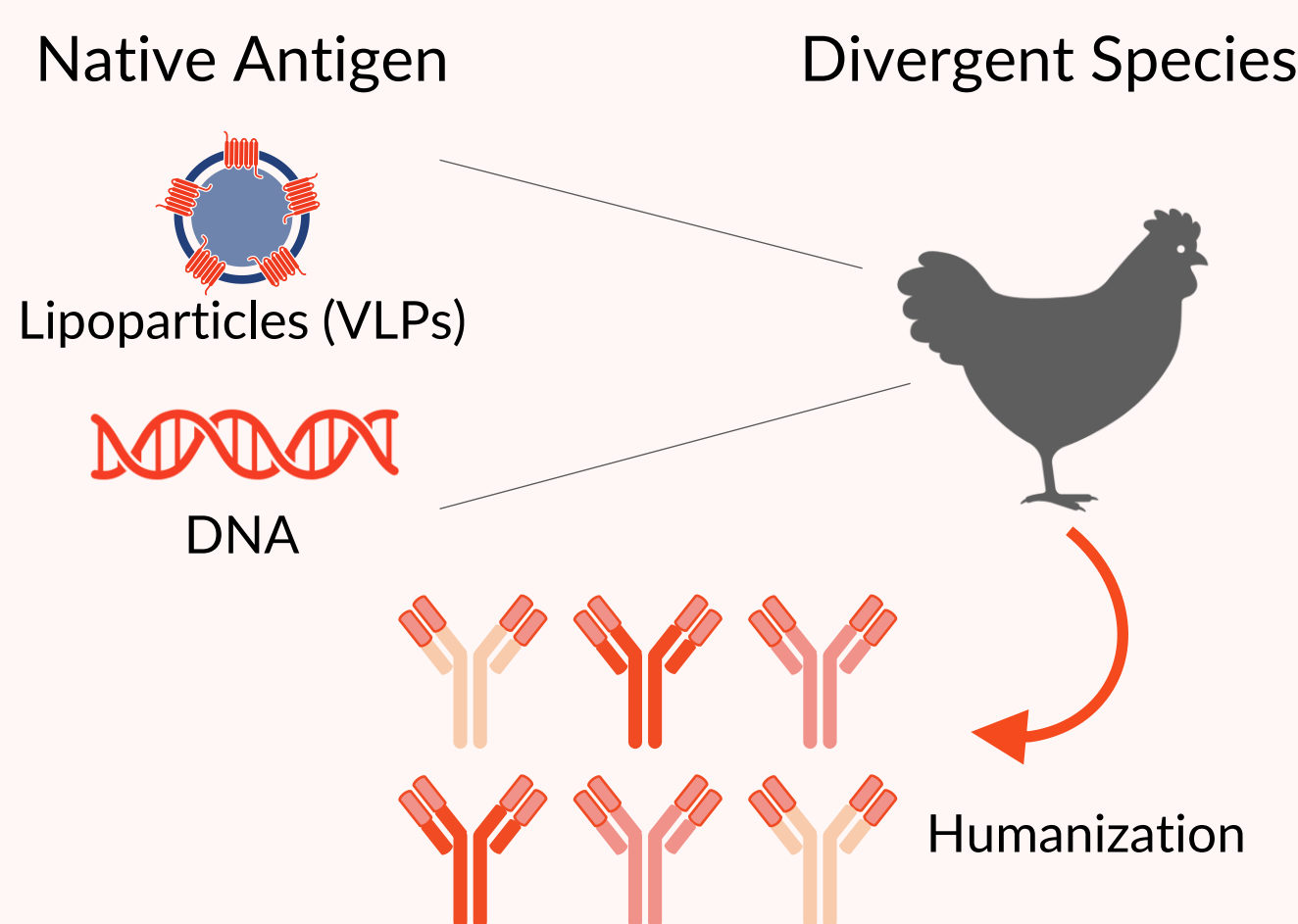


GPRC5D in Multiple Myeloma

- Multiple myeloma is the second most common hematological cancer
- Most treatments fail, leading to relapse
- GPRC5D is expressed in multiple myeloma cells, not in healthy tissue except hair follicles
- Target challenges: complex antigen, small extracellular regions

