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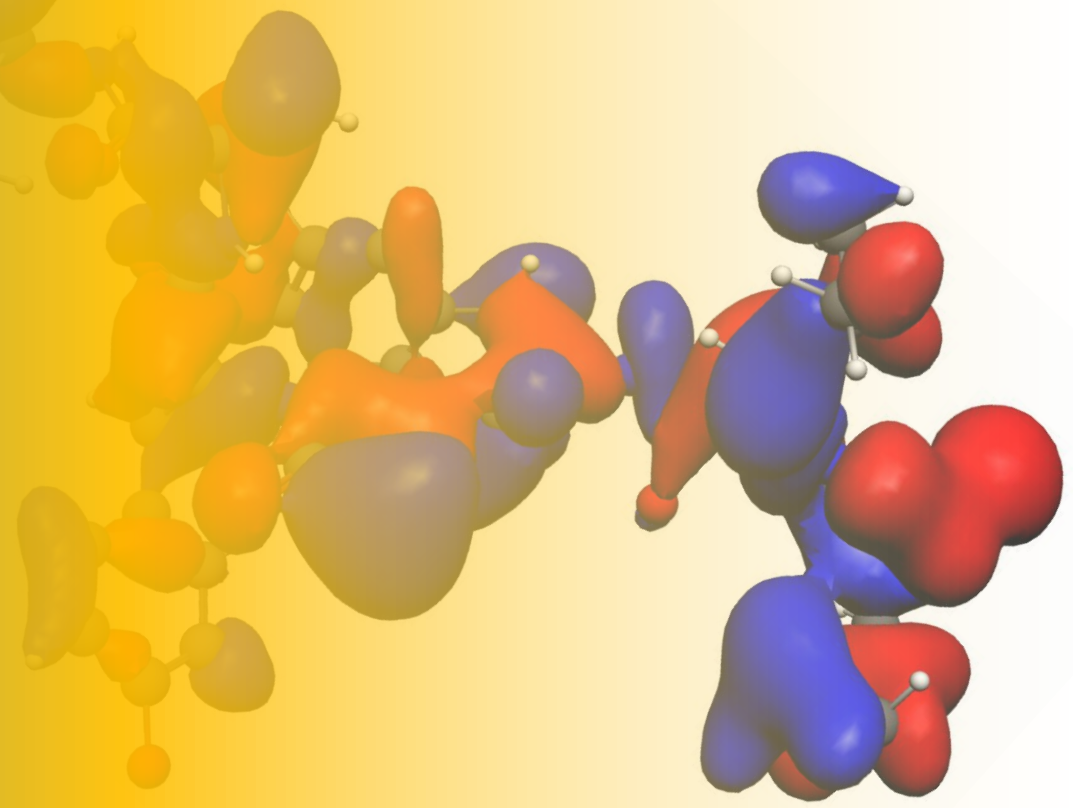
BioRank™: One-shot TCR engineering for TCR-T personalized immunotherapy



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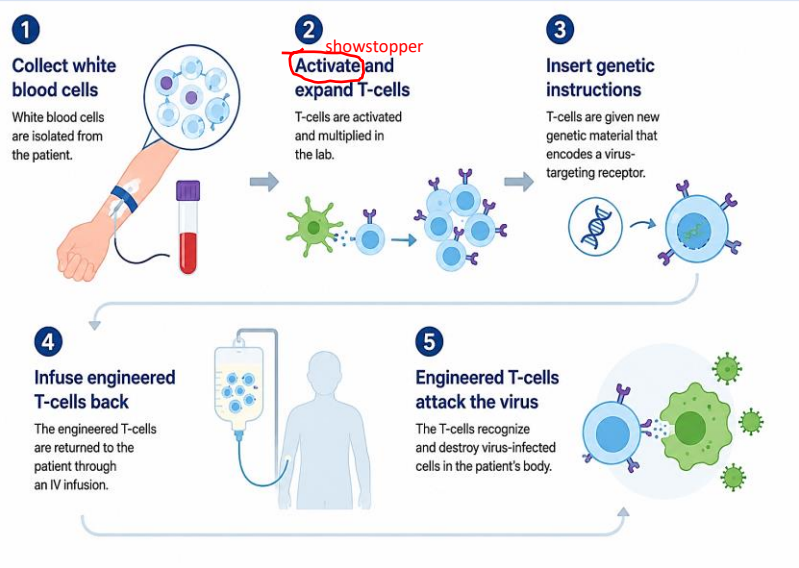
TCR-T therapy and engineering: Current state, showstoppers and our solution

