论著·专家述评

人工智能重塑疫苗研发新范式:效率革命与精准设计

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[摘要] 人工智能(artificial intelligence, AI)通过整合深度学习架构与多组学数据,正在系统性地重塑疫苗研发全链条,推动其从传统依赖试错的"经验驱动"模式,向以"数据驱动"和"算法生成"为核心的理性设计新范式转型。尽管面临数据异质性、模型"黑箱"、算法偏见以及监管框架滞后等多重挑战,AI技术通过与免疫机理的深度结合,推动疫苗设计从"结构模拟"向"功能创造"跨越,为疫苗研发提供了全新范式。本综述系统梳理了AI在疫苗研发多个关键环节的创新应用与典型进展,包括疫苗靶标挖掘、抗原设计、疫苗佐剂、工艺开发、临床试验、疫苗犹豫等,尤其汇总了近年来用于疫苗理性设计的相关工具、核心架构、主要特点和典型案例,为后续疫苗开发中AI技术的应用提供借鉴。

[关键词] 人工智能;深度学习;疫苗;佐剂

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Artificial intelligence reshaping vaccine development: a new paradigm of efficiency revolution and precision design

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[**Abstract**] Artificial intelligence (AI) is systematically reshaping the entire vaccine research and development pipeline through integrating deep learning architectures with multi-omics data. This facilitates a paradigm shift from traditional trial-and-error empirical approaches to a novel rational design framework centered on *data-driven* and *algorithm-generated* methodologies. Despite challenges including data heterogeneity, model opacity, algorithmic bias, and lagging regulatory frameworks, AI enables a transformative leap from *structural mimicry* to *functional innovation* in vaccine design *via* deep integration with immunological mechanisms. This review comprehensively analyzes AI applications across key vaccine development stages: target identification, antigen design, adjuvant screening, process optimization, clinical trial design, and vaccine hesitancy mitigation. We particularly summarize recent tools, core architectures, functional features, and representative cases for AI-powered rational vaccine design, providing actionable references for future AI implementation in vaccinology.

[**Key words**] artificial intelligence; deep learning; vaccine; adjuvants

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疫苗是人类公共卫生领域最重大的成就之一,在控制与消除传染病方面发挥着不可替代的作用。传统疫苗研发普遍周期漫长、成本高昂、成功率低。一款疫苗从早期探索到最终上市平均需耗时10年以上,且超过90%的候选疫苗在临床前或临床阶段失败[1]。这一事实凸显当前疫苗研发体系中明显的效率瓶颈和方法局限。人工智能(artificial intelligence, AI)技术发展逐步成为推动疫苗研发范式转型的关键力量。在21世纪初,反向疫苗学开启了基于基因组信息的抗原计算筛选时代。通过对B群脑膜炎奈瑟菌的系统性挖掘,预测并筛选了数百种表面抗原,远超传统手段效率,助力成功研发Bexsero®和Trumenba®这2款创新疫苗。随着深度学习算法的演进与多组学数据的积累,AI在疫苗靶标识别、抗原设计、佐剂开发等方面展现出前所未有的优势,不断推动疫苗研发从"经验驱动"向"数据与模型驱动"演进。本综述系统地梳理了AI在疫苗研发中的应用进展,并展望其发展趋势与挑战。

1 疫苗与疫苗靶标的特点

抗原是能够被免疫系统识别并激发特异性免疫反应的大分子,而表位(又称抗原决定簇)是抗原上被抗体或T细胞受体特异性结合的小片段或空间构象区域,是免疫识别的基本单位[2]。每个抗原通常含有多个表位,其独特的结构特性决定了免疫应答的特异性与强度。在疫苗研发中,疫苗靶标特指那些能够诱导保护性免疫反应的抗原或其关键表位,即保护性抗原与保护性表位[3]。筛选并优化这些保护性成分是疫苗设计的核心环节,它们通过诱导的功能性抗体或细胞免疫有效阻断病原体感染或清除肿瘤细胞。目前广泛应用的重组乙肝疫苗,其成功的关键在于发现了疫苗保护性抗原——乙肝病毒表面抗原HBsAg。同样地,基于反向疫苗技术鉴定出的保护性抗原fHBA、NHBA成功催生了B群脑膜炎奈瑟菌疫苗Bexsero®和Trumenba®。

