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AI-Driven Predictive Modeling for Accelerated Development of Cell and Gene Therapy Products

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ABSTRACT

Cell and gene therapies (CGTs) offer curative potential for intractable diseases but face significant hurdles, including manufacturing costs exceeding $400,000 per dose, 40% clinical hold rates for IND applications, and lengthy vein-to-vein timelines. Artificial intelligence (AI) and machine learning (ML) are emerging as critical tools to optimize the CGT lifecycle. This review examines predictive modeling applications in target identification, vector engineering, manufacturing, and clinical outcome prediction.

We discuss key methodologies such as deep learning, protein language models, and reinforcement learning. Case studies highlight the efficacy of these tools, notably Dyno Therapeutics' AAV capsid engineering, which increased viability from <1% to 55%, and the AIDPATH digital twin initiative for decentralized manufacturing. Additionally, the review navigates the evolving regulatory landscape, including the FDA's 2025 draft guidance on AI credibility.

By integrating multi-omics data, quantum computing, and explainable AI (XAI), the next generation of CGTs aims for enhanced safety and scalability. This article provides a comprehensive roadmap for stakeholders to leverage AI in accelerating the development of advanced therapeutic medicinal products (ATMPs) while addressing essential ethical and data governance frameworks.

Keywords: Artificial Intelligence, Machine Learning, Cell and Gene Therapy, CAR-T Cell Manufacturing, AAV Capsid Engineering, Predictive Modeling, Digital Twin, CRISPR Guide RNA Design, Process Analytical Technology, Computer System Validation, Explainable AI, FDA Regulatory Science, Quality by Design, Good Manufacturing Practice, Immunogenicity Prediction

1. INTRODUCTION

Cell and gene therapies (CGTs) have emerged as one of the most promising frontiers in modern medicine, offering the potential for curative treatments across a broad spectrum of genetic disorders, cancers, and degenerative diseases [1]. Unlike conventional small-molecule drugs or biologics that manage symptoms, CGTs aim to address the root cause of disease at the cellular or genetic level. According to FDA data, the agency has approved a growing number of CGT products, with 35 approved as of 2024, and projections suggest 10 to 20 new approvals per year by 2025 [2]. The global cell and gene therapy market was valued at approximately $14.2 billion in 2023 and is projected to exceed $80 billion by 2032, reflecting a compound annual growth rate (CAGR) of approximately 22% [2]. Despite this progress, CGT development remains encumbered by significant technical, manufacturing, and regulatory challenges that limit the pace at which these therapies reach patients.

The development of a CGT product involves a complex, multi-step pipeline that differs fundamentally from traditional drug development. For gene therapies, this includes the identification of therapeutic targets, the design and engineering of viral or non-viral delivery vectors, preclinical efficacy and safety testing, scalable manufacturing under good manufacturing practice (GMP) conditions, and multi-phase clinical trials [3]. For cell therapies such as chimeric antigen receptor T-cell (CAR-T) products, additional layers of complexity arise from the autologous nature of many products, where each patient's cells must be individually harvested, genetically modified, expanded, and reinfused [4]. The manufacturing cost for a single autologous CAR-T product can exceed $400,000, creating significant barriers to widespread access [5].

The traditional approach to CGT development relies heavily on iterative laboratory experimentation, empirical optimization, and extensive trial-and-error processes. Designing an adeno-associated virus (AAV) capsid with optimal tissue tropism, for instance, involves screening vast combinatorial libraries of capsid variants. The combinatorial sequence space for a 28-amino acid capsid segment alone exceeds 10^{36} possible variants, a process that can take years using conventional directed evolution methods and yields functional capsids at rates below 1% [6]. Similarly, optimizing CAR construct design requires balancing multiple interrelated parameters, including antigen binding affinity, co-stimulatory domain selection (CD28 vs. 4-1BB), hinge

length, and tonic signaling characteristics, each of which influences therapeutic efficacy and safety in ways that are difficult to predict empirically [7].

Artificial intelligence (AI) and machine learning (ML) offer a paradigm shift in addressing these challenges. AI encompasses a broad range of computational techniques that enable machines to learn from data, identify patterns, and make predictions or decisions with minimal human intervention [8]. In the context of CGT development, AI-driven predictive modeling can dramatically reduce the time and cost associated with vector design, process optimization, and clinical outcome prediction. Deep learning architectures, including convolutional neural networks (CNNs), recurrent neural networks (RNNs), and transformer models, have demonstrated remarkable capabilities in processing complex biological data such as protein sequences, genomic information, and single-cell transcriptomic profiles [9].

The objective of this review is to provide a comprehensive examination of AI-driven predictive modeling applications across the cell and gene therapy development lifecycle. We discuss the foundational AI methodologies employed, review critical applications in vector engineering, cell manufacturing, and clinical translation, present case studies demonstrating real-world impact, and address the ethical and regulatory landscape. By synthesizing the current literature and identifying gaps, this work aims to provide a practical roadmap for researchers, engineers, and regulatory professionals engaged in advancing CGT products through the integration of artificial intelligence.

2. LITERATURE REVIEW

2.1 Overview of the Cell and Gene Therapy Landscape

Cell and gene therapies encompass a diverse array of therapeutic modalities. Gene therapies involve the introduction, alteration, or replacement of genetic material within a patient's cells to treat or prevent disease. These therapies can be delivered using viral vectors such as AAV, lentivirus, and adenovirus, or through non-viral methods including lipid nanoparticles and electroporation [10]. Cell therapies involve the transplantation of human cells to replace or repair damaged tissue or to augment immune function. CAR-T cell therapy, in which a patient's T-cells are genetically engineered to express chimeric antigen receptors targeting specific tumor antigens, has achieved remarkable clinical success in hematologic malignancies [11]. As of late 2024, six

CAR-T products had received FDA approval, treating conditions including B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, and multiple myeloma [2].

Despite clinical successes, the CGT field faces substantial hurdles. Manufacturing complexity and cost remain primary barriers. For autologous CAR-T therapies, the vein-to-vein time from patient leukapheresis to product infusion typically ranges from two to four weeks, during which manufacturing failures can occur in an estimated 1-14% of cases depending on patient disease burden and manufacturing platform [5]. Gene therapy vectors, particularly AAV, face challenges related to pre-existing immunity in an estimated 50-70% of the human population, limited packaging capacity of approximately 4.7 kilobases, and the need for tissue-specific targeting [6]. Furthermore, according to FDA data, approximately 40% of all clinical holds in recent years have been issued for CGT studies. Among the 585 CGT INDs newly submitted between 2021 and 2023, approximately 126 (roughly 20%) were placed on clinical hold within the initial 30-day review period, despite CGTs constituting approximately 8% of all drugs in development [2]. These statistics highlight the safety concerns inherent to these products and the urgent need for predictive tools that can identify potential issues earlier in the development lifecycle.

2.2 AI Methodologies Applicable to CGT Development

The AI methodologies most relevant to CGT development span several categories of computational approaches. Machine learning algorithms, including supervised methods such as support vector machines (SVMs), random forests, and gradient boosting, are employed for classification and regression tasks in biological data analysis [8]. Unsupervised learning techniques, including k-means clustering and principal component analysis, enable the identification of hidden patterns in high-dimensional datasets such as single-cell RNA sequencing data [12].