Immunization & Humanization



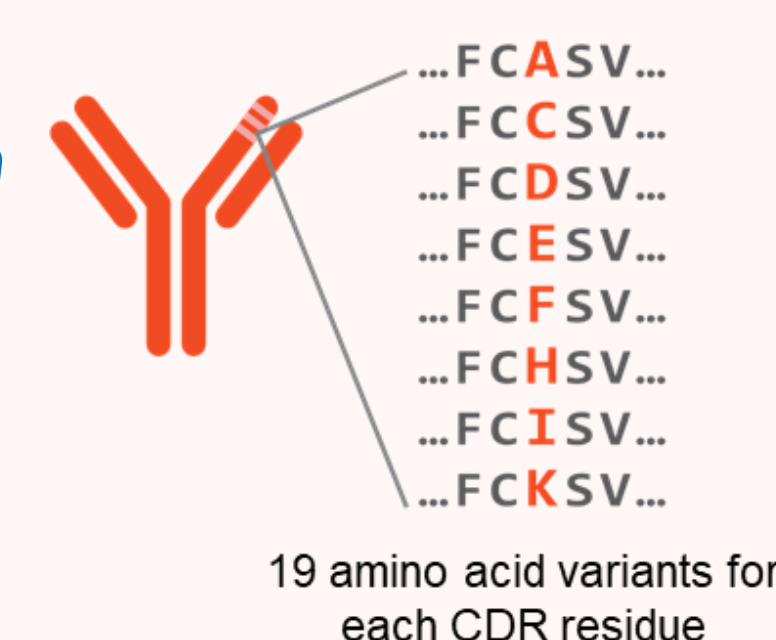
- 74 unique hits, 34 VH CDR3 families
- 99% humanization (excluding CDR regions)

