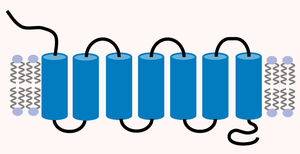
Engineering GPRC5D Multispecific Antibodies

Parallel Engineering to Optimize Affinity, Developability, Species Reactivity & IP

Trevor Barnes, Hayley Roth, Daniel Rogers, Sabyasachi Sen, Ileine Sanchez, Valerie Fiers, Breanna Tyrell, Amelia M. Snyder, Alexander Hobby, Kyle Doolan, Benjamin J. Doranz, Ross Chambers, and Joseph B. Rucker

Integral Molecular, Philadelphia, PA

GPRC5D in Multiple Myeloma



Expressed in multiple myeloma cells

Not expressed in most healthy tissues

GPRC5D MAb Discovery

Native Antigen

On virus-like particles (VLPs)

DNA

74 unique hits,
34 VH CDR3 families

Divergent Species

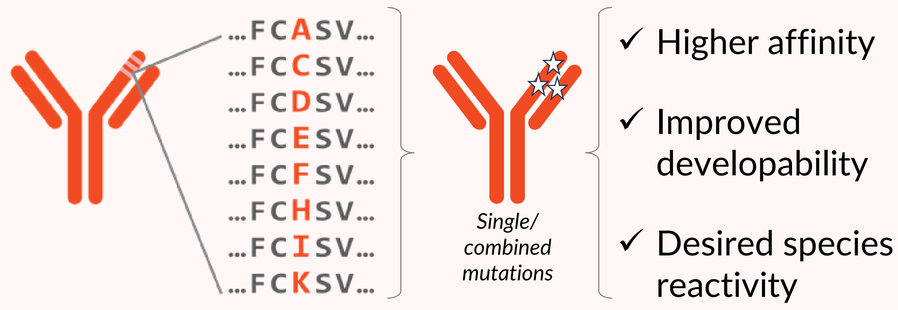
In Vivo

Control

Treatment

Tumor inhibition with bispecific or trispecific molecule

Antibody Engineering and New IP Creation Using CDR-Scanning



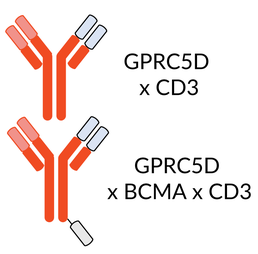
19 amino acid variants for each CDR residue

- ✓ Higher affinity
- ✓ Improved developability
- ✓ Desired species reactivity

GPRC5D Antibody Discovery

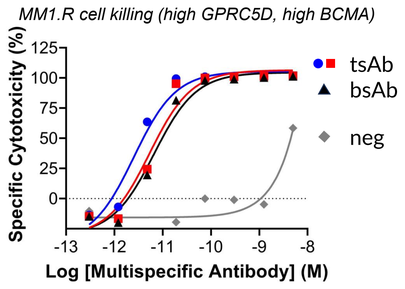
In Vitro: Detailed Analysis of Lead Candidates

Bi/Trispecific



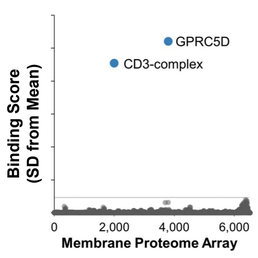
Potent Target Cell Killing

MM1.R cell killing (high GPRC5D, high BCMA)



