Immunoengineering by design: generative AI and high throughput cell screening to develop therapeutic TCR-guided bispecifics against multiple targets

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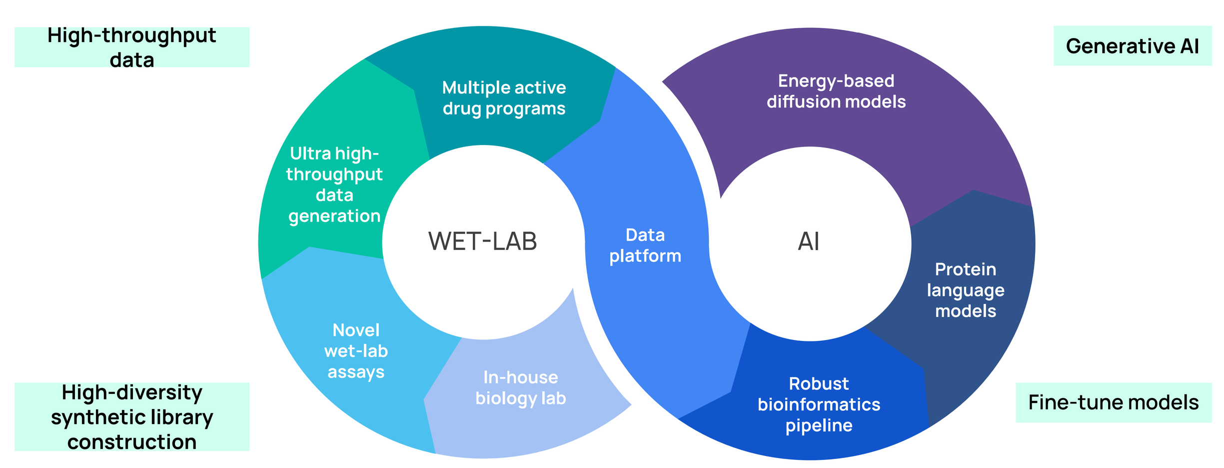
INTRODUCTION

T cell receptors (TCRs) are a unique class of targeting molecule. Through highly specific interactions with peptide:HLA complexes present on the cell-surface, they offer a means of therapeutically targeting any protein, with this specificity highlighted by their ability to selectively recognise cancer-associated single amino acid mutations.

Identifying TCRs that have the desired specificity toward a target peptide has traditionally been challenging

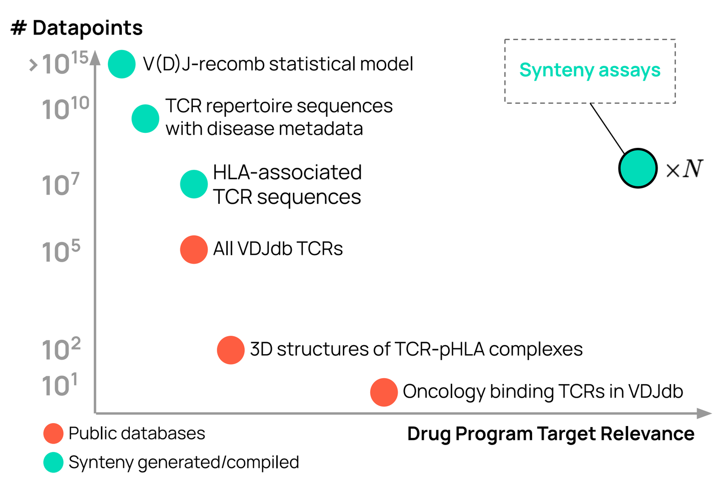
To increase the speed and success of TCR discovery, we have developed an *in silico* TCR design process leveraging recent advances in machine learning for protein sequences with rapid cell-based screening, where both specificity and selectivity are considered at the point of design.



