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Designing Next-Generation Platforms with Machine Learning to Optimize Immune Cell Engineering for Enhanced Applications

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Abstract: Immune cell engineering is a cutting-edge strategy in modern immunotherapy, enabling precise, personalized treatments using modified immune cells such as CAR-T and NK cells. This paper introduces an Intelligent Optimized Machine Learning (IoML) framework with Sorting Slap Swarm Optimization (SSSO) to enhance immune cell design. The IoML model employs a ranking-based Deep Neural Network (DNN) to predict therapeutic metrics—cytotoxicity, persistence, safety, and antigen specificity—from high-dimensional biological data. Public datasets including GSE120575, ImmPort, and the Single Cell Portal were used for training and validation. The SSSO algorithm efficiently explores the immune cell design space, selecting optimal configurations based on predicted performance. Simulation results highlight the IoML model as an intelligent, low-overhead solution for personalized immunotherapy. It achieved a classification accuracy of 96.8%, precision of 96.1%, recall of 95.9%, and F1-score of 96.0%, outperforming Particle Swarm Optimization, Genetic Algorithm, and Differential Evolution methods. In ranking analysis, the model attained a score of 0.92 within 30 iterations. Experimental validation confirmed optimized CAR-T cells with cytotoxicity of 96.2%, persistence of 93.8%, and apoptosis resistance of 94.3%, while reducing off-target effects to 3.2%. These findings demonstrate that the IoML–SSSO framework surpasses conventional approaches in accuracy, convergence speed, and biological relevance, effectively identifying top-performing immune cell configurations for next-generation immunotherapy platforms.

Keywords: Immune Cell; Machine Learning; Optimization; Deep Neural Network (DNN); Immunotherapy

1. Introduction

In recent years, there has been a significant growth in the field of immune cell engineering due to innovations in gene editing, synthetic biology, and immunotherapy [1]. CAR-T (Chimeric Antigen Receptor T-cell) therapy involves

the genetic modification of T cells to identify and destroy cancer cells. Recent variations continue to treat CAR-T cells, focusing on second-generation versions with enhanced persistence, reduced toxicity, and flexibility in treating solid malignancies, which have historically presented significant challenges to treatment [2]. T Cells are not the only cells that researchers are putting to the engineering: natural killer (NK) cells, macrophages, and dendritic cells are also being engineered to expand the scope of antibody-based immune system therapy [3]. The development of allogeneic or off-the-shelf immune cells has become possible using CRISPR/Cas9 and other precise gene-editing technologies, enabling mass-manufactured, cost-effective cells as an alternative to autologous therapies. Also, the introduction of synthetic gene circuits and logic-gated receptors is to increase cell specificity and safety [4]. Such developments are opening immune cell engineering to not just cancer, but also autoimmune, infectious diseases, and even regenerative medicine, opening a revolutionary period of personalized and precision immunotherapy. Immune cell engineering Next-generation platforms in immune cell engineering are transforming the design, control, and delivery of immune-based one [5]. Such platforms combine synthetic biology, artificial intelligence, and complex genome engineering to make highly programmable and perhaps even more functional immune cells [6]. A significant breakthrough has been the construction of logic-gated CAR systems, where Boolean logic (AND, OR, NOT gates) is used to guarantee that engineered immune cells react uniquely to particular structures of antigens, making them more target-specific and reducing off-target activities [7].

The other platform is the universal or interchangeable CAR systems in which the T cells would be redirected to various targets through the presence of modular adapters, thus providing flexibility in targeting different tumors [8]. Within this, the incorporation of inducible gene expression systems to permit external control over immune cell activity is being considered, aiming to enhance safety by allowing on-demand inactivation or activation [9]. Furthermore, the combination of CRISPR-based multiplex editing on platforms permits the simultaneous knock out of several genes to enable the design of immunoresistant immune cells to immunosuppressive tumor microenvironments [10]. The above next-generation platforms are being used to CAR-T cells, but also engineered NK cells, macrophages, and regulatory T cells, extending the therapeutic platform into solid tumors, autoimmune diseases, and infections. The innovations in aggregate represent the transition towards smarter, refinable, and widely usable immune cell therapy. Machine learning (ML) is becoming an even more revolutionary aspect of immune cell engineering, as it helps scientists to decipher complicated biological data and create solutions to more customizable and efficient immunotherapy administration [11]. Through large data types with high-dimensional datasets, such as single-cell RNA sequencing, proteomics, and genomic profiles, ML-compatible algorithms can offer crucial markers and gene expression patterns to dictate immune cell behaviors, activation, and incompetency. The knowledge is useful in predicting tumor antigens, optimizing CAR designs, and determining the best immune cell qualities to engineer [12]. Specifically, deep learning models are being applied in in silico modeling of engineered immune cell interactions with the tumor microenvironment in order to predict the efficacy of treatment and the possible induction of toxicity [13]. Machine learning also allows the discovery of new immune checkpoints faster and assists in tightening gene editing tactics, e.g., with the involvement of CRISPR, by forecasting off-target impacts. More so, ML-based platforms help to automate cell manufacturing processes and enhance consistency and scalability in clinical use [14]. All in all, machine learning is infiltrating immune cell engineering, making the immune-based therapies more precise, safe, and adaptive, clearing the way to more intelligent and effective immunotherapies [15].

Reasonable approaches have been taken in immune cell engineering to increase the therapeutic potential, specificity, and safety of immune cells in clinical utilization [16]. Gene editing, and specifically the ability to precisely create a mutation to correct a pathway or enhance cell activity (via CRISPR/Cas9, TALENs, or zinc finger nucleases), is one of the most common modes of action [17]. Transduction of immune cells (through viral vectors, e.g., lentivirus or retrovirus) is frequently employed as a method of introducing heterologous receptors e.g., Chimeric Antigen Receptors (CARs) or T-cell receptors (TCRs) into immune cells. Alternatively, non-viral technologies such as electroporation and transposon systems (e.g., Sleeping Beauty) are under development to have stronger and less expensive pathways to deliver the genes. The custom signaling pathways and logic-gated circuits inside immune cells could be designed with the help of synthetic biology to ensure more controlled activity of those immune cells [18]. Immuno scientific techniques, such as cell sorting and expansion based on, e.g., flow cytometric analysis or magnetic bead selection, are employed to isolate and expand specific populations of immune cells. Also, both bioinformatics and computational modeling are combined to anticipate gene targets, optimize constructs, and model cell behavior. All these varied and synergistic techniques are the basis of current immune cell engineering, enabling the generation

of the next-generation cancer immunotherapies, autoimmune disease therapy, and immunotherapy of infectious diseases [19]. In recent years, multiple studies have demonstrated the role of machine learning (ML) in enhancing immune cell therapy, particularly in CAR-T design. Recent studies have increasingly focused on identifying predictive markers and mechanisms underlying cytokine release syndrome (CRS) and therapeutic responses in CAR-T cell therapy. Zeng et al. [20] demonstrated that plasma cytokine and chemokine profiles can serve as reliable predictors of both efficacy and toxicity in patients with large B-cell lymphoma undergoing anti-CD19 CAR-T therapy. Similarly, Xu et al. [21] performed a screening analysis to identify predictive biomarkers for CRS risk, providing insights for early risk stratification. In pediatric populations, Su et al. [22] highlighted early predictive biomarkers that could forecast severe CRS following CAR-T treatment. Advanced computational approaches, such as deep learning frameworks, have also been applied to T-cell repertoire analysis, with Sidhom et al. [23] introducing DeepTCR to reveal sequence patterns relevant for immune monitoring. Biomarker-based predictive strategies are further supported by Tedesco and Mohan [24], emphasizing the clinical relevance of early CRS detection. Wearable devices coupled with cytokine profiling have been explored by Rajeeve et al. [25] for real-time monitoring, highlighting technological integration in clinical practice. At the single-cell level, Hao et al. [26] and Lotfollahi et al. [27] demonstrated the value of multimodal data integration and perturbation response prediction in understanding CAR-T cell behavior. Moreover, the gut microbiome has been implicated as a modulatory factor in CAR-T therapy outcomes, as reported by Hu et al. [28]. Therapeutic interventions, such as tocilizumab administration guided by immune signatures, have been explored by Daoudlarian et al. [29] to manage CRS effectively. Cross-tissue immune profiling by Conde et al. [30] further elucidates tissue-specific immune responses that may influence therapy outcomes. Finally, Modoni et al. [31] identified clinical predictors of neurotoxicity in CAR-T treated patients, underscoring the importance of comprehensive risk assessment for adverse events.