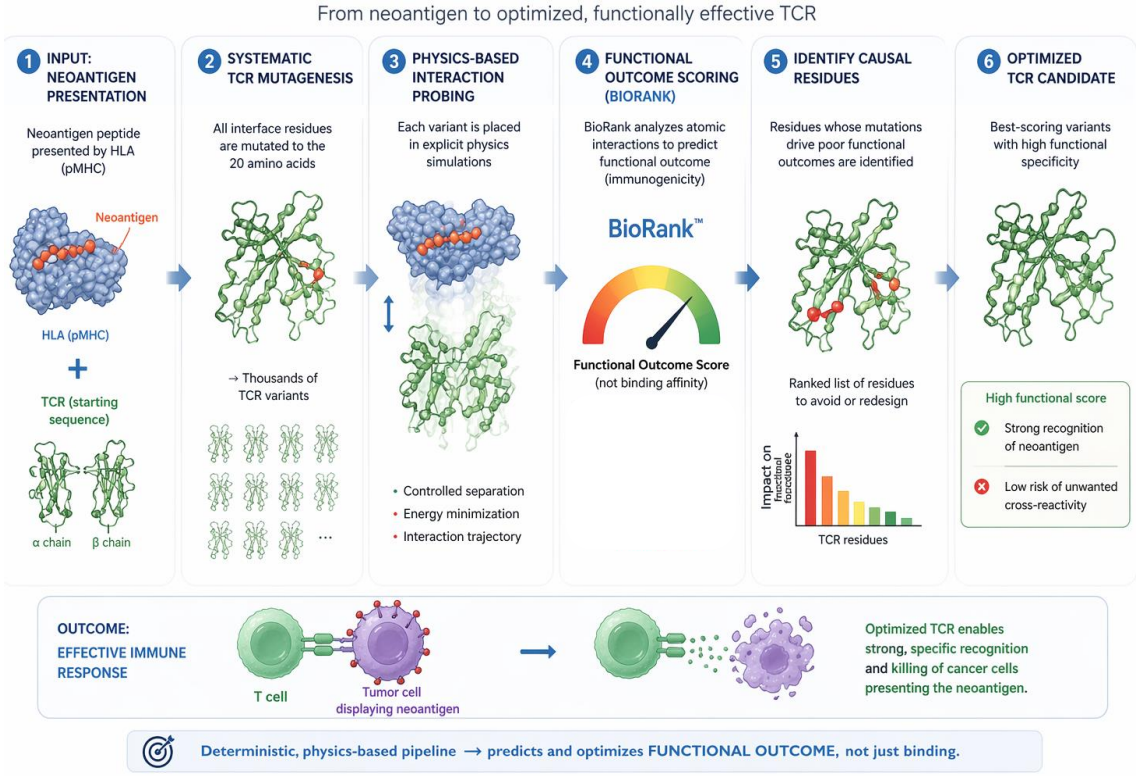
A. Current state. How TCR-T Cell Therapy works. Patient T cells are collected, genetically enhanced, expanded, reinfused, and then precisely recognize and eliminate disease (e.g. cancer, virus, infection)-target cells.



