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# Gene-Modified Immunotherapy and Predictive Modeling in Biomedical Research: A Survey

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## Abstract

Gene-modified immunotherapy has emerged as a transformative approach in biomedical research, offering promising advancements in treating cancer and autoimmune diseases. This survey explores the integration of gene-editing techniques with comprehensive databases, clinical trials, omics data, and predictive modeling to enhance immune system responses. The study underscores the pivotal role of genetic engineering in augmenting the efficacy of cell-based therapies, particularly through the modification of regulatory T cells (Tregs) and tumor-infiltrating lymphocytes (TILs). The integration of omics data and functional genomics provides a deeper understanding of the molecular mechanisms driving immune responses, facilitating the identification of novel therapeutic targets. Predictive modeling further enhances this framework by enabling the estimation of treatment outcomes and personalization of therapeutic strategies. Despite the potential, challenges such as off-target effects, scalability, and cost constraints persist, necessitating continued research and innovation. The survey highlights the importance of hybrid delivery systems and advanced manufacturing processes in overcoming these challenges, ultimately paving the way for more effective and accessible gene-modified therapies. By embracing an integrated approach, researchers are poised to advance the field of personalized medicine, improving patient outcomes through precise and tailored therapeutic interventions.

## 1 Introduction

### 1.1 Significance of Gene-Modified Immunotherapy

Gene-modified immunotherapy is a significant advancement in biomedical research and treatment, particularly for cancer and autoimmune diseases. This innovative approach utilizes genetic engineering to enhance the immune system's ability to identify and eliminate malignant cells, addressing critical challenges in treatment efficacy. For example, melanoma treatment has evolved considerably with various immunotherapies and targeted therapies, yet challenges such as safety, acquired resistance, and the balance between toxicity and effectiveness persist, especially in high-risk resected melanoma patients [1].

The potential of gene-modified immunotherapy to disrupt the cancer immunity cycle further emphasizes its significance in advancing cancer treatment strategies [2]. Beyond oncology, this approach shows promise in treating autoimmune diseases and managing antidrug antibody responses by modifying antigen-specific human regulatory CD4<sup>+</sup> T cells (Tregs) [3]. Additionally, gene delivery strategies in immunoengineering have been demonstrated to significantly enhance immune responses against various diseases, particularly cancer, underscoring the transformative potential of these technologies [4].

The limitations of existing leukemia cell-derived exosomes in eliciting effective immune responses highlight the critical role of gene-modified immunotherapy in boosting anti-leukemia immunity [5]. The integration of advanced bioscience models and precision medicine is essential for overcoming the

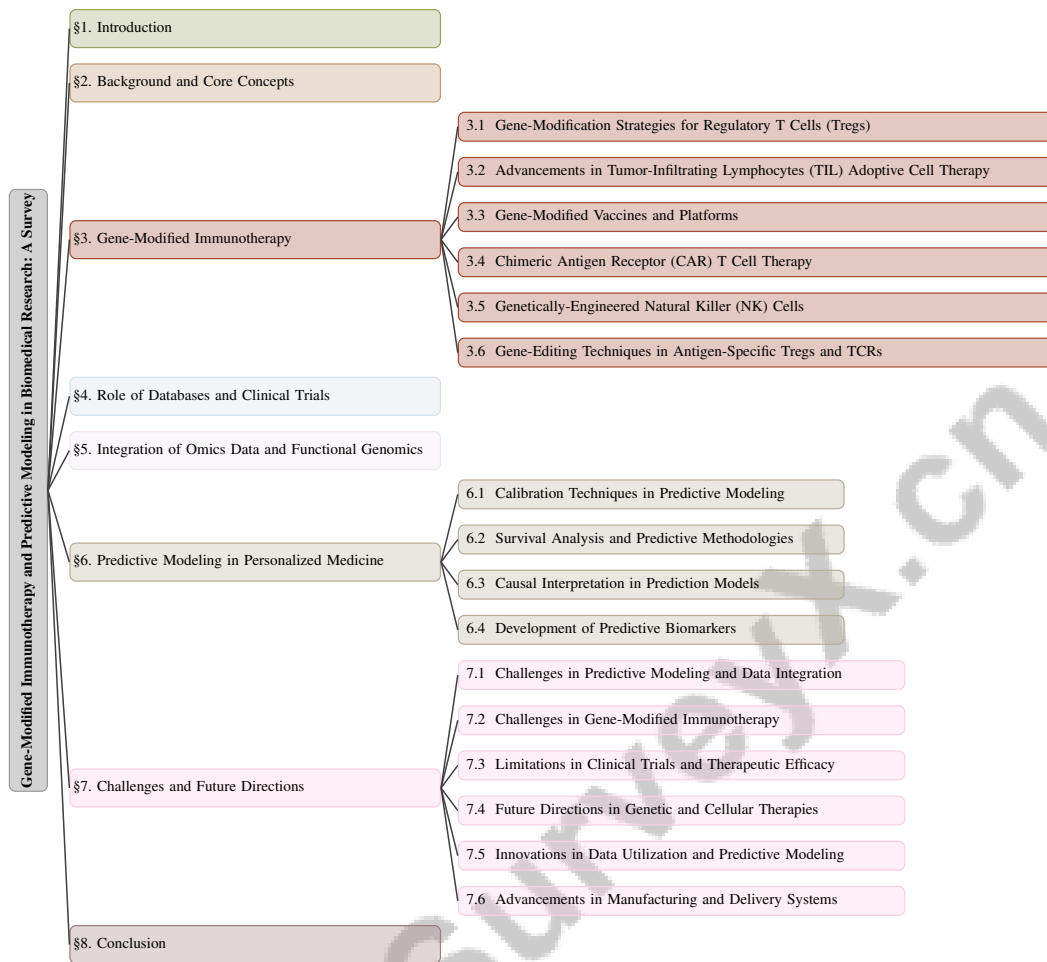


Figure 1: chapter structure

limitations of current methodologies, thereby fostering the development of more effective therapeutic strategies [6]. Furthermore, accurate B-cell epitope prediction, as illustrated in SARS-CoV-2 vaccine development, is vital for progressing biomedical research and treatment, emphasizing the necessity of reliable predictive models in this field [7].

## 1.2 Integration of Key Components

Integrating databases, clinical trials, omics data, and predictive modeling creates a comprehensive framework that significantly enhances immune responses in gene-modified immunotherapy. This multifaceted approach is crucial for navigating the complexities of immune system modulation and optimizing therapeutic outcomes. Databases serve as repositories for extensive biomedical data, facilitating the storage, retrieval, and analysis of genetic, clinical, and molecular information vital for advancing immunotherapeutic strategies. Advanced predictive modeling techniques, including Support Vector Machines and causal inference methods, allow researchers to uncover intricate patterns within biological datasets, guiding the development of more targeted and effective treatments for various diseases. By synthesizing insights from observational studies and clinical trials, these methodologies enhance risk estimation under hypothetical interventions, improving clinical decision support systems and therapeutic outcomes [8, 4, 9].

Clinical trials are essential for evaluating the safety and efficacy of gene-modified therapies, providing empirical evidence to validate the therapeutic potential of interventions such as checkpoint inhibition and CAR T cell therapy, which are pivotal for enhancing immune responses [10]. Systematic assessments of these therapies contribute to refining treatment protocols and identifying optimal therapeutic combinations.