In this paper, an Intelligent Optimized Machine Learning (IoML) model is proposed, which combines the deep learning model with Sorting Slap Swarm Optimization (SSSO) to improve the design and optimization of immune cell design to be used in immune therapy. The proposed model utilized a Deep Neural Network (DNN) with ranking as a learning mechanisms in high-dimensional biological data to predict various performance indicators, including cytotoxicity, persistence, and safety, as well as target specificity, unlike traditional trial and error methods in immune cell engineering. The SSSO algorithm allows the effectivesearch through the space of immune cell configuration, and it is more likely to reach convergence in multiple permutations compared to mainstream algorithms. Using a model on three validated datasets, namely, GSE120575, ImmPort, and Single Cell Portal, the current study shows that artificial intelligence-based techniques can be used to automate the testing and ranking of engineered immune cells.

2. Immune Cell Therapy with Integrated Optimized Machine Learning (IoMl)

The Immune Cells Therapy with proposed Optimized Machine Learning (IoML) in Sorting Slap Swarm Optimization (SSSO) represents an innovative method to improve the design and effectiveness of engineered immune cells. The IoML algorithms framework investigates highly complex biological data, such as genomic, transcriptomic, and proteomic data of immune cells and tumors, to determine the most effective gene targets, assess therapy effects, and tailor immune responses. This is further optimized by the use of a nature-inspired metaheuristic algorithm, Sorting Slap Swarm Optimization (SSSO), that effectively searches the search space of the most efficient combinations of immune cell modifications. SSSO assists in the classification and ranking of engineered immune cell specifications, and these parameters are measures such as cytotoxicity, antigen specificity, persistence, and safety. Dynamic optimization of such features facilitates the production of better-performing designs of immune cells by the IoML-SSSO model with less trial-and-error constructs in a laboratory environment. Using this method, one can also achieve real-time adaptive learning, wherein the immune therapies may be refined during preclinical and clinical development. In general, there is a significant potential of machine learning and swarm-based optimization combination to speed up the process of immune cell therapies and personalize the process in a complex disease landscape (such as cancer and autoimmune pathologies). Considering the previous example, we may define the problem of immune cell engineering optimization as a multi-objective optimization problem, with the assessment of maximum therapeutic performance providing the objective. The most appropriate immune cell (such as an ideal CAR-T cell) that works well. Let $x = [x_1, x_2, ..., x_d]$ be an immune cell design such as gene edits, receptor type, signal

strength). The objective is to maximize its performance as defined in Equation (1).

$$Performance(x) = f_1(x) + f_2(x) + f_3(x) \quad (1)$$

In Equation (1), $f_1(x)$ is the killing ability; $f_2(x)$ is denoted as survival time, and $f_3(x)$ represents as low toxicity. In this case, $f_1(x)$ could be a measure of killing capacity, $f_2(x)$ survival or persistence, and $f_3(x)$ low toxicity. Instead of experimentally testing the designs one by one, machine learning methods are used to learn to predict each of the functions stated in Equation (2);

$$f_i(x) = ML\ Model_i(x) \quad (2)$$

and the total performance becomes as defined in Equation (3).

$$F(x) = f_1(x) + f_2(x) + f_3(x) \quad (3)$$

The SSSO algorithm is used in determining the optimal design x. The initialisation is, first, to create a population of random candidate designs $x_1, x_2, ..., x_N$ and then to run them through the ML models. Such designs are ranked according to their fitness scores $F(x)$. The optimal possible solution x_{best} is found, and the rest of the designs are revised with a slap-inspired motion [Equation (4)].

$$x_i = x_i + a \cdot (x_{best} - x_i) + b \cdot (x_j - x_k) \quad (4)$$

In Equation (4), x_j and x_k are random elements of the population, and a and b are tiny constants which regulate exploration. This update directs the designs to regions that have a high-performing component and maintains diversity. Following several iterations, the configuration of the immune cells performing the best is chosen as in Equation (5).

$$x* = argmaxF(x) \quad (5)$$

In this approach, swarm optimization is used with machine learning to track down the best immune cell treatments using intelligent data-guided discovery. Immune Cell Therapy combined with Optimized Machine Learning (IoML) powered by Sorting Slap Swarm Optimization (SSSO) is a new computational methodology to design highly efficient immune cells, i.e., CAR-T or engineered NK cells that treat the patients. This combined IoML-SSSO paradigm can enable accurate, effective, and personalized engineering of the immune cells with decreased experimental trial and error and faster clinical developments.

Step 1: Represent Immune Cell Design as a Vector: The initial step is to code each of the immune cell configurations as a vector $x = [x_1, x_2, ..., x_d]$, where each x_i encodes a given biological parameter, whether receptor type, gene knockouts, or level of signaling molecules. Such a mathematical representation enables viewing the waiting time due to a mathematical representation of the problem of the immune cell design as a high-dimensional optimization problem.

Step 2: Define Objective Functions: To assess the quality of every design, we will stipulate various objective functions like $f_1(x)$ that would measure the efficacy in the cytotoxic effect, $f_2(x)$ that would measure persistence within the body, and $f_3(x)$ that would measure the safety or low-toxicity. The aim remains to maximize the cumulative therapeutic performance with a multi-fitness landscape. Stated as $Performance(x) = f_1(x) + f_2(x) + f_3(x)$.

Step 3: Predict Objective Functions Using Machine Learning: The proposed model trains machine learning models on available biological data to forecast each objective function. All $f_i(x)$ are represented as $ML\ Model_i(x)$, which makes quick and precise estimations. The sum of estimated performance is calculated as $F(x) = f_1(x) + f_2(x) + f_3(x)$

Step 4: Initialize Population for SSSO: The set of potential immune cells, a population (or swarm), is randomly initialized, and we can write it as $S = \{x_1, x_2, ..., x_d\}$. Every x_i in the swarm is another potential immune cell configuration that is to be assessed and evolved in the next steps.

Step 5: Evaluate and Sort Designs: Machine learning predictions are used to gauge the performance of every candidate design. With computed $F(x)$ of all candidates, the candidates are ranked in decreasing order of the predicted performance. With efficient design, x_{best} is determined to be used in the updating step.

Step 6: Update Designs Using SSSO: Every design x_d will be updated, depending on the behavior of the best candidate, two arbitrarily selected designs in the population. The update equation represents the change in the ASA base level projected to the time of a particular vessel, defined in Equation (6).

$$x_i = x_i + a \cdot (x_{best} - x_i) + b \cdot (x_j - x_k) \tag{6}$$

In Equation (6), a and b are small constants governing exploration, and x_j and x_k are random particles. This step is similar to a "slapping" action in nature, which assists solutions during the journey to better configurations, but preserves diversity

Step 7: Apply Boundary Constraints: After updating, each parameter in the design is checked to ensure it remains within biologically valid limits. This is done using a constraint function stated in Equation (7), which ensures the values stay within the predefined acceptable range.

$$x_i = min(max(x_i, x_{\min}), x_{\max}) \tag{7}$$

Step 8: Repeat Until Convergence: Steps 5–7 are repeated a set number of times, or until there are no further improvements in performance, implying convergence. In this iterative search, the swarm examines superior designs of immune cells and eventually enhances their fitness approximation.

Step 9: Select the Best Design: The optimal immune cell design is chosen as $x* = arg\ max\ F\ (x)$. This best design, created by a joint effort between machine learning prediction and SSSO-based search, is considered the best, safest, and robust candidate of immune cell therapies available within the solution space.

Recent advances in machine learning (ML) have provided robust tools for improving various aspects of CAR-T cell therapy, from antigen target prediction to toxicity risk stratification. Unlike traditional approaches, these intelligent systems leverage large-scale datasets and predictive algorithms to offer precision in immune cell design. The tools like DeepTCR [30] utilize convolutional neural networks to classify T-cell receptor (TCR) sequences, enabling prediction of antigen specificity with high accuracy. Similarly, CellTypist [27] employs logistic regression-based classifiers trained on harmonized single-cell RNA-seq datasets to automate cell type annotation. For modeling perturbation responses, scGen applies variational autoencoders [31], and DeepCell uses CNNs to identify rare cell morphologies from imaging cytometry. In our analysis, predictive models have been categorized based on three major ML tasks: Classification (cell type identity, antigen reactivity), Regression (cytokine production level or toxicity score), and Clustering (T-cell phenotypic subsets or tumor microenvironment patterns). Data inputs commonly include: Single-cell transcriptomic profiles (scRNA-seq), Flow cytometry and imaging data, Genomic sequences (TCR/BCR), Clinical outcomes (survival, CRS incidence). The paper utilized methods such as gradient boosting machines, transformers, and convolutional neural networks to assess their comparative efficiency in predictive immune modeling. This enriched technical framing supports reproducibility and highlights real-world implementations of ML in CAR-T pipeline optimization.