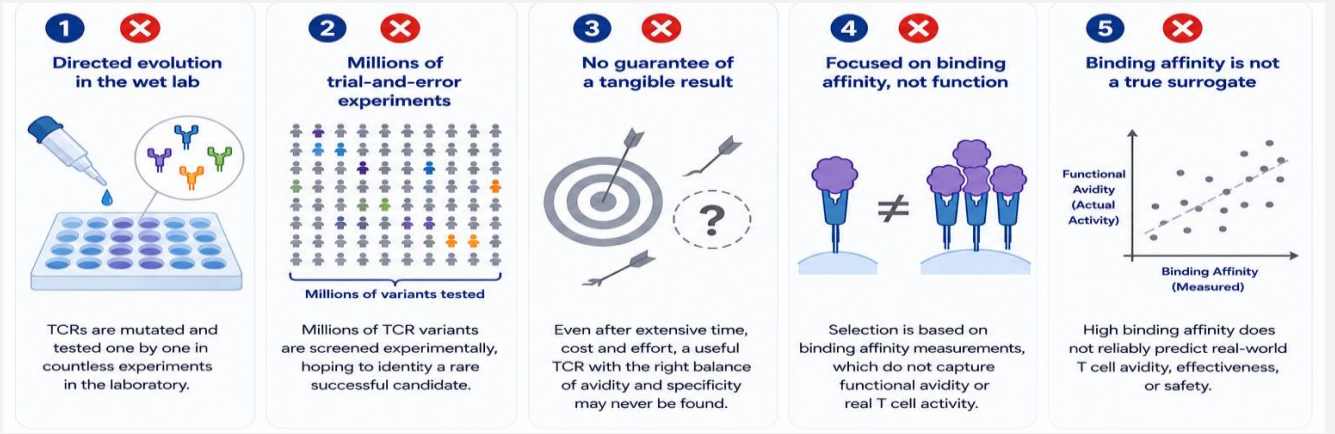
C. Our solution. BioRank™: a platform for one-shot engineering and optimization of therapeutic TCR assets for TCR-T applications.

BioRank™ can detect if TCRs are suboptimal and can design more avid/specific candidates through our breakthrough epistatic landscape navigation technology. This leads to improved TCR asset performance within ultra-short discovery timeframes.

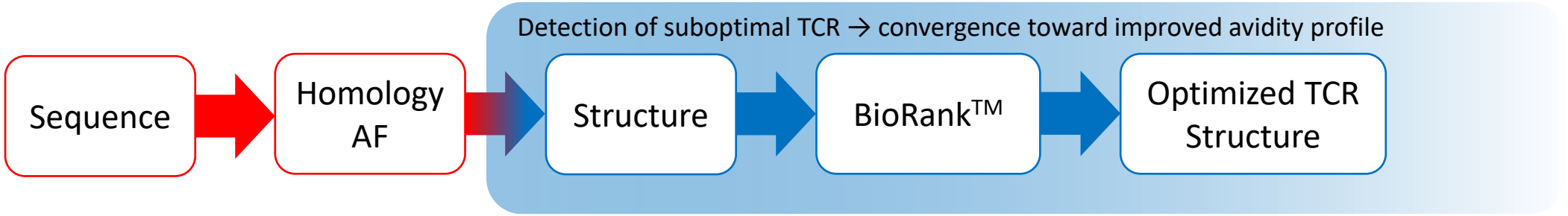
BioRank™ can high throughput-process multiple TCR engineering campaigns and includes the ability to address off-target reactivity in the same design pipeline.



B. Showstoppers. TCR engineering, epistasis and directed evolution blind tests. T-cell activation proceeds when their T-cell receptor (TCR) surface molecules efficiently interact with antigenic proteins on the surface of infected cells. Unfortunately, this interaction – particularly for cancer neoantigens – does not occur naturally. To force it, TCRs can be engineered in-vitro by artificially mutating their structure. However, this, in turn, is blocked by the epistasis problem: i.e. it is impossible to know which TCR positions to mutate and what functional outcome these mutations will produce. The only existing solution is suboptimal: to experimentally conduct an enormous number of costly and time-consuming (1-2 years) trial-and-error mutations (directed evolution blind tests) which only target binding rather than T-cell activation and do not guarantee positive outcomes.



