HIGH-THROUGHPUT DISCOVERY OF HIGH-AFFINITY TCRs FROM SYNTHETIC YEAST-BASED LIBRARIES

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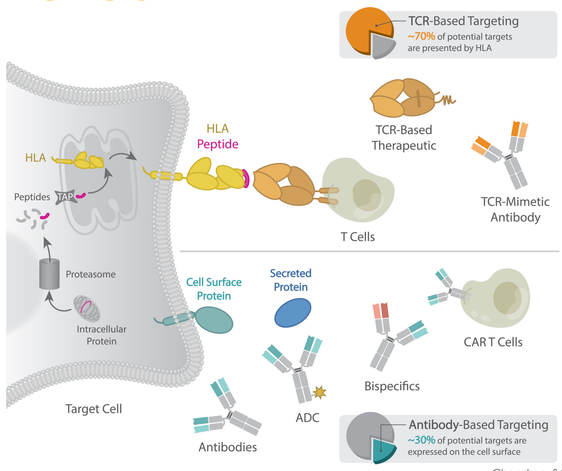
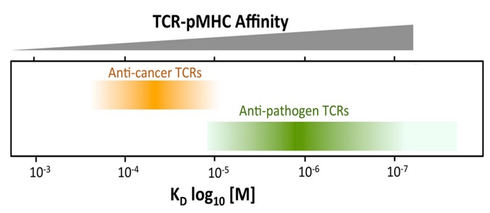
ADIMAB

BACKGROUND

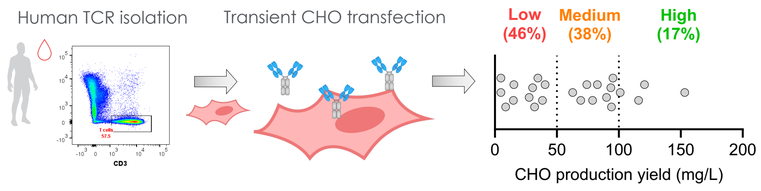


Cites data from Chandran, S.S. & Klebanoff, C.A. (2019) Immunol Rev

TCR-based therapeutics enable targeting of otherwise inaccessible intracellular antigens via peptide-HLA recognition.