Antibody Engineering

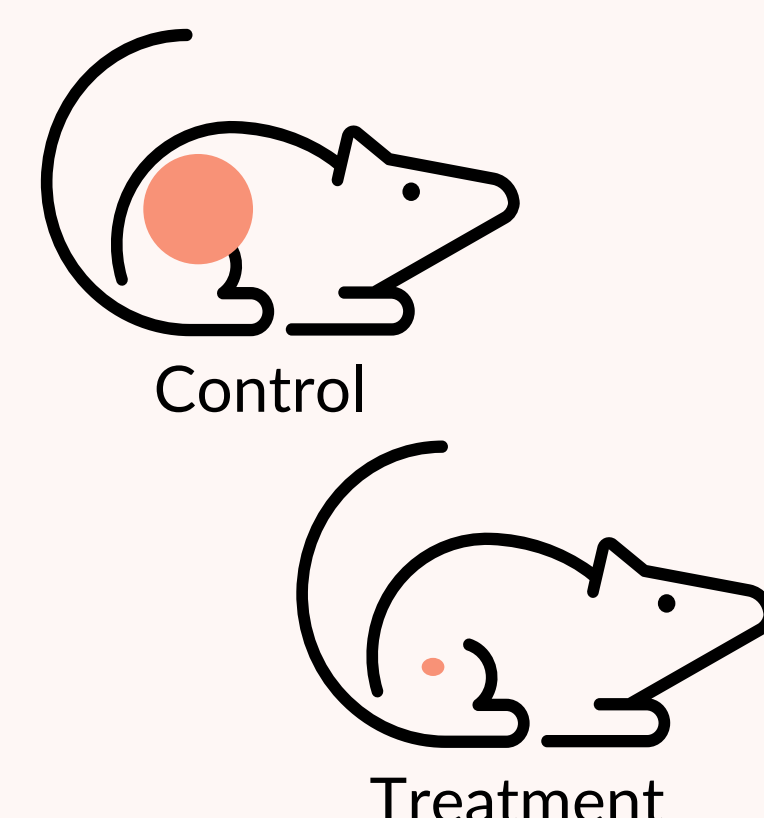
Multispecific Formats



Affinity Maturation by Comprehensive CDR-Scanning



In Vivo Efficacy

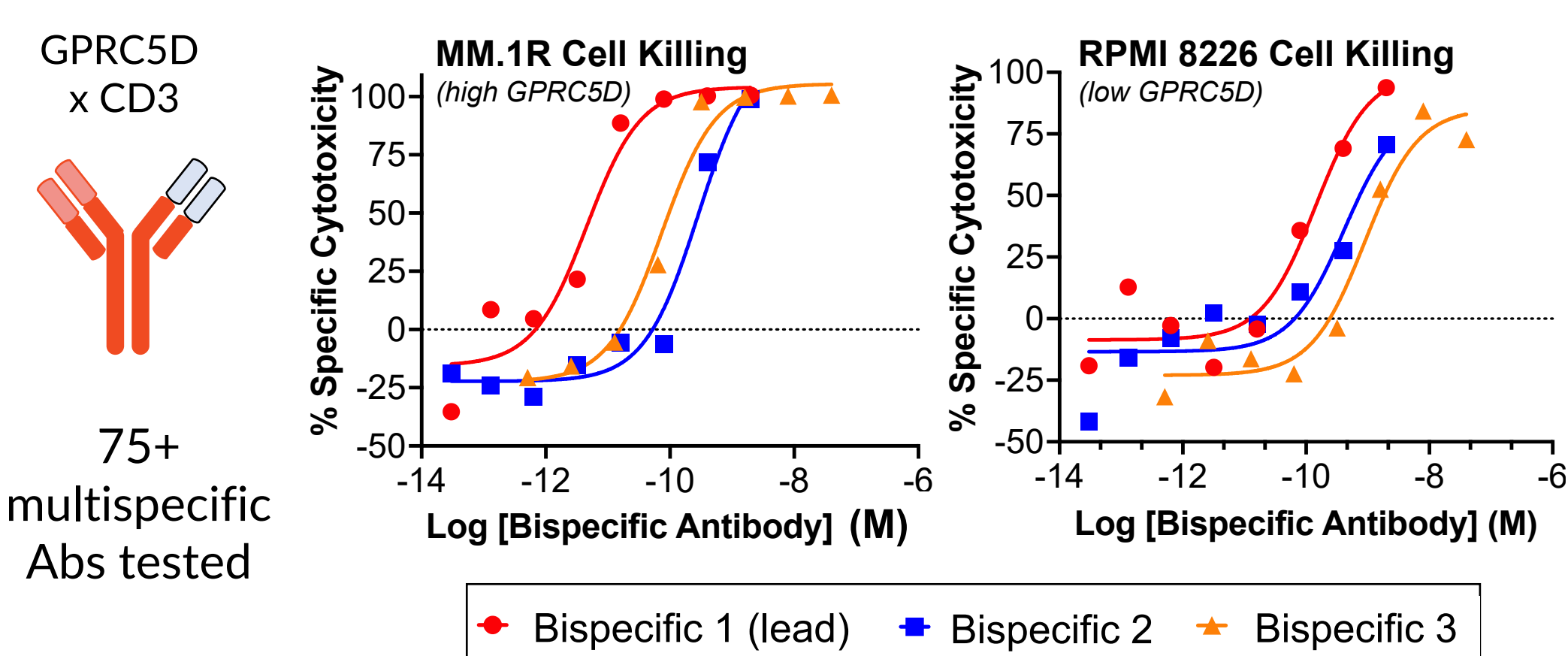


- Tumor inhibition with bispecific or trispecific molecule

