



OmnidAb™:

Heavy Chain-Only Transgenic Chickens Produce Human Antibodies with Robust Immune Repertoires and High-Affinity Binding

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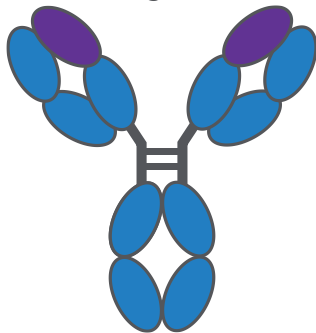
December 14, 2023

What is a Single-Domain Antibody (sdAb)?

ALSO KNOWN AS V_H H ANTIBODIES OR NANOBOBODIES®

Conventional antibody (IgG)

Comprised of 2 heavy chains and 2 light chains



Total MW ~150kD
Binding domain is $V_H \times V_L$

sdAb

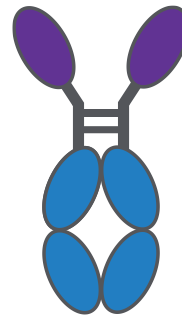
V_H domain of HcAb can be expressed independently as an autonomous sdAb unit



Compact format of sdAb (~15kD) opens new and important opportunities

Heavy chain-only antibody (HcAb)

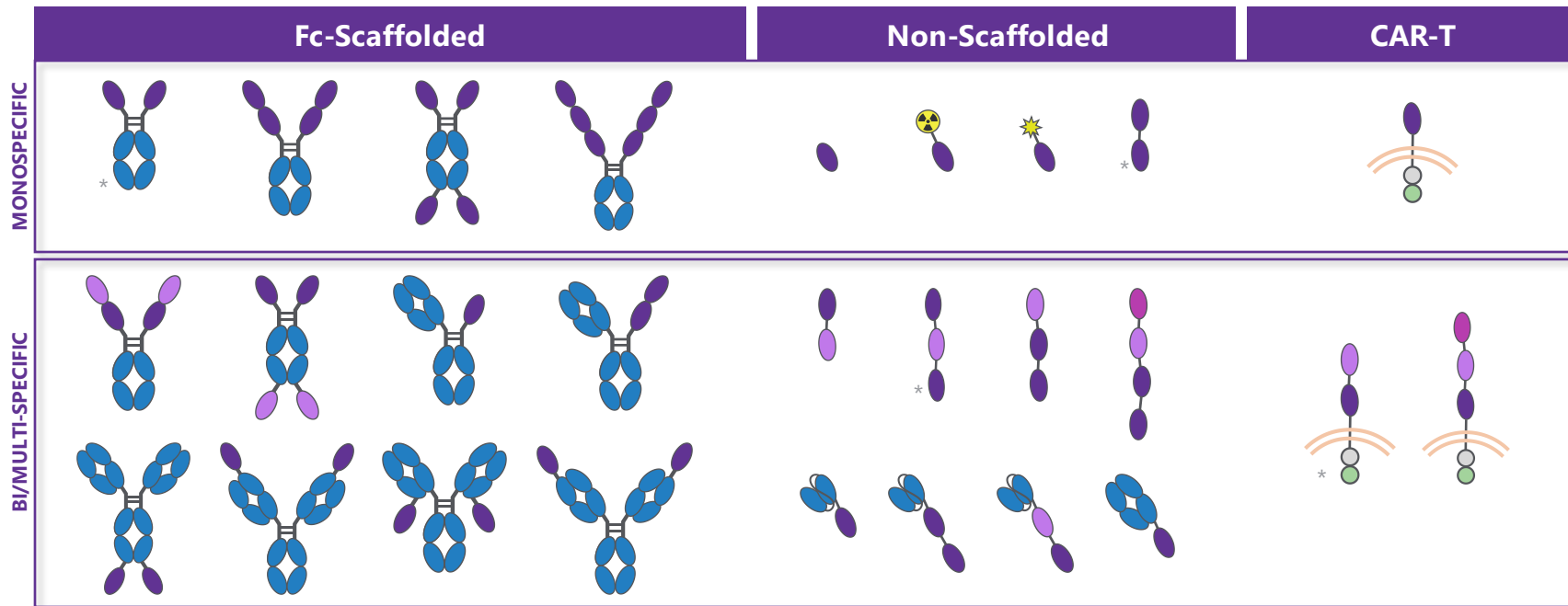
Found naturally in camelids, comprised of 2 heavy chains, no light chain



Total MW ~100kD
Binding domain is V_H only

sdAbs Provide Modular Building Blocks

sdABs CAN BE ASSEMBLED INTO VARIOUS FORMATS TO “FIT THE BIOLOGY” OF AN APPLICATION



- Assembly into larger or custom formats unlocks versatility to “fit the biology”; also well-suited to bi/multi-specifics
- Small formats enable convenient routes of administration (inhalable & oral), penetration, and fast clearance, compatible with the decay half-life of radio-isotopes used in imaging, diagnostics, and radiotherapy