BioRank™: workflow and engagement modes

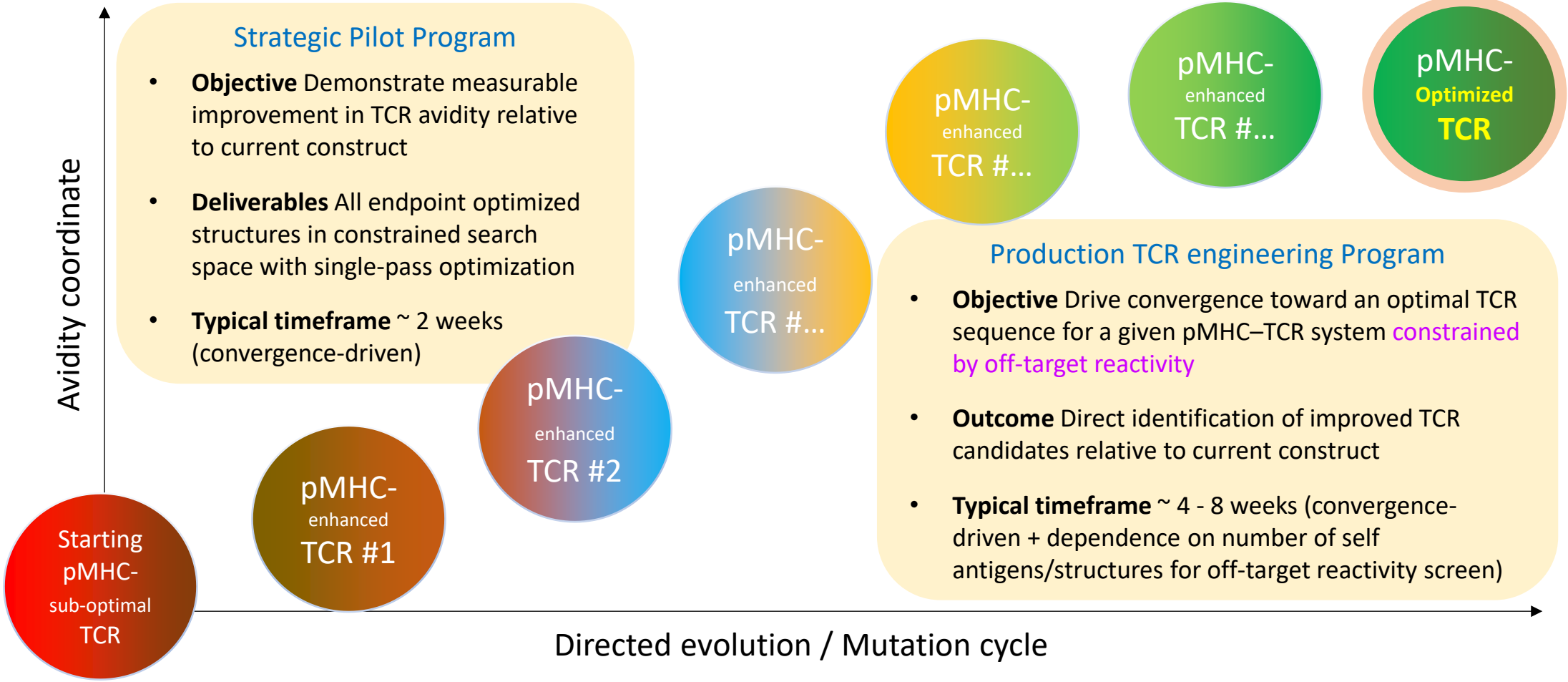


Strategic Pilot Program

- **Objective** Demonstrate measurable improvement in TCR avidity relative to current construct
- **Deliverables** All endpoint optimized structures in constrained search space with single-pass optimization
- **Typical timeframe** ~ 2 weeks (convergence-driven)

Production TCR engineering Program

- **Objective** Drive convergence toward an optimal TCR sequence for a given pMHC–TCR system constrained by off-target reactivity
- **Outcome** Direct identification of improved TCR candidates relative to current construct
- **Typical timeframe** ~ 4 - 8 weeks (convergence-driven + dependence on number of self antigens/structures for off-target reactivity screen)



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BioRank™ biological validation