GENERATIVE MODELLING

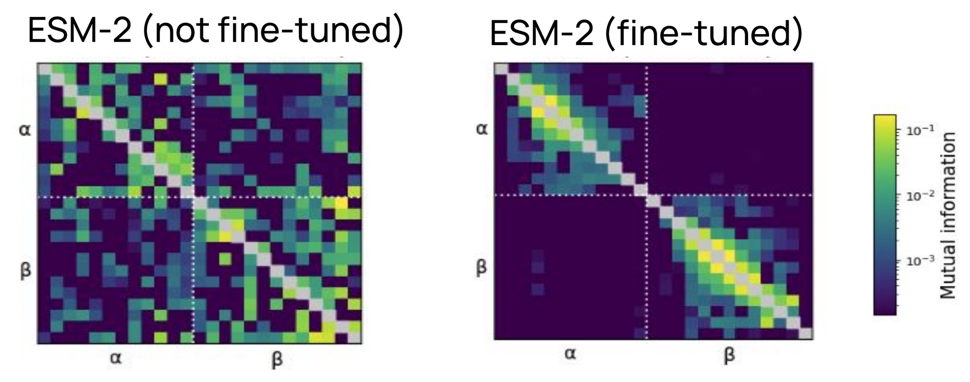
Conditional generative AI recommends TCRs to satisfy desirable binding and developability characteristics

Generative models are trained on a mixture of public and proprietary data of several modalities.



At the heart of the generative models are **protein language models** (pLMs).

- Fine-tuning on experimental data captures binding specificities between known TCRs and their peptide ligands, learning meaningful latent representations of both peptide and TCR sequences