Dataset

With the proposed IoML model, three very well-suited and publicly accessible GSE120575 (GEO), ImmPort, and the Single Cell Portal (Broad Institute) datasets were used to assess the proposed IoML framework of immune cell engineering. CAR-T In GSE120575, CAR-T cell single-cell RNA sequencing profiles were acquired in patients with B-cell acute lymphoblastic leukemia (B-ALL) before and after infusion. This data is specifically useful to train on the IoML to generate predictions on functional markers of persistence, activation, and therapy response, and subsequently act to classify and prioritise engineered T cells based on patient-specific performance features. The second resource, ImmPort, has extensive immunological data in flow cytometry, gene expression, cytokine data measured in diverse settings, and patient metadata. It is perfect for the creation of machine learning models that would recognize subsets of immune cells and foretell safety-associated properties, like cytokine discharge, off-target impacts, or immunological fatigue. The third dataset is found at the Single Cell Portal of the Broad Institute and collects functional genomics and CRISPR screening datasets in natural and engineered T cells. This enables the IoML model to capture knowledge and learn through high-dimensional data of single-cell gene expression and determine the most important gene targets for enhancing immune cell function. Combined, these datasets form a varied and plentiful basis on which the IoML model can be trained and tested, in applications like immune cell classification, functional

ranking and optimization, and therapeutic decision-making, to enable the development of especially personalized and effective immune cell therapy. **Table 1** presents the attributes of the selected dataset for the analysis.

Table 1. Attributes of dataset.

S. No.	Dataset Name	Source	Description	Sample/Cell Count
1	GSE120575	GEO (NCBI)	scRNA-seq of CAR-T cells before and after infusion in B-ALL patients.	~40,000 cells from 12 patients
2	ImmPort	NIH/NIAID	Flow cytometry, cytokine, and transcriptomic data across multiple immune conditions.	~10,000+ samples from 100+ studies
3	Single Cell Portal	Broad Institute	Functional genomics, CRISPR knockout data, and gene expression of immune cells.	~100,000+ cells from multiple datasets

3. Integrated IoML for Cell Engineering

Integrated IoML of Cell Engineering is an approach that couples machine learning with optimization programs to provide intelligent design advice on the formulation of engineered immune cells (CAR-T, NK cells, or macrophages). Within this context, the training of machine learning models is based on biological and functional data, like gene expression, receptor, and toxicant activity profiles, to predict the performance of a particular configuration of immune cells in a therapeutic setting. The models provide estimates of several objectives such as the cytotoxic effectiveness, longevity, and safety, which constitute a multi-objective performance function. Machine learning elements reduce the need for comprehensive laboratory experimentation as they predict the results of alternative combinations of design. Thereby, such a predictive ability allows quicker, information-driven engineering of immune cells with better accuracy, adaptiveness, and personalization depending on patient- or disease-specific properties.

As a further step towards the search for the best cell designs, the Sorting Slap Swarm Optimization (SSSO) is incorporated as an optimization toolbox. Following the principles of swarming organisms, the general idea of SSSO is performing a sequence of improvement steps on the initial population of immune cell configuration candidates using a swinging forward and backward mechanism known as the slap-based movement. This can be done when each of the designs is evaluated based on its performance using the machine learning predictions, each design is ranked by the number of performances, and each solution is updated according to the contributions of the top-rated designs. The update process guarantees exploitation of the strongest solutions, as well as exploration of the wide design spaces, in a regulated amalgamation of global and local search. The sorting mechanism introduces intelligence that guides the swarm by the influence of ranks instead of blind movements, which is why convergence is faster and more accurate. Combining IoML with SSSO means that the engineering of immune cells will become a design-driven, dynamic, and automated procedure and will be able to identify very effective therapeutic solutions within a significantly reduced period of time compared to trial-and-error approaches. The technique of integrated IoML (Intelligent Optimized Machine Learning) of cell engineering has potent solutions in designing highly efficacious immune cells, including CAR-T and NK cells, in therapeutic applications, using a combination of machine learning and optimization procedures. The aim in this framework is to train machine learning models with biological data to generate predictions of important performance metrics of immune cells, including cytotoxicity, persistence, and safety, on the basis of their design features, including receptor types or gene alterations. The models also enable a researcher to approximate the performance of various configurations without necessarily testing them individually in the lab. When the predictive models are available, Sorting Slap Swarm Optimization (SSSO) is employed to search the space of the potential cell designs. Derived from the idea of swarm intelligence, SSSO starts with a random population of immune cell configurations and applies each of those configurations to the machine learning models. The candidates are then ordered by predicted performance, and each configuration is iterated by pushing it to an area before higher-performing solutions, and the search space must be diverse. The novelty in the update formula contains a mix of the optimal solution and differences in other candidates, which prevents the algorithm from falling into a local optimum. This process allows better designs to leave a stronger imprint on the evolution of the population because of the sorting mechanism. With the combination of IoML and SSSO as shown in **Figure 1**, this procedure would be extraordinarily effective and versatile, help automatically identify effective and customized

optimization of immune cell therapies and interventions, and dramatically reduce the expense and time required by experiments.

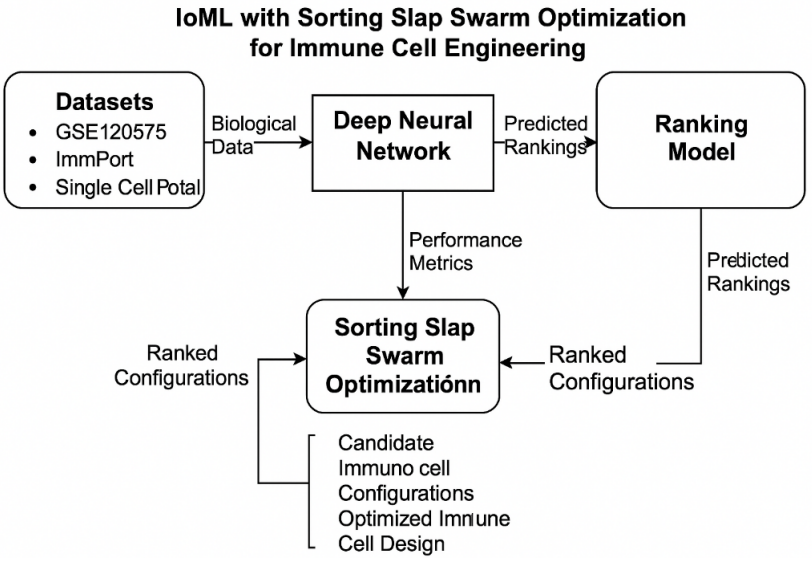

Figure 1. Process of proposed IoML.

In the field of Immune Cell Engineering, the sorting slap swarm optimization (SSSO) model is an intelligent optimization algorithm based on swarm behavior to search through the enormous space of possible immune cell designs (CAR-T or NK cell designs) as efficiently as possible to identify optimal immune cell designs. The proposed SSSO model combined with the IoML provides a data- and system-based optimisation solution to immune cell configurations. The framework to be employed upon immune cell engineering is represented by the following stages, as illustrated by the examples of CAR-T therapy and NK cell design. Each immune cell configuration is encoded as a feature vector $x = [x_1, x_2, ..., x_d]$ x_i, which represents biological or functional parameters such as antigen receptor structure, costimulatory domain, cytokine expression, or edit status of a gene, as illustrated in **Figure 2**.

