doi.org/10.1016/j.compbiolchem.2025.108389
93. H. W. Davidson, C. Watts. Epitope-directed processing of specific antigen by B lymphocytes. *J. Cell Biol*., **1989**, *109,* 85. https://doi.org/10.1083/jcb.109.1.85
94. R. Vita, N. Blazeska, D. Marrama, IEDB Curation Team Members, S. Duesing, J. Bennett, J. Greenbaum, M. D. A. Mendes, J. Mahita, D. K. Wheeler, J. R. Cantrell, J. A. Overton, D. A. Natale, A. Sette, B. Peters. The Immune Epitope Database (IEDB): 2024 update. *Nucleic Acids Res*., **2024**, *53,* D436. https://doi.org/10.1093/nar/gkae1092
95. B. Liu, M. Bai, F. Zheng, M. Yan, E. Huang, J. Wen, Y. Li, J. Wang. The Identification of Dual T-Cell and B-Cell Epitopes Within Viral Proteins Utilizing a Comprehensive Peptide Array Approach. *Vaccines,* **2025**, *13,* 239. https://doi.org/10.3390/vaccines13030239
96. M. Bhattacharjee, M. Banerjee, A. Mukherjee. Advanced in silico design of an optimized multi-epitope peptide vaccine employing immunoinformatics and reverse vaccinology strategies on the model of Listeria monocytogenes. *J. Proteins*

Proteom., **2025**, *16*, 213. https://doi.org/10.1007/s42485-025-00185-9
97. A. Saihar, A. R. Yaseen, M. Suleman, R. Parveen, H. Bashir. From bytes to bites: In-silico creation of a novel multi-epitope vaccine against Murray Valley Encephalitis Virus. *Microb. Pathog*., **2025**, *198*. https://doi.org/10.1016/j.micpath.2024.107171
98. Z. Bayat, Z. Majidi, A. Taherkhani, L. Samie. Engineering a Novel T-Cell Epitope-Based Vaccine Targeting PRAME in Cancer Immunotherapy. *Pept. Sci*., **2025**, *117.* https://doi.org/10.1002/pep2.24393
99. V. Vaghasia, L. K. Snehkant, P. Saumya, J. Das. Epitopes mapping for identification of potential cross-reactive peptide against leptospirosis. *J. Biomol. Struct. Dyn*., **2025**, *43,* 20. https://doi.org/10.1080/07391102.2023.2279285
100. V. Ahlawat, K. Sura, M. Dangi, A. K. Chhillar. Designing of multi-valent epitope vaccine displaying interactions with diverse HLA alleles against Candida auris using immuno-informatics. *J. Genet. Eng. Biotechnol*., **2025**, *23.* https://doi.org/10.1016/j.jgeb.2025.100474
101. D. R. L. Agnila, R. Jain, M. J. Diaz, T. R. Hudlock, R. A. Eakins, A. Chobrutskiy, B. I. Chobrutskiy, G. Blanck. TCR CDR3 chemical complementarity to HPV epitopes is associated with a better outcome for cervical cancer. *Mamm. Genome.,* **2025,** *36,* 683. https://doi.org/10.1007/s00335-025-10127-x
102. M. Nahian, M. Shahab, M. R. Khan, S. Akash, T. A. Banu, M. H. Sarkar, B. Goswami, S. F. Chowdhury, M. A. Islam, A. A. Rus'd, S. Bgum, A. Habib, A. A. Shaikh, J. I. N. Oliveira, S. Akter. Development of a broad-spectrum epitope-based vaccine against Streptococcus pneumoniae. *PloS one*, **2025**, *20.* https://doi.org/10.1371/journal.pone.0317216
103. F. F. Gonzalez-Galarza, A. McCabe, E. J. M. Dos Santos,J. Jones, L. Takeshita, N. D. Ortega-Rivera, G. M. D. Cid-Pavon, K. Ramsbottom, G. Ghattoraya, A. Alfirevic, D. Middleton, A. R. Jones. Allele frequency net database (AFND) 2020 update: gold-standard data classification, open access genotype data and new query tools. *Nucleic Acids Res*., **2019**, *48,* D783. https://10.1093/nar/gkz1029
104. I. Doytchinova, D. Flower. VaxiJen: a server for prediction of protective antigens, tumour antigens and subunit vaccines. *BMC Bioinformatics,* **2007**, *8*, 4. https://doi.org/10.1186/1471-2105-8-4
105. T. L. Nguyen, T. B. Nguyen, H. Kim. Computational identification of B and T-cell epitopes for designing a multi-epitope vaccine against SARS-CoV-2 spike glycoprotein. *J. Struct. Biol*., **2025**, *217*, 108. https://doi.org/10.1016/j.jsb.2025.108177
106. R. D. Huby, R. J. Dearman, I. Kimber. Why are some proteins allergens? *Toxicol. Sci*., **2000**, *55*, 235. https://doi.org/10.1093/toxsci/55.2.235
107. F. Huan, S. Gao, Y. Gu, L. Ni, M. Wu, Y. Li, M. Liu, Y. Yang, A. Xiao, G. Liu. Molecular Allergology: Epitope Discovery and Its Application for Allergen-Specific Immunotherapy of Food Allergy. *Clinic. Rev. Allerg. Immunol*., **2025**, *68*, 37. https://doi.org/10.1007/s12016-025-09052-3
108. I. Dimitrov, I. Bangov, D. R. Flower, I. Doytchinova. AllerTOP v.2--a server for in silico prediction of allergens. *J. Mol. Model*., **2014**, *20,* 2278. https://doi.org/10.1007/s00894-014-2278-5
109. M. N. Nguyen, N. L. Krutz, V. Limviphuvadh, A. L. Lopata, G. F. Gerberick, S. Maurer-Stroh. AllerCatPro 2.0: a web server for predicting protein allergenicity potential. *Nucleic Acids Res.,* **2022**, *50*, W36. https://doi.org/10.1093/nar/gkac446