* Indicates a regulatory body currently-approved format

Opportunities for sdAbs in Medicine



Alternate routes of administration

Injectable, inhalable, & oral



Penetration + fast/tunable clearance

Tissues and tumors



Imaging + diagnostics

Small size compatible with PET/CT imaging radiolabels

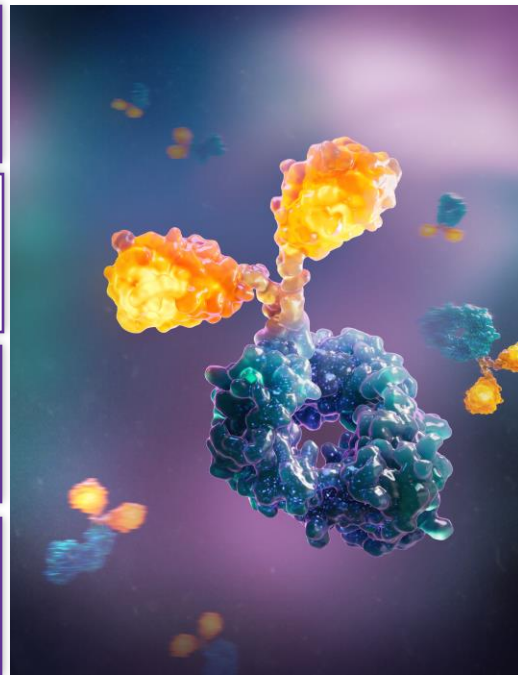


Broad therapeutic applications

Central nervous system and neurodegenerative diseases

Infectious and Autoimmune diseases

Cancer (especially bi/multi-specifics & CAR-T)



Unique physical properties of sdAbs can be leveraged for important applications

Clinical Landscape for Therapeutic sdAbs

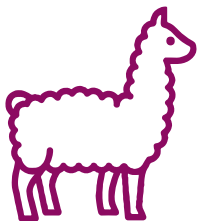
ROBUST AND GROWING CLINICAL PIPELINE OF SINGLE-DOMAIN ANTIBODIES

Clinical Phase	Number of VHH-based Drugs
Approved	4
Phase 3	2
Phase 2	8
Phase 1	10

Jin et al, Int. J. Mol. Sci. 2023; Clinicaltrials.gov: www.antibodysociety.org

- VHH-products comprise a growing segment of the Ab market
- 4 approved VHH-based drugs
- 20 VHH-based products in clinic
- Used to treat cancer, autoimmune, infectious diseases
- Various molecular formats:

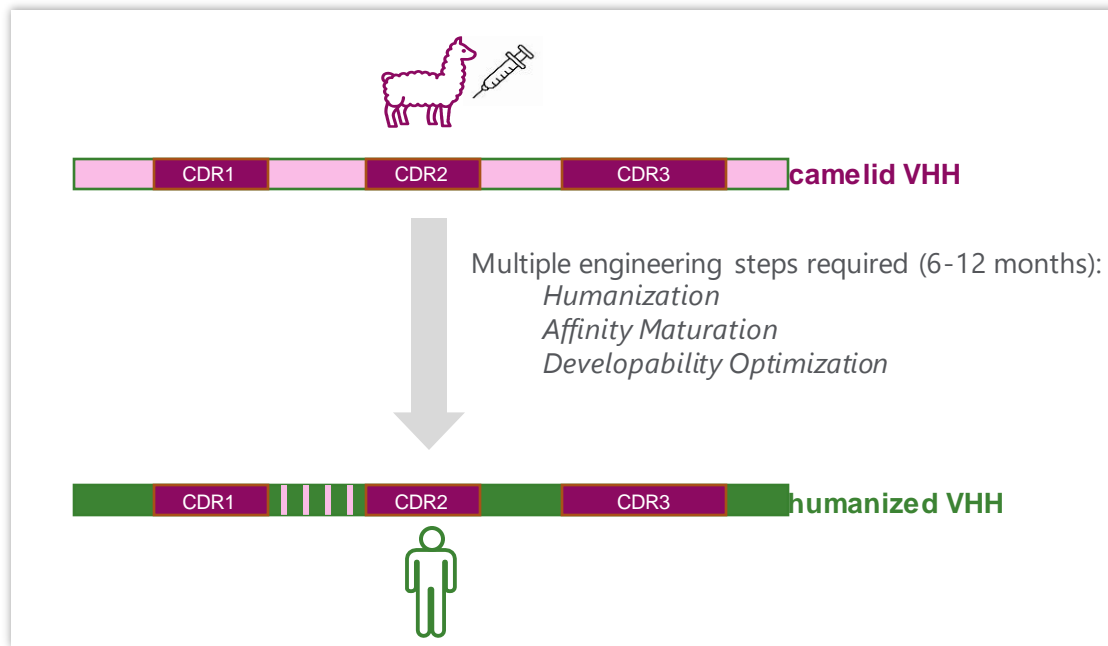
Tandem VHH-VHH, VHH-Fc, VHH-albumin, bi/multi-specific, CAR-T, VHH cocktails...



Currently approved VHH-based drugs: Cablivi, Caplacizumab EU 2018, US 2019 (Sanofi); ENWEIDA, Envafolimab China 2021 (Simcere); Nanozora, Ozoralizumab Japan 2022 (Sanofi); CARVYKTI, Ciltacabtagene autoleucel US 2022 (Janssen)

