Epitope-Targeted Antibody Discovery With AI-Designed Structural Immunogens

Alexander Taguchi, Cody Moore, Gao Liu, Hari Hara S. Potula, Tom Hsu, Tam Phuong, Cory Schwartz, Matthew Dent, Utsav Joshi, Lufei Hu, John Chen, Dillon Phan, Martin Brenner, Matthew Greving
iBio, 11750 Sorrento Valley Rd., San Diego, CA 92121

The Problems

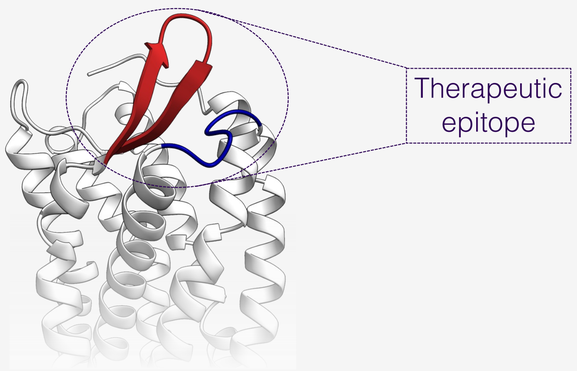
The efficacy of an antibody drug is strongly determined by the epitope to which it binds. Epitope-specific antibody discovery has been hindered by several problems:

- Dominant-epitope antibodies that may not be efficacious inundate traditional discovery approaches[1, 2, 3]
- Low/zero antibody discovery yield for high-value, challenging therapeutic epitopes[4]
- Limited availability of immunogen scaffolds that stabilize the epitope structure[5]

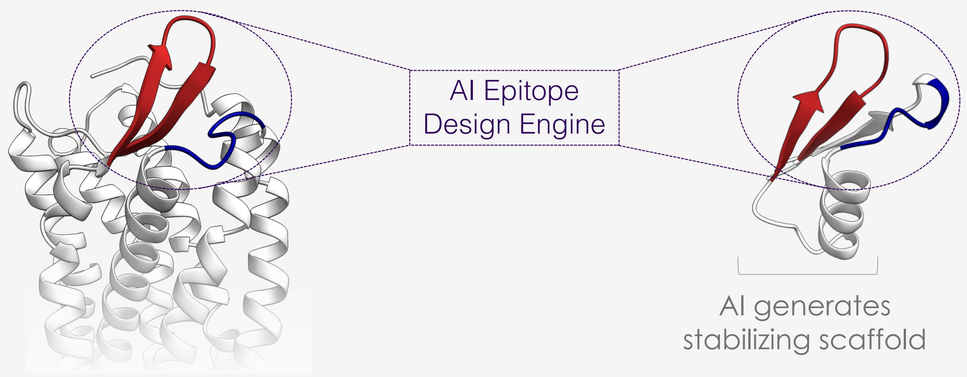
(1)Wicker *et al., Eur. J. Immunol.* (1984)14, p.447
(2)Victora *et al., Cell* (2015) 163, p.545
(3)Nakra *et al., J. Immunol.* (2000) 164, p.5615
(4) Trkulja *et al., Sci. Adv.* (2021) 7:16, p.eabe6397
(5)Sesterhenn *et al., Science* (2020) 368, p. eaay5051