110. S. Saha, G. P. Raghava. AlgPred: prediction of allergenic proteins and mapping of IgE epitopes. *Nucleic Acids Res.,* **2006**, *34*, W202. https://doi.org/10.1093/nar/gkl343
111. I. Dimitrov, L. Naneva, I. Doytchinova, I. Bangov. AllergenFP: allergenicity prediction by descriptor fingerprints. *Bioinformatics,* **2014**, *30*, 846. https://doi.org/10.1093/bioinformatics/btt619
112. I. Dimitrov, I. Doytchinova. An Alignment-Independent Platform for Allergenicity Prediction. *In: Tomar N, ed. Immunoinformatics, New York, NY: Springer US.* **2020**, *147*. https://doi.org/10.1007/978-1-0716-0389-5_5
113. T. Sisay, N. Maina, S. Wachira, V. A. Mobegi. In-silico evaluation of fungal and bacterial L-asparaginases allergenicity. *Inform. Med. Unlocked,* **2023**, *43*, 101398. https://doi.org/10.1016/j.imu.2023.101398
114. S. Basith, N. T. Pham, B. Manavalan, G. Lee. SEP-AlgPro: An efficient allergen prediction tool utilizing traditional machine learning and deep learning techniques with protein language model features. *Int. J. Biol. Macromol*., **2024**, *273,* 133085. https://doi.org/10.1016/j.ijbiomac.2024.133085
115. N. Cristianini, E. Ricci. Support Vector Machines. *In: Kao M-Y, ed. Encyclopedia of Algorithms. Boston, MA: Springer US*, **2008**, *928*. https://doi.org/10.1007/978-0-387-30162-4_415
116. S. Gupta, P. Kapoor, K. Chaudhary, A. Gautam, R. Kumar, OSDDC, G. P. S. Raghava. In silico approach for predicting toxicity of peptides and proteins. *PloS one,* **2013**, *8*. https://doi.org/10.1371/journal.pone.0073957
117. G. Reena, R. Ranjani, K. D. Goutham, K. Sangeetha. In silico screening of plant peptides against the envelope protein of dengue virus. *Trop. Biomed*., **2023**, *40,* 124. https://doi.org/10.47665/tb.40.2.001
118. X. Pan, J. Zuallaert, X. Wang, H. Shen, E. P. Campos, D. O. Marushchak, W. D. Neve. ToxDL: deep learning using primary structure and domain embeddings for assessing protein toxicity. *Bioinformatics*, **2021**, *36*, 5159. https://doi.org/10.1093/bioinformatics/btaa656
119. J. N. Clifford, M. H. Høie, S. Deleuran, B. Peters, M. Nielsen, P. Marcatili. BepiPred-3.0: Improved B-cell epitope prediction using protein language models. *Protein Sci*., **2022**, *31,* e4497. https://doi.org/10.1002/pro.4497
120. S. Saha, G. P. Raghava. Prediction of continuous B-cell epitopes in an antigen using recurrent neural network. *Proteins,* **2006**, *65*, 40. https://doi.org/10.1002/prot.21078
121. H. Singh, H. R. Ansari, G. P. Raghava. Improved method for linear B-cell epitope prediction using antigen's primary sequence. *PloS one,* **2013**, *8*, e62216. https://doi.org/10.1371/journal.pone.0062216
122. M. Collatz, F. Mock, E. Barth, M. Hölzer, K. Sachse, M Marz. EpiDope: a deep neural network for linear B-cell epitope prediction. *Bioinformatics,* **2020**, *37*, 448. https://doi.org/10.1093/bioinformatics/btaa773
123. Y. El-Manzalawy, D. Dobbs, V. Honavar. Predicting linear B-cell epitopes using string kernels. *J. Mol. Recognit.,* **2008**, *21*, 243. https://doi.org/10.1002/jmr.893
124. M. H. Høie, F. S. Gade, J. M. Johansen, C. Würtzen, O. Winther, M. Nielsen, P. Marcatili. DiscoTope-3.0: improved B-cell epitope prediction using inverse folding latent representations. *Front. Immunol*., **2024**, *15*, 1322712. https://doi.org/10.3389/fimmu.2024.1322712
125. J. Ponomarenko, H. H. Bui, W. Li, N. Fusseder, P. E. Bourne, A. Sette, B. Peters. ElliPro: a new structure-based tool for the prediction of antibody epitopes. *BMC bioinformatics,* **2008**, *9*, 514. https://doi.org/10.1186/1471-2105-9-514
126. M. J. Sweredoski, P. Baldi. PEPITO: improved discontinuous B-cell epitope prediction using multiple distance thresholds and half sphere exposure. *Bioinformatics*, **2008**, *24*, 1459. https://doi.org/10.1093/bioinformatics/btn199

127. U. Kulkarni-Kale, S. Bhosle, A. S. Kolaskar. CEP: a conformational epitope prediction server. *Nucleic Acids Res*., **2005**, *33*, W168. https://doi.org/10.1093/nar/gki460
128. J. Sun, D. Wu, T. Xu, X. Wang, X. Xu, L. Tao, Y. X. Li, Z. W. Cao. SEPPA: a computational server for spatial epitope prediction of protein antigens. *Nucleic Acids Res*., **2009**, *37,* W612. https://doi.org/10.1093/nar/gkp417