Deep learning architectures have proven particularly powerful for CGT applications. Convolutional neural networks excel at processing spatial and structural data, making them suitable for analyzing protein structures and molecular interactions [9]. Recurrent neural networks and their variants, including long short-term memory (LSTM) networks, are effective for sequential data analysis, relevant to nucleotide sequence optimization and temporal bioprocess data [13]. Transformer models, originally developed for natural language processing, have been adapted for biological sequence analysis through protein language models such as ESM

(Evolutionary Scale Modeling) and genomic language models such as Evo, which have been applied to predict protein function and design novel sequences [14].

Generative AI models, including generative adversarial networks (GANs) and variational autoencoders (VAEs), enable the de novo design of biological molecules by learning the underlying distribution of functional sequences and generating novel candidates with desired properties [15]. Reinforcement learning, which optimizes decision-making through reward-based feedback, has been applied to adaptive bioprocess control and clinical trial design optimization [5]. These diverse AI approaches are increasingly being combined into integrated pipelines that can address multiple aspects of CGT development simultaneously.

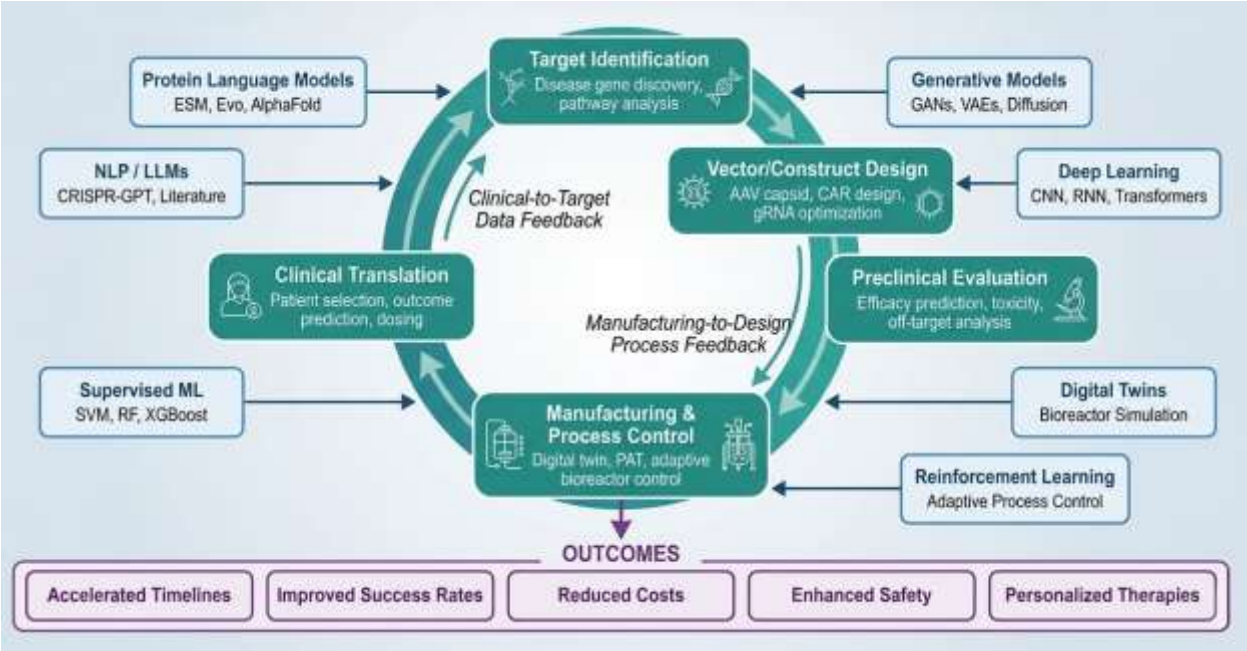

Figure 1. *The Interconnected, AI-Powered CGT Development Lifecycle*
An iterative cycle where AI continuously optimizes stages and drives feedback from improved outcomes

2.3 Data Sources and Infrastructure for AI in CGT

The effectiveness of AI models in CGT development is fundamentally dependent on the quality, diversity, and volume of training data. Key data sources include genomic and transcriptomic databases such as the Human Genome Project, ENCODE, and single-cell atlases that provide reference gene expression profiles for healthy and diseased tissues [16]. Protein structure databases, including the Protein Data Bank (PDB) and AlphaFold Protein Structure Database, provide three-dimensional structural information critical for vector engineering and therapeutic

protein design [17]. Chemical and bioactivity databases such as ChEMBL and PubChem supply compound-activity relationship data relevant to small-molecule components used in CGT manufacturing media and formulations.

Clinical data from electronic health records (EHRs), clinical trial registries (ClinicalTrials.gov), and real-world evidence (RWE) platforms provide patient-level information on treatment responses, adverse events, and long-term outcomes [18]. Manufacturing process data, including bioreactor sensor measurements, analytical quality control results, and batch records, constitute an increasingly important data source for AI-driven process optimization [5]. The integration of these heterogeneous data types through multi-omics approaches and federated learning architectures represents a significant frontier for AI in CGT, enabling comprehensive modeling of the relationships between product attributes, process parameters, and clinical outcomes [19].

2.4 Model Training, Validation, and Optimization Strategies

Training AI models for CGT applications involves several critical steps. Data preprocessing, including normalization, missing value imputation, and feature engineering, is essential for ensuring data quality and model performance [8]. For biological sequence data, preprocessing may involve encoding strategies such as one-hot encoding, k-mer frequency representation, or learned embeddings from pre-trained language models [14]. Feature selection methods, including recursive feature elimination and LASSO regularization, help identify the most informative variables while reducing dimensionality and overfitting risk.

Model validation is paramount in CGT applications where predictions directly impact patient safety. Cross-validation strategies, including k-fold and leave-one-out approaches, are standard for internal validation [8]. External validation on independent datasets is critical for assessing generalizability, particularly given the patient-to-patient variability inherent in autologous cell therapies [20]. Performance metrics including accuracy, precision, recall, F1-score, area under the receiver operating characteristic curve (AUC-ROC), and mean squared error are employed depending on the prediction task. Importantly, model interpretability techniques such as SHapley Additive exPlanations (SHAP) and Local Interpretable Model-agnostic Explanations (LIME) are increasingly required to provide mechanistic understanding of model predictions, which is essential for regulatory acceptance [21].

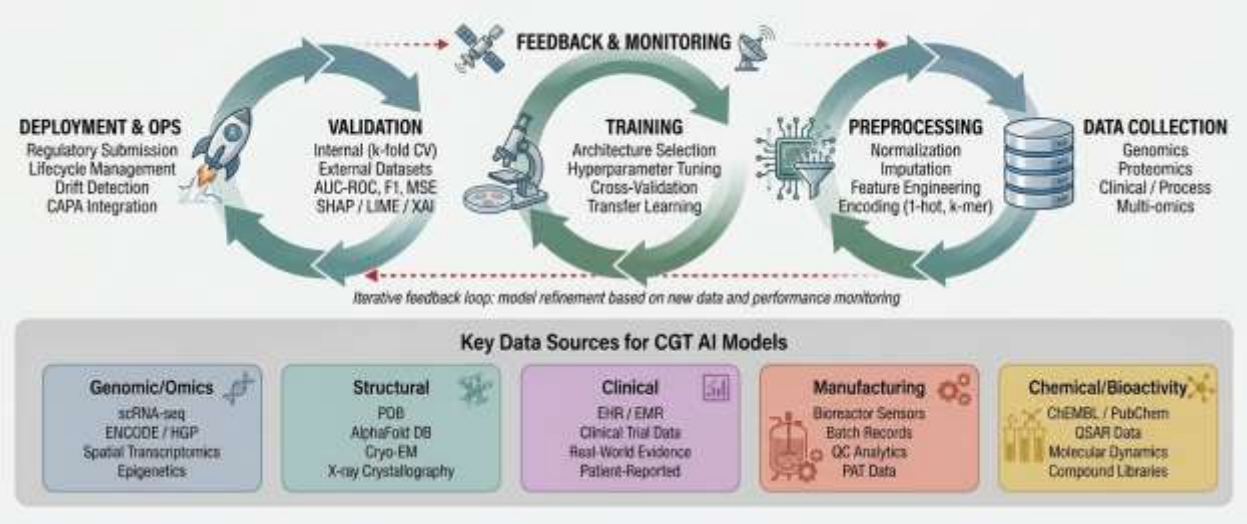

Figure 2. *AI Model Training, Validation, and Optimization Workflow for CGT Applications*