2 AI在疫苗靶标挖掘中的应用

疫苗靶标的挖掘是疫苗研发的核心环节。基于AI表位预测方法的核心优势是其处理大规模数据集并从中提取复杂生物学规律的能力。目前,以卷积神经网络(convolutional neural network,CNN)、循环神经网络(recurrent neural network,RNN)及其变体长短期记忆网络(long short-term memory,LSTM)、Transformer与图神经网络(graph neural network,GNN)为代表的深度学习架构,已成为驱动该领域发展的关键技术引擎[4]。这些模型挖掘疫苗靶标通常遵循共同的计算学习范式:首先将原始的生物序列或结构数据编码为模型可处理的数值化张量,随后在训练阶段通过多层非线性变换,自动学习从序列特征到免疫学表征的复杂映射关系。这一映射关系的建立依赖损失函数的优化与反向传播算法,目标是使模型能够精准区分表位与非表位。经过训练的模型能够对任意输入的候选肽段或抗原区域,输出其成为免疫表位的概率或免疫原性评分[5-8]。

不同的模型架构因其独特的信息处理机制,在挖掘与验证针对特定病原体或疾病的疫苗靶标时展现出明确优势与价值。CNN擅长捕捉局部序列模式,在整合多源信息进行免疫原性综合评判方面效果显著。DeepImmuno通过整合肽序列信息与HLA背景,采用基于β-二项式分布进行预测。该工具用于登革病毒、SARS-CoV-2病毒及肿瘤新抗原预测,其效能优于普通预测算法[9]。RNN和LSTM因有效建模序列的长程依赖关系,在预测肽段与MHC的连续结合模式中优势明显。MHCnuggets利用LSTM处理长肽,可同时预测常见和罕见的MHC I/II类等位基因的结合力。基于该模型在肿瘤基因组图谱(The Cancer Genome Atlas,TCGA)涵盖的26种癌症的高通量分析中,发现了新抗原负载与$CD8^+$T细胞浸润的显著关联[10]。Transformer架构通过自注意力机制实现序列上下文感知,深度解析氨基酸残基间相互作用。基于此架构可采用多实例学习框架,解析卷积质谱数据中肽段与MHC等位基因的对应关系,结合在蛋白质序列的自监督预训练,在MHCⅡ类表位与细胞表面呈递预测上优势突出[11]。比如基于Transformer的deepBCE-Parasite,从肝片形吸虫亮氨酸氨基肽酶(leucine aminopeptidas,LAP)中成功挖掘出7个保护性表位,为应对结构复杂寄生虫疫苗提供基础[12]。

GNN及相关图计算方法将分析维度从序列延伸至三维空间,直接处理结构图或序列图谱以捕捉构象依赖性表位。比如,GraphBepi整合了AlphaFold2预测的蛋白质三维结构与ESM-2序列表征,通过GNN与BiLSTM分别捕捉空间结构与序列信息,在标准测试集中其AUC与AUPR值较仅基于序列方法分别提升5.5%

与44.0%[13]。BigMHC方法包含一个由7个泛等位基因深度学习神经网络组成的集合,先用质谱鉴定的肽-MHC洗脱配体数据训练这些网络,并用抗原特异的免疫反应分析数据使其进行迁移学习,从而显著提高MHC Ⅰ类表位呈递预测精度,为解决个性化肿瘤疫苗新抗原表位筛选提供强大工具[14]。通过整合免疫信息学预测工具与分子动力学模拟,从tRNA编码肽(tRNA-encoded peptide,tREP)中筛选并验证了针对Mamastrovirus 3和Norovirus GⅡ的潜在表位疫苗,为病毒疫苗研发提供了新思路[15]。AI正通过强大的模式识别与预测能力,快速革新疫苗靶标发现的方法,显著提升了研发的精准度和效率。