129. M. Atanasova, A. Patronov, I. Dimitrov, D. R. Flower, I. Doytchinova. EpiDOCK: a molecular docking-based tool for MHC class II binding prediction. *Protein Eng. Des. Sel*., **2013**, *26,* 631. https://doi.org/10.1093/protein/gzt018
130. P. A. Reche, E. L. Reinherz. PEPVAC: a web server for multi-epitope vaccine development based on the prediction of supertypic MHC ligands. *Nucleic Acids Res*., **2005**, *33*, W138. https://doi.org/10.1093/nar/gki357
131. I. Dimitrov, P. Garnev, D. R. Flower, I. Doytchinova. EpiTOP—a proteochemometric tool for MHC class II binding prediction. *Bioinformatics*, **2010**, *26*, 2066. https://doi.org/10.1093/bioinformatics/btq324
132. P. Guan, C. K. Hattotuwagama, I. A. Doytchinova, D. R. Flower. MHCPred 2.0: an updated quantitative T-cell epitope prediction server. *Appl. Bioinformatics*, **2006**, *5,* 55. https://doi.org/10.2165/00822942-200605010-00008
133. C. A. Mirkin, R. Langer, M. Mrksich, A. Margolin, A., S. H. Petrosko, & N. Artzi. Blueprints for Better Drugs: The Structural Revolution in Nanomedicine. *ACS Nano,* **2025**, *19,* 18889. https://doi:10.1021/acsnano.5c06380
134. D. T. Ouologuem, F. O. Maiga, A. Dara, A. Djimdé, D. A. K. Traore, E. Nji. Hands-on training in structural biology, a tool for sustainable development in Africa series 4. *Biology open*. **2022**, *11.* http://doi.org/10.1242/bio.059487
135. E. Nji, A. F. A. Moumbock, K. C. Cramer, N. V. Rüffin, J. Davis, O. A. Asojo, J. J. Griese, A. A. Larbi, M. N. Fodje. Supporting structural biologists in Africa requires resources and capacity building. *Nat. Struct. Mol. Biol.*, **2024**, *31,* 1814. https://doi.org/10.1038/s41594-024-01438-9
136. J. Jumper, R. Evans, A. Pritzel, T. Green, M. Figurnov, O. Ronneberger, K. Tunyasuvunakool, R. Bates., A. Žídek, A. Potapenko, A. Bridgland, C. Meyer, S. A. A. Kohl, A. J. Ballard, A. Cowie, B. Romera-Paredes, S. Nikolov, R. Jain, J. Adler, T. Back, S. Petersen, D. Reiman, E. Clancy, M. Zielinski, M. Sterinegger, M. Pacholska, T. Berghammer, S. Bodenstein, D. Silver, O. Vinyals, A. W. Senior, K. Kavukcuoglu, P. Kohli, D. Hassabis. Highly accurate protein structure prediction with AlphaFold. *Nature,* **2021**, *596,* 583. https://doi.org/10.1038/s41586-021-03819-2
137. M. Mirdita, K. Schütze, Y. Moriwaki, L. Heo, S. Ovchinnikov, M. Steinegger. ColabFold: making protein folding accessible to all. *Nat. Methods,* **2022**, *19*, 679. https://doi.org/10.1038/s41592-022-01488-1
138. S. Park, S. Myung, M. Baek. Advancing protein structure prediction beyond AlphaFold2. *Curr. Opin. Struct. Biol*., **2025**, *90*, 102985. https://doi.org/10.1016/j.sbi.2025.102985
139. M. Torrisi, G. Pollastri, Q. Le. Deep learning methods in protein structure prediction. *Comput. Struct. Biotechnol. J*., **2020**, *18*, 1301. https://doi.org/10.1016/j.csbj.2019.12.011
140. J. Jänes, P. Beltrao. Deep learning for protein structure prediction and design—progress and applications. *Mol. Syst. Biol*., **2024**, *20,* 162. https://doi.org/10.1038/s44320-024-00016-x
141. C. Chen, X. Chen, A. Morehead, T. Wu, J. Cheng. 3D-equivariant graph neural networks for protein model quality assessment. *Bioinformatics,* **2023**, *39*. https://doi.org/10.1093/bioinformatics/btad030
142. L. Kong, F. Ju, W. M. Zheng, J. Zhu, S. Sun, J. Xu, D. Bu. ProALIGN: Directly Learning Alignments for Protein Structure Prediction via Exploiting Context-Specific Alignment Motifs. *J. Comput. Biol*., **2022**, *29,* 92. https://doi.org/10.1089/cmb.2021.0430
143. C. Zhang, Q. Wang, Y. Li, A. Teng, G. Hu, Q. Wuyun, W. Zheng. The Historical Evolution and Significance of Multiple Sequence Alignment in Molecular Structure and Function Prediction. *Biomolecules*, **2024**, *14,* 1531. https://doi.org/10.3390/biom14121531
144. R. S. Aal, E. Ali, J. Meng, M. E. I. Khan, X. Jiang. Machine learning advancements in organic synthesis: A focused exploration of artificial intelligence applications in chemistry. *Artif. Intell. Chem.,* **2024**, *2,* 100049. https://doi.org/10.1016/j.aichem.2024.100049
145. J. Koehler Leman, G. Künze. Recent Advances in NMR Protein Structure Prediction with ROSETTA. *Int. J. Mol. Sci*., **2023**, *24,* 7835. https://doi.org/10.3390/ijms24097835