Current Discovery Strategy for Therapeutic sdAbs

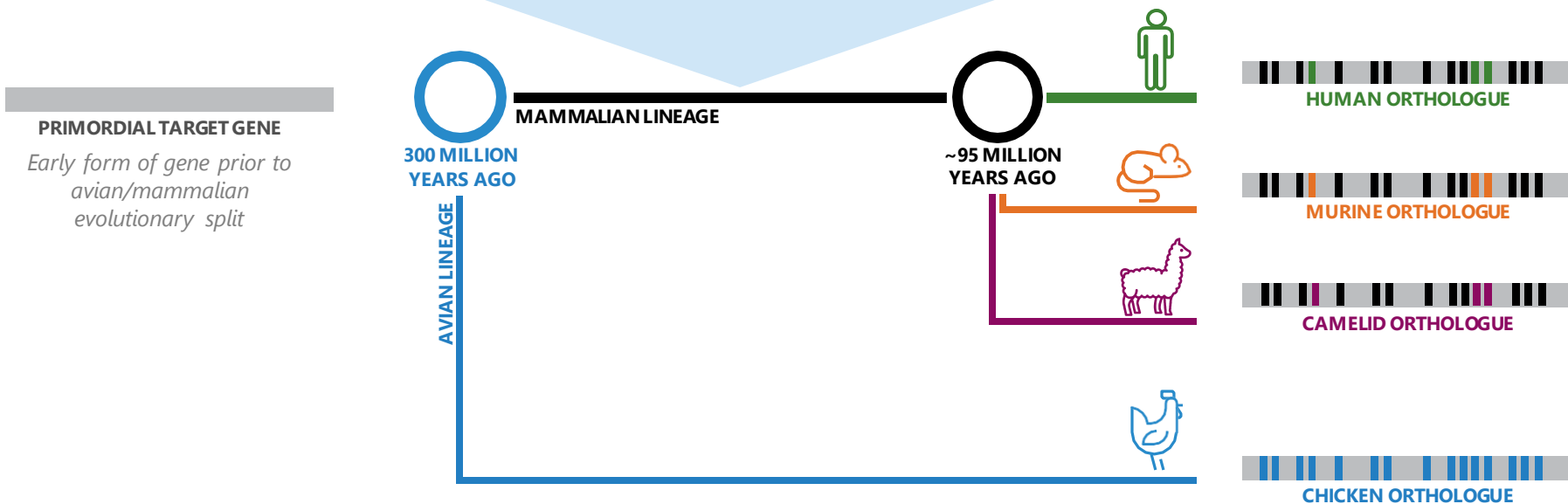
Current process requires large animal immunization, as well as engineering - including humanization and optimization, which adds time and can increase risks



Camelid immune hosts may be limited by target homology, and recovered mAbs require humanization

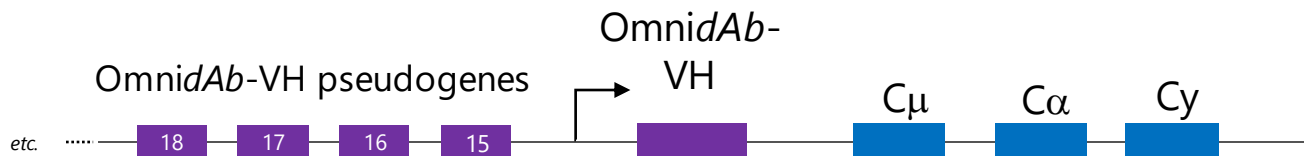
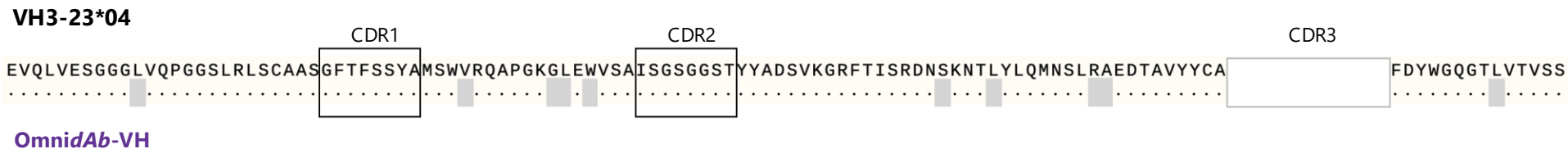
Chicken Platforms: Powered by Evolution

GREATER EVOLUTIONARY DISTANCE YIELDS
GREATER IMMUNOGENICITY AND MORE ANTIBODY DIVERSITY



OmnidAb™ Platform: Transgene Design

HUMAN VH3-23 WITH 10 STABILIZING MUTATIONS IN THE FRAMEWORKS



OmnidAb™ Pseudogene Array: Diversity Through Gene Conversion

STABILIZED FRAMEWORKS, CDR DIVERSITY

Stabilizing mutations maintained in FRs	CDR1*	CDR2*	CDR3**
15	---D·Y	S---SSY	RDR·GIAAQ---DTH
16	---NAW	KSKTD·T	·KD·TV·W---YRAL·QH
17	---V·NY	YS	·KDLGYYYS·DYG---GSRGM·V
18	---W	KQ·D·SKK	·KPEG·RGAAA·PF---DA·II
19	---DHY	TRNKANSYT	·KDGIAA·HT---RARGS
20	---S·DD	W·NS·II	·RSKEDYDILT·YNLQYYYGGM·V
21	---YSIS·G·Y	YH---S	·KENNRHG·W·TFGGVLTSPH
22	---DD·T	GT·A·DTY	·KIS·DIVVYPA---AFH
23	---F	NW·N	·KGA·RN·LI---PY·L
24	---GY·P	WY·D·SNK	·KD·AY·EVRGV---ITNW·P
25	---YSIS·NW	RSKANSYA	·KIP·LA·YFDTFT---GRGA·Q
26	---GSISS·GD·Y	YY---II	·KDYRANDRAT·GY---WDDA·II
27	---GS·G·Y	ITH	·KDPF·YSNY·F---DY·A
28	---GSISS·Y	NS·D·S	·KNSDKWEL---RDA·II

*From human VH3 germline genes

**From human VH3 somatic sequences



Gene conversion provides diversity to the CDRs and maintains the optimized single framework

