Design of Enhanced TCRs against Cancer Antigens Using an AI System

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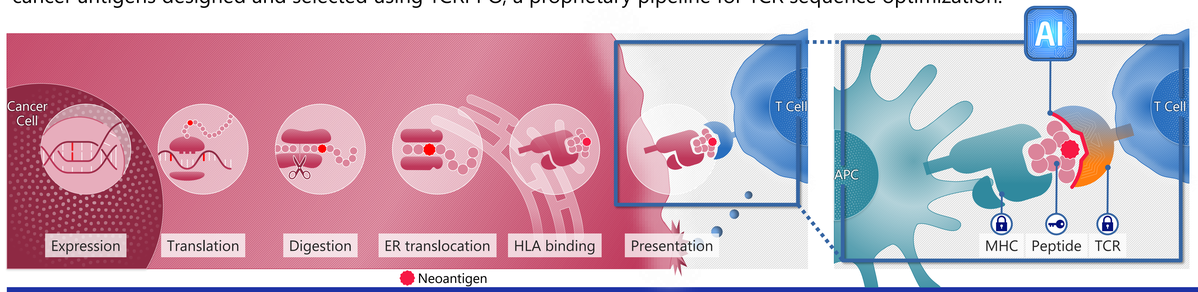
Background

Naturally occurring TCR targeting cancer antigens are associated with relatively low affinity comparatively to TCR targeting external pathogens. This might be explained by the proximity of cancer specific sequences to self. Engineering of modified affinity enhanced TCR constitutes a possible solution, however, TCR binding remains challenging to model using structural biology approaches because of the conformational flexibility of the TCR complex. The use of machine learning based methods constitutes a promising approach to design TCR of higher affinity. Herein, we report enhanced affinity TCR sequences against cancer antigens designed and selected using TCRPPO, a proprietary pipeline for TCR sequence optimization.



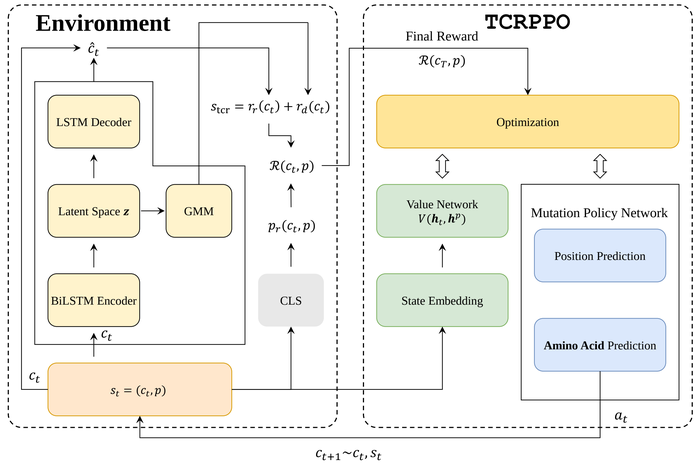
Methods

The TCRPPO Framework

TCRPPO is a reinforcement-learning framework based on proximal policy optimization to optimize TCRs through a mutation policy. Briefly after training the system on a series of TCR sequences known to bind a given target, TCRPPO introduces mutations on existing sequence to achieve higher affinity guided by a reward function factoring in affinity of the new sequence and the likelihood for this sequence to be a valid TCRs.

The reinforcement learning framework is formulated as follows:

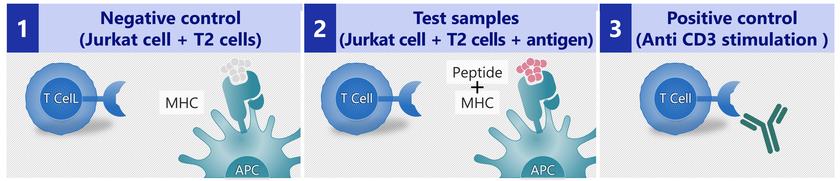
• **State**	The CDR3β and peptide sequence
• **Action**	Choosing a position to mutate, then choose the mutant amino acid
• **Reward**	Predicted interaction score with the target antigen from an ensemble of pre-trained classifiers + TCR validity score from a pre-trained autoencoder



The model learns a policy network that determines the optimal action based on the current state (sequence) that maximizes expected rewards.

Experimental Validation

To validate our approach, we designed a series of candidate TCR sequences against known clinically relevant cancer antigen MART-1 and evaluated their biological functional potency. Starting TCR or engineered TCR together with NFAT-Luc reporter gene were expressed on the ΔTCR Jurkat cell line. The cells were cultured in the presence of antigen presenting cells with or without target peptide to assess biological activity of TCRs.

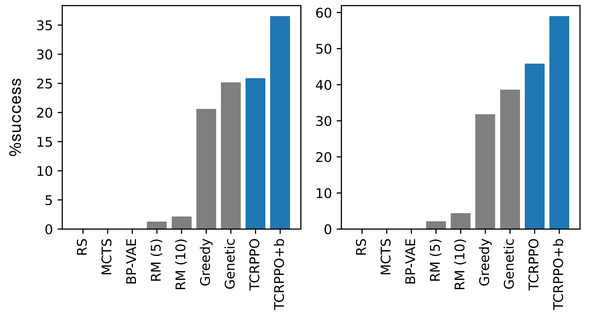


TCRs used for this validation experiment

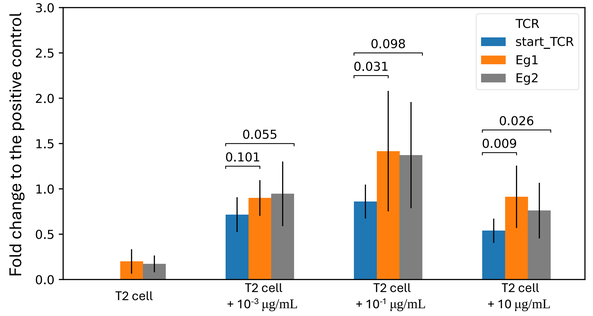
	CDR3 beta
Start TCR	CASSYSATGGEQYF
Engineered #1 (Eg1)	CASS**XXXX**GG**X**QYF
Engineered #2 (Eg2)	CASS**XXXX**GGEQYF

Results

We benchmark our methods on public datasets VDJDB and McPAS-TCR, achieving higher performance than the baseline methods. %success denotes the success rate of optimizing test TCRs *in silico*.



We run our method on the β chain of a weak binder to MART-1 epitope and selected two engineered sequences. Both engineered sequences (Eg1 and Eg2) display higher biological activity than the endogenous TCR and are dissimilar from known TCRs.



Conclusion and Future Work

We successfully engineered TCRs to have better antigen recognition. The enhanced TCRs warrant further characterization to evaluate their therapeutic potential. This AI model might contribute to improving the efficacy of TCR-T therapy in the future. Beyond this case, our approach constitutes a pipeline that might be applied to other targets for which alternative TCRs are required.

For building more effective and robust TCR engineering AI models, we are actively seeking more accurate and generalizable interaction classifiers to enable the optimization towards rare and novel antigens, and seeking to engage in collaborations to validate engineered TCR in relevant models. For more information, please contact Martin at renqiang@nec-labs.com