146. M. Baek, F. DiMaio, I. Anishchenko, J. Dauparas, S. Ovchinnikov, G. R. Lee, J. Wang, Q. Cong, L. N. Kinch, R. D. Schaeffer, G. R. Lee, J. Wang, Q. Cong, L. N. Kinch, R. D. Schaeffer, C. Millán, H. Park, C. Adams, C. R. Glassman, A. DeGiovanni, J. H. Pereira, A. V. Rodrigues, A. A. V. Dijk, A. C. Ebrecht, D. J. Opperman, T. Sagmeister, C. Buhlheller, T. Pavkov-Keller, M. K. Rathinaswamy, U. Dalwadi, C. K. Yip, J. E. Burke, K. C. Garcia, N. V. Grishin, P. D. Adams, R. J. Read, D. Bekar. Accurate prediction of protein structures and interactions using a three-track neural network. *Science*, **2021**, *373*, 871. https://doi.org/10.1126/science.abj8754
147. Q. Wuyun, Y Chen, Y Shen, Y. Cao, G. Hu, W. Cui, J. Gao, W. Zheng. Recent Progress of Protein Tertiary Structure Prediction. *Molecules*, **2024**, *29,* 832. https://doi.org/10.3390/molecules29040832
148. J Rey, S Murail, S de Vries, P Derreumaux, P Tuffery. PEP-FOLD4: a pH-dependent force field for peptide structure prediction in aqueous solution. *Nucleic Acids Res.*, **2023**, *51*, W432. https://doi.org/10.1093/nar/gkad376
149. C. T. Mant, R. S. Hodges. Design of peptide standards with the same composition and minimal sequence variation to monitor performance/selectivity of reversed-phase matrices. *J. Chromatogr. A*., **2012**, *1230*, 30. https://doi.org/10.1016/j.chroma.2012.01.053
150. A. Mondal, L. Chang, A. Perez. Modelling peptide-protein complexes: docking, simulations and machine learning. *QRB Discov*., **2022**, *3*, e17. https://doi.org/10.1017/qrd.2022.14
151. B. Raveh, N. London, O. Schueler-Furman. Sub-angstrom modeling of complexes between flexible peptides and globular proteins. *Proteins*, **2010**, *78*, 2029. https://doi.org/10.1002/prot.22716
152. M. Ciemny, M. Kurcinski, K. Kamel, A. Kolinski, N. Alam, O. Schueler-Furman, S. Kmiecik. Protein–peptide docking: opportunities and challenges. *Drug Discov. Today,* **2018**, *23*, 1530. https://doi.org/10.1016/j.drudis.2018.05.006
153. O. Trott, A. J. Olson. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem.,* **2010**, *31,* 455. https://doi.org/10.1002/jcc.21334
154. M. L. Verdonk, J. C. Cole, M. J. Hartshorn, C. W. Murray, R. D. Taylor. Improved protein-ligand docking using GOLD. *Proteins,* **2003**, *52*, 609. https://doi.org/10.1002/prot.10465
155. J. Patra, A. K. Keshari, R. R. Bhandare, A. B. Shaik, M. Parrot, S. Lin. Discovery of Novel Multiangiogenic Agents Targeting VEGFR2, EphB4, FGFR-1, and TIE-2: Receptor-Based Pharmacophore Modeling, Virtual Screening, and Molecular Modeling Studies. *ACS omega*, **2025**, *10*, 13880. https://doi.org/10.1021/acsomega.4c08366
156. S. Huang, D. Gu, W. Xiong. Exploring the functional and prognostic roles of EPHX4 in pancreatic cancer: Insights from

bioinformatics and experimental validation. *Gene*, **2025**, *959*, 149504. https://doi.org/10.1016/j.gene.2025.149504
157. H. Lee, L. Heo, M. S. Lee, C. Seok. GalaxyPepDock: a protein-peptide docking tool based on interaction similarity and energy optimization. *Nucleic Acids Res*., **2015**, *43*, W431. https://doi.org/10.1093/nar/gkv495
158. A. Obarska-Kosinska, A. Iacoangeli, R. Lepore, A. Tramontano. PepComposer: computational design of peptides binding to a given protein surface. *Nucleic Acids Res*., **2016**, *44,* W522. https://doi.org/10.1093/nar/gkw366
159. I. Johansson-Åkhe, C. Mirabello, B. Wallner. InterPep2: global peptide–protein docking using interaction surface templates. *Bioinformatics,* **2020**, *36,* 2458. https://doi.org/10.1093/bioinformatics/btaa005
160. R. V. Honorato, M. E. Trellet, B. Jiménez-García, Jörg J. Schaarschmidt, M. Giulini, V. Reys, P. I. Koukos, J. P. G. L. M. Rodrigues, E. Karaca, G. C. P. V. Zundert, J. Roel-Touris, C. W. V. Noort, Z. Jandová, A. S. J. Melquiond, A. M. J. J. Bonvin. The HADDOCK2.4 web server for integrative modeling of biomolecular complexes. *Nat. Protoc*., **2024**, *19,* 3219. https://doi.org/10.1038/s41596-024-01011-0
161. P. Zhou, B. Jin, H. Li, S. Y. Huang. HPEPDOCK: a web server for blind peptide-protein docking based on a hierarchical algorithm. *Nucleic Acids Res.,* **2018**, *46,* W443. https://doi.org/10.1093/nar/gky357
162. D. A. Antunes, M. Moll, D. Devaurs, K. R. Jackson, G. Lizée, L. E. Kavraki. DINC 2.0: A New Protein-Peptide Docking Webserver Using an Incremental Approach. *Cancer Res*., **2017**, *77*, e55. https://doi.org/10.1158/0008-5472.can-17-0511
163. E. Donsky, H. J. Wolfson. PepCrawler: a fast RRT-based algorithm for high-resolution refinement and binding affinity, estimation of peptide inhibitors. *Bioinformatics*, **2011**, *27*, 2836. https://doi.org/10.1093/bioinformatics/btr498