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Omics data—including genomics, proteomics, and metabolomics—offers a comprehensive view of the biological mechanisms driving immune responses, facilitating a deeper understanding of the molecular interactions and cellular processes that influence immune system functionality and disease pathology [11, 4, 12, 8, 2]. Integrating omics data into immunotherapy research is instrumental in identifying novel therapeutic targets and biomarkers for personalized medicine.

Predictive modeling further enhances this integrative approach by enabling the estimation of treatment outcomes and the personalization of therapeutic strategies. The survey by [9] categorizes existing research into two methodological approaches: enriching prediction models with causal effects from clinical trials and meta-analyses, and estimating both prediction models and causal effects directly from observational data. These methodologies are crucial for developing robust models that can accurately forecast patient responses to gene-modified therapies, optimizing treatment plans and improving patient outcomes.

### 1.3 Structure of the Survey

This survey is meticulously organized to provide a comprehensive exploration of gene-modified immunotherapy and its integration with predictive modeling in biomedical research. The paper is structured into several key sections, each addressing specific components and aspects of this multidisciplinary field.

The survey begins with an **Introduction** that highlights the synergistic integration of diverse data sources, including clinical trial results, omics data, and functional genomics, along with advanced predictive modeling techniques, to enhance immune system responses and improve the efficacy of cancer immunotherapy approaches, such as those utilizing gene-modified tumor cells [8, 13, 2].

Following the introduction, the **Background and Core Concepts** section provides essential definitions and explanations of key concepts such as gene-modified immunotherapy, databases, clinical trials, omics data, cell therapy, functional genomics, and predictive modeling, establishing a foundational understanding of the terms and technologies that underpin the survey.

The subsequent section, **Gene-Modified Immunotherapy**, delves into the role of gene-editing techniques in immunotherapy, exploring their applications, advancements, and challenges. Subsections within this part cover diverse topics such as gene-modification strategies for regulatory T cells, advancements in tumor-infiltrating lymphocyte adoptive cell therapy, and the development of gene-modified vaccines and platforms.

The **Role of Databases and Clinical Trials** section discusses the importance of databases and clinical trials in evaluating gene-modified immunotherapy, highlighting the role of databases in storing and analyzing biomedical data, the significance of gene delivery systems in clinical trials, and tools used to validate clinical trial outcomes.

Next, the **Integration of Omics Data and Functional Genomics** section examines how omics data and functional genomics contribute to improving gene-modified immunotherapy outcomes, exploring insights into tumor-infiltrating lymphocyte behavior and the use of CRISPR/Cas9 in genetically-engineered cells.

The section on **Predictive Modeling in Personalized Medicine** discusses the use of predictive modeling to forecast treatment outcomes and personalize therapeutic strategies, explaining calibration techniques, survival analysis, causal interpretation, and the development of predictive biomarkers.

Towards the end of the survey, the **Challenges and Future Directions** section identifies challenges in integrating gene-modified immunotherapy with databases, omics data, and predictive modeling. It discusses limitations in clinical trials and therapeutic efficacy, as well as potential innovations and future directions in genetic and cellular therapies.

Finally, the **Conclusion** summarizes the key points discussed in the paper, emphasizing the importance of an integrated approach in advancing biomedical research and treatment. The survey employs a structured methodology to comprehensively assess the current landscape and future prospects of gene-modified immunotherapy, particularly in the context of predictive modeling, by examining various gene delivery strategies and their implications for enhancing immune responses against diseases such as cancer and autoimmune disorders [4, 13, 2, 12]. The following sections are organized as shown in Figure 1.

## 2 Background and Core Concepts

### 2.1 Genetic Engineering and Cell Therapy

Genetic engineering is integral to advancing cell therapy, particularly in immunotherapy, by enhancing the effectiveness of treatments for cancer and autoimmune disorders. Regulatory T cells (Tregs) are a focal point due to their role in maintaining immune balance, with gene modification strategies crucial for optimizing their therapeutic function [12]. The development of antigen-specific Tregs illustrates genetic engineering's application in cell therapy, showing promise in treating hemophilia A and multiple sclerosis through enhanced specificity and efficacy [3]. This targeted modulation of immune responses aims to reduce adverse effects associated with conventional therapies.

The success of genetic engineering in cell therapy hinges on effective gene delivery systems. Current cancer therapies' limitations necessitate innovative delivery approaches. Advances in viral and non-viral vectors, such as polymeric, lipid-based, and inorganic nanoparticles, address these challenges by facilitating precise genetic material introduction into target cells, thereby enhancing the therapeutic potential of gene-modified cells [4]. Clinical trials, like those for the AGI-101H vaccine targeting high-risk melanoma, exemplify the integration of genetic engineering with cell therapy to improve patient outcomes [1]. Continued development of efficient gene delivery systems is essential for overcoming existing therapeutic limitations and advancing cell therapy [14].

### 2.2 Predictive Modeling in Biomedical Research

Predictive modeling is crucial in biomedical research, offering frameworks for forecasting treatment outcomes and personalizing therapies. By employing statistical and computational techniques to analyze complex biological data, researchers can predict disease progression and treatment efficacy. A significant challenge is developing models that estimate outcomes under hypothetical interventions, addressing the limitations of traditional models lacking causal interpretations [9]. Integrating predictive modeling with gene-modified immunotherapy enhances the ability to tailor treatments to individual profiles. For example, models for the AGI-101H vaccine have provided insights into its effectiveness and re-induction therapy's impact on outcomes, underscoring the importance of robust metrics in evaluating interventions [1].

Predictive modeling is also vital in vaccine development, as demonstrated during the COVID-19 pandemic. Identifying linear B-cell epitopes from protein sequences is crucial for vaccine design, and models have been employed to address this challenge, aiding in developing effective vaccines against emerging pathogens [7]. However, the utility of predictive models is often constrained by inconsistent support and interpretations of modeling languages like SED-ML across software tools, which hampers simulation experiments [6]. The lack of reliable validation tools for SED-ML files exacerbates this issue, leading to errors and inconsistencies that impede effective simulation and modeling efforts [6].

## 3 Gene-Modified Immunotherapy

| Category   | Feature                      | Method       |
|--|------------------------------|--------------|
| Gene-Modified Vaccines and Platforms                       | Prediction Reliability       | CUE-BEP[7]   |
| Gene-Editing Techniques in Antigen-Specific Tregs and TCRs | Gene-Modification Strategies | Bria-OTS+[2] |

Table 1: This table provides a summary of the methods employed in gene-modified immunotherapy, focusing on two main categories: gene-modified vaccines and platforms, and gene-editing techniques in antigen-specific Tregs and TCRs. It highlights the specific features and methods associated with each category, referencing key studies that have contributed to advancements in these areas.

Table 2 presents a comprehensive comparison of various gene-modification strategies in immunotherapy, detailing the target cells, modification techniques, and therapeutic applications across different immune cell types. The integration of gene-modified techniques in immunotherapy has significantly advanced the precision and efficacy of immune cell functions. This section delves into innovative gene-modification strategies, focusing on their impact on regulatory T cells (Tregs) within immunotherapy. These strategies are pivotal for enhancing therapeutic outcomes across diverse clinical scenarios, as discussed in the subsequent subsections. Table 1 presents a concise overview of

the methods applied in gene-modified immunotherapy, detailing the categories, features, and methods that underpin current research and development efforts in this field. ?? illustrates the hierarchical categorization of gene-modified immunotherapy strategies, highlighting key advancements and challenges across different immune cell types and therapeutic approaches. This visual representation not only complements the discussion but also provides a clear framework for understanding the complexities involved in the implementation of these strategies.