3 AI在疫苗抗原设计中的应用

抗原结构决定了其免疫原性,因此对于抗原特别是蛋白抗原结构的精准认识是疫苗设计的关键。除了直接通过X晶体衍射、冷冻电镜等技术测定抗原结构外,抗原结构的精准预测对疫苗的设计和优化尤为重要。通过对蛋白质结构进行精准预测,AI加速了疫苗的设计与优化进程。蛋白质结构预测主要基于3种核心理论框架:比较建模、折叠识别与从头预测[16-18]。

比较建模通过同源模板结构和序列比对构建抗原三维模型,适用于具有高相似性模板的抗原蛋白设计[19-20]。AlphaFold 2通过注意力机制神经网络精准预测残基间距离与二面角(两个氨基酸残基平面的夹角),实现了从序列到结构的高精度预测,显著提升了抗原尤其是孤儿蛋白(orphan protein)的结构预测精度[21-24]。折叠识别基于蛋白质折叠类型的保守性,将目标抗原序列与已知结构库进行匹配,适用于序列相似性低但可能具有类似三维折叠的抗原识别,有助于发现远缘同源结构[25]。ThreaderAI通过将模板-查询序列比对问题构建为视觉像素分类任务,整合序列谱、预测残基接触图等多维特征,显著提升远缘同源蛋白的结构对齐精度。其采用的深度残差神经网络能够有效解析弱同源信号,为缺乏近缘同源模板的抗原提供高精度的三维结构预测[26]。

而对于无模板或模板信息极少的场景,从头预测方法通过物理能量函数与构象采样直接预测结构,为全新抗原设计提供了可能[27-29]。具体而言,DMPfold通过深度学习综合预测原子间距离、主链氢键网络等多源结构约束,以迭代方式构建高精度蛋白结构模型,适用于针对序列多样性高、同源性低的病毒表面蛋白进行保守表位鉴定与构象稳定化设计,大幅扩展可预测结构的抗原范围[30]。RoseTTAFold通过其三通道神经网络,依次处理一维序列、二维距离图谱与三维坐标,通过跨层次信息传递与精修,能够快速准确地预测抗原及其复合物的三维结构[31]。trRosettaX-Single引入监督变换器蛋白质语言模型获取高质量的序列嵌入,并借助知识蒸馏技术将大模型能力迁移至轻量模型,在保证效率的同时维持高性能。该融合策略通过多尺度网络进一步优化,显著提高了残基间距离与方向的预测准确度,从而为大规模抗原结构的快速筛选与评估提供了高效可靠的技术路径[32]。

借助AI对疫苗抗原精准预测,抗原设计在全流程计算化、个体化、抗原组装等方面得到发展。AstraMEV通过系统筛选56个传染性支气管炎病毒(infectious bronchitis virus,IBV)基因组,鉴定其保守的B、T细胞表位,实现了多表位疫苗全流程计算设计[33]。在个性化疫苗领域,AI技术通过分析复杂的生物数据集,精准设计靶向肿瘤相关抗原与新生抗原的表位、优化mRNA或DNA疫苗序列,预测特异性免疫反应,提高疫苗设计的精准度和治疗效果[34]。在抗原组装与载体设计方面,基于Rosetta程序化以三聚体蛋白为模块成功构建蛋白质纳米笼,突破天然蛋白质组装的对称性限制,提供了全新的、可精准设计的纳米疫苗平台[35]。层次化伪对称计算方法成功构建240、540、960个亚基组成的超大型20面体纳米笼,突破了传统严格对称性的限制,显著拓宽了可设计蛋白质纳米结构的尺寸与复杂度范围[36]。流感病毒血凝素抗原偶联至基于AI设计的自组装蛋白纳米颗粒,在小鼠中诱导出强效中和抗体应答[37]。