164. B. Raveh, N. London, L. Zimmerman, O. Schueler-Furman. Rosetta FlexPepDock ab-initio: simultaneous folding, docking and refinement of peptides onto their receptors. *PloS one* **2011**, *6,* e18934. https://doi.org/10.1371/journal.pone.0018934
165. X. Xu, C. Yan, X. Zou. MDockPeP: An ab-initio protein-peptide docking server. *J. Comput. Chem*., **2018**, *39*, 2409. https://doi.org/10.1002/jcc.25555
166. X. Xu, X. Zou. Predicting Protein–Peptide Complex Structures by Accounting for Peptide Flexibility and the Physicochemical Environment. *J. Chem. Inf. Model.,* **2022**, *62*, 27. https://doi.org/10.1021/acs.jcim.1c00836
167. C. E. M. Schindler, S. J. de Vries, M. Zacharias. Fully Blind Peptide-Protein Docking with pepATTRACT. *Structure*, **2015**, *23*, 1507. https://doi.org/10.1016/j.str.2015.05.021
168. M. Kurcinski, M. Jamroz, M. Blaszczyk, A. Kolinski, S. Kmiecik. CABS-dock web server for the flexible docking of peptides to proteins without prior knowledge of the binding site. *Nucleic Acids Res.,* **2015**, *43*, W419. https://doi.org/10.1093/nar/gkv456
169. N. Alam, O. Goldstein, B. Xia, K. A. Porter, D. Kozakov, O. Schueler-Furman. High-resolution global peptide-protein docking using fragments-based PIPER-FlexPepDock. *PLoS. Comput. Biol.,* **2017**, *13*, e1005905. https://doi.org/10.1371/journal.pcbi.1005905
170. Y. Zhang, M. F. Sanner. AutoDock CrankPep: combining folding and docking to predict protein-peptide complexes. *Bioinformatics,* **2019**, *35,* 5121. https://doi.org/10.1093/bioinformatics/btz459
171. A. Khramushin, Z. Ben-Aharon, T. Tsaban, J. K. Varga, O. Avraham, O. Schueler-Furman. Matching protein surface structural patches for high-resolution blind peptide docking. *Proc. Natl. Acad. Sci*., **2022**, *119,* e2121153119. https://doi.org/10.1073/pnas.2121153119
172. E. Ayan. Computational insights into the allosteric behavior of mini proinsulin driven by C peptide mobility. *Sci. Rep*., **2025**, *15*, 8065. https://doi.org/10.1038/s41598-025-92799-8
173. S. Subhadarshini, H. Tandon, N. Srinivasan, R. Sowdhamini. Normal Mode Analysis Elicits Conformational Shifts in Proteins at Both Proximal and Distal Regions to the Phosphosite Stemming from Single-Site Phosphorylation. *ACS omega,* **2024**, *9,* 24520. https://doi.org/10.1021/acsomega.4c00523
174. R. Ma, B. Du, C. Shi, L. Wang, F. Zeng, J. Han, H. Guan, Y. Wang, K. Yan. Molecular basis for the regulation of human phosphorylase kinase by phosphorylation and Ca2+. *Nat. Commun*., **2025**, *16,* 3020. https://doi.org/10.1038/s41467-025-58363-8
175. B. Ganesh, A. Banerjee, L. Guruprasad. Evaluating the ability of in silico identified hit compounds to bind Staphylococcus aureus LcpA(SA) using steered molecular dynamics simulations. *Mol. Divers.,* **2025**. https://doi.org/10.1007/s11030-025-11155-0
176. S. P. D. Sidhanta, R. Sowdhamini, N. Srinivasan. Comparative analysis of permanent and transient domain-domain interactions in multi-domain proteins. *Proteins,* **2025**, *93*, 197. https://doi.org/10.1002/prot.26581
177. E. Ayan, M. Türk, Ö. Tatlı, S. Bostan, E. Telek, B. Dingiloğlu, B. Z. Doğan, M. I. Alp, Ahmet Katı, Gizem Dinler-Doğanay, H. Demirci. X-ray crystallographic and hydrogen deuterium exchange studies confirm alternate kinetic models for homolog insulin monomers. *PloS one*, **2025**, *20*, e0319282. https://doi.org/10.1371/journal.pone.0319282
178. S. Subhadarshini, S. Sahoo, M. K. Jolly, M. Rashid. An integrative molecular systems approach unravels mechanisms underlying biphasic nitrate uptake by plant nitrate transporter NRT1.1. *bioRxiv*. **2025**. https://doi.org/10.1101/2025.01.28.635294
179. D. M. Krüger, A. Ahmed, H. Gohlke. NMSim web server: integrated approach for normal mode-based geometric simulations of biologically relevant conformational transitions in proteins. *Nucleic Acids Res.,* **2012**, *40*, W310. https://doi.org/10.1093/nar/gks478
180. J. R. López-Blanco, J. I. Aliaga, E. S. Quintana-Ortí, P. Chacón. iMODS: internal coordinates normal mode analysis server. *Nucleic Acids Res*., **2014**, *42* (Web Server issue), W271. https://doi.org/10.1093/nar/gku339
181. E. Eyal, G. Lum, I. Bahar. The anisotropic network model web server at 2015 (ANM 2.0). *Bioinformatics*, **2015**, *31*, 1487. https://doi.org/10.1093/bioinformatics/btu847
182. D. Van Der Spoel, E. Lindahl, B. Hess, G. Groenhof, A. E. Mark, H. J. Berendsen. GROMACS: fast, flexible, and free. *J. Comput. Chem.,* **2005**, *26*, 1701. https://doi.org/10.1002/jcc.20291