OmnidAb™ Platform: sdAb VH and tLC Transgenes

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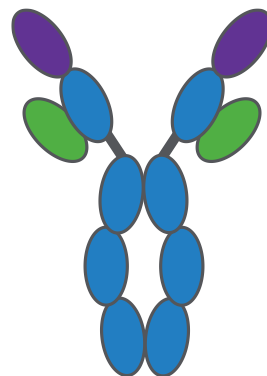
VH3-23*04



OmnidAb-VH

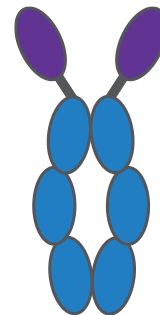
- Birds express VH, but no VL
- Spliced to WT chicken heavy chain constant region (Fc)
- Spontaneous CH1 deletion

Predicted:
OmnidAb-VH
Truncated Light Chain



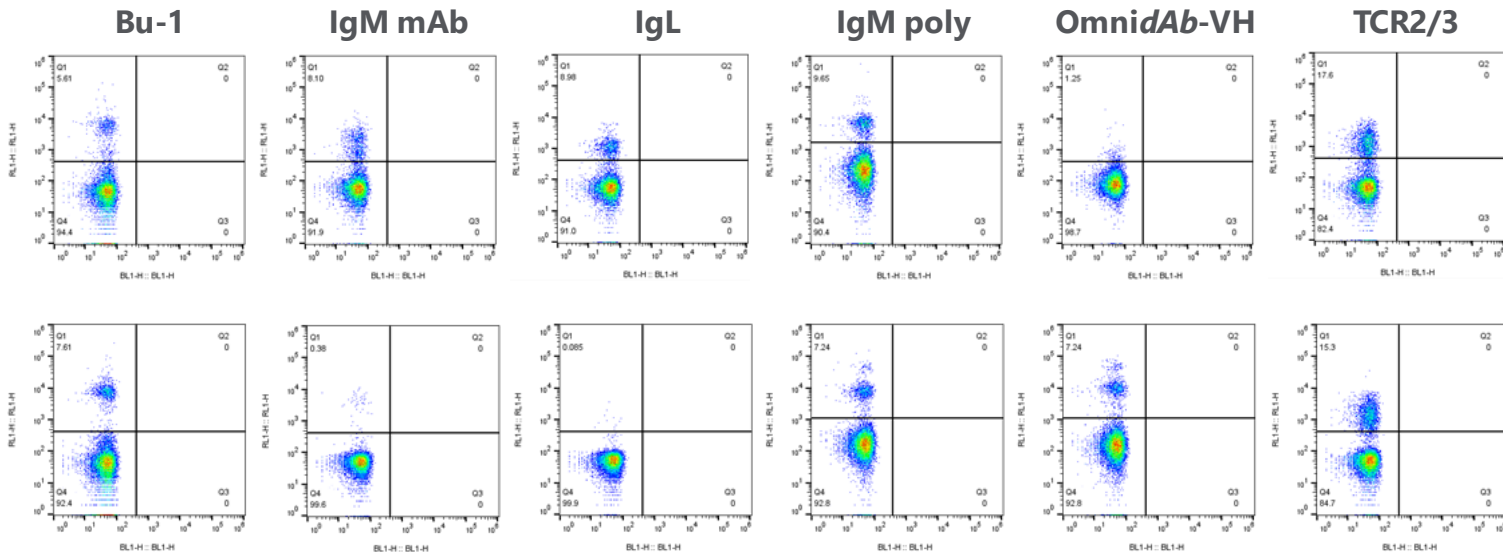
CH1-deletion →

Observed:
OmnidAb-VH



B Cell Development in *OmnidAb*TM Chickens

Wild type



CH1-deletion:
IgM epitope is in CH1

No IgL

Robust B cell development in *OmnidAb*TM chickens

OmniAb™ Immunizations

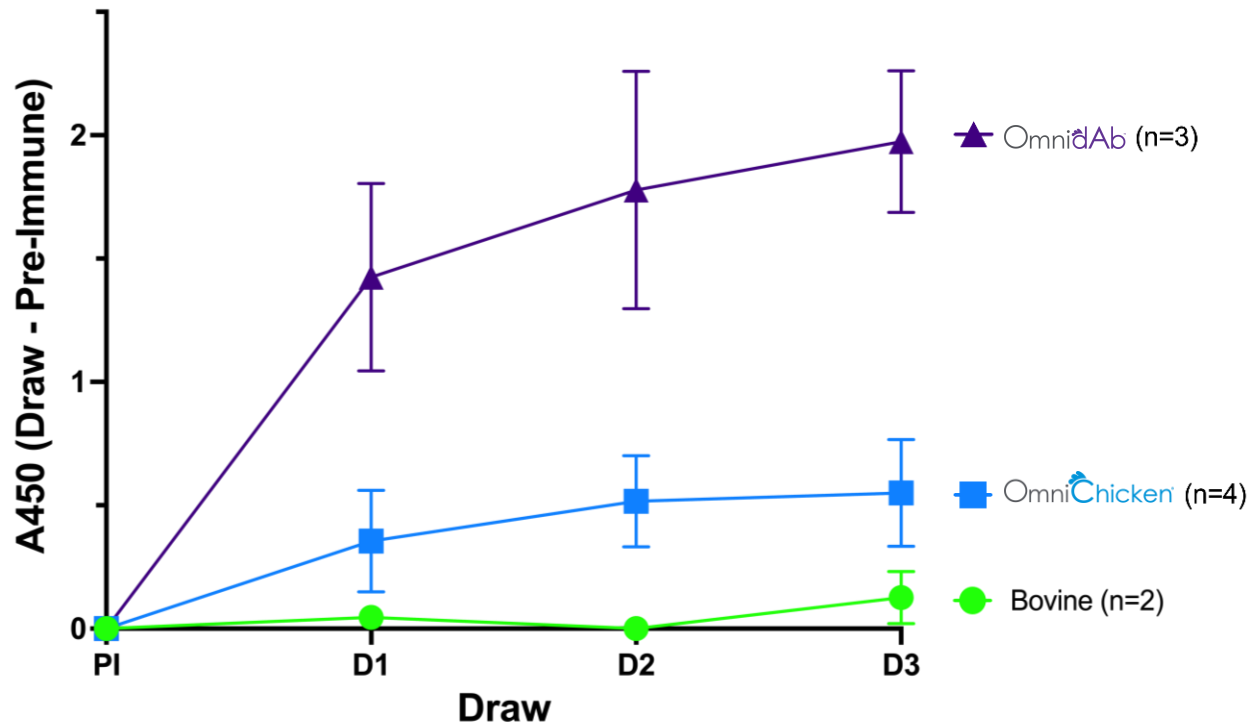
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THREE COHORTS: NKp46, TIGIT+PGRN COCKTAIL, Kv1.3