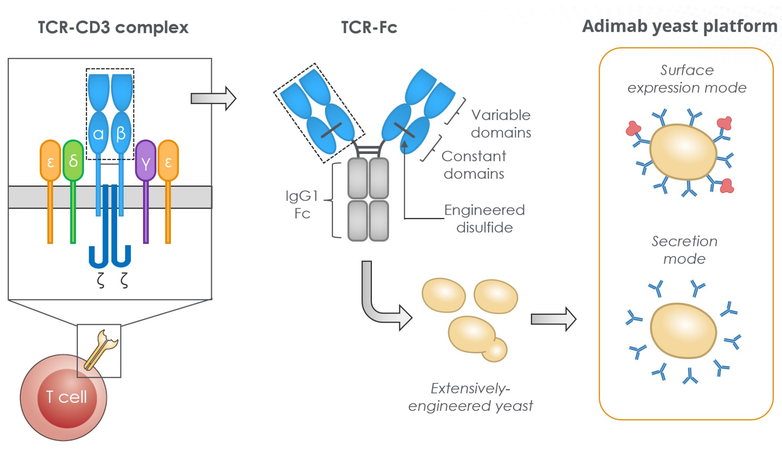


Adapted from Dolton, G. et al. (2018) Front Immunol



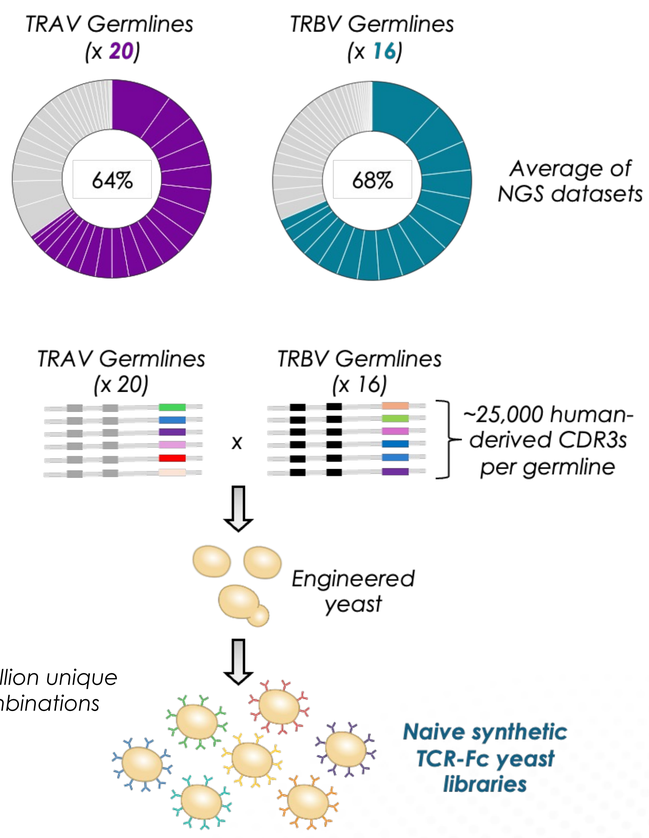
Natural TCRs possess weak affinities towards many disease-relevant pHLA antigens due to central tolerance and have poor expression in mammalian cells as TCR-Fc molecules.

METHODS - Platform



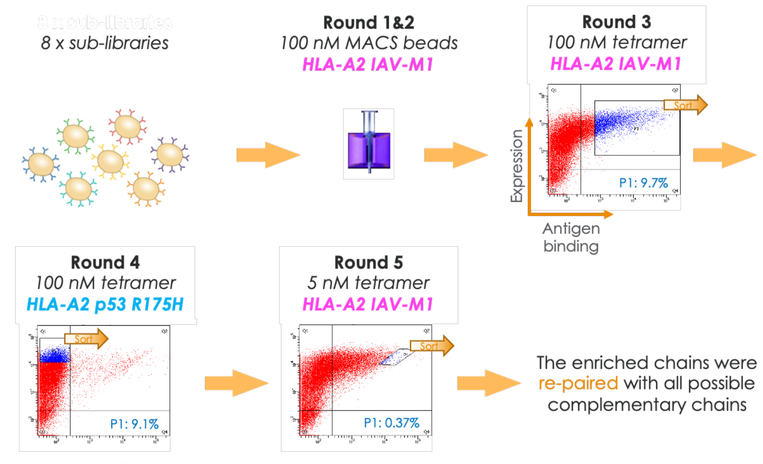
Yeast-based platform for high-throughput TCR discovery and engineering in bivalent IgG-like format capable of surface expression and soluble secretion.

METHODS - Libraries

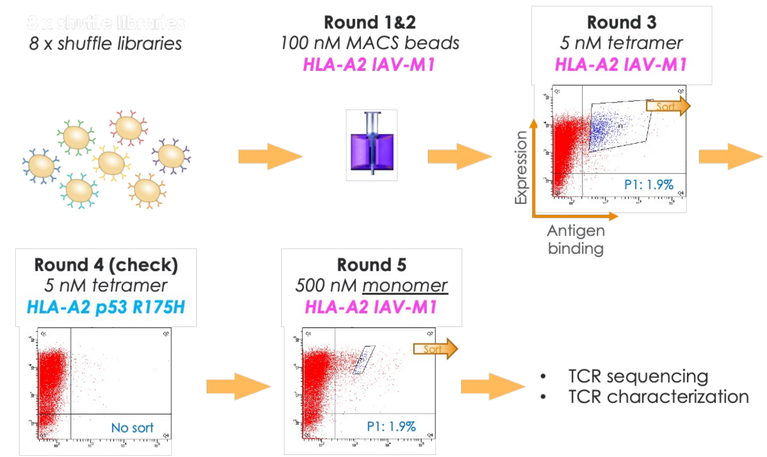


High frequency TCR a and β variable domains were paired with large diversities of human CDR3 sequences to generate synthetic TCR libraries in yeast.