### 3.1 Gene-Modification Strategies for Regulatory T Cells (Tregs)

Gene-modification of Tregs is a critical area in improving immunotherapy for cancer, autoimmune diseases, and transplantation [12]. Despite their role in immune homeostasis, Tregs' immunosuppressive nature can hinder anti-tumor responses, prompting research to enhance their therapeutic utility while reducing off-target effects [15]. Strategies include engineering leukemia cell-derived exosomes to upregulate costimulatory molecules like CD80 and CD86, thereby boosting CD4+ T cell stimulation and anti-leukemia immunity [? ]. Challenges persist in expanding genetically modified TILs under GMP standards [? ]. Techniques such as TCRs, CARs, and BARs are employed to enhance Treg specificity, though TCR-pMHC affinity remains a critical factor in determining T-cell reactivity, necessitating precise target identification [3, 11].

As illustrated in Figure 2, the gene-modification strategies for regulatory T cells (Tregs) highlight their therapeutic potential, the techniques employed, and the challenges faced, alongside potential solutions. This visual representation underscores the complexity and multifaceted nature of Treg engineering, providing a comprehensive overview that complements the textual discussion.

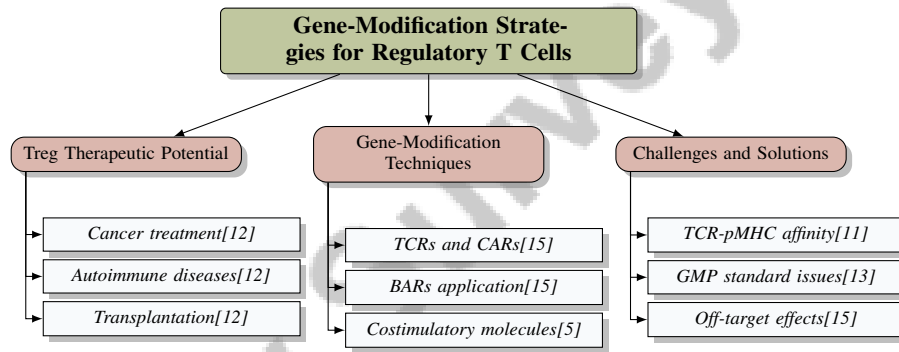


Figure 2: This figure illustrates the gene-modification strategies for regulatory T cells (Tregs), focusing on their therapeutic potential, techniques employed, and challenges faced, alongside potential solutions.

### 3.2 Advancements in Tumor-Infiltrating Lymphocytes (TIL) Adoptive Cell Therapy

Advancements in TIL adoptive cell therapy (ACT) have focused on overcoming TIL exhaustion and the immunosuppressive tumor microenvironment, which limit therapeutic efficacy [? 2]. Genetic modifications, such as CARs and modified TCRs, enhance TIL specificity and potency [? ]. Cytokine support, particularly IL-2, is crucial for TIL survival and function, while novel culture systems improve TIL expansion and capacity. Clinical trials have shown promising results for genetically modified TILs in various cancers, highlighting their potential to deliver durable responses in advanced malignancies [10? , 15, 2].

### 3.3 Gene-Modified Vaccines and Platforms

Gene-modified vaccines represent a significant advancement in immunotherapy for infectious diseases and cancer. Utilizing genetic engineering to enhance immune responses, these vaccines introduce modified antigens that elicit robust immune activity. The modified Rapid Expansion Protocol (REP) is crucial for scaling vaccine production [? ]. Accurate B-cell epitope prediction, enhanced by uncertainty estimation, is vital for vaccine design against rapidly mutating viruses like SARS-CoV-2 [7]. Advanced gene delivery methods improve vaccine efficacy by modulating immune cells, offering personalized cancer immunotherapy strategies [4, 2].

### 3.4 Chimeric Antigen Receptor (CAR) T Cell Therapy

CAR T cell therapy, a transformative approach in cancer immunotherapy, involves engineering T cells to express CARs that target tumor antigens, significantly advancing ACT for various cancers [32, 16, 10, 15]. The process includes isolating patient T cells, modifying them with CARs via viral vectors, and expanding them ex vivo under GMP conditions for reinfusion [112, 102, 15]. Innovations focus on second and third-generation CARs to improve efficacy and safety, with retroviral vectors enhancing CAR T cell migration and activity [2]. Efforts to apply CAR T therapy to solid tumors, exemplified by the Bria-OTS+ platform, highlight its potential in overcoming the tumor microenvironment [2]. The versatility of CAR T therapy is further demonstrated by exploring genetically-modified TCRs and BARs to enhance specificity and efficacy [15, 3].

### 3.5 Genetically-Engineered Natural Killer (NK) Cells

Genetically-engineered NK cells offer a promising approach in cancer immunotherapy, enhancing innate immune responses against tumors [27, 16, 11]. Despite challenges from the tumor microenvironment, genetic modifications improve NK cell cytotoxicity and persistence [16]. CARs are introduced to increase specificity, while cytokine receptor integration, such as IL-15, enhances survival and proliferation [112, 16]. Gene-editing technologies like CRISPR/Cas9 facilitate modifications that enhance NK cell functionality, paving the way for more effective therapies [24, 16].

### 3.6 Gene-Editing Techniques in Antigen-Specific Tregs and TCRs

Gene-editing techniques have transformed immunotherapy by enabling precise modifications of antigen-specific Tregs and TCRs, enhancing their therapeutic potential [11, 32, 12, 15]. Enhancing Treg specificity and suppressive function is crucial for autoimmune and transplantation contexts, reducing non-specific immunosuppression [11, 3, 4, 122]. CRISPR/Cas9 facilitates precise Treg modifications, while TCR gene modification focuses on optimizing TCR-pMHC affinity for improved safety and function [11]. The Bria-OTS+ method exemplifies the integration of gene-editing with advanced strategies to improve immune activation [2]. Additionally, NK-92MI cells with chimeric receptors enhance ADCC, showcasing gene-editing's versatility in augmenting immune cell cytotoxicity [17].

| Feature                | Gene-Modification Strategies for Regulatory T Cells (Tregs) | Advancements in Tumor-Infiltrating Lymphocytes (TIL) Adoptive Cell Therapy | Gene-Modified Vaccines and Platforms |
|------------------------|---|--|--------------------------------------|
| Target Cells           | Regulatory T Cells  | Tumor-Infiltrating Lymphocytes   | Immune Cells                         |
| Modification Technique | Tcrs, Cars, Bars  | Cars, Tcrs   | Gene Delivery                        |
| Therapeutic Focus      | Cancer, Autoimmune, Transplantation                         | Cancer   | Infectious Diseases, Cancer          |

Table 2: This table provides a comparative analysis of gene-modification strategies employed in immunotherapy, focusing on regulatory T cells (Tregs), tumor-infiltrating lymphocytes (TIL), and gene-modified vaccines. It highlights the target cells, modification techniques, and therapeutic focus of each strategy, offering insights into their application in cancer, autoimmune diseases, and infectious diseases.

## 4 Role of Databases and Clinical Trials

### 4.1 Importance of Databases in Biomedical Research

Databases are crucial in biomedical research, serving as repositories for extensive genetic, clinical, and molecular data. Their role is particularly significant in immunotherapy, facilitating the identification and analysis of immunogenic components. The Immune Epitope Database (IEDB), for instance, is vital for storing B-cell epitope data, essential for vaccine development and understanding immune responses [7].