	NKp46	TIGIT PGRN	Kv1.3
Immunogen	Protein	Protein	Solubilized Protein Nanodiscs DNA mRNA-LNP
OmniAb	3 birds	4 birds	13 birds
2-3 boosts (4-5 injections)			(in process)

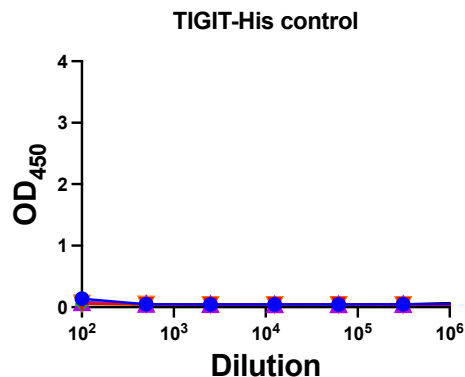
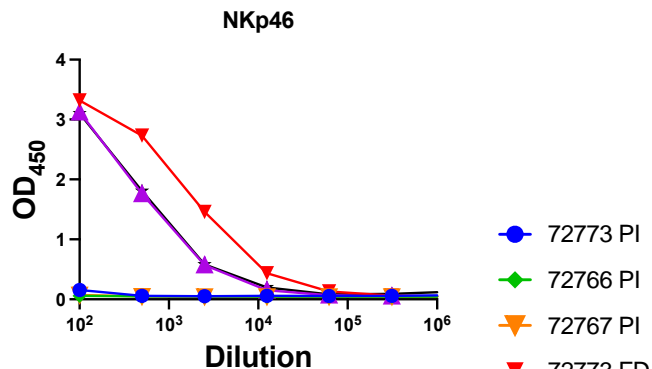
Preliminary Response Data to Kv1.3 Ion Channel

Species	% Homology to Human
Chicken	76.3%
Bovine	95.3%
Alpaca	97.7%
Mouse	96.6%

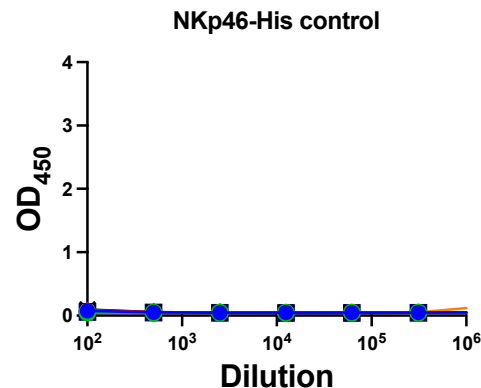
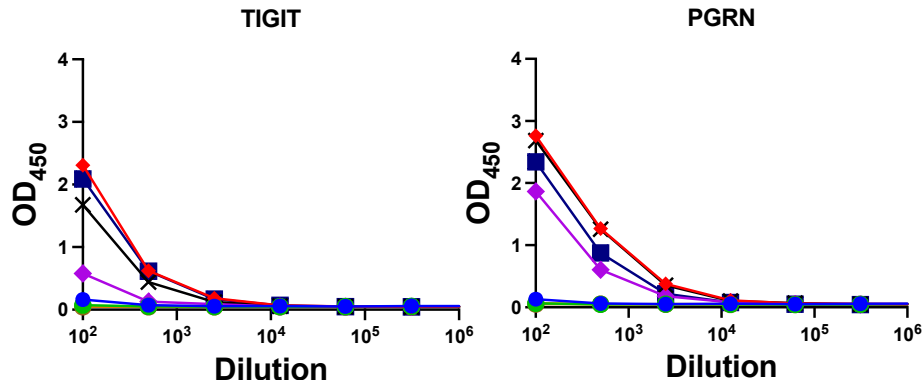