RESULTS - Selections

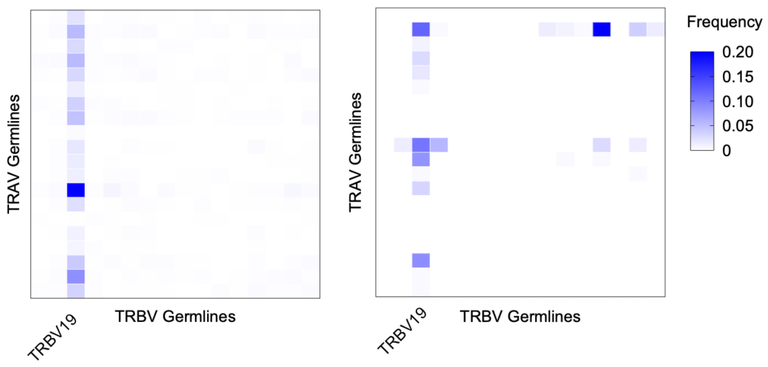


Synthetic TCR libraries were selected for specific pHLA binders.

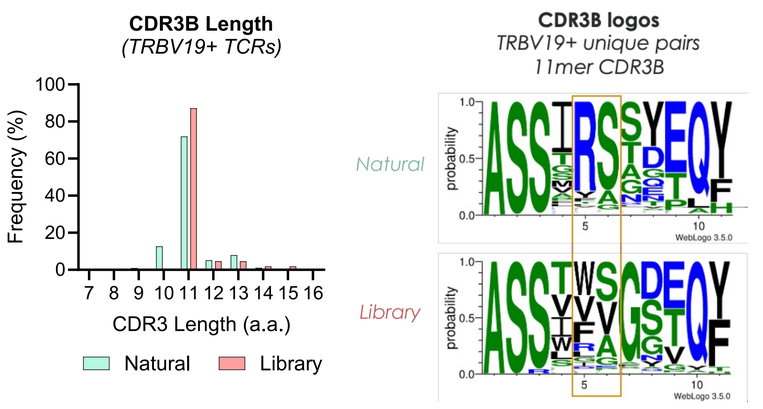


Chain shuffle libraries were selected under more stringent conditions to enrich high-affinity and specific pHLA binders.

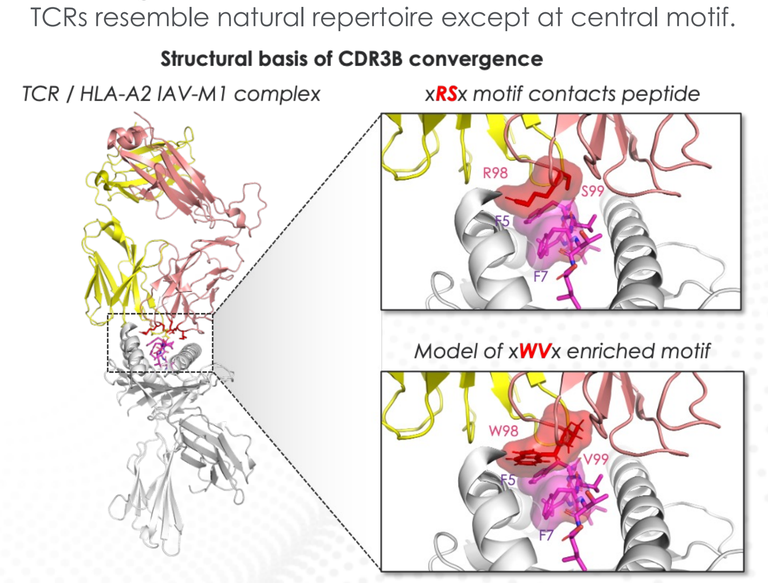
RESULTS - Sequences



TCRs selected from synthetic yeast libraries resemble the predominance of TRBV19+ TCRs in natural repertoires, with additional TRBV/TRAV germline pairing hotspots.