183. D. A. Case, H. M. Aktulga, K. Belfon, D. S. Cerutti, G. A. Cisneros, V. W. D. Cruzeiro, N. Forouzesh, T. J. Giese, A. W. Götz, H. Gohlke, S. Izadi, K. Kasavajhala, M. C. Kaymak, E. King, T. Kurtzman, T. S. Lee, P. Li, J. Liu, T. Luchko, R. Luo, M. Manathunga, M. R. Machado, H. M. Nguyen, K. A. O'Hearn, A. V. Onufriev, F. Pan, S. Pantano , R. Qi, A. Rahnamoun, A. Risheh, S. Schott-Verdugo, A. Shajan, J. Swails, J. Wang, H. Wei, X. Wu , Y. Wu, S. Zhang, S. Zhao, Q. Zhu, 3rd T. E. Cheatham, D. R. Roe, A. Roitberg, C. Simmerling, D. M. York, M. C. Nagan, Jr. K. M. Merz. AmberTools. *J. Chem. Inf. Model*., **2023**, *63,* 6183. https://doi.org/10.1021/acs.jcim.3c01153
184. B. R. Brooks, 3rd C. L. Brooks, Jr. A. D. Mackerell, L. Nilsson, R. J. Petrella, B. Roux, Y. Won, G. Archontis, C. Bartels, S. Boresch, A. Caflisch, L. Caves, Q. Cui, A. R. Dinner, M. Feig, S. Fischer, J. Gao, M. Hodoscek, W. Im, K. Kuczera, T.

Lazaridis, J. Ma, V. Ovchinnikov, E. Paci, R. W. Pastor, C. B. Post, J. Z. Pu, M. Schaefer, B. Tidor, R. M. Venable, H. L. Woodcock, X. Wu, W. Yang, D. M. York, M. Karplus. CHARMM: the biomolecular simulation program. *J. Comput. Chem.*, **2009**, *30,* 1545. https://doi.org/10.1002/jcc.21287

185. R. Qi, G. Wei, B. Ma, R. Nussinov. Replica Exchange Molecular Dynamics: A Practical Application Protocol with Solutions to Common Problems and a Peptide Aggregation and Self-Assembly Example. *Methods Mol. Biol.*, **2018**, *1777*, 101. https://doi.org/10.1007/978-1-4939-7811-3_5
186. G. Boggarapu, A. Banerjee, L. Guruprasad. Evaluating the ability of in silico identified hit compounds to bind Staphylococcus aureus LcpASA using steered molecular dynamics simulations. *Mol. Divers.,* **2025**. https://doi.org/10.1007/s11030-025-11155-0
187. J. Wang, A. Ishchenko, W. Zhang, A. Razavi, D. Langley. A highly accurate metadynamics-based Dissociation Free Energy method to calculate protein-protein and protein-ligand binding potencies. *Sci. Rep.,* 2022. *12*, **2024**. https://doi.org/10.1038/s41598-022-05875-8
188. M. S. Valdés-Tresanco, M. E. Valdés-Tresanco, P. A. Valiente, E. Moreno. gmx_MMPBSA: A New Tool to Perform End-State Free Energy Calculations with GROMACS. *J. Chem. Theory. Comput.*, **2021**, *17*, 6281. https://doi.org/10.1021/acs.jctc.1c00645
189. D. K. Vo, K. T. L. Trinh. Molecular Farming for Immunization: Current Advances and Future Prospects in Plant-Produced Vaccines. *Vaccines*, **2025**, *13,* 191. https://doi.org/10.3390/vaccines13020191
190. B. Pudhuvai, B. Koul, A. K. Mishra. Insights into the world of edible vaccines: From lab to reality. *Curr. Res. Biotechnol.,* **2025**, *9,* 100290. https://doi.org/10.1016/j.crbiot.2025.100290
191. A. Mozafari, J. Amani, J. S. Shahsavandi, A. Hatef Salmanian. A Novel Multi-Epitope Edible Vaccine Candidate for Newcastle Disease Virus: In Silico Approach. *Iran J. Biotechnol.*, **2022**, *20*, e3119. https://doi.org/10.30498/ijb.2022.298822.3119
192. Y. Devarakonda, A. D. Rajratna, A. Ray, K. Syal. Novel edible multi-epitope vaccine construct against Enterococcus faecalis. *Nucleus*, **2025**, *68*, 113. https://doi.org/10.1007/s13237-024-00478-2
193. C. Campbell, E. Azagra. Edible mRNA vaccine in lettuce chloroplasts. *Nat. Rev. Bioeng.*, **2025**, *3*, 264. https://doi.org/10.1038/s44222-025-00299-1
194. M. May. How mRNA is powering a personalized vaccine revolution. *Nat. Med.,* **2024**, *30*, 2097. https://doi.org/10.1038/d41591-024-00052-y
195. M. G. Jiji, M. A. Ninan, V. P. Thomas, B. T. Thomas. Edible microalgae: potential candidate for developing edible vaccines. *Vegetos*, **2024**, *37*, 788. https://doi.org/10.1007/s42535-023-00636-y
196. Z. T. Buriev, S. E. Shermatov, D. E. Usmanov, M. K. Mirzakhmedov, K. A. Ubaydullaeva, V. S. Kamburova, B. K. Rakhmanov, M. S. Ayubov, A. N. Abdullaev, J. B. Eshmurzaev, B. O. Mamajonov, A. A. Tulanov, A. A. Ismailova, T. A. Petrova, R. J. Rozumbetov, T. U. Aripova, M. I. Muminov, K. Y. Ermatova, D. A. Dalimova, S. U. Turdikulova, A. Abdukarimov, I. Y. Abdurakhmonov. Tomato-made edible COVID-19 vaccine TOMAVAC induces neutralizing IgGs in the blood sera of mice and humans. *Front. Nut.,* **2024**, *10*, 1275307. https://doi.org/10.3389/fnut.2023.1275307
197. A. R. Kumar, S. Ajay, K. Anusha, B. Nair, A. R. Devan, G. Sethi, and L. R. Nath. Emerging Role of Plant-Derived Products in Immunotherapy: Plausible Exposition for HCC Treatment. *bioRxiv*. Liver Cancer Phytomed., **2025**, *2025,* 443.