In gene-modified immunotherapy, databases assess the efficacy and safety of novel strategies, such as costimulatory molecule gene-modified exosomes that enhance leukemia cell-derived exosome immunogenicity [5]. These repositories enable systematic evaluation of gene modifications' impact on immune responses, informing the development of more effective therapies.

Additionally, databases validate computational models in biomedical research. Tools like the SED-ML Validator ensure compliance with SED-ML specifications, highlighting databases' importance

in maintaining simulation experiments' accuracy [6]. This framework enhances the integration of predictive modeling with empirical data, improving biomedical research precision.

Gene delivery systems' successful application in clinical trials further exemplifies research strengths facilitated by comprehensive databases [4]. These repositories aggregate and analyze trial data, offering insights into gene delivery systems' performance and potential to enhance immune responses, refining therapeutic strategies in gene-modified immunotherapy.

## 4.2 Gene Delivery Systems and Clinical Trials

Gene delivery systems are fundamental to advancing immunotherapy clinical trials, enabling genetic material introduction into cells to enhance or modify their function. The choice between viral and non-viral systems depends on transfection efficiency, target specificity, safety profiles, and potential immune response and insertional mutagenesis risks associated with viral vectors. Non-viral methods, including polymeric and lipid-based nanoparticles, offer alternatives that mitigate immunogenic risks while achieving effective gene transfer for immunoengineering and cancer therapy applications [14, 11, 4, 13, 5].

Figure 3 illustrates the categorization of gene delivery systems into viral and non-viral vectors, highlighting their characteristics and clinical implications in immunotherapy. Viral vectors, known for high transfection efficiency and host genome integration, pose challenges such as immune response elicitation and insertional mutagenesis risks, potentially leading to oncogenesis [14]. These safety concerns necessitate rigorous clinical trial evaluations to ensure therapeutic benefits outweigh potential risks.

Non-viral vectors, including lipid-based and polymeric nanoparticles, present lower immune activation and insertional mutagenesis risks, though typically exhibit lower transfection efficiencies compared to viral vectors [14]. Ongoing research aims to enhance non-viral systems' delivery efficiency for clinical applications.

The Bria-OTS+ Immunotherapy Platform exemplifies gene delivery systems' clinical implications, utilizing intradermal injection of modified tumor cells to stimulate immune activation [2]. This method evaluates gene-modified immunotherapies' efficacy, directly influencing the immune system's tumor cell recognition and targeting ability.

Furthermore, genetically modifying NK-92MI cells to express chimeric receptors binding human immunoglobulins illustrates gene delivery systems' potential to enhance immune cell cytotoxicity [17]. This modification enables NK cells to effectively target and destroy tumor cells, emphasizing gene delivery's role in optimizing immune cell function for therapeutic applications.

The immunosuppressive tumor microenvironment presents additional challenges for gene-modified therapies' clinical application. Strategies to overcome these barriers are essential for translating preclinical findings into clinical practice [10]. Clinical trials are pivotal in systematically evaluating gene delivery systems' safety and efficacy, ultimately informing more effective immunotherapeutic strategy development.

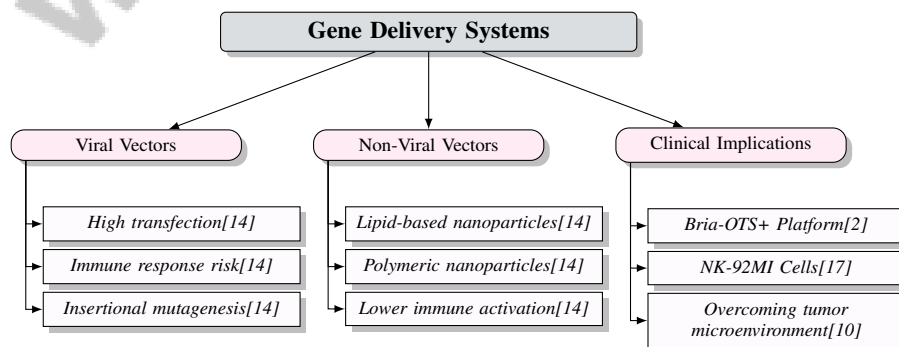


Figure 3: This figure illustrates the categorization of gene delivery systems into viral and non-viral vectors, highlighting their characteristics and clinical implications in immunotherapy.

### 4.3 Validation Tools in Clinical Trial Evaluation

| Benchmark   | Size | Domain   | Task Format       | Metric  |
|-------------|------|----------|-------------------|---------|
| AGI-101H[1] | 196  | Oncology | Survival Analysis | DFS, OS |

Table 3: This table presents a representative benchmark utilized in the evaluation of clinical trial outcomes, particularly in the context of gene-modified therapies. It details the benchmark name, size, domain, task format, and the metrics used for assessing survival analysis, thereby highlighting the tools essential for validating therapeutic efficacy and safety in oncology.

Validation tools are crucial in clinical trial evaluation, ensuring outcome accuracy and reliability, which inform effective therapeutic strategy development. These tools encompass methodologies and technologies designed to assess clinical interventions' safety, efficacy, and reproducibility. In gene-modified immunotherapy, validating trial outcomes is paramount due to these strategies' innovative nature, including genetically modified tumor-infiltrating lymphocytes (TILs) and optimized T-cell receptor (TCR) affinity. Rigorous evaluation is necessary to ensure efficacy and safety, especially given recent findings highlighting potential serious adverse events linked to off-target effects in TCR-based therapies [13, 11].

A key aspect of clinical trial validation is using computational models to simulate biological processes and predict treatment outcomes. Integrating computational tools, such as the SED-ML Validator, is critical for validating simulation experiments by ensuring SED-ML specifications compliance [6]. This process enhances trial result reliability by ensuring robust computational models capable of accurately predicting patient responses.

Moreover, validating gene-modified therapies often involves using biomarkers as surrogate endpoints to assess therapeutic efficacy. Predictive biomarkers from comprehensive omics data and advanced functional genomics techniques provide insights into molecular mechanisms governing treatment responses. By leveraging machine learning models and causal inference methods, researchers enhance these biomarkers' predictive relevance, improving risk estimations for outcomes under hypothetical interventions and optimizing therapeutic strategies, such as TCR gene-modified therapies [7, 11, 12, 8, 9]. These biomarkers enable monitoring gene-modified interventions' biological effects and validate clinical outcomes, facilitating therapeutic refinement.

Clinical trials also employ statistical methods to validate outcomes, ensuring statistically significant results not due to chance. Techniques like survival analysis and causal interpretation evaluate gene-modified therapies' impact on patient survival and disease progression, providing a comprehensive treatment efficacy assessment [9]. Table 3 provides an overview of a benchmark used in clinical trial validation, particularly focusing on survival analysis in the oncology domain, which is critical for assessing the efficacy and safety of gene-modified therapies. These methodologies are integral to the validation process, offering a rigorous framework for interpreting clinical trial data.

Validation of clinical trial outcomes is further enhanced through integrating real-world evidence, analyzing routine clinical practice data. This approach assesses clinical interventions' applicability and effectiveness in diverse patient populations, bridging the gap between controlled clinical trial settings and everyday healthcare scenarios. By utilizing causal inference methods, researchers refine prediction models to estimate outcomes under hypothetical interventions, improving decision-making processes in clinical settings [6, 8, 9]. Integrating real-world evidence with clinical trial data validates trial outcomes' generalizability and applicability, enhancing research findings' translation into clinical practice.