3. APPLICATIONS IN GENE THERAPY

3.1 AI-Driven AAV Capsid Engineering

Adeno-associated virus vectors represent the most widely used platform for in vivo gene therapy. As of December 2024, the FDA had approved seven AAV-mediated gene therapy drugs, and approximately 331 AAV gene therapy clinical trials were listed on ClinicalTrials.gov, accounting for approximately 12% of all gene therapy trials worldwide [6]. However, natural AAV serotypes exhibit limitations including pre-existing neutralizing antibodies in 50-70% of the human population, suboptimal tissue tropism, and a limited single-stranded DNA packaging capacity of approximately 4.7 kilobases [22]. Engineering improved AAV capsids through conventional directed evolution methods is constrained by the vast sequence space: a 28-amino acid segment of the VP1 capsid protein alone represents a combinatorial space exceeding 10^{36} possible variants, of which only a minuscule fraction are functional [22].

Machine learning has transformed AAV capsid engineering by enabling the prediction of capsid viability and function from sequence data alone. In a landmark study published in Nature Biotechnology, Bryant et al. (2021) at Dyno Therapeutics, in collaboration with Google Research and Harvard's Wyss Institute, applied deep learning to design 201,426 variants of the AAV2 capsid protein, yielding 110,689 viable engineered capsids [22]. Of these, 57,348 variants surpassed the average diversity of natural AAV serotype sequences, with some containing up to 29 amino acid substitutions in the targeted 28-residue region. This ML-guided approach achieved a viability rate

of approximately 55%, compared to less than 1% with conventional random mutagenesis, representing a greater than 50-fold improvement in design efficiency [22]. The models were trained on relatively modest initial datasets and employed multiple neural network architectures to predict packaging viability across highly diverse sequences.

More recently, the Fit4Function framework published in Nature Communications by Zhu et al. (2024) demonstrated a generalizable ML approach for engineering multi-trait AAV capsids that simultaneously optimize for tissue targeting, manufacturability, and immune evasion [23]. By combining six separate sequence-to-function models trained on mouse in vivo and human in vitro screening data, the team designed a multi-trait capsid library in which 88% of variants met all six predetermined functional criteria, including liver tropism and manufacturing yield. Notably, models trained exclusively on rodent data accurately predicted capsid biodistribution in non-human primates, suggesting robust cross-species generalizability of ML-guided vector engineering approaches.

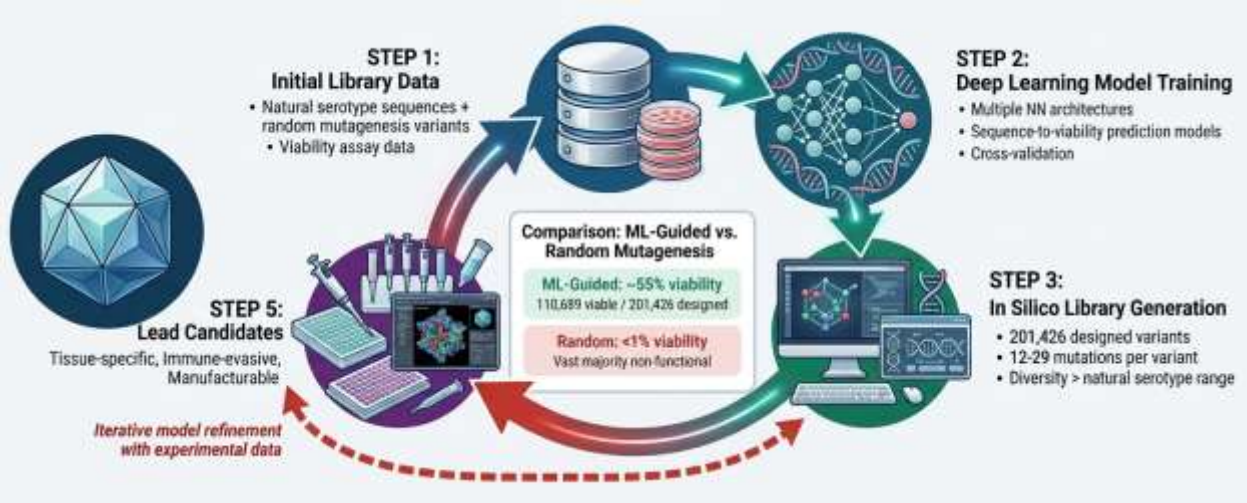

Figure 3. *ML-Guided AAV Capsid Engineering Pipeline: from sequence library design through functional screening and iterative model refinement*

3.2 CRISPR Guide RNA Design and Off-Target Prediction

Gene editing technologies, particularly CRISPR-Cas systems, represent another critical area where AI is accelerating CGT development. Designing effective guide RNAs (gRNAs) that maximize on-target editing efficiency while minimizing off-target activity is a complex optimization problem that has benefited significantly from ML approaches [24]. Early algorithms for gRNA design relied on hard-coded binding rules, but newer models based on deep learning, trained on large-scale

experimental data, substantially outperform rule-based approaches. Examples include the ML model Azimuth 2.0 and the deep learning models DeepCRISPR and DeepSpCas9, which predict gRNA efficiency and specificity with high accuracy [24].

A notable advancement is CRISPR-GPT, developed at Stanford University, which integrates 11 years of expert knowledge from published CRISPR experiments into an AI agent capable of automating experimental design [25]. CRISPR-GPT functions as an interactive assistant that predicts optimal editing strategies, identifies potential off-target sites, and assesses the likelihood of unintended genetic effects. By encoding domain expertise into a large language model, CRISPR-GPT lowers the barrier to effective use of gene editing technology and has the potential to significantly accelerate the design phase of gene therapy development.

3.3 AI for Reducing Immunogenicity of Gene Therapy Products

Immunogenicity of therapeutic proteins and viral vectors remains a critical challenge in gene therapy. AI-driven approaches are being developed to design therapeutic proteins with reduced immunogenic potential while maintaining functional activity. In a 2025 study led by Xiaojing Gao at Stanford University's School of Engineering, a team demonstrated the use of three independent machine learning algorithms to engineer zinc finger proteins for gene therapy applications with reduced predicted immunogenicity [26]. The first algorithm predicted new DNA-binding targets for zinc finger arrays, the second algorithm (MARIA, developed by co-author Ash Alizadeh) screened for protein junctions unlikely to trigger immune detection, and the third predicted overall protein function. According to lead author Eric Wolsberg, the AI-enhanced zinc fingers increased gene production by two- to six-fold compared to original proteins in lab-based validation tests while maintaining low predicted immunogenicity, representing a significant advance toward safer gene therapy constructs [26].