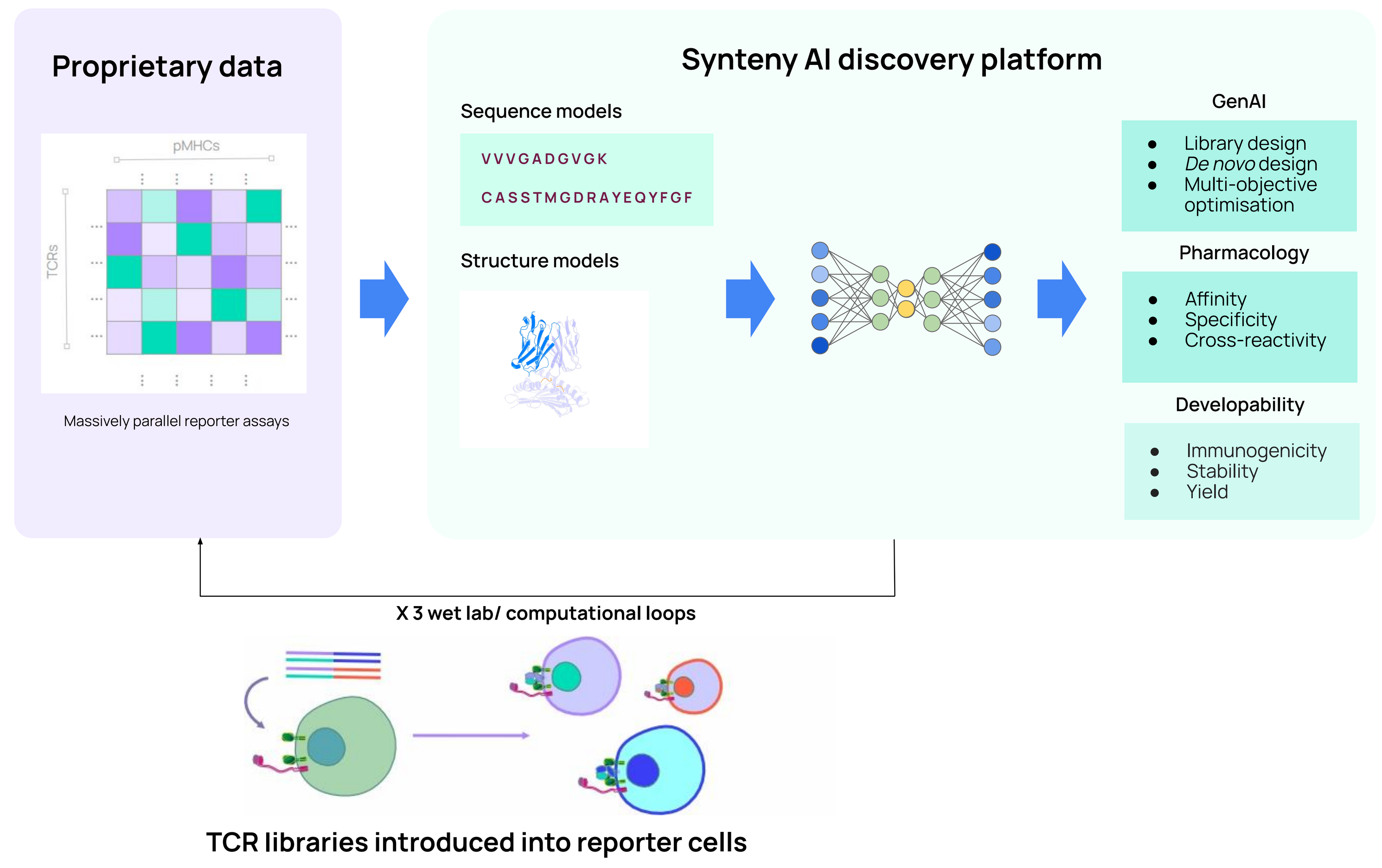


(Cornwall *et al.*, NeurIPS 2023 GenBio Workshop)

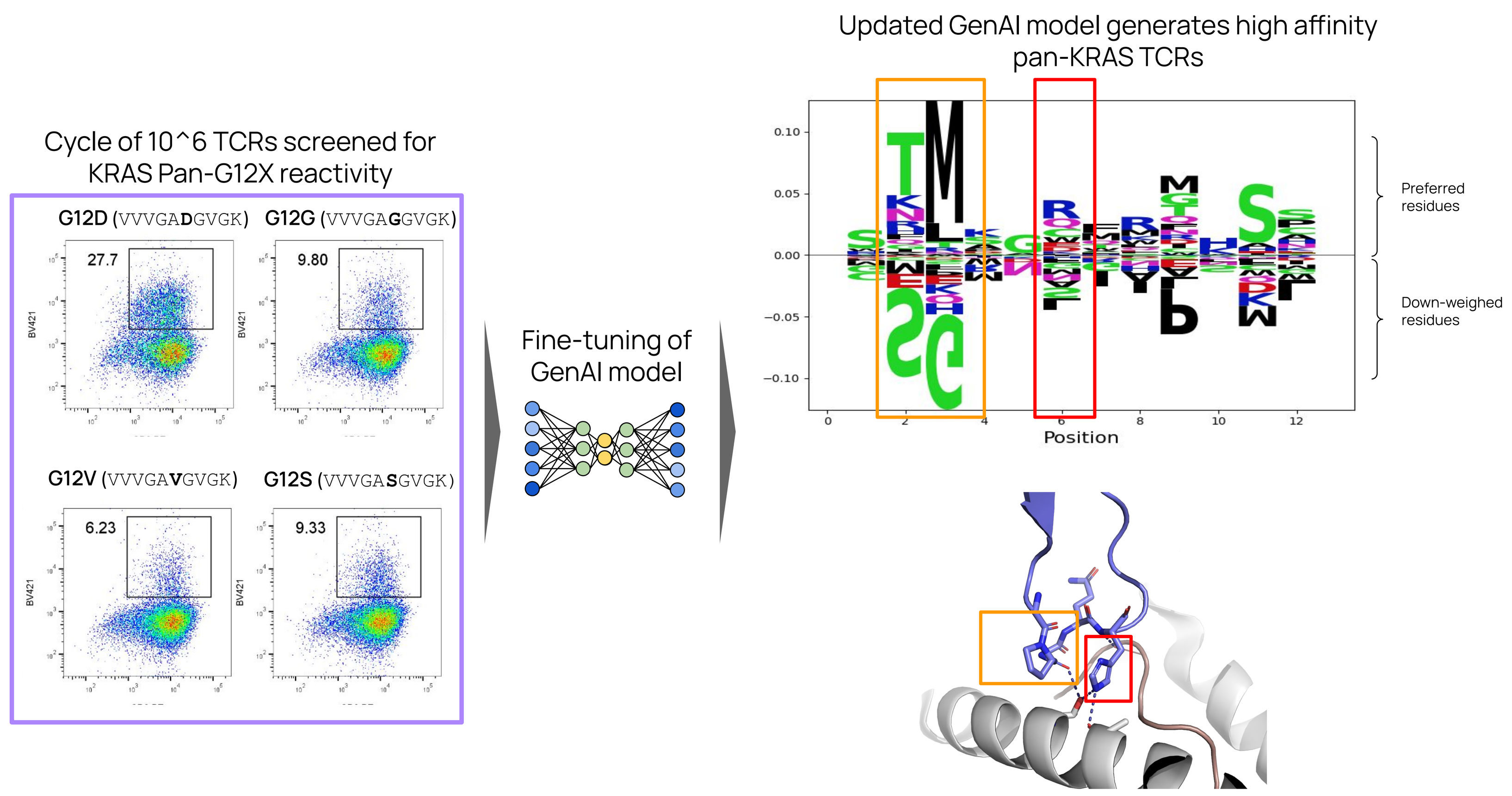
The generative models are highly capable of recovering unseen TCRs with known specificity