### 4.4 Examples of Innovative Clinical Trials

Innovative clinical trials have been pivotal in advancing gene-modified immunotherapy, providing empirical evidence of novel therapeutic strategies' efficacy and safety. A notable example is the re-induction therapy clinical trial, demonstrating significant survival improvements for patients, particularly in Trial 5, showcasing statistically significant effects underscoring re-induction therapy's potential to enhance treatment outcomes in high-risk melanoma patients [1]. This trial emphasizes exploring novel therapeutic regimens' importance, integrating with existing protocols to improve patient survival and quality of life.



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The field of T-cell receptor (TCR)-modified T cell therapies is witnessing increased interest, evidenced by numerous ongoing clinical trials evaluating their efficacy against various cancers. These trials reflect a growing investment in TCR-modified therapies, driven by engineered T cells' potential to target specific tumor antigens with high precision [15]. Exploring TCR-modified T cells in clinical settings demonstrates advancements in genetic engineering technologies enabling immune cells' customization to enhance anti-tumor activity while minimizing off-target effects.

These groundbreaking clinical trials illustrate gene-modified immunotherapy's significant potential to revolutionize cancer treatment. Employing innovative techniques to generate and expand clinical-grade, genetically modified tumor-infiltrating lymphocytes (TILs), researchers successfully translate advanced research into practical applications, such as metastatic melanoma treatment. This approach enhances adoptive cell therapy efficacy and exemplifies how targeted gene delivery methods optimize immune responses against tumors, ultimately improving patient outcomes [14, 4, 13, 12, 2]. By rigorously evaluating gene-modified therapies' safety and efficacy through well-designed clinical trials, researchers pave the way for integrating these novel treatments into standard clinical practice, ultimately improving outcomes for patients with challenging malignancies.

## **5 Integration of Omics Data and Functional Genomics**

### **5.1 Functional Genomics and TIL Behavior**

Functional genomics has profoundly enhanced our understanding of tumor-infiltrating lymphocytes (TILs), crucial for the immune response against cancer. TILs, particularly T cells, play a vital role in recognizing and attacking tumor cells within the microenvironment. Advanced techniques like high-throughput sequencing and gene expression profiling have elucidated the complex molecular interactions and pathways governing TIL behavior, aiding the development of innovative immunotherapeutic strategies [11, 4, 13, 8, 2].

The advent of CRISPR/Cas9 technology has allowed precise gene manipulation in TILs, offering insights into factors affecting TIL persistence and efficacy. By modifying specific genes, researchers enhance TIL cytotoxicity, thereby improving cancer cell eradication. Techniques for large-scale production of genetically modified TILs, such as those using the chemokine receptor CXCR2, are currently under clinical trials for metastatic melanoma at MD Anderson Cancer Center [10, 13, 11].

Functional genomics has also revealed TIL heterogeneity, identifying subpopulations with distinct effector functions and proliferative capacities. Understanding these differences is crucial for optimizing adoptive cell therapies, especially in developing genetically modified TILs for clinical use [13, 11]. The tumor microenvironment influences this heterogeneity, affecting TIL activity and necessitating genomic and transcriptomic profiling for therapeutic optimization.

Epigenetic modifications, such as DNA methylation and histone changes, significantly impact TIL behavior, influencing their functionality and effectiveness in tumor antigen recognition. Understanding these regulatory mechanisms is vital for optimizing adoptive cell therapy strategies, as they affect TILs' ability to mount robust immune responses against cancer cells [13, 11]. By elucidating these mechanisms, interventions can be devised to modulate TIL activity and enhance anti-tumor responses.

### **5.2 CRISPR/Cas9 in Genetically-Engineered Cells**

The CRISPR/Cas9 system has revolutionized genetic engineering, offering precision in modifying genetic material, thereby advancing genetically-engineered cells for improved immunotherapy. This technology enhances immune responses against cancer by editing genes within immune cells, such as T cells and NK cells, to boost their anti-tumor activity and persistence. Successful applications of genetically modified TILs in clinical trials for metastatic melanoma illustrate this advancement [11, 4, 13, 12, 5].

CRISPR/Cas9 has facilitated the development of chimeric antigen receptor (CAR) T cells with improved specificity and efficacy. By precisely modifying CAR constructs, researchers enhance antigen recognition and signaling domains, increasing therapeutic efficacy and expanding potential applications in treating malignancies [15, 16, 3]. This precision engineering allows for CAR T cells tailored to specific tumor antigens, reducing off-target effects and improving patient outcomes.

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In genetically engineering stem cells, CRISPR/Cas9 holds promise for regenerative medicine and treating genetic disorders, enabling precise genome modifications that enhance cell functionality and therapeutic efficacy [4, 14, 16, 12]. By correcting mutations or introducing beneficial modifications, CRISPR/Cas9 generates stem cells with enhanced therapeutic properties for cell-based therapies, offering new avenues for treating a range of diseases.

### 5.3 Multi-faceted Approach to T-cell Activation

A multi-faceted approach to T-cell activation is essential for optimizing immunotherapeutic strategies, leveraging insights from omics data and genomic studies to enhance T-cell efficacy and specificity. This approach requires a comprehensive understanding of T-cell receptor (TCR) structure and signaling, integrating genomic data to inform clinical applications [15]. Recent studies advocate for a broader evaluation beyond TCR-pMHC affinity, considering signaling pathways, co-stimulatory signals, and the tumor microenvironment [11].

Omics data, encompassing genomics, transcriptomics, and proteomics, provide valuable insights into regulatory networks involved in T-cell activation. By integrating diverse biological data, researchers can identify genes and proteins modulating T-cell function, serving as targets for genetic modifications or pharmacological interventions. This approach enhances the therapeutic efficacy of TCR gene-modified T-cells in cancer treatment and addresses off-target effects observed in clinical trials [11, 3, 13, 12, 15].

Genomic insights are instrumental in refining manufacturing processes, ensuring the reliable production of high-quality T-cell products, such as genetically modified TILs and engineered TCRs, essential for effective adoptive cell therapy in treating conditions like metastatic melanoma [13, 15, 14, 16]. Understanding genetic factors influencing T-cell expansion and persistence allows optimization of culture conditions and genetic modifications to produce T-cells with enhanced therapeutic properties, critical for translating laboratory findings into clinically viable therapies.

## 6 Predictive Modeling in Personalized Medicine

Predictive modeling is pivotal in personalized medicine, enabling tailored interventions for individual patients. This section delves into calibration techniques that refine predictive outputs, converting them into meaningful probabilities crucial for clinical decisions. Enhancing model accuracy and interpretability through these techniques is vital for integrating predictive models into personalized medicine.

### 6.1 Calibration Techniques in Predictive Modeling

Calibration techniques are crucial in predictive modeling, particularly in personalized medicine, where precise treatment outcome predictions are essential. Platt's scaling, for example, converts Support Vector Machine (SVM) outputs into probabilities, enhancing interpretability and clinical relevance [8]. This transformation integrates predictive models into clinical decision-making by providing intuitive probabilistic insights.

Platt's scaling involves fitting a logistic regression model to SVM outputs, mapping decision values to a probability scale, thus facilitating causal inference under hypothetical interventions. This integration with probabilistic models in clinical settings supports informed decisions based on causal effects from observational data and clinical trials [8, 9]. Calibrated probability estimates are particularly valuable in personalized medicine, influencing therapeutic decisions based on treatment success likelihood or adverse events.