				Functional assay	BioRank™						
peptide A	HLA A	TCR A	PDB A	A > B	A > B	PDB B	Peptide P	HLA B	TCR B	Same peptide	Same HLA	Same TCR
LLFGYPVYV	HLA-A*02	A6	1AO7	YES	YES	1BD2	LLFGYPVYV	HLA-A*02	B7	TRUE	TRUE	FALSE
LLFGYPVYV	HLA-A*02	A6	1AO7	YES	YES	1QRN	LLFGYAVYV	HLA-A*02	A6	FALSE	TRUE	TRUE
LLFGYPVYV	HLA-A*02	A6	1AO7	YES	YES	1QSE	LLFGYPRYV	HLA-A*02	A6	FALSE	TRUE	TRUE
LLFGYPVYV	HLA-A*02	A6	1AO7	YES	YES	1QSF	LLFGYPVAV	HLA-A*02	A6	FALSE	TRUE	TRUE
LLFGYPVYV	HLA-A*02	A6	1AO7	YES	YES	2GJ6	LLFGKPVYV	HLA-A*02	A6	FALSE	TRUE	TRUE
LLFGYPRYV	HLA-A*02	A6	1QSE	YES	YES	1QRN	LLFGYAVYV	HLA-A*02	A6	FALSE	TRUE	TRUE
LLFGYPRYV	HLA-A*02	A6	1QSE	YES	YES	1QSF	LLFGYPVAV	HLA-A*02	A6	FALSE	TRUE	TRUE
SLLMWITQV	HLA-A*02	1G4	2BNQ	YES	YES	2BNR	SLLMWITQC	HLA-A*02	1G4	FALSE	TRUE	TRUE
ALWGFFPVL	HLA-A*02 W167A	AHIII	2JCC	YES	YES	2J8U	ALWGFFPVL	HLA-A*02 K66A	AHIII	TRUE	FALSE	TRUE
ALWGFFPVL	HLA-A*02 W167A	AHIII	2UWE	YES	YES	2J8U	ALWGFFPVL	HLA-A*02 K66A	AHIII	TRUE	FALSE	TRUE
ALWGFFPVL	HLA-A*02 W167A	AHIII	2UWE	YES	YES	2JCC	ALWGFFPVL	HLA-A*02 W167A	AHIII	TRUE	TRUE	TRUE
HPVGEADYFEY	HLA-B*35	TK3	3MV7	YES	YES	3MV8	HPVGEADYFEY	HLA-B*35	TK3* Q55H	TRUE	TRUE	FALSE
HPVGEADYFEY	HLA-B*35	TK3* Q55A	3MV9	YES	YES	3MV8	HPVGEADYFEY	HLA-B*35	TK3* Q55H	TRUE	TRUE	FALSE
HPVGDADYFEY	HLA-B*35	TK3	4PRH	YES	YES	4PRI	HPVGEADYFEY	HLA-B*35	TK3	FALSE	TRUE	TRUE
EVDPIGHLY	HLA-A*01	MAG-IC3	5BRZ	YES	YES	5BS0	ESDPIVAQY	HLA-A*01	MAG-IC3	FALSE	TRUE	TRUE
YQFGPDFPIA	HLA-A*02	10-6	5C07	YES	YES	5C0A	MVWGPDPLYV	HLA-A*02	10-6	FALSE	TRUE	TRUE
RQWGPDPAAV	HLA-A*02	10-6	5C08	YES	YES	5C0A	MVWGPDPLYV	HLA-A*02	10-6	FALSE	TRUE	TRUE
YLGGPDFPTI	HLA-A*02	10-6	5C09	YES	YES	5C0A	MVWGPDPLYV	HLA-A*02	10-6	FALSE	TRUE	TRUE
RQFGPDFPTI	HLA-A*02	10-6	5C0B	YES	YES	5C0A	MVWGPDPLYV	HLA-A*02	10-6	FALSE	TRUE	TRUE
GILGLVFTL	HLA-A*02	JM22	5HHM	YES	YES	5HHO	GILEFVFTL	HLA-A*02	JM22	FALSE	TRUE	TRUE

BioRank™ was validated across the full range of known (public domain) Class I systems having available functional (not affinity) data - these comprised of 40 blind test groups organized in 20 A >? B pairs, where A and B are complexes (therefore knowing each pair's functional ordering from the literature, BioRank™ was asked to predicted it).