198. Y. Kang, D. S. Kim, H. Hwang, Y. Kim, Y. Seo, P. Hinterdorfer, K. Ko. Plant-derived recombinant macromolecular PAP-IgG Fc as a novel prostate cancer vaccine candidate eliciting robust immune responses. *Transgenic Res.,* **2025**, *34*, 1. https://doi.org/10.1007/s11248-025-00433-0
199. K. Mazur-Włodarczyk, A. Gruszecka-Kosowska, B. Martire, M. F. Mastrototaro, G. Ottaviano, C. Rizzo, M. Sgrulletti, M. M. D. Giudice, V. Moschese. Sustainable Consumption and Production of Edible Plants in the Context of Reaching the EU Climate Neutrality by 2050: A Literature Review. *Sustainability*, **2024**, *16*, 10822. https://doi.org/10.3390/su162410822
200. D. Montin, V. Santilli, A. Beni, G. Costagliola et al. Towards personalized vaccines. *Front. Immunol.,* **2024**, *15,* 1436108. https://doi.org/10.3389/fimmu.2024.1436108
201. D. C. Koboldt, L. Ding, E. R. Mardis, R. K. Wilson. Challenges of sequencing human genomes. *Brief Bioinform.*, **2010**, *11*, 484. https://doi.org/10.1093/bib/bbq016
202. M. Wang, L. Kurgan, M. Li. A comprehensive assessment and comparison of tools for HLA class I peptide-binding prediction. *Brief Bioinform.*, **2023**, *24*, bbad150. https://doi.org/10.1093/bib/bbad150
203. A. L. Kessler, R. F. A. Pieterman, W. A. S. Doff, K. Bezstarosti, R. Bouzid, K. Klarenaar, D. T. S. L. Jansen, R. J. Luijten, J. A. A. Demmers, S. I. Buschow. HLA I immunopeptidome of synthetic long peptide pulsed human dendritic cells for therapeutic vaccine design. *NPJ Vacc.,* **2025**, *10*, 1. https://doi.org/10.1038/s41541-025-01069-1
204. G. Visalli, A. Laganà, D. Lo Giudice, S. Calimeri, D. Caccamo, A. Trainito, A. D. Pietro, A. Facciolà. Towards a Future of Personalized Vaccinology: Study on Individual Variables Influencing the Antibody Response to the COVID-19 Vaccine. *Vaccines*, **2023**, *11,* 217. https://doi.org/10.3390/vaccines11020217
205. Ö. Türeci, M. Löwer, B. Schrörs, M. Lang, A. Tadmor, U. Sahin. Challenges towards the realization of individualized cancer vaccines. *Nat. Biomed. Eng.,* **2018**, *2,* 566. https://doi.org/10.1038/s41551-018-0266-2
206. P. Navaux, A. Lorenzon, M. Serpa. Challenges in High-Performance Computing. *J. Braz. Comput. Soc.,* **2023**, *29,* 51. https://doi.org/10.5753/jbcs.2023.2219
207. S. Duangdangchote, D. S. Seferos, O. Voznyy. Stability and transferability of machine learning force fields for molecular dynamics applications. *Digital Discovery*, **2024**, *3*, 2177. https://doi.org/10.1039/d4dd00140k
208. P. Kovatch, L. Gai, H. M. Cho, E. Fluder, D. Jiang. Optimizing High-Performance Computing Systems for Biomedical Workloads. IEEE International Symposium on Parallel & Distributed Processing, Workshops and Phd Forum: [proceedings] IEEE International Symposium on Parallel & Distributed Processing, Workshops and Phd F. **2020**, *2020,*183. https://doi.org/10.1109/ipdpsw50202.2020.00040
209. L. Song, G. Bai, X. S. Liu, B. Li, H. Li. Efficient and accurate KIR and HLA genotyping with massively parallel sequencing data. *Genome Res.*, **2023**, *33,* 923. https://doi.org/10.1101/gr.277585.122
210. Q. Zhou, M. Ghezelji, A. Hari, M. K. B. Ford, C. Holley, COVNET Consortium, L. Mirabello, S. Chanock, S. C. Sahinalp, I. Numanagićl. Geny: A Genotyping Tool for Allelic Decomposition of Killer Cell Immunoglobulin-Like Receptor Genes. *bioRxiv*. **2024**. https://doi.org/10.1101/2024.02.27.582413
211. A. Cox, H. Cevik, H. A. Feldman, L. M. Canaday, N. Lakes, S. N. Waggoner. Targeting natural killer cells to enhance vaccine responses. *Trends Pharmacol. Sci.*, **2021**, *42,* 789. https://doi.org/10.1016/j.tips.2021.06.004

212. P. Rettman, M. D. Blunt, R. J. Fulton, A. F. Vallejo, L. Y. Bastidas-Legarda, L. España-Serrano, M. E. Polak, A. Al-Shamkhani, C. Retiere, & S. I. Khakoo. Peptide: MHC-based DNA vaccination strategy to activate natural killer cells by targeting killer cell immunoglobulin-like receptors. *J. Immunother. Cancer,* **2021**, *9*, e001912. https://doi.org/10.1136/jitc-2020-001912