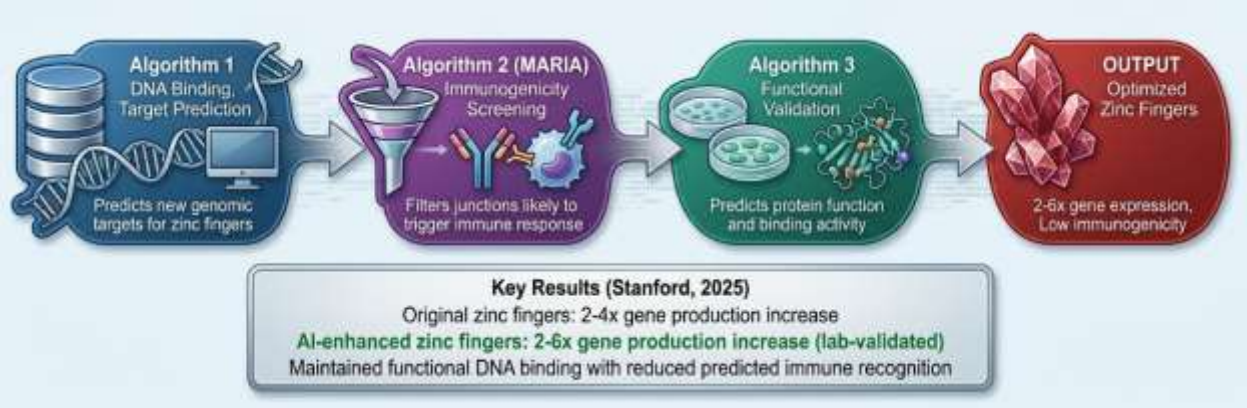

Figure 4. *Multi-Algorithm AI Approach for Low-Immunogenicity Therapeutic Protein Design*

4. APPLICATIONS IN CELL THERAPY

4.1 AI-Optimized CAR Design and Engineering

Chimeric antigen receptor T-cell therapy has achieved remarkable clinical success but continues to face challenges in CAR construct design optimization. The design of an effective CAR requires balancing multiple interrelated parameters, including single-chain variable fragment (scFv) binding affinity, hinge and transmembrane domain selection, co-stimulatory domain configuration, and signaling characteristics [7]. Tonic signaling, the spontaneous activation of CAR molecules in the absence of antigen, represents a particularly significant design challenge that can lead to T-cell exhaustion, reduced persistence, and diminished anti-tumor efficacy [27].

The CAR-Toner platform, developed by Qiu et al. (2024) at ShanghaiTech University, represents a pioneering AI-driven approach to predicting and optimizing CAR tonic signaling [27]. CAR-Toner computes a Positively Charged Patch (PCP) score for CAR protein sequences, a metric that correlates with antigen-independent CAR signaling levels. The platform analyzed PCP scores across four antibody domain types: single-chain variable fragments (scFv), camelid-derived nanobodies (VHH), shark-derived nanobodies (VNAR), and variable lymphocyte receptors (VLR). The analysis revealed that VHH-based CARs consistently fell within the optimal signaling range, providing a computational rationale for domain selection that previously relied on empirical testing [27]. This AI-driven approach substantially reduces the trial-and-error cycles traditionally required for CAR optimization.

Beyond tonic signaling, AI is being applied to predict CAR-T cell efficacy through analysis of the immunological synapse. Research has demonstrated that in vitro ML-based measurements of

CAR-T immunological synapse quality correlate with patient clinical outcomes, providing a potential predictive biomarker that could inform manufacturing and patient selection decisions before treatment [28]. Deep learning models using computer vision have been employed to analyze the morphology and phenotype of CAR cells, while natural language processing techniques extract relevant information from clinical reports to build comprehensive predictive models of treatment response [29].

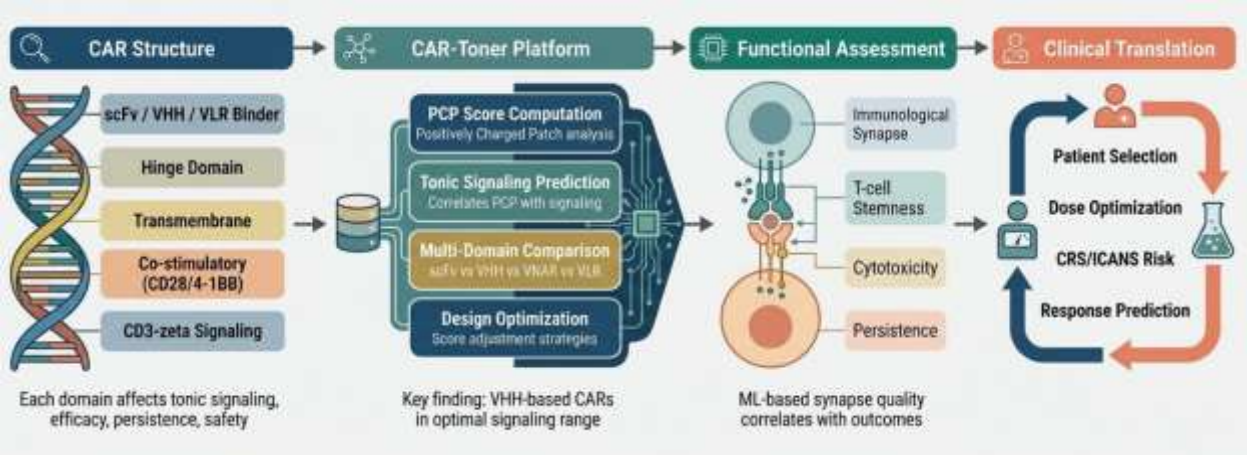

Figure 5. *AI-Driven CAR Construct Optimization Workflow: from sequence analysis through tonic signaling prediction, immunological synapse assessment, and clinical outcome modeling*

4.2 AI-Enhanced Cell Manufacturing and Process Control

The manufacturing of cell therapy products, particularly autologous CAR-T cells, presents unique challenges that are well-suited to AI-driven optimization. The multi-step manufacturing process, encompassing T-cell isolation, activation, genetic modification, expansion, and formulation, involves numerous critical process parameters (CPPs) that influence product quality attributes (CQAs) [5]. Patient-to-patient variability in starting material quality adds an additional layer of complexity that makes standardized manufacturing protocols suboptimal [4].

The AIDPATH (Artificial Intelligence-Driven, Decentralized, Patient-centric, Automated CAR-T cell manufacturing) project, funded by the European Union, exemplifies the integration of AI into CGT manufacturing [5]. AIDPATH is developing a comprehensive platform that employs digital twin technology to model the T-cell expansion bioreactor in real-time. The digital twin combines mechanistic knowledge of cell biology with real-time sensor data to simulate and predict cell growth trajectories. Machine learning soft sensors process streaming bioreactor data, including dissolved oxygen, pH, lactate, and glucose concentrations, to forecast cell expansion over one- to

two-day horizons. These predictions inform optimal harvest timing, identifying when cultures are most likely to reach target cell doses [5].

Beyond process monitoring, AI supports adaptive process control in CAR-T manufacturing. Reinforcement learning algorithms have been applied to optimize resource management across manufacturing campaigns, addressing the complexity of varying production times and resource requirements for individual patients [30]. Prescriptive AI agents can determine optimal harvest times and propose process adjustments to operators, integrating data from multiple physical sensors through ensemble learning approaches [5]. Williams et al. (2023) demonstrated that ML combined with metabolic modeling can implement novel process analytical technology (PAT) in CGT manufacturing, enabling real-time quality assessment without destructive sampling [31].