Advanced calibration techniques, such as isotonic regression and beta calibration, further enhance model accuracy, especially with imbalanced datasets or outliers [8, 6, 9]. These methods correct biases in probability estimates, aligning predicted probabilities with observed outcomes, thus improving predictive models' utility in clinical practice for accurate risk stratification and treatment personalization.

Calibration techniques are integral to predictive models in personalized medicine, converting raw outputs into interpretable probabilities and enhancing models' relevance and application in clinical decision-making. This transformation is essential for predictions under hypothetical interventions,

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integrating causal inference methods that improve risk estimation and clinical decision support systems. Techniques like Platt's scaling mitigate uncertainties and biases, increasing clinician confidence in predictions, vital for advancements in vaccine development and personalized medicine [7, 13, 9, 8, 6].

## **6.2 Survival Analysis and Predictive Methodologies**

Survival analysis is integral to predictive modeling in personalized medicine, focusing on time-to-event data to estimate patient prognosis and optimize therapeutic strategies. Integrating survival analysis with advanced predictive methodologies, particularly those incorporating causal inference techniques, enables comprehensive models estimating patient survival probabilities under hypothetical interventions. This integration enhances clinical decision-making by providing insights based on causal relationships from observational data and clinical trials, addressing traditional prediction models' limitations and supporting clinical decision support systems [8, 9].

Key aspects of survival analysis involve evaluating model performance using metrics such as precision, sensitivity, and the area under the curve (AUC). These metrics assess predictive models' accuracy and reliability in estimating survival outcomes. Comparing uncalibrated and calibrated models underscores calibration techniques' importance in enhancing model performance, ensuring predictions are accurate and clinically relevant [8]. Employing these metrics allows refinement of predictive models to capture survival data complexities, improving their applicability in personalized medicine.

Predictive methodologies in survival analysis utilize advanced statistical and machine learning techniques, including Cox proportional hazards models, random survival forests, and deep learning approaches. These methodologies incorporate covariates like genetic, clinical, and demographic factors, providing comprehensive patient risk assessments. Integrating diverse data types into survival models is advantageous in personalized medicine, facilitating individualized risk assessments that inform treatment decisions. This approach enhances prediction precision and leverages causal inference methods to evaluate potential outcomes under hypothetical interventions. Advanced techniques like marginal structural models and g-estimation allow clinicians to understand various treatment options' impacts, ultimately improving patient outcomes. Addressing data imbalance and model calibration challenges enhances predictive models' reliability, guiding clinical decision-making [8, 9].

Developing predictive models incorporating causal inference methodologies enhances survival analysis interpretability. Applying causal inference methods to observational data allows researchers to estimate hypothetical interventions' effects on survival outcomes more accurately. This approach improves treatment efficacy understanding and allows predictive models incorporating estimated causal effects, offering a comprehensive clinical decision-making perspective. Methods like marginal structural models and g-estimation facilitate insights integration from clinical trials and meta-analyses into prediction models, improving clinical decision support systems' operationalization [8, 9]. Integrating causal inference with predictive modeling represents a significant advancement, providing a holistic survival analysis approach aligned with personalized medicine goals.

## **6.3 Causal Interpretation in Prediction Models**

Causal interpretation in prediction models is crucial in personalized medicine, where understanding causal relationships between variables is essential for effective decision-making. Integrating causal inference methodologies with predictive models enables researchers to forecast outcomes and gain insights into mechanisms driving these outcomes, particularly under hypothetical interventions. This approach enhances model predictive relevance by incorporating causal effects from clinical trials and meta-analyses and estimating causal relationships from observational data. Methodologies like marginal structural models and g-estimation support clinical decision-making by addressing dynamic treatment regimes and multiple interventions complexities, though validating causal prediction models remains an evolving research area [8, 9]. This dual capability is vital for developing effective interventions tailored to individual patient needs.

Deriving causal interpretations from prediction models involves using causal graphs and structural equation modeling. These methods map causal pathways between variables, providing visual relationship representations that guide model development and interpretation. Explicitly modeling causal pathways allows researchers to systematically identify and account for potential confounding

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variables, enhancing prediction accuracy and validity. This approach facilitates developing prediction models estimating outcomes under hypothetical interventions. Recent literature highlights that employing causal inference methods—such as marginal structural models and g-estimation—yields more robust predictions, particularly in clinical settings where decision-making relies on understanding various interventions' effects. Integrating insights from clinical trials and observational data enriches these models, leading to improved clinical decision support systems [8, 6, 9].

Counterfactual reasoning compares predicted outcomes under different hypothetical scenarios, estimating specific interventions' causal effects. This approach provides insights into how changes in one variable might influence overall outcomes. Counterfactual reasoning is crucial in personalized medicine, enabling healthcare providers to assess various treatment options' potential outcomes, optimizing therapeutic strategies. This approach is essential for developing predictive models incorporating causal inference, allowing more accurate risk estimations under hypothetical interventions. Integrating insights from clinical trials and observational data enables healthcare professionals to make informed decisions tailored to individual patient needs, improving treatment efficacy and outcomes [8, 7, 9].

Applying causal inference in prediction models involves advanced statistical techniques, such as instrumental variable analysis and propensity score matching. These methods address endogeneity and selection bias issues, which can distort causal estimates and lead to incorrect conclusions. Incorporating advanced causal inference techniques into models achieves more precise causal interpretations, improving findings' validity and applicability in clinical practice. Techniques include enriching prediction models from observational studies with causal effects from clinical trials and meta-analyses and directly estimating causal effects from observational data. This methodological enhancement addresses traditional prediction models' limitations and facilitates more informed decision-making in clinical settings, leading to better patient outcomes [8, 6, 9].

Causal interpretation in prediction models represents a significant advancement in personalized medicine, providing a deeper understanding of complex relationships between variables and their impact on patient outcomes. Integrating causal inference methodologies with predictive modeling enhances models' robustness and informational value, enabling more accurate clinical outcomes predictions under hypothetical interventions. This approach supports effective clinical decision-making and addresses the need for risk estimation in patient care by leveraging causal effects from observational data and clinical trials. Ultimately, these advancements contribute to developing clinical decision support systems that adapt to dynamic treatment regimes and improve patient outcomes [8, 7, 9].

#### **6.4 Development of Predictive Biomarkers**

Developing predictive biomarkers is pivotal in advancing personalized medicine, allowing therapeutic interventions tailored to individual patient profiles. Predictive biomarkers provide insights into likely treatment responses, enabling precise and effective healthcare strategies. Cutting-edge genetic and molecular methodologies have significantly contributed to discovering and validating clinically relevant biomarkers, enhancing their application in patient care and treatment strategies. This advancement is evident in adoptive cell therapy (ACT), where optimizing genetically modified tumor-infiltrating lymphocytes (TILs) has enhanced therapeutic potential in treating conditions like metastatic melanoma [8, 13, 11].

Advancements in predicting B-cell epitopes exemplify predictive biomarkers' role in personalized medicine. Methods improving prediction accuracy and providing insights into uncertainty in B-cell epitope predictions are crucial for developing effective vaccines and immunotherapies [7]. These advancements underscore predictive biomarkers' importance in guiding therapeutic decisions and optimizing patient outcomes.

In cancer immunotherapy, refining TIL therapies highlights predictive biomarkers' potential to enhance anti-tumor efficacy. Future research should focus on refining methods and exploring additional gene modifications to optimize TILs' therapeutic potential [13]. Identifying biomarkers predicting TIL responsiveness can improve patient selection and treatment efficacy.