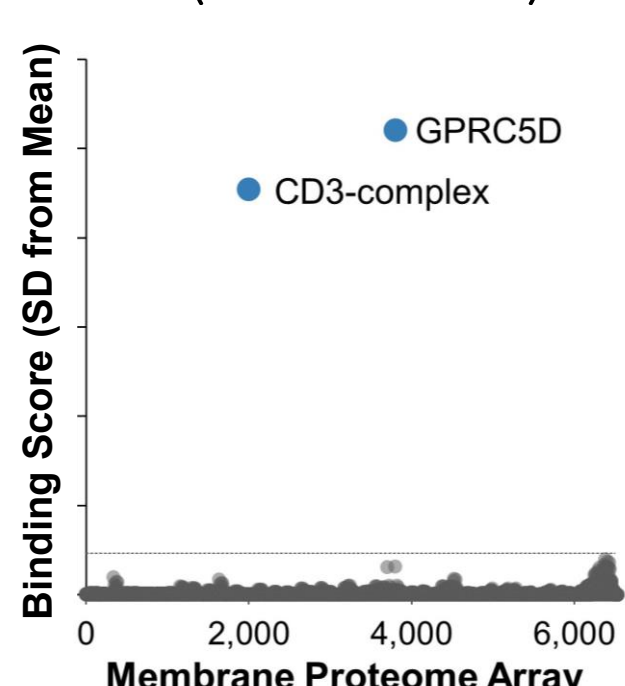
Bi- and Tri-Specific Antibody Discovery

In Vitro Efficacy: Detailed Analysis of Lead Candidates

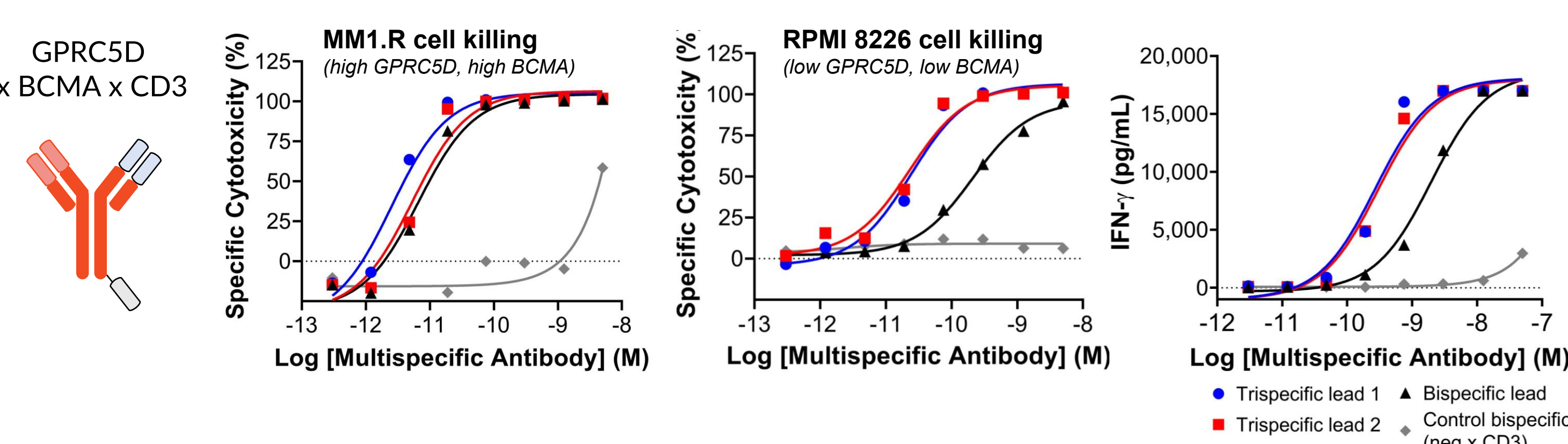
Bispecific



Exquisite Specificity (lead molecule)