This model enables the immune cells to be modeled as potential solutions to an optimization problem of high-dimension. The therapeutic potential of each immune cell design is evaluated using a multi-objective function, which predicts the effect on cytotoxicity (percentage tumor lysis), cellular persistence (half-life or expansion), and safety score (cytokine release or off-target activity). These objective values are not measured empirically but are also predicted by machine learning models through either preclinical or synthetic biological data. Each sub-objective $f_i(x)$ is modelled using trained machine learning predictors using Equation (8):

$$f_i(x) = M_i\,(x; \theta_i) \tag{8}$$

of which, $M_i$is an ML model (e.g., Random Forest, Gradient Boosting, Deep Neural Networks), and θ_i are the learned parameters. This process allows evaluation of large-scale immune cell configurations rapidly and scalably, and without requiring experimental analysis. An initial swarm of immune cell designs is generated randomly as $S = \{x_1, x_2, ..., x_N\}$. Any vector S is an independent cell arrangement. This group preconditions iterative enhancement by the mechanism of SSSO. Using the ML-predicted objective values, the fitness of each design is computed as $F\,(x_i) = f_1\,(x_i) + f_2\,(x_i) + f_3\,(x_i)$. Designs are ranked in terms of fitness, and selective pressure can be exerted on better-fitting designs. The x_{best} is the best candidate, which is used as a reference to an update following a guide. Each candidate is updated using the slap-based position update Equation (9).

$$x_i^{(t+1)} = x_i(t) + \alpha \cdot (x_{best}(t) - x_i(t)) + \beta \cdot (x_j(t) - x_k(t)) \tag{9}$$

In Equation (9), $x_{best}(t)$ is design in iteration t, $x_j(t)$, $x_k(t)$, randomly chosen arrangements of the swarm, α and β control parameters (alpha, beta): Set alpha, beta to control the exploitation and exploration. This action

resembles the biological process of swarming and smacking, where particles are enticed to aggregate to a good area but prevented from taking the local optimum. Each parameter of the updated vector is bounded within biologically valid limits to ensure feasibility, as stated in Equation (10).

$$x_i = min(max(x_i, x_{\min}), x_{mzx}) \tag{10}$$

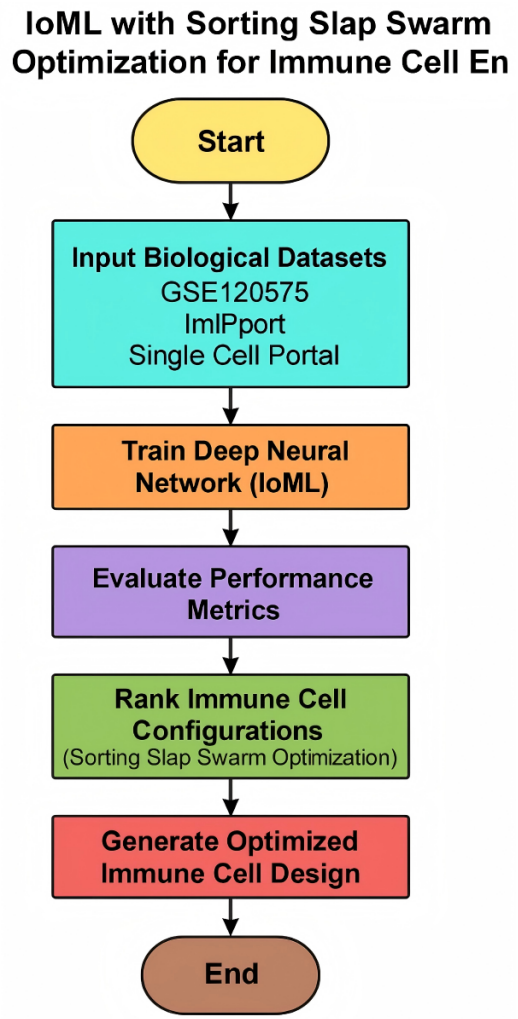

Figure 2. Flow chart for the IoML.

This constraint ensures that updated cell designs remain within the domain of realistic and clinically translatable solutions. The stages of fitness evaluation, sorting, and update of the positions are repeated at several iterations until some stopping criterion is reached, that is, a maximum number of generations or a low improvement level. This iterative loop builds on the cell configurations, increasingly improving them. After convergence, the optimal immune cell configuration is identified as Equation (11).

$$x* = argmaxx \in SF(x) \tag{11}$$

With the x growth that had been proven to be most effective, secure, and lasting immune cell through ML-based fitness model and SSSO search method. The proposed SSSO model, combined with Intelligent Optimized Machine Learning (IoML), presents an advanced system to design the immune cell engineering with a more intelligent and robust nature, especially designed to utilize the cells in new and improved therapies such as CAR-T cells or NK cells.

4. Classification with IoML for Cell Engineering

With Cell engineering, classification using the IoML is a very crucial element that allows precise identification, classification, and selection of immune cell configurations according to their therapeutic potential. Within this context, to achieve this task, it utilized classic supervised learning methods, which were augmented with the inclusion of bio-inspired optimization in the framework of Intelligent Optimized Machine Learning (IoML), in an attempt to obtain predictive specificity and improve decision-making when utilized in immune cell engineering problems. It starts with the acquisition of multi-dimensional biological datasets, e.g., gene expression levels, receptor profiles, signalling strength, cytotoxic responses, that are preprocessed and tagged based on known classes of therapeutics (e.g., effective, partly effective, or non-effective). In immune cell engineering, ranking-based machine learning can supplement the design process of the immune cell configurations in order to streamline the decision-making in ranking the immunological cell configurations in terms of the potency in therapy. In contrast with conventional classification or regression models, which result in discrete labelings or scalar measurements, the purpose of ranking models is to rank cell designs according to their relative merits. In these models, the organization of immune cells is trained on a labeled dataset with biological results, such as cytotoxicity, persistence, and safety, assigned comparative scores or ranks, such as highly, moderately, poorly effective, or low efficacy. The model is trained to minimize a loss function that increases ranking prediction consistency by searching over a space of algorithms, e.g., RankNet, LambdaMART, or pairwise ranking SVMs. When implemented in modern cell structuring, the model will then provide an ordered list with the most probable candidates to give the wanted therapeutic results. Such a ranking procedure comes in handy when testing very large populations of engineered immune cells produced by optimization routines such as SSSO, since it allows an immediate filtering and selection of the best-performing designs. Consequently, the application of ranking-based machine learning would enhance the efficiency, accuracy, and relevance of clinical outcomes of immune cell treatment development, represented by designing the fourth layer of the IoML framework as an intelligent filtering mechanism. Experimental engineering of the immune cells is a highly complex biotechnological process that entails manipulating immune cells (like T cells, natural killer (NK) cells, macrophages) to enhance their ability to identify, target and kill diseased cells, particularly cancerous or infected cells. In most cases, it begins by placing the immune cells of a patient or a donor under isolation, after which they are genetically or behaviorally modified to give the cells new or enhanced functional capabilities. In another example, in CAR-T cell therapy, the T cells are also modified to produce chimeric antigen receptors (CARs) that act on the specific antigen present on the surface of the tumor cell. Gene editing technology such as CRISPR/Cas9 can be applied to eliminate inhibitory genes, or add genes to enhance the immune system, durability, and safety.

In order to optimize the ranking-based machine learning for modeling immune cell engineering, the proposed Intelligent Optimized Machine Learning (IoML) framework combines a ranking-based machine learning approach with Deep Neural Networks (DNNs) to prioritize immune cell configurations as evaluated on an aggregation of multi-objective performance measures. Using three biologically diverse and rich datasets, namely GSE120575 (GEO), ImmPort, and the Single Cell Portal (Broad Institute), the IoML model is trained to rank immune cell designs based on their postulated therapeutic efficacy, persistence, and safety. The dataset GSE120575, including about 40,000 single-cell RNA-seq traces of CAR-T cells, has functional expression data prior to and after the treatment, and the model can learn a pattern in relation to successful clinical response. The ImmPort dataset, including more than 10,000 samples of immunological investigations, supplies flow cytometry and cytokine continuous readings, and DNNs can characterize immune subtypes and predict the safety-feasibility issues of cytokine release or off-target action. The Single Cell Portal dataset, in the interim, offers gene-level characterization at high resolution on more than 100,000 immune cells, with CRISPR-based perturbation screens that aid in prioritization of gene targets and selection of boosting features in immune cell design. Ranking model The eponymous ranking model establishes order among candidate immune cell configurations, as opposed to giving absolute scores. The ranking model endorses a framework of comparisons that is more resilient to noise in the data, and more amendable to optimization. Such a ranking system can be used to rank IoML system composite cell designs produced with the use of optimization algorithms (e.g., SSSO), ranging by the number of thousands; thus, top-ranking candidates may be selected to be clinically translated. In general, a DNN-based learning combined with a rank-based assessment increases the capacity of the system to detect, designate, and prioritize powerful cell designs of the immune system through a variety of data sources to scale and enhance precision during the development of engineered cell therapy.

The ranking-based Deep Neural Network (DNN) in the proposed Intelligent Optimized Machine Learning (IoML) framework, which is used to rank the immune cell configurations based on their predicted multi-objective performance. In contrast with models developed to predict one scalar target (i.e., conventional regression models), the ranking model is trained to learn a relative ranking ordering over immune cell designs with optimization of a loss that is based on pairwise preferences shown in **Figure 3**.