The specificity and safety of T-cell receptor (TCR) engineering are critical in developing predictive biomarkers for TCR-modified T cells. Enhancing TCR specificity and developing safer engineering techniques are essential for improving these therapies' efficacy across various malignancies [15].

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Predictive biomarkers assessing TCR functionality and safety can guide TCR design optimization, ensuring therapeutic interventions are effective and safe.

Genetic modifications have enhanced natural killer (NK) cells' functions, making them safer and more effective therapeutic options [16]. Identifying biomarkers predicting genetically-modified NK cells' efficacy can facilitate developing personalized immunotherapies, enabling optimal treatment strategy selection for individual patients.

Future research should continue exploring TCR design optimization by considering factors like CD8 requirements, TCR expression levels, and antigen density's impact on T-cell function [11]. Developing predictive biomarkers accounting for these variables can refine TCR-based therapies, enhancing their therapeutic potential and expanding their applicability to a broader range of diseases.

## **7 Challenges and Future Directions**

### **7.1 Challenges in Predictive Modeling and Data Integration**

The integration of predictive modeling in personalized medicine is challenged by the complexity of heterogeneous datasets. Support Vector Machines (SVMs) are particularly sensitive to imbalanced datasets and multicollinearity, which can skew predictions and reduce accuracy [8]. Addressing these issues requires advanced algorithms that manage data imbalance and collinearity to ensure equitable outcomes across diverse patient groups.

Predicting outcomes under hypothetical interventions is complicated by treatment drop-in, residual confounding, and the need for precise estimand definitions [9]. Such complexities hinder causal inference from observational data, crucial for evaluating therapeutic strategies. Therefore, robust methodologies are necessary to enhance the reliability of treatment effect predictions.

Data integration also faces challenges, particularly in simulation experiments. While standardized modeling languages like SED-ML are essential for reproducibility and interoperability, the lack of reliable validation tools can lead to errors, impeding collaboration and data sharing among researchers [6]. Tools like the SED-ML Validator are crucial for debugging simulation experiments and ensuring the integrity of integrated data analyses.

### **7.2 Challenges in Gene-Modified Immunotherapy**

Gene-modified immunotherapy faces several challenges limiting its clinical application. A significant concern is unintended off-tumor or off-target cross-reactivity from affinity-enhanced T-cell receptors (TCRs), which can cause severe adverse events, including death [11]. This necessitates precise target identification and strategies to mitigate off-target effects.

The instability of genetic materials and risks associated with delivery methods further complicate gene-modified therapies [4]. Ensuring reproducible results is critical for clinical translation, as stability and specificity are vital for therapeutic efficacy and minimizing adverse effects.

Scalability is another hurdle, particularly in producing regulatory T cells (Tregs) and other gene-modified cells, with current studies facing challenges in scaling production for larger populations [3]. Additionally, antibody-mediated interference with bispecific T-cell engagers (BAR Tregs) poses challenges to their long-term efficacy.

The high cost and risk of severe autoimmune side effects are critical concerns affecting accessibility and safety [10]. Strategies to reduce costs and improve safety are essential to enhance the accessibility of these interventions.

Moreover, the potential loss of expression of engineered receptors, such as CD64, over time may impact the long-term efficacy of modified cells [17]. Strategies to ensure sustained expression and functionality are needed.

### **7.3 Limitations in Clinical Trials and Therapeutic Efficacy**

Clinical trials are vital for developing and validating gene-modified immunotherapies, yet they face limitations affecting therapeutic efficacy. One major challenge is the complexity and variability of patient responses, complicating trial result interpretation and treatment efficacy assessment. Factors

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like imbalanced datasets and high multicollinearity can skew results, while traditional prediction models often lack causal interpretability, complicating predictions under hypothetical interventions [8, 9].

Translating preclinical findings into clinical outcomes is hindered by causal inference complexities and the need for robust prediction models capable of accounting for hypothetical interventions. Despite methodological advancements, operationalizing models in clinical decision support systems remains underdeveloped, highlighting the gap between observational data and clinical applications [14, 4, 13, 8, 9].

Clinical trial design and execution also pose challenges, particularly in patient recruitment and retention. Stringent inclusion criteria and complex treatment protocols can limit enrollment and increase dropout rates. The high costs and logistical demands can compromise trial scope and duration, impacting the validity and generalizability of findings, especially regarding robust prediction models under hypothetical interventions [8, 4, 7, 9].

Assessing therapeutic efficacy is complicated by the lack of standardized endpoints and biomarkers. Traditional metrics like overall survival may not adequately reflect the complex immune responses generated by gene-modified therapies, particularly considering factors like T-cell receptor affinity [5, 4, 13, 11]. Developing novel biomarkers that accurately reflect therapeutic efficacy is essential for improving clinical trial evaluations.

The evolving regulatory landscape presents additional challenges for trial design and implementation. Advances in gene delivery methods and increasing therapeutic strategy complexity necessitate navigating dynamic regulatory requirements [14, 4, 12, 8, 15]. Regional variations in regulatory requirements create barriers to harmonizing clinical trial practices and timely therapy approvals.

#### **7.4 Future Directions in Genetic and Cellular Therapies**

The future of genetic and cellular therapies promises advancements through refining existing techniques and exploring novel strategies. Developing hybrid delivery systems that integrate viral and non-viral methods is a key focus, enhancing gene delivery efficiency and safety [4].

In regulatory T cell (Treg) therapies, future research should refine gene-modification techniques to ensure purity and efficacy. Investigating Treg therapies' long-term effects is crucial for understanding their impact on immune homeostasis and disease progression [12].

Exploring combinatorial gene manipulation strategies, including CRISPR/Cas9, represents a promising direction for enhancing natural killer (NK) cell therapeutic potential [16]. These advanced techniques can improve NK cell cytotoxicity and persistence, expanding their applications against cancer cells.

Immunotherapy advancements will include refining strategies and developing predictive biomarkers to enhance patient selection and treatment outcomes [10]. These efforts will facilitate more personalized and targeted therapies.

Validating causal prediction models and exploring dynamic treatment strategies are critical for advancing predictive modeling in personalized medicine [9]. Addressing the complexities of multiple interventions will enhance predictive model accuracy and applicability in clinical decision-making.

Expanding validation tools, such as the SED-ML Validator, to support new features and file types will improve simulation experiment reliability [6]. Ensuring the integrity and reproducibility of computational models is essential.

Future research should prioritize larger, randomized trials to validate current study findings and explore biomarkers predicting patient responses to therapies [1]. These trials will provide insights into the efficacy and safety of novel therapeutic approaches.

#### **7.5 Innovations in Data Utilization and Predictive Modeling**

Innovations in data utilization and predictive modeling are reshaping personalized medicine by enabling more accurate, individualized therapeutic strategies. Integrating causal inference methodologies with predictive models enhances understanding of causal relationships within complex datasets [9].

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Predictive modeling has greatly benefited from machine learning techniques, facilitating large-scale omics data analysis to identify patterns that inform treatment decisions. For instance, calibrated uncertainty estimation in predicting B-cell epitopes has improved vaccine development reliability [7].

The development of tools like the SED-ML Validator has improved computational model validation, ensuring reproducibility and compliance with standards [6]. These tools are essential for accurately integrating predictive models with empirical data.

Data utilization has progressed through standardized modeling languages, such as SED-ML, enhancing data sharing and integration across platforms. Although SED-ML's effectiveness has been limited by inconsistent support among modeling tools, advancements in causal inference methods are enabling prediction models that estimate outcomes under hypothetical interventions [8, 9, 6].