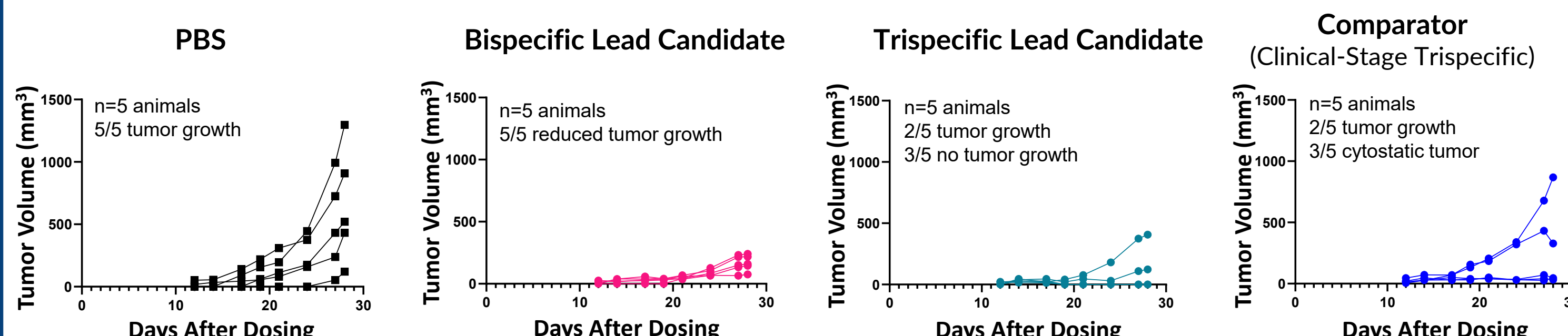
Trispecific



- Clinical background:** Individual bispecifics targeting BCMA or GPRC5D (J&J) show high objective response rates for patients with multiple myeloma and combination therapeutics show even better responses in Phase 1 testing
- Current findings:** Trispecific antibody targeting GPRC5D, CD3 and BCMA shows potent (pM) killing of hGPRC5D expressing target cells with modest levels of cytokine release (IFN- γ), providing a beneficial therapeutic window

Excellent *in vitro* properties of multispecific antibodies including potency, target specificity and low cytokine release