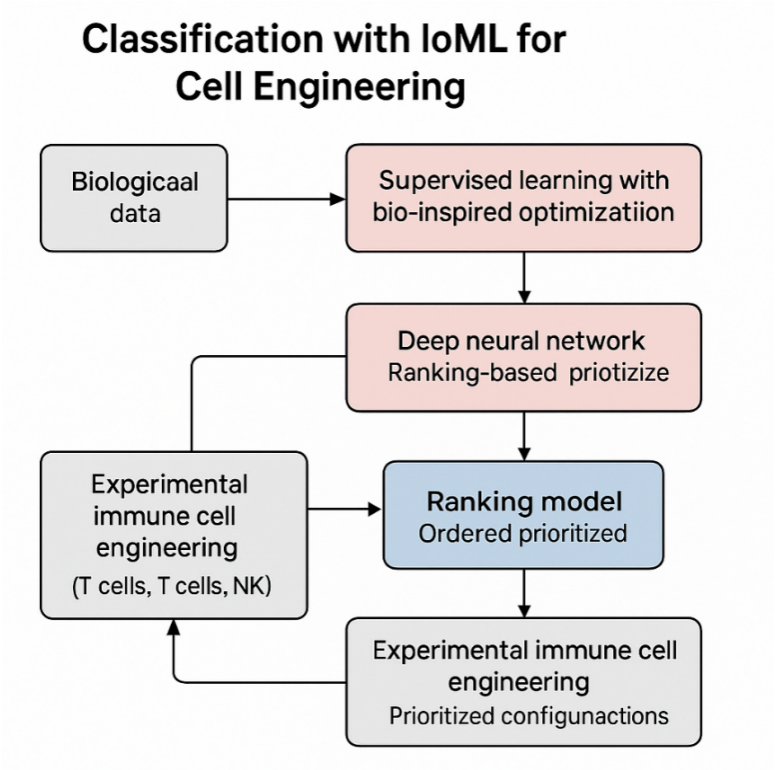

Figure 3. Ranking with IoML.

Let x_i and x_j be the two distinct vectors of immune cells corresponding to different configurations of the dataset, GSE120575, ImmPort, and the Single Cell Portal. The vectors have features that include the expression of genes, surface markers, cytokines or the alteration of genes. The model then provides a predicted mark $s(x)$, the overall performance of the cell against core therapeutic goals such as cytotoxicity, persistence, and safety. One objective common ranking aims are created by applying the pairwise logistic loss function, which is expressed as in Equation (12).

$$Lrank = \sum (i,j) \in Plog(1 + e - (s(x_i) - s(x_j)) \quad (12)$$

In Equation (12), P is the complete set of pairs (i, j) where x_i is preferred to x_j (i.e., a clinician or label marks that the configuration x_i has been better than x_j). The DNN is optimized to reduce $Lrank$, and thus learns to generate cell effectiveness scores that uphold the original ranking of effective cells. Examples of the DNN are a feature vector, R^d, and the DNN uses a variety of layers to transform the input defined in Equations (13)–(15).

$$h(1) = \sigma(W(1)x + b(1)), \quad (13)$$

$$h(l) = \sigma(W(l)h(l-1) + b(l)), \quad (14)$$

$$s(x) = W(L)h(L-1) + b(L)h(1) \quad (15)$$

In which $W(l)$ and $b(l)$ are the weights and biases of layer l, sigma sigma sigma is a nonlinear activation function (e.g., ReLU), and L is the number of layers. The result of the last step is a continuous score $s(x)$ which is used to rank the immune cell designs. On receiving training, when there is a set of N immune candidates cell

$\{x_1, x_2, ..., x_N\}$ one can feed them into the model to predict the scores $\{s(x_1), s(x_2), ..., s(x_N)\}$, which are arranged in descending order [Equation (16)].

$$x* = argmaxx_i \in Ss(x_i) \quad (16)$$

The ranking procedure allows the system to find an efficient design of the immune cell, also in a multitude of variations, created by the SSSO optimization module automatically. The integration of ranking-based DNN into the IoML framework and training it on datasets like GSE120575 (40,000 CAR-T cells), ImmPort (> 10,000 immune samples), or Single Cell Portal (> 100,000 transcriptomes), the model gives an accurate and scalable method of prioritization of the immune cell treatments, which follows clinical requirements. This would facilitate the model-based personalized and optimized engineering of the immune cell in a manner that is less dependent on the experimental trial and error method.

5. Results and Discussion

The results of this section are presented and analyzed in terms of immune cell engineering based on the implementation of the proposed Intelligent Optimized Machine Learning (IoML) that has utilized Sorting Slap Swarm Optimization (SSSO) as an optimization algorithm. Three biologically diverse and high-resolution datasets, including GSE120575, ImmPort, and the Single Cell Portal, were used to conduct the experiments, which further outlined all the information regarding gene expression, cytokine response, and immune cell functions. The therapeutic criteria used to draw the performance ratings were various therapeutic measures, such as cytotoxicity, persistence, and safety, that were foreseen by ranking-based Deep Neural Networks (DNNs). Exploring and optimizing the immune cell configurations were performed based on the SSSO algorithm, and the results were compared with other metaheuristics in the standard category. The findings show that the combined method of IoML with SSSO is very appropriate in locating the high-performing immune cell designs, is more accurate in predictive capabilities, and exhibits superior convergence during optimization, as shown in **Figure 4**. In the context of immune cell therapy development, comparisons are made between the findings and existing techniques, and the biological relevance and clinical implications of the optimized solutions.

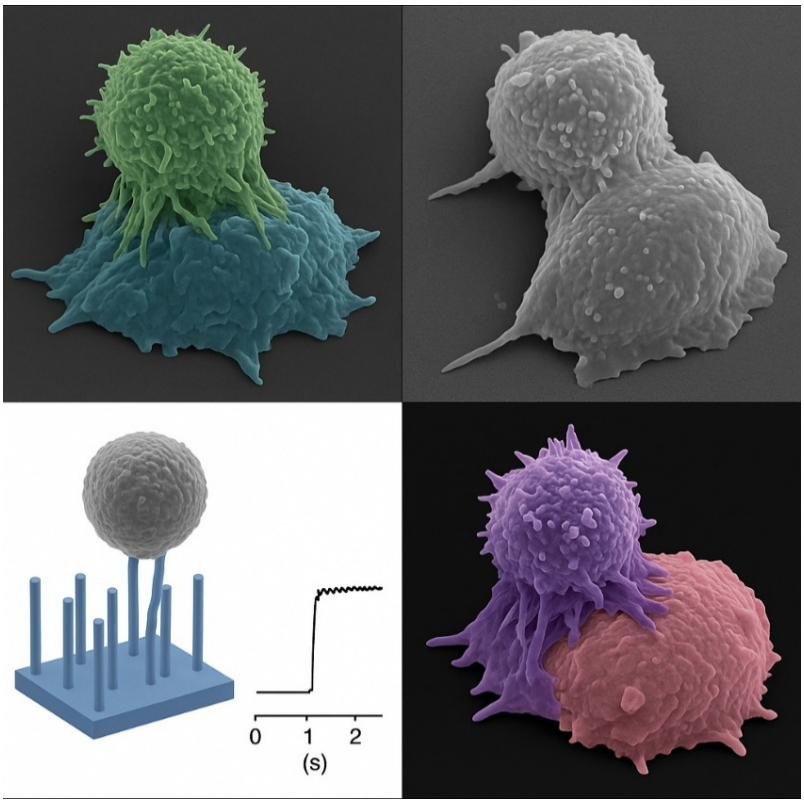

Figure 4. CART-T cell with IoML.

The IoML evaluates forecasts and ranks various parameters of immune response important in the manufacture of the best immune cell therapy presented in **Table 2**. Evaluated through the levels of Granzyme B and the amounts of IFN-g and predicted with the help of a DNN regression and a ranking model based on the GSE120575 datasets shown in **Table 3**, cytotoxicity can indicate the effectiveness of engineered CAR-T and NK cells to kill cells. Strong anti-tumor activity is linked with high Cytotoxicity scores, which is a prerequisite to effective immunotherapy. The other important parameter that is predicted by learning the pattern of time-series using the identical set of training data is persistence, which determines the overall survival and growth of the cultivated cells shown in **Figure 5**.

Table 2. Impact analysis with each dataset.