Our Solution

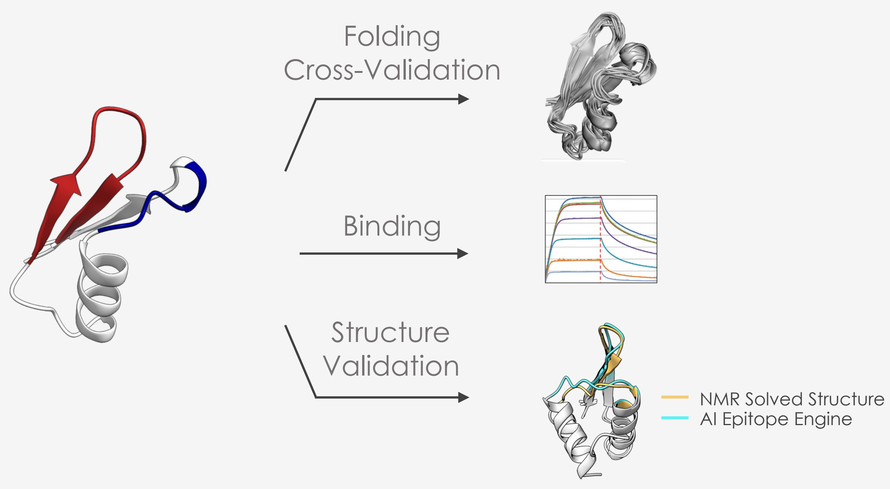
1. Start with an epitope



2. Design structural immunogens for that epitope

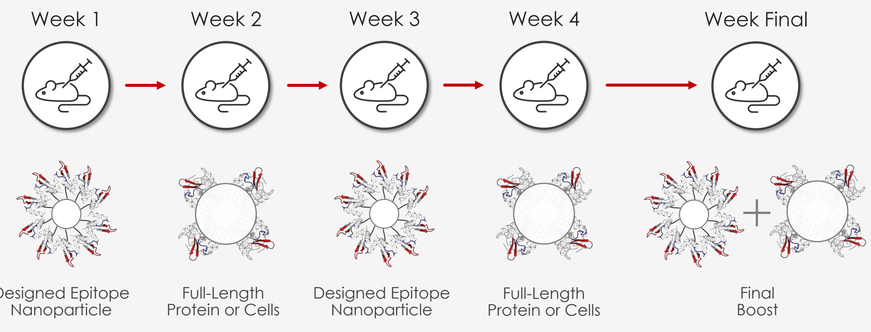


3. Verify designed immunogen

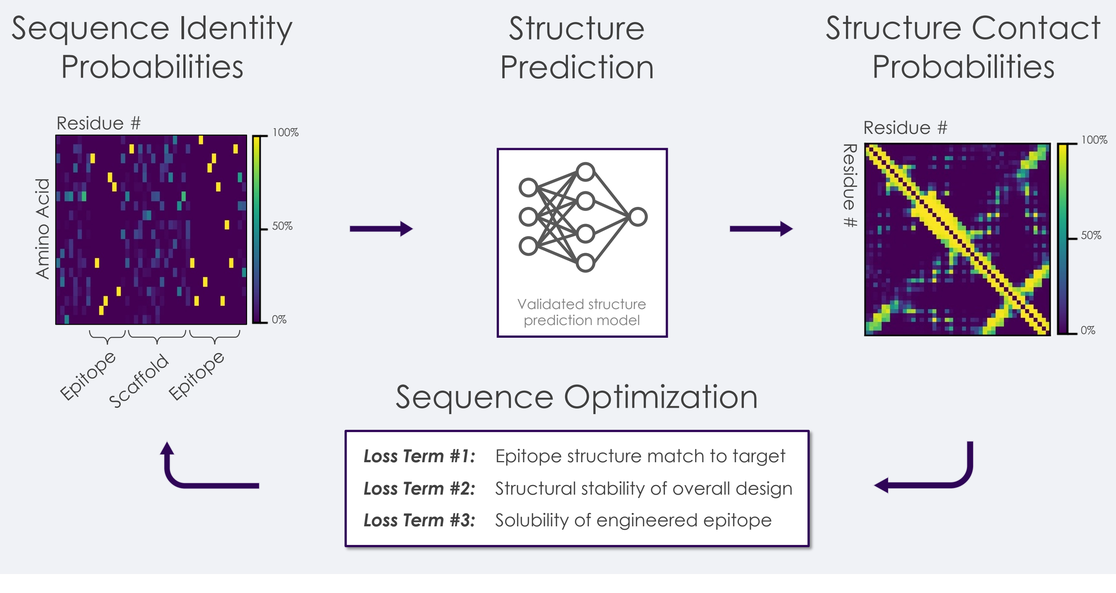


Predicted vs. Actual epitope structure
Backbone RMSD: 1.6 Å

4. Use designed immunogen in epitope-targeted discovery



AI Epitope Design

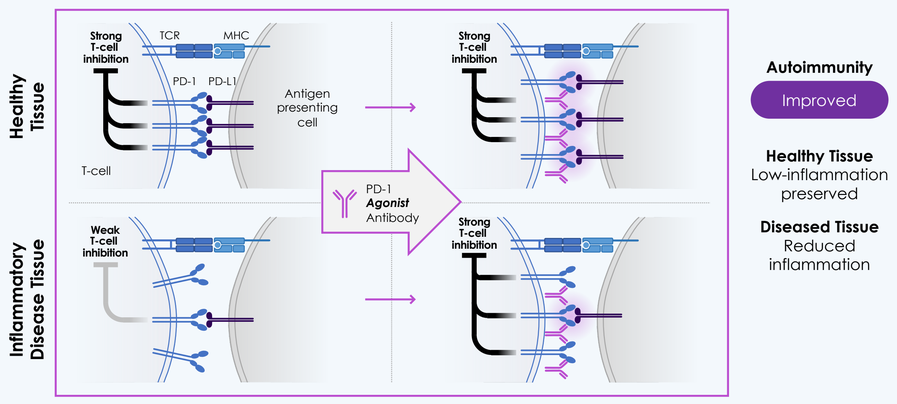


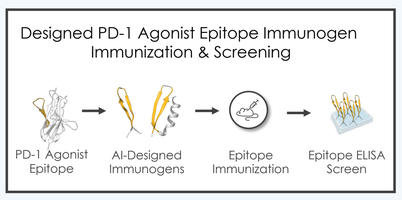
Validation

Epitope-targeted antibody discovery has been applied to several challenging targets. Two epitope targeted examples are below: 1) Agonist epitope and 2) Tumor specific (TSA) epitope.