4 AI在疫苗佐剂筛选中的应用

佐剂是疫苗保护性免疫应答必要组分,AI技术正凭借其多维数据整合与分析能力,推动该领域迈向新突破。目前多种AI算法已深度融合至佐剂的发现流程中。贝叶斯主动学习(Bayesian active learning)融合主动学习与高通量计算,构建了可自我迭代的筛选循环,能以最低计算成本高效锁定目标分子;已成功用于高通量筛选免疫佐剂,验证可能激活关键免疫通路的候选分子,加速高效佐剂的发现[29]。此外,基于定量构效关系(quantitative structure-activity relationship,

QSAR)的建模方法通过特征选择与机器学习分类,高效预测候选分子的生物活性,在CDK2抑制剂筛选中表现出高分类准确率,用于疫苗佐剂的虚拟筛选与早期活性-安全性评估[38]。在机制研究方面,“计算预测-实验验证”整合策略通过高分辨液相色谱-质谱联用(high-resolution liquid chromatography-mass spectrometry, HR-LC/MS)鉴定活性成分,并利用Cytoscape构建“成分-靶点-通路”网络,预测其对Toll样受体(Toll-like receptor,TLR)等信号通路的调控潜力,最终通过体内实验进行功能确认[39]。在应用研究方面,基于分子设计与机器学习技术,研究人员从46种TLR靶向激动剂中筛选出两种新型广谱纳米佐剂,在黑色素瘤与乳腺癌模型中均能激活多个TLR通路,显著抑制肿瘤生长与转移[40]。以TLR4为靶点,基于其结构模拟、分子对接和动力学模拟,优选出苯甲酰化菊糖作为高效激动剂,其纳米制剂在体内诱导的抗体与T细胞应答均优于传统铝佐剂[41]。

5 AI在疫苗研发其它环节中应用

在疫苗工艺开发阶段,AI可用于分析生产数据,从而优化关键工艺参数[42]。计算模型能够模拟疫苗在体内的释放动力学与免疫应答动态,为控释剂型和新型递送平台的设计提供理论指导[43]。在安全性评价环节,结合AI的预测能力,研究者可通过整合实验数据、计算模型与迭代优化策略,评估疫苗的安全性。2024年美国食品药品监督管理局宣布允许采用基于AI的毒性计算机模型,辅以体外细胞系和类器官毒性测试,部分替代传统的动物安全性评价实验。

在临床试验研究环节引入AI可优化关键流程,涵盖患者招募、试验设计、过程监测与数据分析等多个方面。预测分析与数据建模有助于改进试验方案设计、患者筛选标准及终点评估方法,从而提升试验的整体成功率。AI系统能够实时监测试验进展,早期识别不良事件,并提供实时数据分析,支持对试验设计的动态调整。此外,借助对电子健康记录和基因组数据的智能解析,AI可精准识别适合参与临床试验的患者群体,显著提高招募效率,并增强研究队列的多样性与代表性[44]。AI算法还可用于模拟不同试验场景、预测潜在结果并确定最佳研究终点,从而大幅降低疫苗开发的周期与成本[45]。

AI在疫苗领域的应用还深入到卫生信息沟通。借助情感分析与自然语言处理技术,研究人员能够实时监测并解析公众舆论动向,精准识别误导性信息,从而有效解决疫苗犹豫问题。AI驱动的聊天机器人及对话系统可提供实时、个性化的信息支持,有助于澄清误解、减轻公众对疫苗接种的顾虑。这些技术不仅提升了民众对疫苗的认知与信任水平,也为实现更高的疫苗免疫覆盖率奠定了重要基础。综上所述,AI已渗透至疫苗研发的靶标挖掘、抗原设计、佐剂筛选及临床试验优化等全链条环节(表1)。

6 挑战与机遇

当前疫苗研发所依赖的数据涵盖基因组序列、蛋白质组学、蛋白质结构、免疫反应谱及临床结果等多个模态,具有单细胞、空间和时间等多个尺度特征。然而,这些数据往往呈现碎片化、不完整或存在偏倚,且缺乏统一的质量控制,从而影响AI模型的鲁棒性与可靠性[45]。训练数据中对某些人群覆盖不足可能引入算法偏见,导致疫苗在不同群体中的效力出现差异,进而引发公平性质疑。此外,深度学习等复杂算法因其架构与决策过程不透明,常被视为“黑箱”,使得疫苗设计建议的合理性难以得到充分解释[46]。伦理与监管同样是当前的重要挑战,疫苗具有显著的公共健康属性与规模效应,AI应用必须妥善应对涉及公平性、透明度、隐私保护与个体自主权等一系列伦理议题。美国食品药品监督管理局、欧洲EMA等监管机构针对AI驱动疫苗研发的指导框架仍处于初步构建阶段,亟需进一步明确与拓展[47]。