TCR DISCOVERY PLATFORM

Our TCR discovery platform involves multiple rapd cycles of generational AI and experimentation using high throughput reporter assays. Our generative models are specifically designed to simultaneously guide towards TCR sequences that bind one or more target peptide sequence(s), whilst avoiding any number of specific off-target peptides. Our models are able to do this whilst also considering multiple other parameters, such as preserving a desired motif, or maximizing for a specific property such as stability.



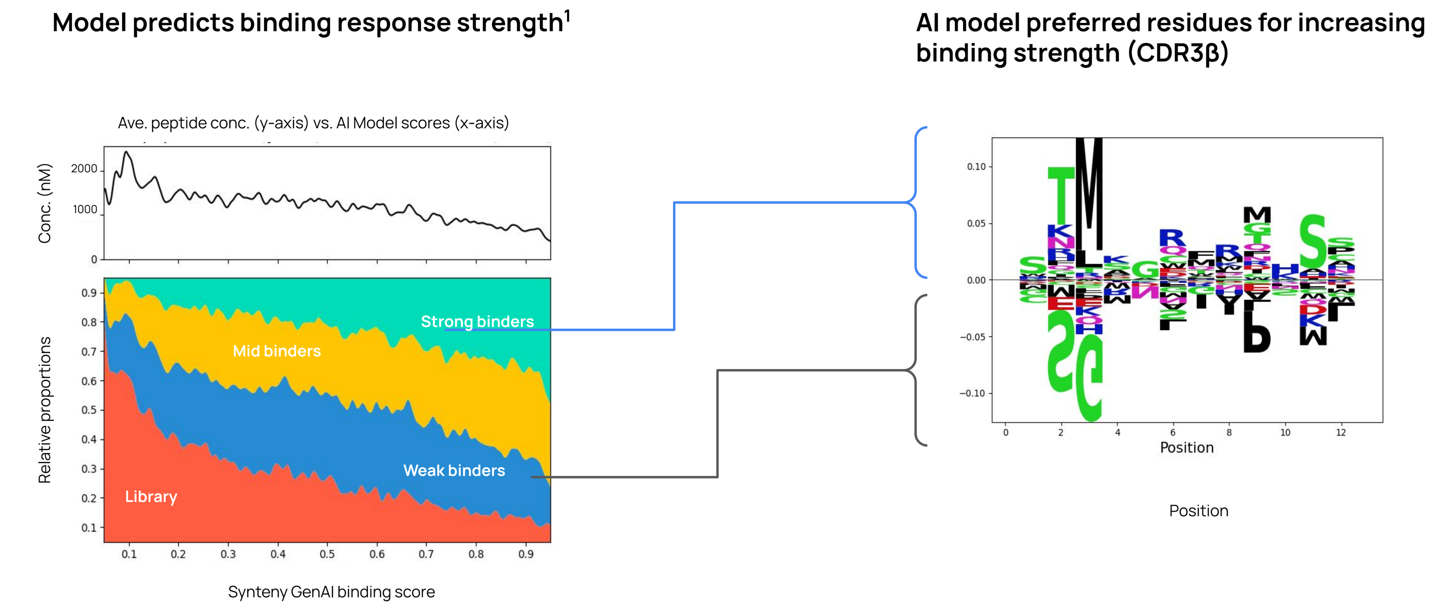
In our early cycles both model-generated and naive permutations are synthesised and expressed in a cell-based high throughput screen; providing a data-rich training environment for subsequent cycles which focus in around specific structures.