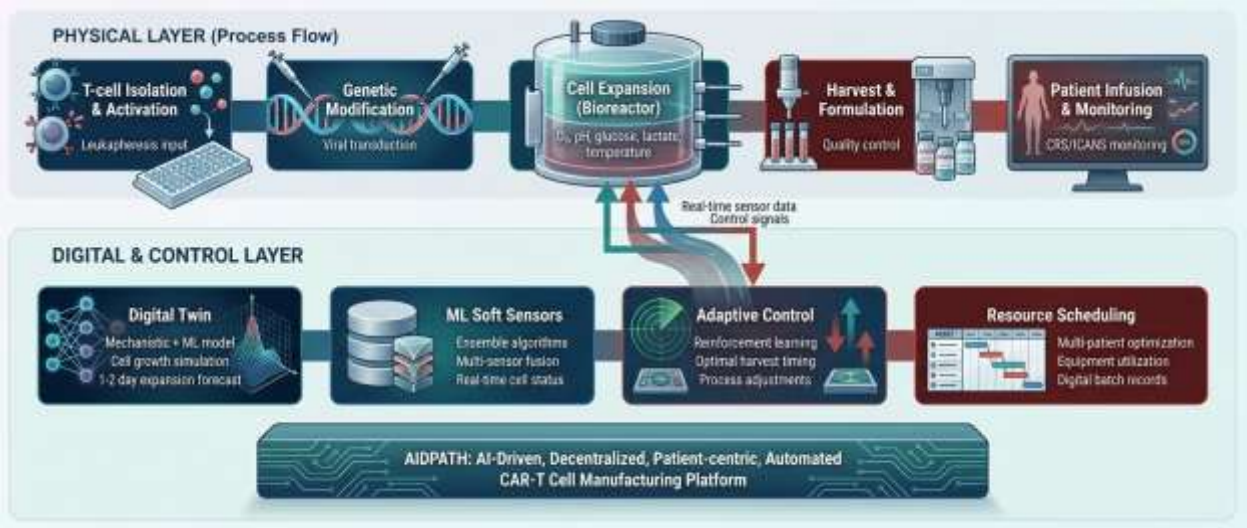

Figure 6. *Digital Twin Architecture For AI-Driven CAR-T Cell Manufacturing: integration of real-time sensor data, predictive modeling, and adaptive process control*

4.3 Predictive Modeling for Clinical Outcomes and Patient Selection

AI-driven predictive modeling is increasingly being applied to optimize patient selection and predict clinical outcomes for CGT products. ML algorithms can analyze patient clinical profiles, including genetic backgrounds, tumor characteristics, and immune status, to identify those most likely to respond to therapy and to predict the risk of severe adverse events such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) [29]. These predictions can inform dose optimization and guide clinical monitoring strategies.

For gene therapies, AI models trained on clinicogenomic databases can predict patient-specific responses based on the interaction between the therapeutic vector and the individual's genetic background [24]. Spatial transcriptomics, which visualizes gene expression patterns at single-cell resolution within tissues, provides a spatial dimension to these analyses, enabling the identification of novel therapeutic targets and the prediction of treatment-specific effects on the tumor microenvironment [24]. The integration of multi-modal data sources, including imaging, genomic, proteomic, and clinical data, through AI-driven analysis pipelines represents a powerful approach for developing comprehensive predictive models of CGT clinical outcomes.

5. CASE STUDIES

5.1 Dyno Therapeutics: ML-Guided AAV Capsid Library Design

Dyno Therapeutics, in collaboration with Google Research and Harvard University, demonstrated the transformative potential of deep learning for AAV capsid engineering [22]. The team focused on a 28-amino acid segment of the AAV2 VP1 capsid protein that encompasses regions critical for both immune recognition and cell tropism. Starting from a modest initial dataset, multiple deep learning architectures were trained to predict capsid viability from sequence alone. The trained models were then used to generate a library of 201,426 diverse capsid variants. Experimental validation revealed that 110,689 variants (approximately 55%) successfully packaged DNA payload, representing a dramatic improvement over the less than 1% viability rate achieved through random mutagenesis. More than 57,000 variants exhibited diversity exceeding that of natural AAV serotypes, with some containing up to 29 mutations in the targeted region. This work established that ML can effectively navigate the vast sequence space of viral capsid proteins to identify functional variants that would be inaccessible through conventional engineering approaches.

5.2 CAR-Toner: AI-Driven CAR Tonic Signaling Optimization

The CAR-Toner platform developed at ShanghaiTech University (Qiu et al., 2024) represents a significant advance in computational CAR design [27]. By establishing the relationship between positively charged patches on CAR protein surfaces and tonic signaling behavior, the team created a predictive framework that can evaluate candidate CAR constructs before any experimental testing. The platform's analysis across four antibody domain architectures provided actionable

design principles, particularly the finding that VHH-based CARs exhibit optimal signaling characteristics. While the platform cannot fully predict all potential side effects and laboratory validation remains essential, CAR-Toner substantially reduces the number of design iterations required to achieve optimized constructs. The team is developing an expanded AI platform intended to generate ready-to-use, optimized CAR designs for any specified target antigen [27].

5.3 AIDPATH: Digital Twin for Decentralized CAR-T Manufacturing

The AIDPATH consortium represents an ambitious effort to develop AI-integrated, decentralized CAR-T manufacturing capabilities suitable for deployment in hospital settings [5]. The platform integrates multiple AI applications along the manufacturing and therapy process. A digital twin tracks the product through the entire manufacturing workflow, performing simulations of cell behavior based on real-time sensor data. ML soft sensors predict cell expansion trajectories from metabolic measurements, enabling proactive harvest timing decisions. Adaptive scheduling algorithms, powered by reinforcement learning, optimize resource utilization across multiple parallel manufacturing campaigns. The platform also generates digital batch records automatically, reducing documentation burden while maintaining regulatory compliance. The AIDPATH initiative demonstrates how AI can address the scalability and cost challenges that currently limit CAR-T therapy access, potentially enabling a transition from centralized manufacturing facilities to the decentralized smart manufacturing hospitals [5].

Table 1. *Summary of key AI applications in cell and gene therapy development*

Case Study	AI Application	Methodology	Key Metric	Outcome
Dyno Therapeutics AAV Engineering	Capsid protein variant design	Deep neural networks	55% viability vs <1% random	110,689 viable capsids from 201,426 designs
CAR-Toner (ShanghaiTech)	CAR tonic signaling prediction	PCP score computation	Optimized signaling range	VHH-based CARs identified as optimal
AIDPATH Digital Twin	Bioreactor process optimization	Digital twin, RL, ensemble ML	1-2 day expansion prediction	Adaptive harvest timing and process control
Fit4Function (Zhu et al.)	Multi-trait AAV capsid design	Six combined ML models	88% multi-criteria pass rate	Cross-species prediction validated in NHP
Stanford Zinc Finger Engineering	Low-immunogenicity protein design	Three integrated ML models	2-6x gene expression increase	Functional zinc fingers with

				reduced immunogenicity

6. ETHICAL AND REGULATORY CONSIDERATIONS

6.1 Ethical Implications of AI in CGT Development

The integration of AI into CGT development raises several important ethical considerations that must be addressed to ensure responsible and equitable deployment of these technologies. Bias in AI models represents a primary concern, as training data that inadequately represent diverse patient populations can lead to models that perform poorly for underrepresented groups [21]. In the context of CGT, where treatments are often personalized based on individual patient characteristics, biased models could result in suboptimal treatment selection or manufacturing protocols for certain demographic groups. For example, AI models trained predominantly on data from Western populations may exhibit lower predictive accuracy for patients of East Asian or African descent, potentially exacerbating existing health disparities [21].