为应对上述挑战,AI驱动的疫苗抗原设计正经历从“结构模拟”到“功能创造”的范式跃迁。当前的核心挑战在于突破静态结构的局限,将动态免疫识别、抗原加工递呈等生物学机制转化为可计算的设计原则。下一代AI模型需具备融合多组学数据与免疫规则的能力,在原子维度与系统层面协同优化,精准平衡免疫原性、安全性与成药性。这要求生成式AI与免疫学机理的深度融合,实现从“计算机辅助设计”向“AI理性设计”的根本性转变。同时,亟需同步构建跨学科协作生态与适应性监管框架,以破解数据质量、模型可解释性及伦理公平性等核心瓶颈。最终,AI将作为关键使能技术,助力人类构筑起更精准、更迅捷的疫苗研发新体系。

利益冲突 本文所有作者声明不存在利益冲突

表1 AI驱动的疫苗理性设计进展

Table 1 AI-driven advances in rational vaccine design

Tool name	Core architecture	Input type	Main features	Validation case
DeepImmuno	CNN	Peptide sequence	Employs β-binomial distribution	Dengue virus, cancer neoantigens, SARS-CoV-2 [9]
MHCnuggets	LSTM	Peptide sequence, MHC Ⅰ/Ⅱ alleles	Single-model universal prediction	Neoantigen prediction across 26 cancer types [10]
BERTMHC	Transformer	Peptide sequence, MHC sequence	Excellent performance in MHC-II binding and presentation prediction	Improved accuracy in predicting MHC-II molecular interactions [11]
GraphBepi	EGNN, BiLSTM	Protein structure, ESM-2 sequence	Integrates 3D structural and sequence information	Validated on B-cell epitope datasets [13]
BigMHC	DNN Ensemble	Peptide–MHC mass-spectrometry data, etc	Integrates seven pan-allelic models	Epitope presentation prediction on 45 000 MHC-eluted ligand samples mixed with 900 000 negative samples [14]
deepBCE-Parasite	Transformer	Peptide sequence	Optimized for parasitic pathogens	B-cell epitope prediction for Fasciola hepatica LAP protein [12]
ThreaderAI	Deep ResNet	structural features	Improved accuracy for distantly homologous protein structure modeling	Demonstrated excellent performance across multiple benchmarks [26]
DMPfold	Iterative Modeling	Amino acid sequence	Low sequence-number requirement	High-accuracy model prediction based on CASP12 domain sequences [30]
RoseTTAFold	Three-track Neural Network	Amino acid sequence	Integration of sequence and structural information	Achieved structure-prediction accuracy close to DeepMind in CASP14; aids in solving modeling challenges [31]
trRosettaX-Single	Supervised transformer protein language model	Amino acid sequence	Optimized for single-sequence input	Prediction accuracy surpasses AlphaFold2 and RoseTTAFold on orphan and designed proteins [32]
AstraMEV	RFdiffusionProteinMPNN	Genomic sequence	Conservative epitope screening	Multi-epitope vaccine design against infectious bronchitis virus [33]
Rosetta	Physics-based energy function	Protein structure	Rational design of self-assembling protein nanostructures	Design of symmetric four-component protein nanocages [35]
Bayesian Active Learning	Bayesian optimization	Material descriptors	Active learning cycle	Successfully applied to screening 3 119 two-dimensional hexagonal binary compounds [29]
QSAR moodel	support vector machine	Compound structural descriptors	Uses SA algorithm to screen the most discriminative molecular descriptors	Applied to classification and activity prediction of CDK2 inhibitors [38]

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