The pipeline was able to

1. **Generalize out-of-the box: 100% A > B predictability.**
2. **Explain differences and A > B ordering arising from peptide, HLA and TCR mutations <u>with a single model</u>. To the best of our knowledge, there is currently no competing technology that offers comparable capabilities.**

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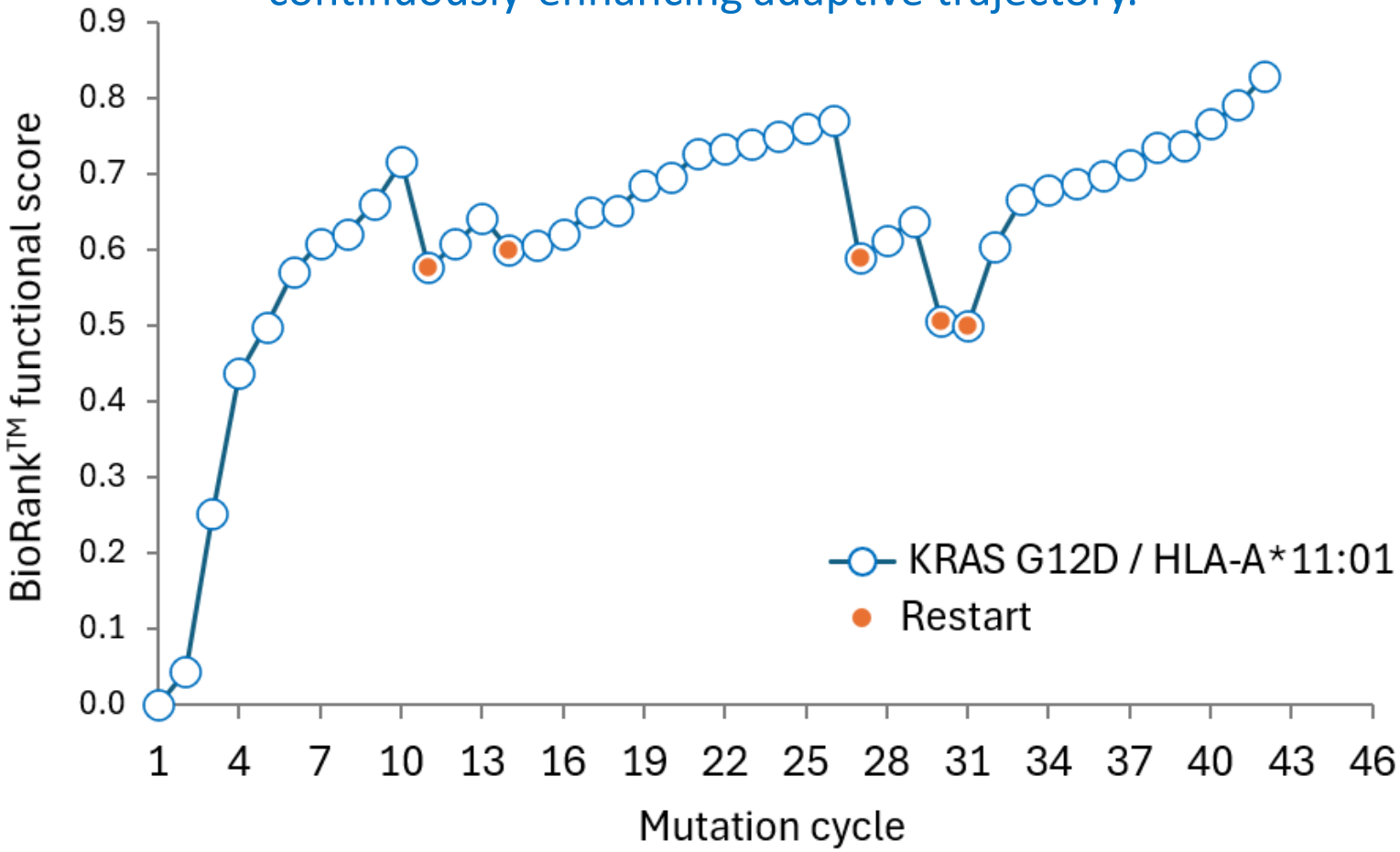
Use case: The KRAS G12D / HLA-A*11:01 cancer mutation

We showcased that the affinity-enhanced JDIa41b1 TCR variant bound to the KRAS G12D / HLA-A*11:01 neoantigen complex (PDB ID 7OW6) **is suboptimal**: BioRank™ achieved > 80% avidity enhancement/same specificity vs. JDIa41b1 along a continuously-enhancing adaptive trajectory.



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