OmniAb™ Birds Raise Robust, Specific Immune Responses

NKp46-immunized



TIGIT/PGRN-immunized

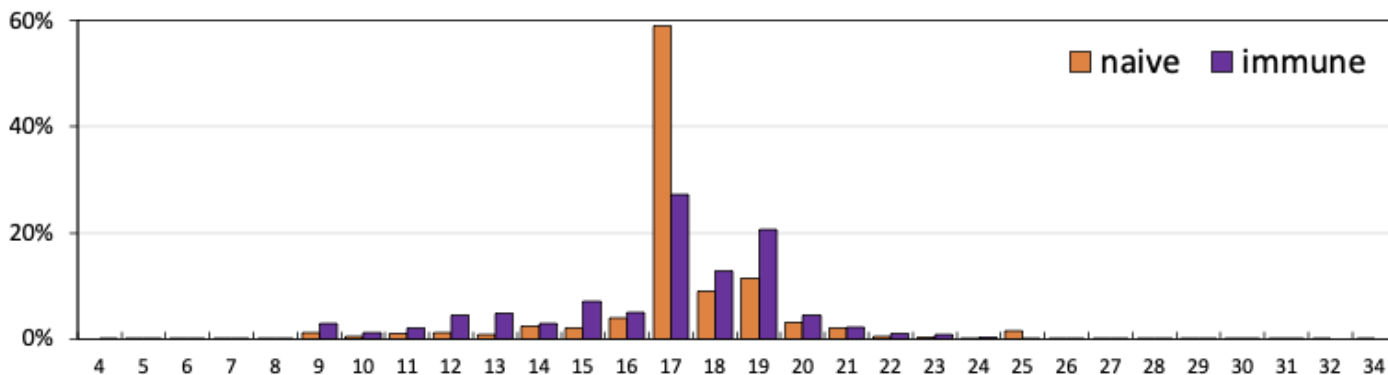


PI = pre-immune
FD = final draw

NGS: Diversity Increases Upon Immunization

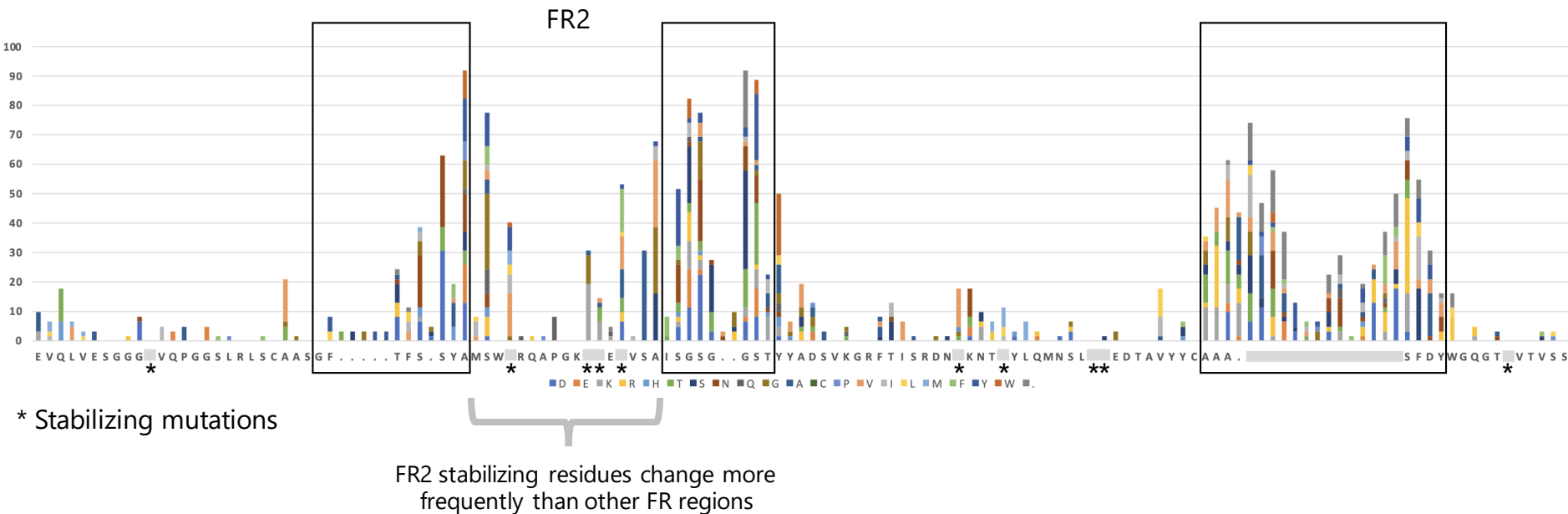
Bird ID:		72766	72767	72773	72776	72806	72809	72847
Naïve PBMC	# lineage:	176	50	163	247	315	500	45
	# unique seq:	19323	25764	14061	6565	9948	8855	17094
Immunized splenocyte	# lineage:	1270	2099	3490	5190	3252	3266	604
	# unique seq:	35240	23160	35890	30810	17693	29436	17551

CDR-H3 length:



