Fully Human & Developable Antibody Optimization Libraries Using Human-Sequence Trained AI and Mammalian Display

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The Problems

In vitro phage-display antibody libraries are a rich source of antibody diversity and are compatible with sophisticated selections that are difficult or impossible to perform with immunization. However, in vitro phage-display libraries can increase downstream risks such as:

- Low expression in production mammalian cell lines⁽¹⁾
- Instability and aggregation⁽¹⁾
- Immunogenicity due to non-human diversity⁽²⁾

Validation

PD-1 Agonist

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



In vitro mammalian-display antibody libraries can minimize the downstream expression and instability risks.⁽³⁾ However, mammalian-display has limited capacity for library diversity.⁽⁴⁾

(1) Kaleli et al. Proteins (2019) 87 p.607
(2) Walsh et al. MABS (2020) 12(0) p.e176482955
(3) Dyson et al. MABS (2020) 12(1) p.e1829335
(4) Valldorf et al. Biol. Chem. (2022) 403(5-6) p.455

Our Solution

1. Train AI on human antibody sequence space

Antibody Database

StableHu Al



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>1 billion curated human antibody sequences



AI trained to predict fully human CDR from masked CDR



PD-1 Agonism Reporter Assay

Starting from a mouse antibody template, StableHu AI & mammalian-display identified a more potent PD-1 agonist antibody



CCR8 GPCR ADCC

Depletion of CCR8+ Treg cells can evoke tumor immunity



2. Use AI model to predict fully human focused diversity from a template antibody to be optimized



3. Produce a mammalian-display library using AI-predicted focused diversity



Mammalian Display Library





Sorted Cells

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





4. Single-cell screen mammalian-display library for expression and binding

Single-Cell Sorting



Starting from a mouse antibody template, StableHu AI & mammalian-display identified a more potent EGFRvIII+ cell killing antibody

EGFRvIII ADCC Cell Killing Assay