## 7.6 Advancements in Manufacturing and Delivery Systems

Advancements in manufacturing and delivery systems for gene-modified therapies are crucial for enhancing treatment efficacy and scalability. Developing hybrid delivery systems that combine viral and non-viral vectors' strengths is a critical focus, maximizing transfection efficiency while minimizing risks like immune activation [4].

Optimizing gene delivery systems is vital for clinical applications. Recent efforts aim to improve precision and stability in gene delivery, ensuring therapeutic genes are accurately introduced into target cells [14, 2].

Advancements in manufacturing processes are instrumental in scaling production to meet clinical demands. Integrating automated and closed-system manufacturing platforms has improved the efficiency of producing clinical-grade genetically modified tumor-infiltrating lymphocytes (TILs) for adoptive cell therapy (ACT) [13, 14].

The integration of advanced analytics and process control technologies has significantly improved product consistency and quality, enhancing therapeutic outcomes through optimized gene delivery methods and adherence to GMP [14, 4, 13, 8, 2].

These advancements are driving the evolution of gene-modified therapies, enabling more precise, scalable, and safe treatment options. By overcoming existing challenges, these developments hold the potential to significantly improve patient outcomes across diverse diseases [4, 13, 14, 12].

## 8 Conclusion

Gene-modified immunotherapy, when integrated with predictive modeling, omics data, and functional genomics, represents a pivotal shift in the landscape of biomedical research and treatment. This comprehensive survey illustrates the transformative potential of gene-modification technologies in enhancing the efficacy of cell therapies for complex diseases. Innovations such as CD4<sup>+</sup> T LEX-CD8086 cells have shown promise in strengthening anti-leukemia immunity, indicating new directions for vaccine development in leukemia immunotherapy.

Platforms like Bria-OTS+ highlight the ability of gene-modified therapies to robustly activate T-cells and NK cells, thus improving anti-tumor immune responses. The clinical potential of gene-modified antigen-specific Tregs in moderating pathogenic immune responses is particularly noteworthy for autoimmune conditions. Additionally, the enhanced cytotoxicity against tumor cells by NK-92MI hCD16 and NK-92MI hCD64 cells, especially when combined with rituximab, underscores their therapeutic promise for diverse tumor types, such as mantle cell lymphoma.

The findings of this survey affirm that immune-based therapies are at the forefront of revolutionizing cancer treatment. Continuous research is essential to refine these therapies for wider clinical application. By integrating advanced gene-modification techniques with comprehensive data analysis and predictive modeling, researchers are poised to develop more precise and effective therapeutic strategies, ultimately advancing personalized medicine and improving patient outcomes.

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## References

- [1] Jacek Mackiewicz, Tomasz Burzykowski, Dariusz Iżycki, and Andrzej Mackiewicz. Re-induction using whole cell melanoma vaccine genetically modified to melanoma stem cells-like beyond recurrence extends long term survival of high risk resected patients-updated results. *Journal for ImmunoTherapy of Cancer*, 6:1–8, 2018.
- [2] Miguel Lopez-Lago, Vikas Bhardwaj, Pravin Kesarwani, Xiaoyi Zheng, Sagarika Pachhal, Patience Cournoo, Renee Cortez, Charles L Wiseman, and William V Williams. Bria-ots immunotherapy platform: Harnessing gene-modified tumor cells to reinvigorate the cancer immunity cycle for precision anti-tumor responses. *AACR 2024 Poster*, 2024.
- [3] Patrick R Adair, Yong Chan Kim, Ai-Hong Zhang, Jeongheon Yoon, and David W Scott. Human tregs made antigen specific by gene modification: the power to treat autoimmunity and antidrug antibodies with precision. *Frontiers in immunology*, 8:1117, 2017.
- [4] Sarah Y Neshat, Stephany Y Tzeng, and Jordan J Green. Gene delivery for immunoengineering. *Current opinion in biotechnology*, 66:1–10, 2020.
- [5] Jiaqi Li, Fang Huang, Yan Jiang, Jie Zhao, Jiangbo Wan, and Siguo Hao. A novel costimulatory molecule gene-modified leukemia cell-derived exosome-targeted cd4+ t cell vaccine efficiently enhances anti-leukemia immunity. *Frontiers in Immunology*, 13:1043484, 2022.
- [6] Bilal Shaikh, Andrew Philip Freiburger, Matthias König, Frank T. Bergmann, David P. Nickerson, Herbert M. Sauro, Michael L. Blinov, Lucian P. Smith, Ion I. Moraru, and Jonathan R. Karr. Sed-ml validator: tool for debugging simulation experiments, 2021.
- [7] Bhargab Ghoshal, Biraja Ghoshal, Stephen Swift, and Allan Tucker. Uncertainty estimation in sars-cov-2 b-cell epitope prediction for vaccine development, 2021.
- [8] Marek Pecha. Balancing predictive relevance of ligand biochemical activities, 2021.
- [9] Lijing Lin, Matthew Sperrin, David A. Jenkins, Glen P. Martin, and Niels Peek. A scoping review of causal methods enabling predictions under hypothetical interventions, 2021.
- [10] Joseph A Trapani and Phillip K Darcy. Immunotherapy of cancer. *Australian family physician*, 46(4):194–198, 2017.
- [11] Timothy T Spear, Yuan Wang, Kendra C Foley, David C Murray, Gina M Scurti, Patricia E Simms, Elizabeth Garrett-Mayer, Lance M Hellman, Brian M Baker, and Michael I Nishimura. Critical biological parameters modulate affinity as a determinant of function in t-cell receptor gene-modified t-cells. *Cancer Immunology, Immunotherapy*, 66(11):1411–1424, 2017.
- [12] Wook-Jin Chae and Alfred LM Bothwell. Therapeutic potential of gene-modified regulatory t cells: from bench to bedside. *Frontiers in Immunology*, 9:303, 2018.
- [13] Marie-Andrée Forget, René J Tavera, Cara Haymaker, Renjith Ramachandran, Shuti Malu, Mingying Zhang, Seth Wardell, Orenthial J Fulbright, Chistopher Leroy Toth, Audrey M Gonzalez, et al. A novel method to generate and expand clinical-grade, genetically modified, tumor-infiltrating lymphocytes. *Frontiers in immunology*, 8:908, 2017.
- [14] Seok-Beom Yong, Jee Young Chung, Yoonsung Song, and Yong-Hee Kim. Recent challenges and advances in genetically-engineered cell therapy. *Journal of Pharmaceutical Investigation*, 48:199–208, 2018.
- [15] Rita Tendeiro Rego, Emma C Morris, and Mark W Lowdell. T-cell receptor gene-modified cells: past promises, present methodologies and future challenges. *Cytotherapy*, 21(3):341–357, 2019.
- [16] May Daher and Katayoun Rezvani. Next generation natural killer cells for cancer immunotherapy: the promise of genetic engineering. *Current opinion in immunology*, 51:146–153, 2018.
- [17] Ying Chen, Fengtao You, Licui Jiang, Jialu Li, Xuejun Zhu, Yangyi Bao, Xiang Sun, Xiaowen Tang, Huimin Meng, Gangli An, et al. Gene-modified nk-92mi cells expressing a chimeric cd16-bb- $\zeta$  or cd64-bb- $\zeta$  receptor exhibit enhanced cancer-killing ability in combination with therapeutic antibody. *Oncotarget*, 8(23):37128, 2017.



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