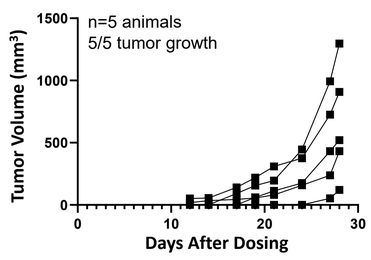
Exquisite Specificity

Lead molecule tested on MPA

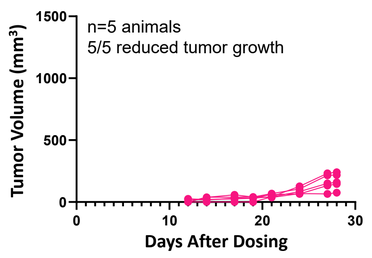


In Vivo: Tumor Inhibition

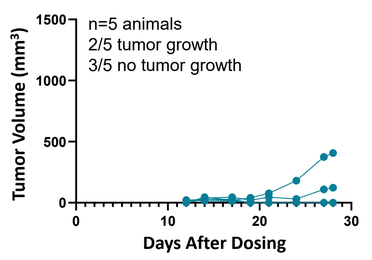
PBS



Bispecific Lead

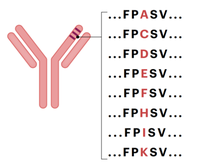


Trispecific Lead



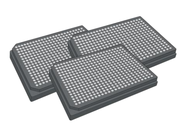
CDR-Scanning Enables Engineering

1 Comprehensive CDR-Scan Library



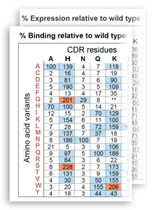
19 variants per CDR residue, Fab or scFv formats

2 High-Throughput Binding Assay



Quantify binding by ELISA, expression + binding

3 Detailed Report



Single mutants with improved binding and developability

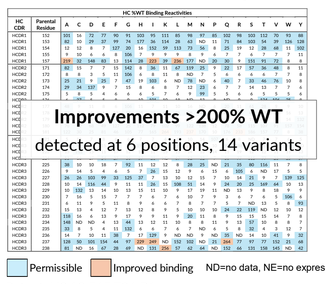
4 Optimized Lead



Optimal variants combined using AI/ML and tested in lab

GPRC5D CDR-Scanning

(986 variants, heavy chain + light chain)

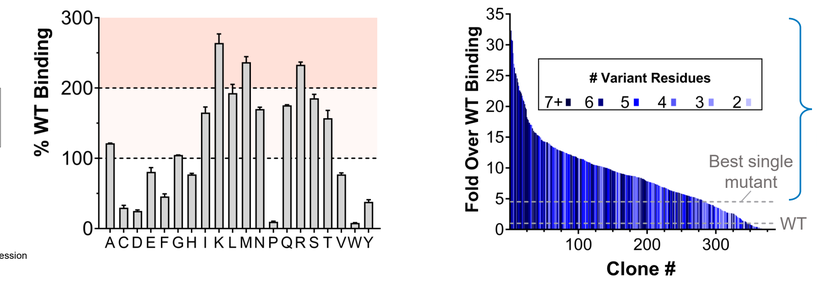


Improvements >200% WT detected at 6 positions, 14 variants

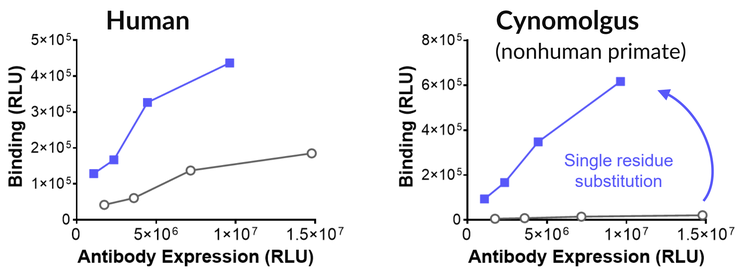
Permissible | Improved binding | ND=no data, NE=no expression

Patent: US 12,545,726 B1

Improved Binding: Saturation & Combination Mutagenesis



Improved variants for better affinity, developability, and novel IP

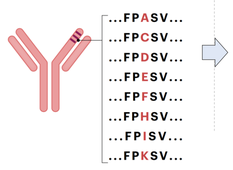


- 986 variants tested with cyno GPRC5D
- 10 improvements identified across 7 amino acid positions