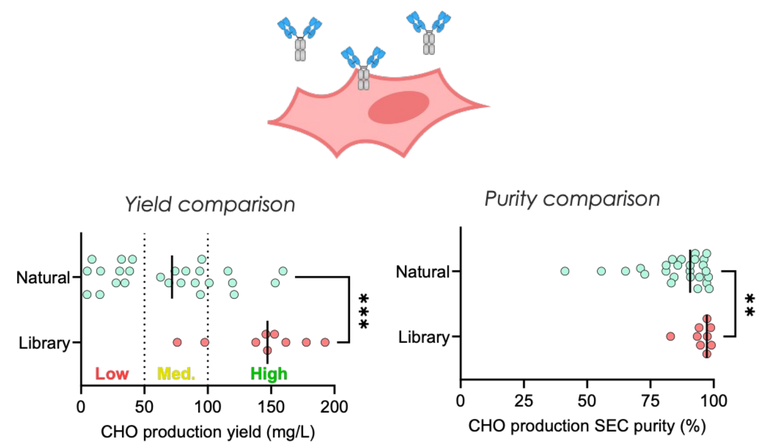
CDR3β lengths and compositions of library-enriched TRBV19+ TCRs resemble natural repertoire except at central motif.



Library-derived TCRs possess distinct CDR3β motifs predicted to improved hydrophobic packing with the peptide.

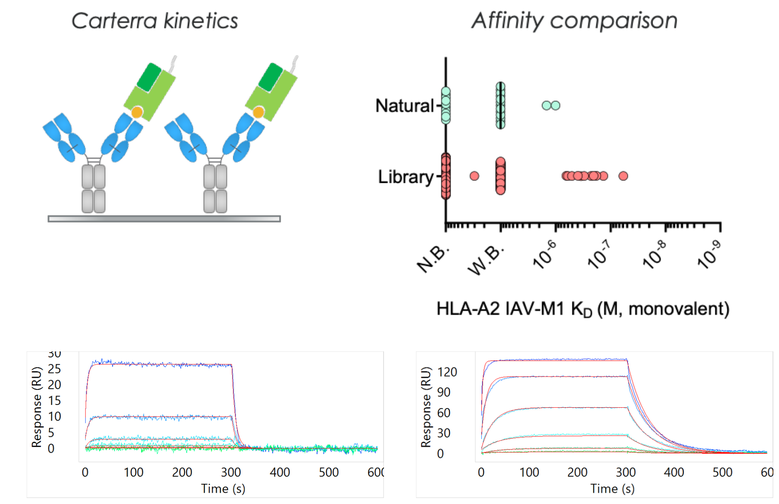
RESULTS - Developability

Transient CHO production



Synthetic library-derived TCRs exhibit significantly improved production titers and qualities in mammalian expression systems compared to natural repertoire TCRs.

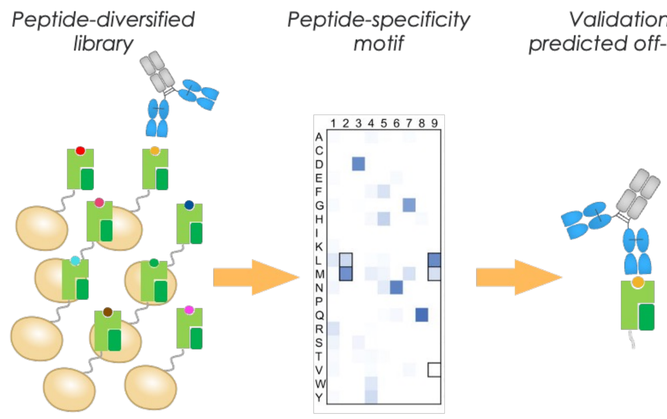
RESULTS - Kinetics



Synthetic library-derived TCRs display higher target pHLA affinities than antigen-matched TCRs from natural repertoires.

NEXT STEPS - Specificity

pHLA specificity assessments



Specificity motif adapted from Gee, M.V. et al. (2018) Cell

Peptide-binding specificity of library-derived TCRs will be assessed through peptide-diversified pHLA libraries expressed in yeast combined with off-target prediction and validation.

SUMMARY

- TCRs derived from natural repertoires have poor target affinities for and poor developability profiles, complicating the development of soluble TCR-based therapeutics.
- Adimab has developed a high-throughput platform for TCR engineering, including a fully human synthetic TCR library in yeast to identify potent and specific soluble TCRs.
- TCRs derived from synthetic libraries share key sequence features with natural repertoires but surpass natural TCRs in both affinity and mammalian cell expression.
- Next steps: define the specificity of library-derived TCRs and discover TCRs against additional model pHLAs.

ACKNOWLEDGEMENTS

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