Mutational Levels in Cloned sdAbs

DATA FROM PGRN, TIGIT, AND NKp46 CLONES. N = 62



High sequence diversity observed in antigen-specific clones

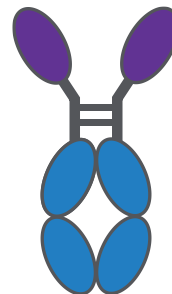
OmnidAb™ sdAbs are Antigen-Specific

sdAB-huFc SUPERNATANTS BIND TO EITHER TIGIT OR PROGRANULIN

TIGIT

Coat: TIGIT-Bio at 2 ug/mL												
Detect: anti-HuFc-HRP at 1:5000												
	1	2	3	4	5	6	7	8	9	10	11	12
A	0.113	0.051	1.757	0.049	0.055	0.052	0.048	0.051	0.052	0.046	0.049	0.05
B	0.07	0.091	0.048	0.053	0.045	0.047	0.083	0.046	0.047	0.046	0.047	0.062
C	0.058	0.049	0.051	0.056	0.049	0.047	0.044	0.052	0.053	0.046	0.046	0.053
D	0.104	0.051	1.982	0.051	0.047	0.049	0.058	0.049	0.045	0.054	0.046	0.047
E	0.063	0.05	0.056	0.047	0.053	0.058	0.053	0.049	0.049	0.051	0.073	0.051
F	0.058	0.051	0.064	0.049	0.046	0.041	0.048	0.052	0.047	0.137	0.068	0.05
G	0.059	0.048	0.056	0.056	0.055	0.049	0.071	0.077	0.045	0.049	0.049	0.05
H	0.082	0.071	0.057	0.061	0.08	0.055	0.067	0.058	0.061	0.06	0.061	1.703
Coat: PGRN-his at 2ug/ml												
Detect: anti-HuFc-HRP at 1:5000												
	1	2	3	4	5	6	7	8	9	10	11	12
A	0.14	0.051	0.048	1.75	0.057	1.732	0.05	0.056	0.048	0.079	0.053	0.175
B	0.063	0.082	0.046	0.06	0.135	0.049	0.052	0.049	0.048	0.049	0.046	0.056
C	0.066	0.047	0.048	0.052	0.059	0.061	0.047	0.047	0.048	0.602	0.059	1.556
D	1.62	0.048	0.048	0.047	0.101	0.048	0.046	0.047	0.05	1.418	1.543	0.052
E	1.749	0.053	0.053	1.122	0.046	0.888	0.046	0.049	0.046	1.689	0.06	0.055
F	0.071	0.048	1.682	0.047	0.046	1.78	0.048	0.063	1.528	0.065	0.051	0.054
G	0.052	0.048	1.723	0.047	1.69	0.047	0.048	0.06	0.24	1.842	1.013	1.689
H	0.061	0.063	0.051	0.881	0.067	0.155	1.68	1.613	1.752	0.057	0.392	0.083