Transparency and interpretability of AI models are essential for maintaining trust among clinicians, patients, and regulators. Many deep learning models function as black-box systems, making it difficult to understand the rationale behind specific predictions [21]. In CGT applications where AI outputs directly influence treatment decisions, such as patient selection for CAR-T therapy or determination of gene therapy dosing, the inability to explain model reasoning poses ethical challenges. Explainable AI (XAI) approaches, including SHAP and LIME, provide methods for quantifying the contribution of individual input features to model outputs, enabling stakeholders to evaluate whether predictions are based on scientifically reasonable factors [21].

Data privacy and protection are particularly salient in CGT applications, which inherently involve sensitive patient genomic information. The use of patient-specific data for AI model training requires robust governance frameworks that balance the need for comprehensive datasets with the protection of individual privacy. Techniques such as federated learning, which enables model training across distributed datasets without centralizing sensitive data, and differential privacy, which adds controlled noise to prevent individual identification, offer promising approaches to this challenge [19].

6.2 Current Regulatory Frameworks and Emerging Guidance

Regulatory agencies are actively developing frameworks to address the use of AI in pharmaceutical and biological product development. In January 2025, the FDA issued a draft guidance titled "Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products," which establishes a risk-based credibility assessment framework for AI models used in regulatory submissions [32]. This framework outlines seven steps: defining the question of interest, specifying the context of use (COU), assessing model risk based on model influence and decision consequence, developing a credibility establishment plan, executing the plan, reporting results, and maintaining the model throughout its lifecycle [32].

The FDA's framework distinguishes between higher-risk and lower-risk AI applications. Models that make final determinations without human intervention, particularly those affecting safety decisions such as patient monitoring during clinical investigations, are classified as higher risk. Lower-risk applications include those where AI identifies potential issues but requires human review and confirmation before corrective action is taken, such as flagging out-of-specification manufacturing batches for human evaluation [32]. This risk-based approach aligns with the agency's broader quality-by-design philosophy and provides a practical pathway for sponsors seeking to incorporate AI into their CGT development programs.

The European Medicines Agency (EMA) has also engaged with AI regulation through its 2024 reflection paper on the use of AI in the medicinal product lifecycle [33]. Internationally, the International Society for Cell and Gene Therapy (ISCT) published a guidance document in 2025 addressing AI, ML, and digitalization systems in the CGT sector, emphasizing the need for standardized terminology, validation methodologies, and regulatory alignment [34]. These emerging frameworks collectively signal a regulatory environment that is supportive of AI integration but demands rigorous validation, transparency, and ongoing monitoring of AI-based systems in CGT development.

Figure 7. *FDA Risk-Based Credibility Assessment Framework for AI in CGT product development (Source: FDA Draft Guidance, January 2025 (Docket No. FDA-224-D-4689)*

6.3 Recommendations for Stakeholders

To facilitate the responsible integration of AI into CGT development, several recommendations are offered to key stakeholders. For industry sponsors, establishing comprehensive data governance policies that ensure data quality, diversity, and privacy protection is fundamental. Building diverse and representative training datasets that include patients across demographic groups, disease stages, and genetic backgrounds will help mitigate model bias and improve generalizability [21]. Implementing explainability requirements for all AI models used in safety-critical applications, and maintaining complete audit trails documenting model development, training, validation, and deployment decisions, will support regulatory compliance and stakeholder trust.

For regulatory agencies, continued development of adaptive regulatory frameworks that keep pace with rapidly evolving AI technology is essential. Providing clear guidance on the validation standards expected for AI models at different risk levels, and establishing mechanisms for post-market surveillance of AI-driven manufacturing and clinical decision-support systems, will support safe and effective CGT product development. Collaboration between regulatory bodies, academic institutions, and industry stakeholders through consortia and public-private partnerships will help ensure that regulatory standards remain aligned with scientific capabilities.

For researchers and technology developers, prioritizing the development of AI models that are not only accurate but also interpretable and robust to domain shift is critical. Investing in federated learning and privacy-preserving computation methods will enable the development of models

trained on broader, more diverse datasets while maintaining patient privacy. Engaging proactively with regulatory agencies through pre-submission meetings and providing detailed documentation of AI model performance and limitations will facilitate the integration of AI tools into the regulatory review process.

7. CONCLUSION

7.1 Summary of Key Findings

This review has demonstrated that AI-driven predictive modeling is rapidly transforming the cell and gene therapy development landscape across multiple dimensions. In gene therapy, machine learning has enabled the design of AAV capsid variants with unprecedented diversity and viability: the Dyno Therapeutics study (Bryant et al., 2021, Nature Biotechnology) achieved approximately 55% capsid viability from 201,426 ML-designed variants, compared to less than 1% with conventional random mutagenesis, representing a greater than 50-fold improvement [22]. The Fit4Function framework (Zhu et al., 2024, Nature Communications) demonstrated 88% multi-criteria success rates for multi-trait capsid engineering [23]. AI-powered CRISPR guide RNA design tools such as CRISPR-GPT have reduced experimental planning timelines from months to days [25], while multi-algorithm approaches at Stanford produced therapeutic zinc finger proteins with two- to six-fold improved gene expression and reduced predicted immunogenicity [26]. In cell therapy, the CAR-Toner platform (Qiu et al., 2024, Cell Research) established the first computational framework for predicting and optimizing CAR construct tonic signaling prior to experimental testing [27], and digital twin technologies within the AIDPATH consortium are enabling one- to two-day predictive horizons for real-time process monitoring and adaptive control of CAR-T cell manufacturing [5].

The regulatory landscape is evolving in parallel with technological advances. The FDA's 2025 draft guidance on AI for drug and biological products provides a structured, risk-based framework for evaluating AI model credibility in regulatory submissions [32]. International bodies including the EMA and ISCT are contributing complementary guidance that collectively establishes the foundation for a harmonized regulatory approach to AI in CGT [33, 34]. These developments provide a clear, if still evolving, pathway for sponsors seeking to leverage AI in their CGT programs.

7.2 Emerging Technologies and Future Directions

Several emerging technologies are poised to further accelerate AI-driven CGT development. Quantum computing offers the potential to dramatically increase computational capacity for molecular simulations and protein folding predictions, potentially enabling the exploration of even larger combinatorial sequence spaces than current classical computing approaches [35]. Multi-omics integration, combining genomic, transcriptomic, proteomic, and metabolomic data through AI models, promises to provide more comprehensive understanding of disease mechanisms and treatment responses, enabling truly personalized CGT products [19].

Foundation models for biology, analogous to large language models in natural language processing, represent an emerging paradigm with significant implications for CGT. Models such as Evo for genomic sequences and ESM for protein sequences, trained on massive biological datasets, can be fine-tuned for specific CGT applications with relatively small amounts of task-specific data [14]. The development of virtual cell models, which integrate multimodal omics data with advanced algorithms to simulate cellular behavior, offers the potential to reduce reliance on animal testing while improving prediction accuracy for human therapeutic responses [21].

The convergence of AI with synthetic biology represents another frontier. Recent work has demonstrated that ML can predict gene circuit design and function, enabling rapid iteration through the Design-Build-Test-Learn (DBTL) cycle for engineering cells with targeted therapeutic responses [36]. This integration has the potential to transform the development of next-generation cell therapies by enabling the computational design of complex genetic programs before any laboratory work begins.