213. A. Conev, R. Fasoulis, S. Hall-Swan, R. Ferreira, L. E. Kavraki. HLAEquity: Examining biases in pan-allele peptide-HLA binding predictors. *iScience*, **2024**, *27,* 108613. https://doi.org/10.1016/j.isci.2023.108613
214. A. Halužan Vasle, M. Moškon. Synthetic biological neural networks: From current implementations to future perspectives. *BioSystems,* **2024**, *237,* 105164. https://doi.org/10.1016/j.biosystems.2024.105164
215. D. Bonnerjee, S. Chakraborty, B. Mukherjee, R. Basu, A. Paul, & S. Bagh. Multicellular artificial neural network-type architectures demonstrate computational problem solving. *Nat. Chem. Biol*., **2024**, *20*, 1524. https://doi.org/10.1038/s41589-024-01711-4
216. P. Stolfi, F. Castiglione, E. Mastrostefano, I. Di. Biase, S. Di Biase, G. Palmieri, & A. Prisco. In-silico evaluation of adenoviral COVID-19 vaccination protocols: Assessment of immunological memory up to 6 months after the third dose. *Front. Immunol*., **2022**, *13*, 998262. https://doi.org/10.3389/fimmu.2022.998262
217. S. Succi, F. Castiglione, M. Bernaschi. Collective Dynamics in the Immune System Response. *Phys. Rev. Lett.,* **1997**, *79,* 4493. https://doi.org/10.1103/PhysRevLett.79.4493
218. Y. Jamali. Modeling the Immune System Through Agent-based Modeling: A Mini-review. *Immunoregulation*, **2024**, *6*, 3. https://doi.org/10.32598/Immunoregulation.6.1.7
219. A. Rezvanian, S. M. Vahidipour, A. M. Saghiri. CaAIS: Cellular Automata-Based Artificial Immune System for Dynamic Environments. *Algorithms,* **2024**, *17*, 18. https://doi.org/10.3390/a17010018
220. F. Chiacchio, M. Pennisi, G. Russo, S. Motta, F. Pappalardo. Agent-based modeling of the immune system: NetLogo, a promising framework. *Biomed. Res. Int.,* **2014**, *2014,* 1. https://doi.org/10.1155/2014/907171
221. K. S. Corbett, D. K. Edwards, S. R. Leist, O. M. Abiona, S. B. Barnum, R. A. Gillespie, S. Himansu, A. Schäfer, C. T. Ziwawo, A. T. DiPiazza, and K. H. Dinnon. SARS-CoV-2 mRNA vaccine design enabled by prototype pathogen preparedness. *Nature,* **2020**, *586,* 567. https://doi.org/10.1038/s41586-020-2622-0
222. U. Sahin, A. Muik, E. Derhovanessian, I. Vogler, L. M. Kranz, M. Vormehr, A. Baum, K. Pascal, J. Quandt, D. Maurus, and S. Brachtendorf. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature,* **2020**, *586,* 594. https://doi.org/10.1038/s41586-020-2814-7
223. P. Tebas, S. Yang, J. D. Boyer, E. L. Reuschel, A. Patel, A. Christensen-Quick, V. M. Andrade, M. P. Morrow, K. Kraynyak, J. Agnes, M. Purwar, A. Sylvester, J. Pawlicki, E. Gillespie, I. Maricic, F. I. Zaidi, K. Y. Kim, Y. Frase. Dia, D. Frase, P. Pezzoli, L. M. Humeau. Safety and immunogenicity of INO-4800 DNA vaccine against SARS-CoV-2: A preliminary report of an open-label, Phase 1 clinical trial. *EClinicalMedicine*, **2021**, *31,* 100689. https://doi.org/10.1016/j.eclinm.2020.100689
224. C. Y. Wang, K. P. Hwang, H. K. Kuo, W. J. Peng, Y. H. Shen, B. S. Kuo J. H. Huang, H. Liu, Y. H. Ho, F. Lin, S. Ding, Z. Liu, H. T. Wu, C. T. Huang, Y. Lee, M. C. Liu, Y. C. Yang, P. L. Lu, H. C. Tsai, C.H. Lee, T. P. Monath. A multitope SARS-CoV-2 vaccine provides long-lasting B cell and T cell immunity against Delta and Omicron variants. *J. Clin. Invest.,* **2022**, *132,* e157707. https://doi.org/10.1172/JCI157707
225. A. S. De Groot, J. Rayner, W. Martin. Modelling the immunogenicity of therapeutic proteins using T cell epitope mapping. *Dev Biol (Basel).,* **2003**, *112,* 71.
226. D. B. Olawade, J. Teke, O. Fapohunda, K. Weerasinghe, S. O. Usman, A. O. Ige, A. C. David-Olawade. Leveraging artificial intelligence in vaccine development: A narrative review. *J. Microbiol. Methods*, **2024**, *224,* 106998. https://doi.org/10.1016/j.mimet.2024.106998