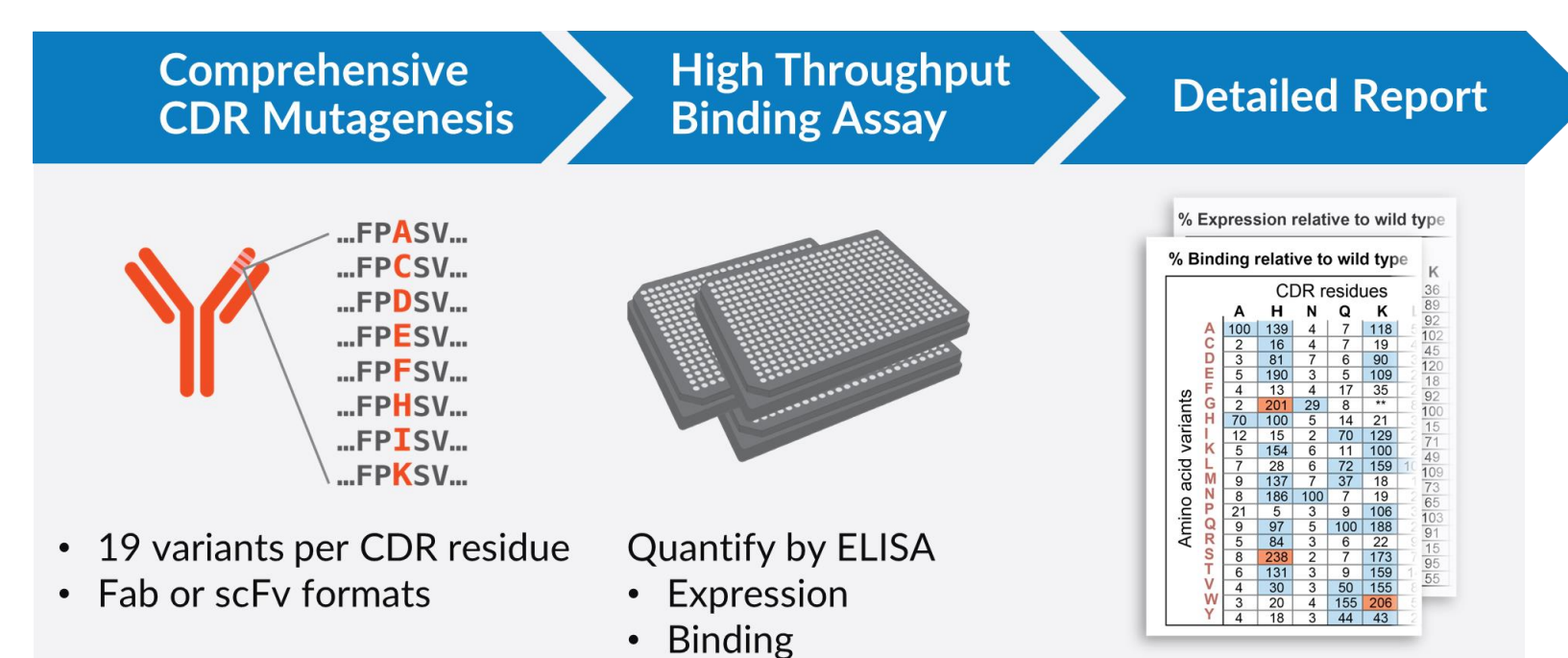
In Vivo Efficacy: Inhibition of Tumor Growth



- Prophylactic tumor model using H929 xenograft in humanized mice (5 mg/kg, dosed biweekly, dose 1 on day 0)
- Treatment well tolerated in mice (not shown)

Engineering By Deep Mutational Scanning

Affinity Maturation Using Paratope-PLUS CDR-Scanning



As described in Banik et al., 2025

Patents naturebiotechnology
Redefining antibody patent protection using paratope mapping and CDR-scanning

- Variations for improved binding and developability
- Draft patent claims based on paratope and functional variants for better IP and enforceability

GPRC5D CDR-Scanning Mutagenesis (986 variants, heavy + light chain variants, human antigen)

		HC WT Binding Residues																			
HC CDR	Parental Residue	A	C	D	E	F	G	H	I	K	L	M	N	P	Q	R	S	T	V	W	
HCDR1	152	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR1	153	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR1	154	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR1	155	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR1	157	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	171	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	172	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	173	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	174	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	175	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	176	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	177	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	178	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	179	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	180	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	181	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	182	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	183	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	184	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	185	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	186	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	187	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	188	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	189	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	190	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	191	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	192	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	193	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	194	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	195	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	196	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	197	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	198	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	199	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	200	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	201	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	202	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	203	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	204	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
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HCDR2	206	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	207	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
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HCDR2	209	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	210	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	211	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
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HCDR2	214	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	215	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	216	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
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HCDR2	218	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	219	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	220	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	221	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	222	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	223	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	224	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	225	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
HCDR2	226	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	227	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	228	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11	
HCDR2	229	10	10	4	6	106	7	9	9	9	9	9	9	9	9	9	9	9	9	9	
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HCDR2	231	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
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HCDR2	235	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
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HCDR2	238	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	239	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
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HCDR2	242	101	16	72	77	90	91	108	95	111	85	98	92	102	98	100	112	70	95	88	
HCDR2	243	82	10	28	37	99	76	177	14	114	148	144	148	144	148	144	148	144	148	144	
HCDR2	244	12	12	8	7	107	20	14	102	10	113	70	140	8	126	19	12	126	148	11</	