Each cycle enables further model refinement for desired binding properties, and therefore subsequent recommendations for novel TCRs. In the case above, the model shows remarkable structural awareness of the key residues driving peptide specificity, enabling us to tune the TCR toward more desirable binding profiles where the TCR is able to bind multiple mutants whilst avoiding binding to the unmutated peptide

LEAD OPTIMISATION

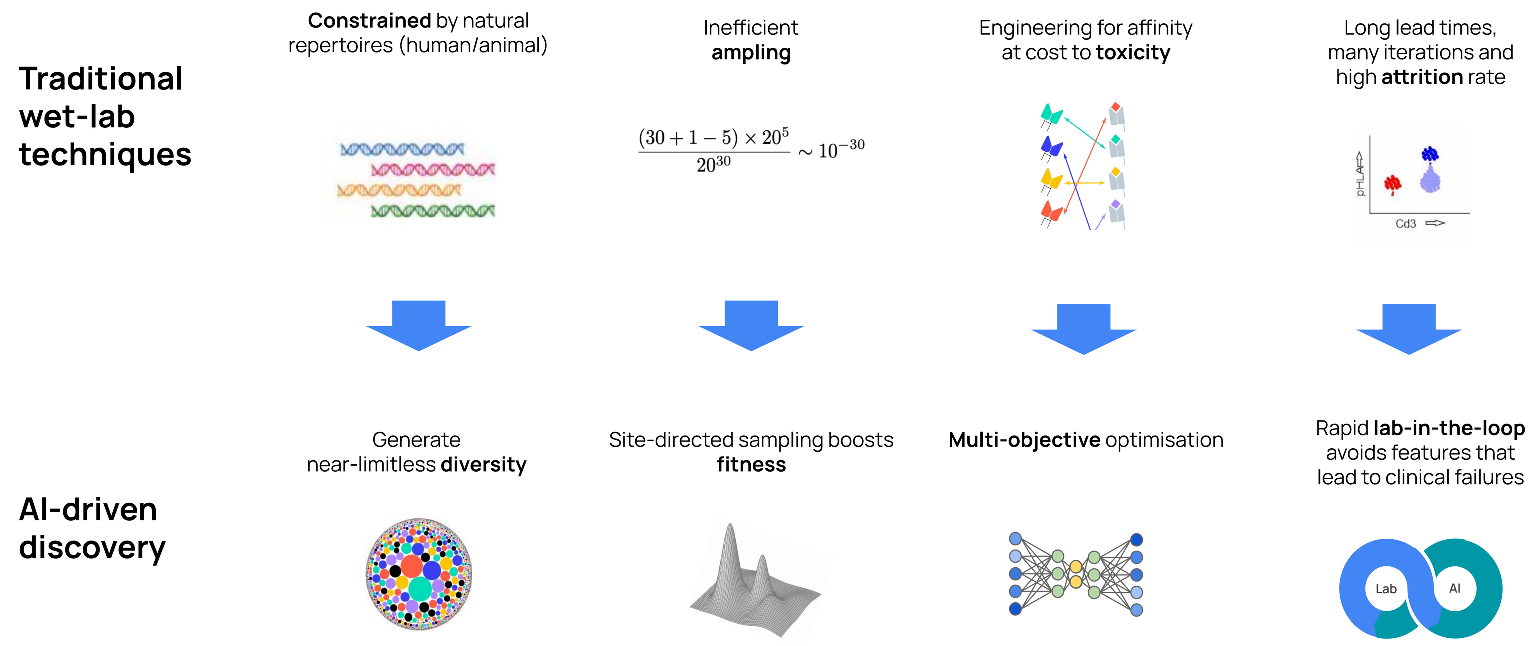
Equally important in our AI-led refinement process is the ability to predict relative binding strength of interaction, in order to select sequences which satisfy the binding requirements of the therapeutic modality



Our generative binding scores correlate well with binding metrics, and allow us to tune our TCR outputs, providing a range of binding affinities that can be adjusted depending on the target peptide density. Our pipeline has been applied to design novel TCRs against both viral targets and public neoantigens including our lead program against the common KRAS mutation at position G12, and undisclosed targets in partnership with a major cancer centre and clinical stage biotech company.

CONCLUSION

Combining state of the art generative AI with high throughput screening approaches empowers a TCR design process that considers both selectivity and specificity, opening up the next generation of TCR-based therapeutics.



ACKNOWLEDGEMENTS

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