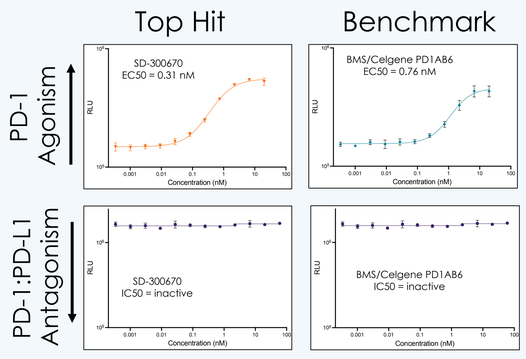
PD-1 Agonist

Agonizing PD-1 without blocking PD-L1 restores activated T-cell suppression



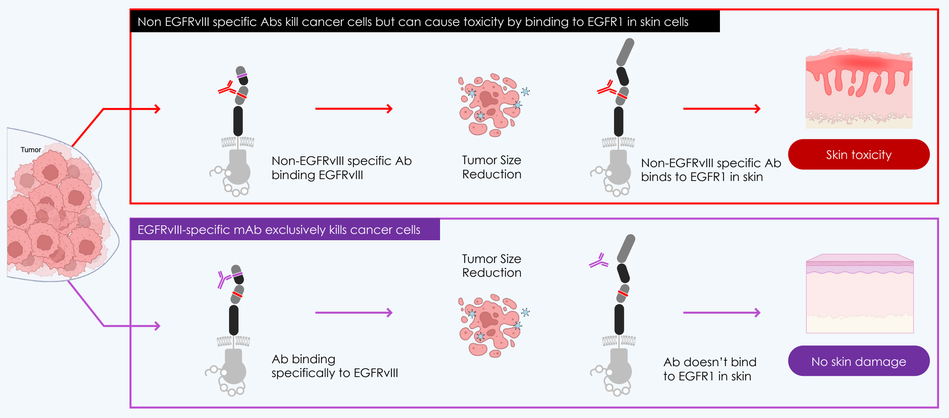


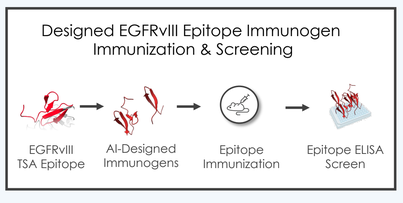
PD-1 agonist epitope-targeted antibodies agonize PD-1 without antagonizing PD-L1



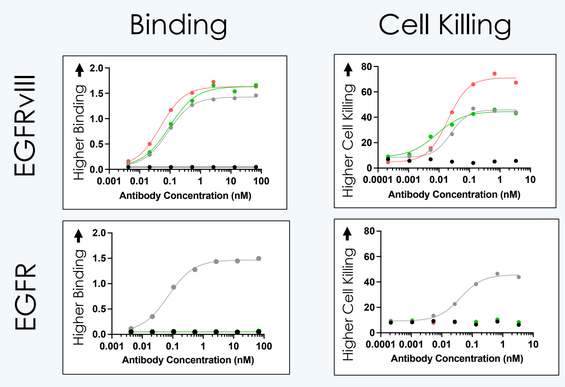
EGFRvIII TSA

The EGFRvIII epitope can be targeted to kill tumor cells and preserve EGFR1 healthy cells





EGFRvIII epitope-targeted antibodies selectively kill EGFRvIII tumor cells without killing EGFR1 healthy cells



Negative control, EC_{50} = no binding
Cetuximab, EC_{50} = 0.018 nM
SD-233883, EC_{50} = 0.008 nM
SD-710726, EC_{50} = 0.020 nM