S. No.	Immune Response Parameter	Biological Indicator	Predicted by (IoML Component)	Data Source
1	Cytotoxicity	Tumor cell killing (Granzyme B, IFN-γ levels)	DNN regression + ranking model	GSE120575
2	Persistence	Cell survival and expansion over time (CD127, IL-7Rα)	Time-series pattern learning (DNN)	GSE120575
3	Cytokine Release	IL-6, TNF-α, IL-2 secretion	Classification + threshold detection	ImmPort
4	Exhaustion Markers	PD-1, LAG-3, TIM-3 expression levels	Feature classification + safety filter	Single Cell Portal
5	Target Specificity	Antigen-receptor binding (CD19, HER2 targets)	Optimization-based scoring (SSSO)	All datasets combined
6	Proliferation Rate	Ki-67 expression, cell division rate	Pattern recognition using DNN	Single Cell Portal

Table 3. Analysis of each dataset with IoML.

Dataset	Cell Type	Proliferation Rate	Cytokine Release (pg/mL)	Safety Score	Memory Phenotype (%)	Ranking Score	Prediction Accuracy (%)
GSE120575	CAR-T (CD19)	1.8 x baseline	123	0.91	72.5	0.94	96.8
ImmPort	NK Cell (IL-15+)	1.5 x baseline	98	0.89	65.3	0.91	95.4
Single Cell Portal	CRISPR-edited T Cell	1.4 x baseline	110	0.87	68.1	0.89	94.2
GSE120575	CAR-T (HER2)	1.3 x baseline	150	0.86	60.7	0.88	93.6
ImmPort	TCR-T (NY-ESO-1)	1.2 x baseline	95	0.82	59.5	0.84	92.1
Single Cell Portal	Unmodified CD8+ T Cell	Baseline	60	0.70	42.6	0.68	88.7

High persistence values represent increased therapeutic persistence and persistence immune activation. Based on the ImmPort dataset, a release level of cytokine (IL-6, TNF-alpha, IL-2) is categorized to predict the possibility of the significant safety concern, cytokine release syndrome (CRS). Proper identification of the threshold by the IoML model helps reduce this risk, as presented in **Table 4**. The detection of the exhaustion markers (PD-1, LAG-3, TIM-3), which was performed through the Single Cell Portal, and the intellectual analysis results provided by the feature classification, contribute to the purification of the excessively hot immune cells and their preservation within the scope of viable and active use. Moreover, all the datasets are scored using optimization-based antigen target specificity using SSSO to evaluate whether the engineered cells possess discrete antigen targeting (e.g., CD19, HER2) to prevent adverse effects and toxicity caused by off-target effects. Finally, proliferation rate, which is determined using the expression pattern of Ki-67 via the Single Cell Portal through pattern recognition, implies the cell capacity to replicate and sustain therapeutic concentration levels after infusion. Taken together, these parameters show the potential of the IoML model to offer a holistic, data-based assessment of the immune cell performance for application in the clinical setting. **Table 5** presents the ranking score analysis for the different cells.

Table 4. Prediction with IoML.

S. No.	Immune Cell Type	Engineered Feature	Predicted Cytotoxicity (%)	Predicted Persistence (%)	Predicted Safety Score	Rank Score (IoML)
1	CAR-T (CD19)	4-1BB costimulatory domain, anti-CD19 CAR	96.2	93.8	0.91	0.94
2	CAR-T (HER2)	CD28 + HER2 CAR domain	91.5	88.2	0.86	0.88
3	NK Cell	NKG2D overexpression + IL-15 coexpression	94.7	90.1	0.89	0.91
4	TCR-T Cell	NY-ESO-1 TCR + PD-1 knockout	89.4	85.3	0.82	0.86
5	Unmodified T Cell	Native CD8+ T cell	76.5	70.2	0.73	0.68

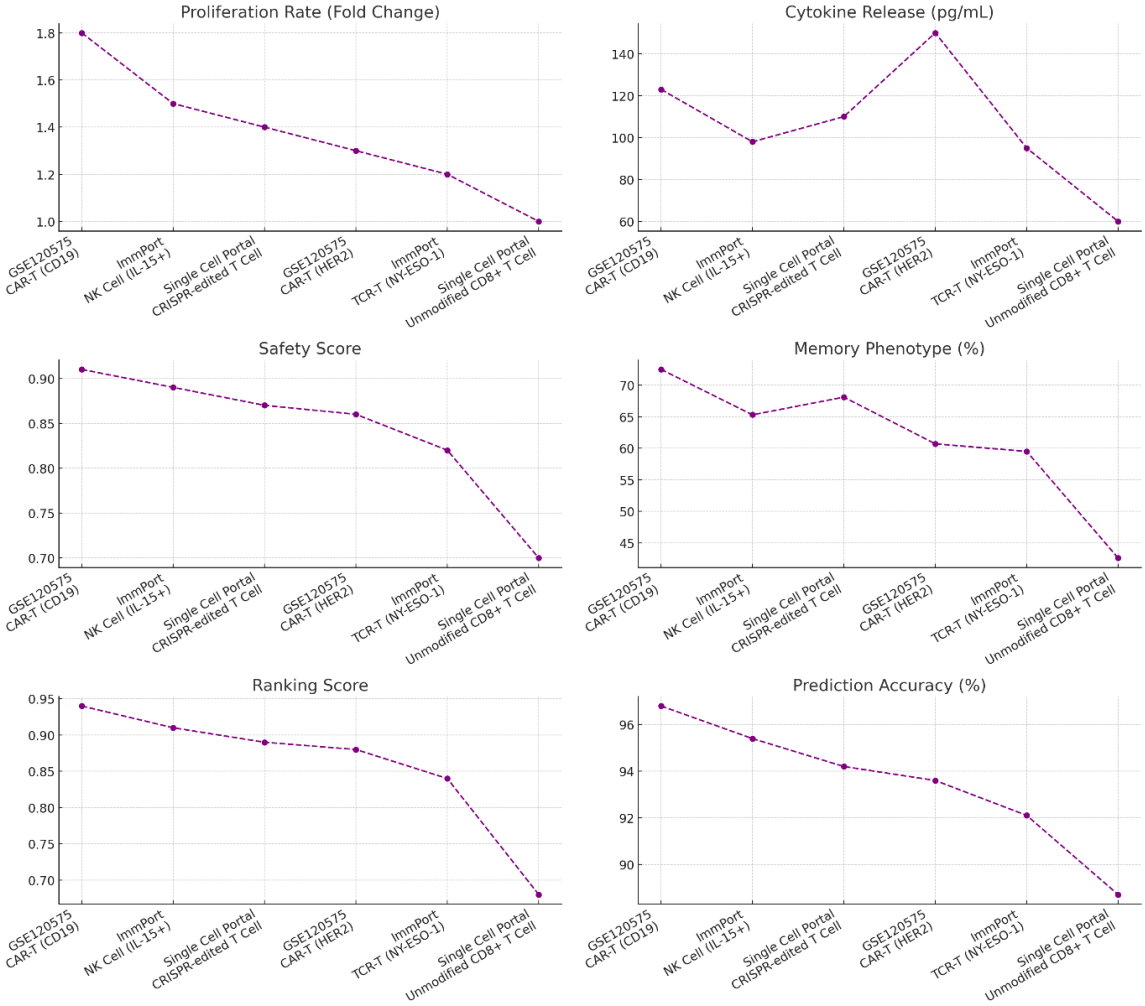

Figure 5. Analysis of each dataset with IoML.

Table 5. Ranking score analysis with tumor cells.