Reactivity to NHP ortholog enables testing in preclinical animal models

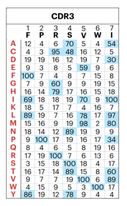
CDR-Scanning Adds Value to Patents

1 CDR-Scan Library



Mutate each CDR residue to 19 other amino acids

2 Permissible Variants



Individually test binding and expression

3 Visualize Genus



Common structural element (paratope) defines genus

4 Claim Genus in Patent

An antibody comprising a heavy chain variable region (HVR) and light chain variable region (LVR), wherein the HVR comprises an…

HCDR3 comprising an amino acid sequence of $X_1PX_2X_3X_4WX_5$, wherein X_1 is an amino acid selected from F,I,L,Y,…

*Parental antibody **PLUS** all permissive CDR variants that permit binding*

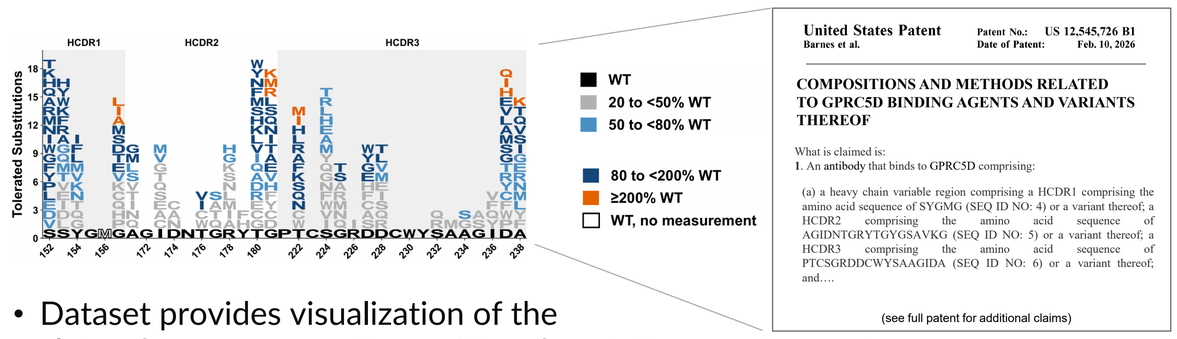
Enablement *teaches how to make* + **Written Description** *demonstrates possession* = **Claimed Genus**

As described in Banik et al., 2025

- Patents claiming only 1 antibody 'species' can be easily circumvented; preferable to claim a 'genus' covering a group of related antibodies
- Antibody patent strategy using extremely broad functional genus claims is no longer viable in the US after the landmark case *Amgen v. Sanofi*

Updated USPTO guidance and case law require developers to use a new strategy to fulfill antibody patent enablement and written description requirements

Patent Issued With Genus Claims Based on CDR-Scanning



- Dataset provides visualization of the claimed genus, supporting written description requirements
- Issued patent protects single and combined substitutions

Integral Molecular's Pipeline Enabled by Membrane Protein Technologies and Antibody Engineering

- Native antigen presentation using **virus-like particles** in conjunction with **DNA/RNA immunization**
- **Divergent** host species enable robust immune responses to complex targets
- **Membrane Proteome Array™** for specificity screening against ~6,000 native membrane proteins
- **Paratope-PLUS®** CDR-Scanning for affinity maturation, species reactivity, and patent protection

Target	Indication	Modality	Discovery	Preclinical	Phase 1	Partner
CLDN6	solid tumors	TCE	CTIM-76			context
Undisclosed	oncology	undisclosed				AstraZeneca
CLDN18.2	solid tumors	ADC				undisclosed
SLC2A4	undisclosed	undisclosed				undisclosed
CLDN18.2	solid tumors	TCE, CAR-T				
GPRC5D	multiple myeloma	TCE				

Additional assets available for licensing include P2X3 (pain), P2X7 (immunity)

v1026

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With 25 years of experience, Integral Molecular is the industry leader in antibody discovery against undruggable protein targets such as complex membrane proteins.

Contact us with licensing inquiries for GPRC5D and additional assets from our therapeutic pipeline.

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