Looking ahead, the successful integration of AI into CGT development will require sustained investment in data infrastructure, workforce development, and cross-disciplinary collaboration. Building large, standardized, and diverse datasets through open-source platforms and data-sharing initiatives will be essential for training robust AI models. Developing regulatory science expertise at the intersection of AI and CGT will be critical for both sponsors and regulatory agencies. Ultimately, the goal is to leverage AI not merely as an efficiency tool, but as a transformative enabler that accelerates the delivery of safe, effective, and accessible cell and gene therapies to patients worldwide.

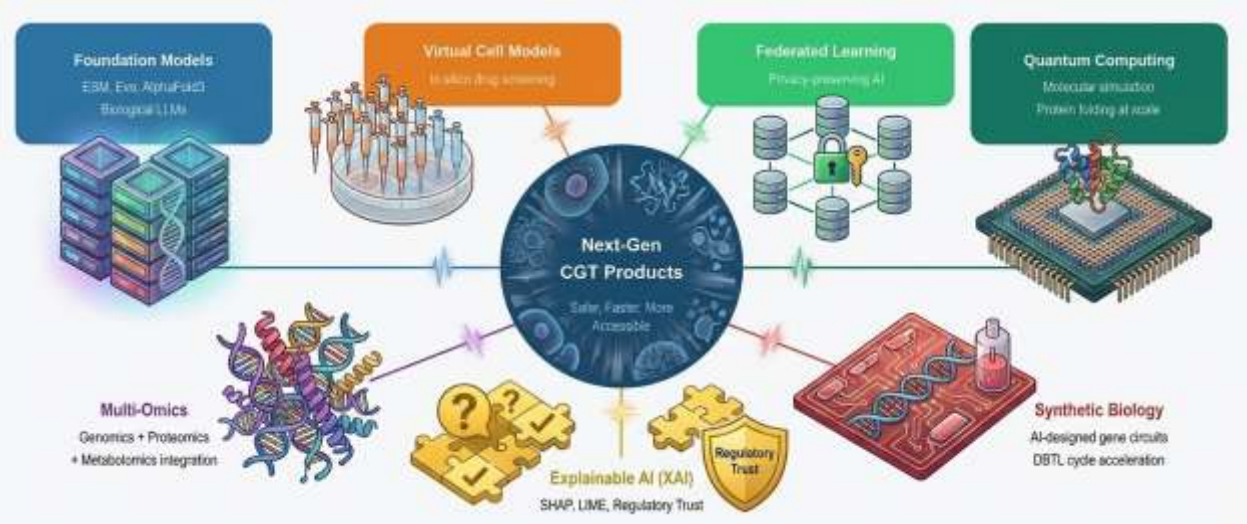

Figure 8. *Future Convergence of AI Technologies for Next-Generation CGT Development: quantum computing, foundation models, multi-omics integration, and synthetic biology*

Table 2. *Comparison of traditional versus AI-driven approaches in CGT development: quantitative performance metrics*

Development Stage	Traditional Approach	AI-Driven Approach	Improvement Factor
AAV Capsid Viability	<1% viable from random mutagenesis	~55% viable from ML-designed libraries	>55x improvement [22]
Multi-trait Capsid Engineering	Iterative selection; low multi-trait success	88% met all 6 criteria simultaneously	Validated cross-species [23]
Zinc Finger Gene Expression	2-4x gene production increase	2-6x gene production increase	Up to 1.5x further improvement [26]
CAR Design Iterations	Dozens of constructs; months of testing	Computational PCP scoring; pre-screening	Reduced experimental cycles [27]
Cell Expansion Forecasting	Empirical observation; reactive decisions	Digital twin with 1-2 day predictive horizon	Proactive harvest timing [5]
CRISPR gRNA Design	Rule-based prediction; months of validation	CRISPR-GPT: automated experimental design	Weeks to days acceleration [25]

GLOSSARY OF KEY TERMS

Adeno-Associated Virus (AAV): A small, non-enveloped virus approximately 25 nm in diameter used as a vector for in vivo gene therapy delivery. As of 2024, seven FDA-approved gene therapies use AAV vectors, with approximately 331 active clinical trials globally [6].

Chimeric Antigen Receptor (CAR): A synthetic receptor engineered to redirect T-cells to recognize and destroy cells expressing a specific target antigen. CAR constructs typically comprise

an extracellular antigen-binding domain (e.g., scFv or VHH), a hinge region, a transmembrane domain, and intracellular co-stimulatory and signaling domains [7].

Digital Twin: A computational model that mirrors a physical manufacturing process in real-time, integrating mechanistic knowledge with sensor data to simulate, predict, and optimize system behavior. In CAR-T manufacturing, digital twins forecast cell expansion trajectories from bioreactor measurements [5].

Explainable AI (XAI): A set of computational methods, including SHAP (SHapley Additive exPlanations) and LIME (Local Interpretable Model-agnostic Explanations), that provide human-interpretable explanations for AI model predictions, essential for regulatory acceptance and clinical trust [21].

Generative Adversarial Network (GAN): A deep learning architecture consisting of two competing neural networks, a generator and a discriminator, used in CGT for de novo design of protein sequences, antibody libraries, and AAV capsid variants [15].

Process Analytical Technology (PAT): A system for designing, analyzing, and controlling manufacturing processes through timely measurements of critical quality and performance attributes. AI-enhanced PAT in CGT manufacturing enables real-time quality assessment without destructive sampling [31].

Tonic Signaling: The spontaneous, antigen-independent activation of CAR molecules on T-cell surfaces, which can lead to T-cell exhaustion, reduced persistence, and diminished anti-tumor efficacy. The CAR-Toner AI platform predicts tonic signaling levels through Positively Charged Patch (PCP) score computation [27].

Transfer Learning: A machine learning technique in which a model pre-trained on a large general dataset is fine-tuned on a smaller domain-specific dataset, enabling accurate predictions even with limited training data, particularly valuable in CGT where patient-specific datasets are small [14].

REFERENCES

[1] Dunbar, C. E., High, K. A., Joung, J. K., Kohn, D. B., Ozawa, K., & Sadelain, M. (2018). Gene therapy comes of age. Science, 359(6372), eaan4672. https://doi.org/10.1126/science.aan4672

[2] Cell & Gene Therapies: An Overview of FDA Regulatory Considerations for 2024. Cell and Gene. Retrieved from https://www.cellandgene.com/doc/cell-gene-therapies-an-overview-of-fda-regulatory-considerations-for-0001

[3] Bulaklak, K., & Gersbach, C. A. (2020). The once and future gene therapy. Nature Communications, 11(1), 5820. https://doi.org/10.1038/s41467-020-19505-2

[4] Bäckel, N., Hort, S., Kis, K. B., et al. (2023). Elaborating the potential of Artificial Intelligence in automated CAR-T cell manufacturing. Frontiers in Molecular Medicine, 3, 1250508. https://doi.org/10.3389/fmmed.2023.1250508

[5] Bäckel, N., Schuster, A., Noll, T., et al. (2022). Toward rapid, widely available autologous CAR-T cell therapy: Artificial intelligence and automation enabling the smart manufacturing hospital. Frontiers in Medicine, 9, 913287. https://doi.org/10.3389/fmed.2022.913287

[6] Tan, X., Fu, X., R., Suo, H., Zhang, J., & Chen, D. (2025). Artificial intelligence-based approaches for AAV vector engineering. Advanced Science, 12, 2411062. https://doi.org/10.1002/advs.202411062