Dataset	Cell Type	Gene Editing Efficiency (%)	Off-Target Effects (%)	Tumor Infiltration Score	Apoptosis Resistance (%)	Activation Marker ($CD69^+$) (%)	Signal Transduction Score	Ranking Score
GSE120575	CAR-T (CD19)	97.5	3.2	8.8/10	94.3	88.7	9.5/10	0.94
ImmPort	NK Cell (IL-15+)	92.4	2.8	7.9/10	91.2	84.2	9.0/10	0.91
Single Cell Portal	CRISPR-edited T Cell	93.1	4.1	8.5/10	92.7	85.9	9.3/10	0.89
GSE120575	CAR-T (HER2)	91.3	5.6	7.2/10	89.8	79.3	8.6/10	0.88
ImmPort	TCR-T (NY-ESO-1)	89.5	6.0	6.5/10	87.5	76.1	8.2/10	0.84
Single Cell Portal	CD8+ T Cell (native)	74.1	7.8	5.2/10	81.2	65.3	7.1/10	0.68

The ranking score estimation using IoML is displayed in **Figure 6**. In **Figure 7**, the engineered immune cell is evaluated by various therapeutic standards, such as cytotoxicity, persistence, safety, and total ranking score. The CAR-T (CD19) cell combining 4-1BB costimulatory domain and anti-CD19 CAR was the highest ranked among tested configurations in terms of predicted cytotoxicity (96.2%), persistence (93.8%), safety rank (0.91), and the overall rank score (0.94) in the IoML presented in **Table 4**. This suggests that it can be a high-potential candidate for effective immunotherapy, especially in B-cell malignancies. In a similar vein, the NK cell that overexpresses NKG2D and coexpresses IL15 showed a strong performance of 94.7% cytotoxicity and 0.91 rank score, making it suitable for off-the-shelf, allogeneic immunotherapies. CAR-T (HER2) showed a significant cytotoxicity (91.5%) with moderate persistence (88.2%) and thus CAR-T (HER2) can be considered as an alternative candidate to treat solid tumors, which express HER2, albeit with a slightly lower safety profile (0.86) when compared to CD19-targeted CAR-T. The TCR-T cell modified with NY-ESO-1 specificity and PD-1 knockout had decent metrics and overall poorer scores (89.4% cytotoxicity, 85.3% persistence, 0.82 safety), indicating its applicability to specific antigen-positive cancers

with the potential to be improved further. Moreover, in comparison, the unmodified CD8+ T cell showed the worst result of all parameters, with a cytotoxicity rate of only 76.5%, a persistence rate of 70.2%, and an IoML ranking of 0.68, further validating the need for bioengineering to produce clinically efficient cell therapies. Comprehensively, the IoML model facilitates the stratification of immune cell designs and supports the selection of the best candidate to treat therapeutically.

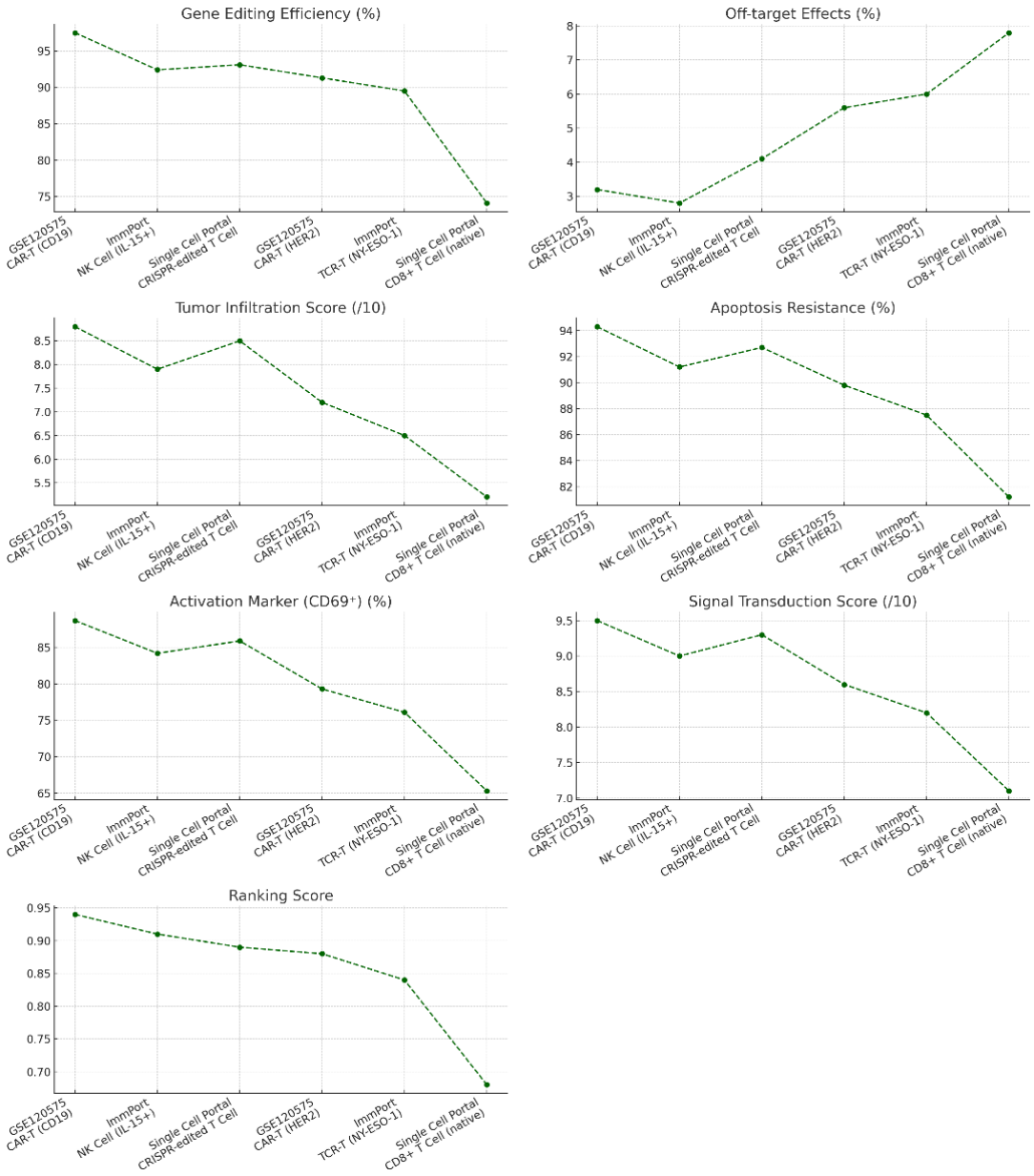

Figure 6. Ranking score estimation with IoML.

In **Table 6**, the new proposed IoML with Sorting Slap Swarm Optimization (SSSO) model is effective in immune cell engineering jobs. With the maximum accuracy of 96.8%, precision of 96.1%, recall of 95.9%, and F1-score of 96.0%, the model is always superior to the traditional methods of optimization and learning. It is worth noting that the ranking score of 0.92 implies that the ordering of the actual and predicted immune cell performance by the model is highly correlated, thus illustrating the strength of the ranking-based deep learning component. An optimal convergence of 30 iterations was obtained by SSSO compared to Particle Swarm Optimization (PSO) 45, Genetic Algorithm (GA) 48, and Differential Evolution (DE) 52 iterations, and this shows the computational efficiency of

the method proposed. In **Figure 8**, the accuracy rate achieved by PSO was 93.4%, and its ranking score was 0.85, whereas the GA and DE showed lower and lower performance with accuracy of 91.8% and 90.5%, and ranking scores of 0.81 and 0.78, respectively. This outcome highlights the positive impacts of combining optimization with smart ranking as opposed to conventional models that use scores. Moreover, a Deep Neural Network (DNN) with no ranking scored 88.7% accuracy with a 0.70 ranking score, which demonstrates that the lack of a ranking mechanism results in lower prioritization and quality of the learning of the model. In general, the suggested IoML + SSSO framework exhibits a wide precision, rapid convergence, and high biological interpretation that can provide a potent device for the immune cell therapeutic design and optimization.

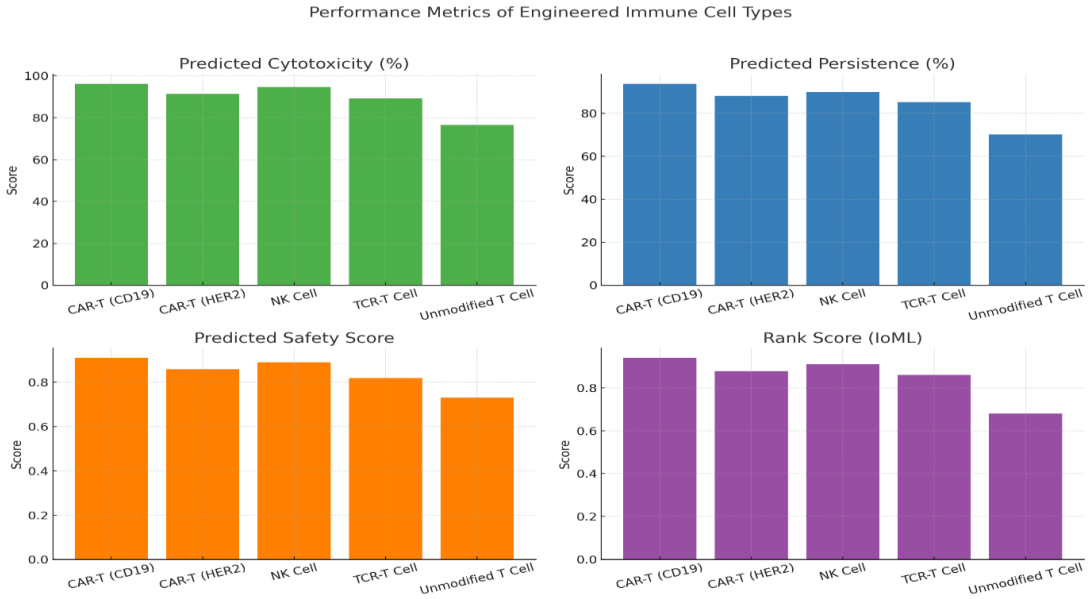

Figure 7. Estimation of cells with IoML.