[7] Labanieh, L., & Mackall, C. L. (2023). CAR immune cells: Design principles, resistance and the next generation. Nature, 614, 635-648. https://doi.org/10.1038/s41586-023-05707-3

[8] Dara, S., Dhamercherla, S., Jadav, S. S., Babu, C. M., & Ahsan, M. J. (2022). Machine learning in drug discovery: A review. Artificial Intelligence Review, 55(4), 1947-1999. https://doi.org/10.1007/s10462-021-10058-5

[9] Jiménez-Luna, J., Grisoni, F., Weskamp, N., & Schneider, G. (2021). Artificial intelligence in drug discovery: Recent advances and future perspectives. Expert Opinion on Drug Discovery, 16(9), 949-959. https://doi.org/10.1080/17460441.2021.1909567

[10] Wang, D., Tai, P. W., & Gao, G. (2019). Adeno-associated virus vector as a platform for gene therapy delivery. Nature Reviews Drug Discovery, 18(5), 358-378. https://doi.org/10.1038/s41573-019-0012-9

[11] June, C. H., O'Connor, R. S., Kawalekar, O. U., Ghassemi, S., & Milone, M. C. (2018). CAR T cell immunotherapy for human cancer. Science, 359(6382), 1361-1365. https://doi.org/10.1126/science.aar6711

[12] Luecken, M. D., & Theis, F. J. (2019). Current best practices in single-cell RNA-seq analysis: A tutorial. Molecular Systems Biology, 15(6), e8746. https://doi.org/10.15252/msb.20188746

[13] Aliper, A., Plis, S., Artemov, A., Ulloa, A., Mamoshina, P., & Zhavoronkov, A. (2016). Deep learning applications for predicting pharmacological properties of drugs and drug repurposing using transcriptomic data. Molecular Pharmaceutics, 13(7), 2524-2530. https://doi.org/10.1021/acs.molpharmaceut.6b00248

[14] Lin, Z., Akin, H., Rao, R., et al. (2023). Evolutionary-scale prediction of atomic-level protein structure with a language model. Science, 379(6637), 1123-1130. https://doi.org/10.1126/science.ade2574

[15] Zhavoronkov, A., Ivanenkov, Y. A., Aliper, A., et al. (2019). Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nature Biotechnology, 37(9), 1038-1040. https://doi.org/10.1038/s41587-019-0224-x

[16] ENCODE Project Consortium. (2012). An integrated encyclopedia of DNA elements in the human genome. Nature, 489(7414), 57-74. https://doi.org/10.1038/nature11247

[17] Jumper, J., Evans, R., Pritzel, A., et al. (2021). Highly accurate protein structure prediction with AlphaFold. Nature, 596(7873), 583-589. https://doi.org/10.1038/s41586-021-03819-2

[18] Kolluri, S., Lin, J., Liu, R., Zhang, Y., & Zhang, W. (2022). Machine learning and artificial intelligence in pharmaceutical research and development: A review. The AAPS Journal, 24(1), 19. https://doi.org/10.1208/s12248-021-00644-3

[19] Luo, Y., Peng, J., & Ma, J. (2022). Next decade's AI-based drug development features tight integration of data and computation. Health Data Science, 2022, 9816939. https://doi.org/10.34133/2022/9816939

[20] Adam, G., Rampášek, L., Safikhani, Z., Smirnov, P., Haibe-Kains, B., & Goldenberg, A. (2020). Machine learning approaches to drug response prediction: Challenges and recent progress. NPJ Precision Oncology, 4(1), 19. https://doi.org/10.1038/s41698-020-0122-1

[21] Chen, Y., et al. (2025). AI-driven virtual cell models in preclinical research: Technical pathways, validation mechanisms, and clinical translation potential. NPJ Digital Medicine. https://doi.org/10.1038/s41746-025-02198-6

[22] Bryant, D. H., Bashir, A., Sinai, S., et al. (2021). Deep diversification of an AAV capsid protein by machine learning. Nature Biotechnology, 39, 691-696. https://doi.org/10.1038/s41587-020-00793-4

[23] Zhu, D., Brookes, D. H., Busia, A., et al. (2024). Systematic multi-trait AAV capsid engineering for efficient gene delivery. Nature Communications, 15, 6602. https://doi.org/10.1038/s41467-024-50555-y

[24] McKinsey & Company. (2022). How artificial intelligence can accelerate research and development for cell and gene therapies. Retrieved from https://www.mckinsey.com/industries/life-sciences/our-insights/how-ai-can-accelerate-r-and-d-for-cell-and-gene-therapies

[25] Cong, L., et al. (2025). CRISPR-GPT: AI-powered CRISPR experimental design. Stanford Medicine. Retrieved from https://med.stanford.edu/news/all-news/2025/09/ai-crispr-gene-therapy.html

[26] Wolsberg, E., Gao, X., et al. (2025). Machine learning-guided zinc finger protein engineering for gene therapy with reduced immunogenicity. Stanford University. Retrieved from https://news.stanford.edu/stories/2025/06/machine-learning-ai-cell-gene-therapies

[27] Qiu, S., Chen, J., Wu, T., et al. (2024). CAR-Toner: An AI-driven approach for CAR tonic signaling prediction and optimization. Cell Research, 34(5), 386-388. https://doi.org/10.1038/s41422-024-00936-1

[28] Naghizadeh, A., Tsao, W. C., Cho, J. H., et al. (2023). In vitro machine learning-based CAR T immunological synapse quality measurements correlate with patient clinical outcomes. Molecular Therapy, 29, 1349-1351.

[29] Shahzad, M., et al. (2024). Artificial intelligence for chimeric antigen receptor-based therapies: A comprehensive review of current applications and future perspectives. Therapeutic Advances in Vaccines and Immunotherapy, 12, 25151355241305856. https://doi.org/10.1177/25151355241305856

[30] Szentpéteri, S., Kis, K. B., & Egri, P. (2024). Reinforcement learning based resource management for CAR T-cell therapies. Procedia CIRP, 125, 154-159.

[31] Williams, T., Kalinka, K., Sanches, R., et al. (2023). Machine learning and metabolic modelling assisted implementation of a novel process analytical technology in cell and gene therapy manufacturing. Scientific Reports, 13, 834. https://doi.org/10.1038/s41598-023-27998-2

[32] U.S. Food and Drug Administration. (2025). Considerations for the Use of Artificial Intelligence to Support Regulatory Decision-Making for Drug and Biological Products; Draft Guidance for Industry. Federal Register, 90 FR 1099. Retrieved from https://www.federalregister.gov/documents/2025/01/07/2024-31542/

[33] European Medicines Agency. (2024). Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle. Retrieved from https://www.ema.europa.eu/en/use-artificial-intelligence-ai-medicinal-product-lifecycle

[34] Song, H. W., Hart, S. J., Sethi, D., et al. (2025). Artificial intelligence, machine learning, and digitalization systems in the cell and gene therapy sector: A guidance document from the ISCT industry committees. Cytotherapy. https://doi.org/10.1016/j.jcyt.2025.05.007

[35] Bai, F., Li, S., & Li, H. (2024). AI enhances drug discovery and development. National Science Review, 11, nwad303. https://doi.org/10.1093/nsr/nwad303

[36] Hill, A., True, J. M., & Jones, C. H. (2025). Advancing cell therapies with artificial intelligence and synthetic biology. Current Opinion in Biotechnology, 91, 103259. https://doi.org/10.1016/j.copbio.2025.103259