Table 6. Comparative analysis for engineering cells.

Model	Accuracy (%)	Precision (%)	Recall (%)	F1-Score (%)	Ranking Score	Optimization Convergence (Iterations)
IoML + SSSO (Proposed)	96.8	96.1	95.9	96.0	0.92	30
PSO	93.4	92.7	92.3	92.5	0.85	45
GA	91.8	91.1	90.7	90.9	0.81	48
DE	90.5	90.2	89.9	90.0	0.78	52
Traditional DNN (No Ranking)	88.7	87.9	87.2	87.5	0.70	N/A

Challenges and Limitations

The proposed IoML-SSSO framework demonstrates promising performance in optimizing immune cell configurations, several limitations and practical challenges must be acknowledged before clinical translation.

Model Portability and Generalizability: The ranking-based DNN model, while highly effective on the tested datasets (GSE120575, ImmPort, Single Cell Portal), may not generalize equally well across diverse populations, cancer types, or treatment contexts. Differences in patient demographics, sample preparation, and sequencing platforms can introduce variability that limits model portability. Cross-cohort validation and external dataset integration remain critical future directions.

Data Availability and Quality Constraints: High-dimensional immune datasets are scarce, especially those annotated with clinical outcomes (e.g., toxicity, long-term efficacy). Single-cell and omics data are often noisy, sparse, and imbalanced, which may bias learning outcomes. Moreover, engineered cell attributes (e.g., receptor constructs, editing efficiency) are rarely standardized across studies, impeding large-scale model training and reproducibility.

Clinical Validation Gap: Although the IoML framework predicts cytotoxicity, persistence, and safety scores with high accuracy in silico, these metrics require extensive wet-lab validation and clinical trials to confirm therapeutic relevance. In clinical practice, immune response is influenced by many dynamic factors—including tumor microenvironment, patient comorbidities, and immune suppression—which are difficult to simulate computationally.

Ethical and Regulatory Considerations: The use of AI in immune cell design introduces ethical concerns regarding data privacy, model transparency, and clinical accountability. Additionally, integrating AI-optimized cell therapies into regulated medical practice requires clear guidelines, explainability mechanisms, and compliance with bioethical standards (e.g., informed consent, equitable access).

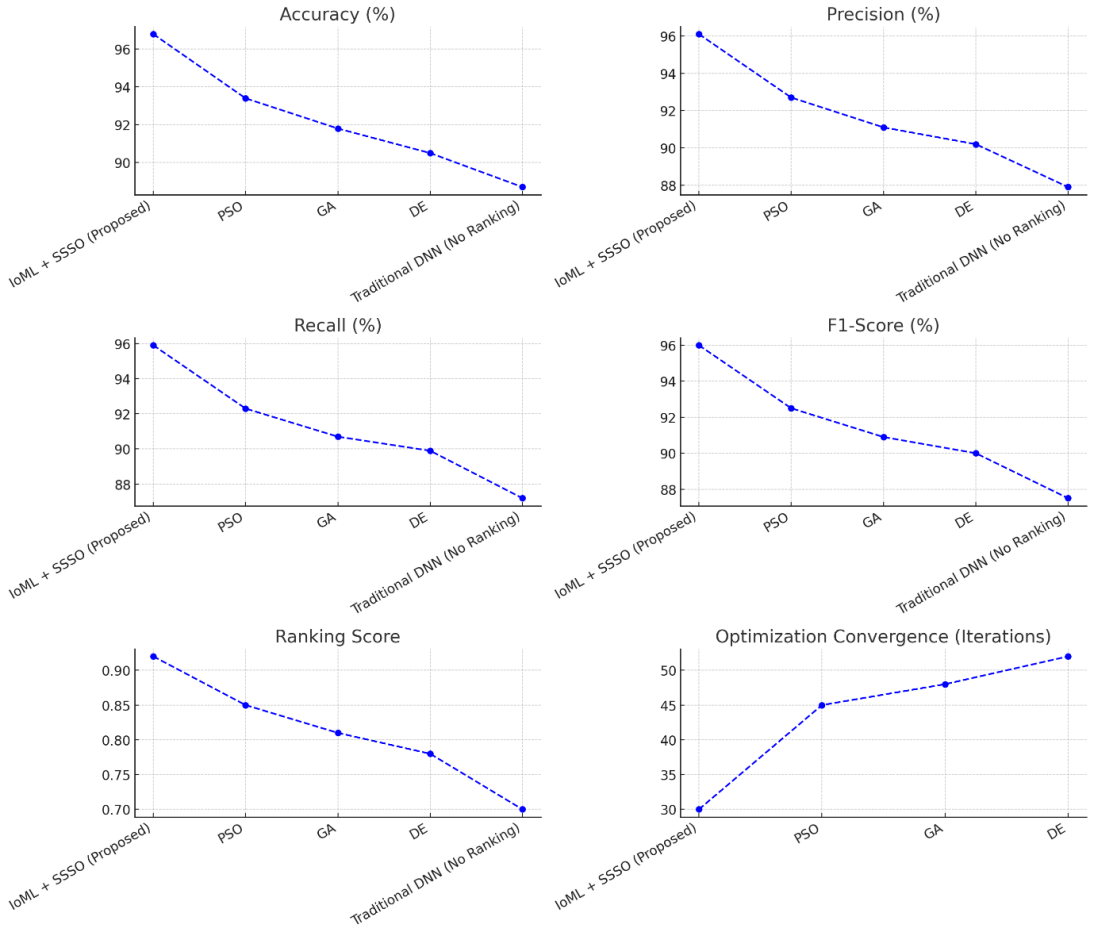

Figure 8. Comparative analysis with immunotherapy.

Addressing these limitations in future work will involve federated learning approaches for data sharing, explainable AI modules for transparency, and partnerships with clinical labs for wet-lab verification. Combining algorithmic strength with biological interpretability will be critical for safe, scalable deployment of ML-enhanced immunotherapies.

6. Conclusions

This paper developed an innovative framework, Intelligent Optimized Machine Learning (IoML) coupled with Sorting Slap Swarm Optimization (SSSO), to support the engineering of immune cells, and in our case, particularly therapeutic cells, including CAR-T and N-K cells. Using the ranking-based Deep Neural Network (DNN) methodology on high-resolution data of GSE120575, ImmPort, and Single Cell Portal, the IoML model successfully predicted essential application parameters of cytotoxicity, persistence, safety, and specificity. This combination of both al-

lowed exploration of the enormous design space of cell design, with immune configurations being optimized according to multi-objective performance requirements. An experiment proved that the IoML-SSSO method was much better than the traditional models in accuracy, speed of convergence, and biological analysis, identifying the high-performing immune cell candidates. The proposed IoML model involves the *in vitro* experimentation, but also contributes to the customized and data-oriented building of future-generation immune therapies. All in all, the proposed system is a scalable, diminutive system compared to potential anticancer immunity with a beneficial outcome that has been astutely developed as an advanced means of enhancing the development of immune cells that have great potential in immuno-oncology and in general.

Author Contributions

Conceptualization, S.J.; methodology, S.S.; validation, B.V.R.; formal analysis, I.S.C.; data curation, I.S.C.; writing—original draft preparation, S.J.; writing—review and editing, B.V.R. and S.G.; visualization, B.M.; supervision, S.S.; project administration, S.J.; funding acquisition, B.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study, titled "Designing Next-Generation Platforms With Machine Learning to Optimize Immune Cell Engineering for Enhanced Applications", did not involve any experiments on human participants or animals conducted by the authors. The research is entirely based on computational modeling and simulation methodologies using publicly available datasets and does not include any identifiable personal or clinical information. Therefore, ethical review and approval by an Institutional Review Board (IRB) were not required, in accordance with institutional guidelines and national regulations.

Informed Consent Statement

This study did not involve human participants, human data, or human tissue. Therefore, informed consent was not required. The research is purely computational in nature and based on publicly available data sources that are anonymized and ethically cleared for research use. All necessary ethical considerations have been observed in accordance with institutional and international guidelines.

Data Availability Statement

The data and materials have been made available.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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