sdAb-huFc



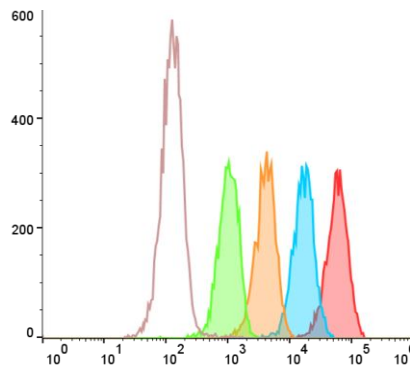
Progranulin

Yield: ~1 mg/ml

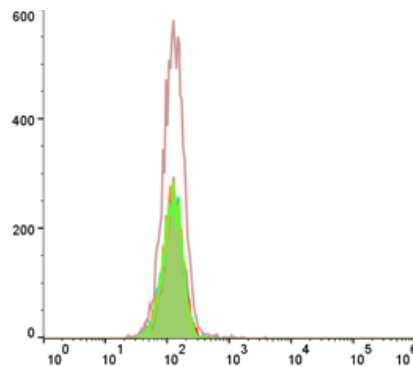
Antibody response is mono-specific

Specific Cell Binding to NKp46-Expressing Cells

Representative *OmniAb*[™] clone in flow cytometry

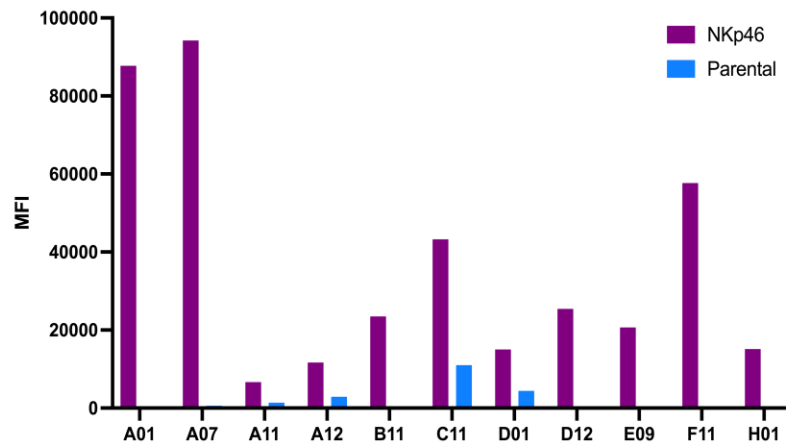


NKp46-expressing cells
staining in dilution series



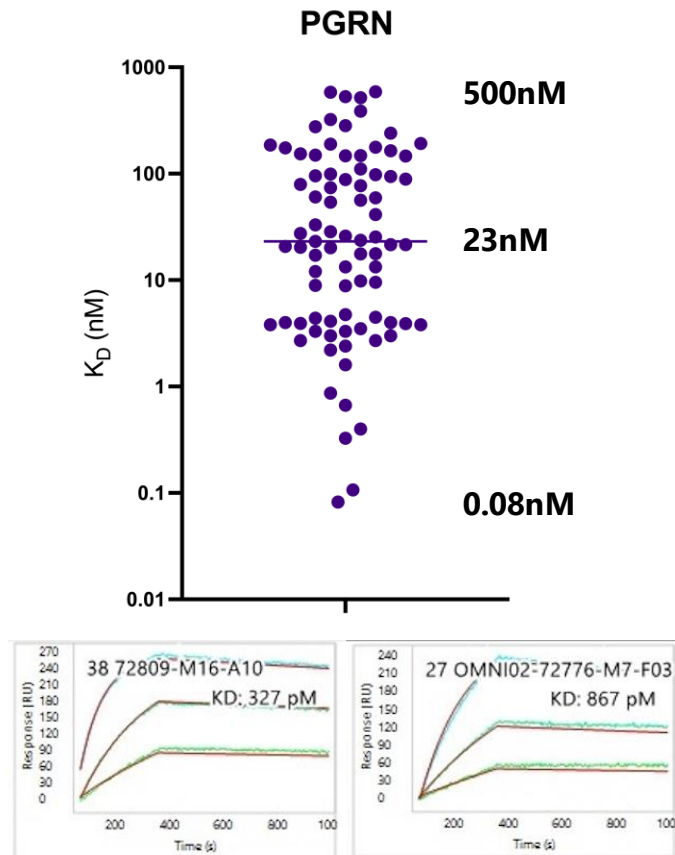
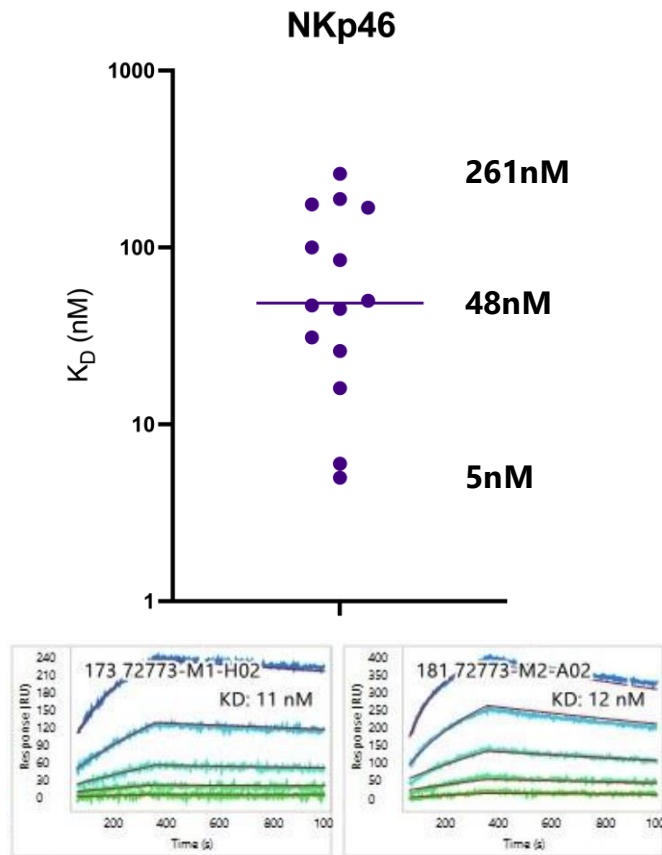
Parental (no NKp46) cells
no staining

Clones show specific binding

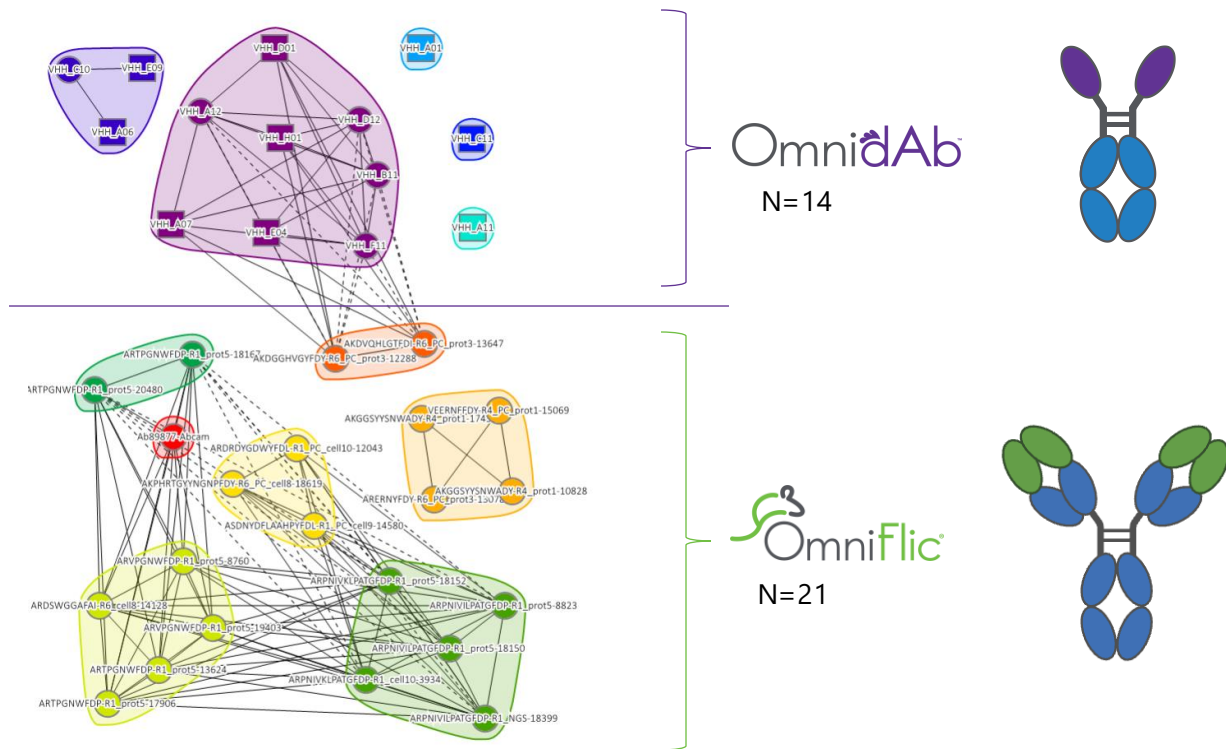


OmniAb™ sdAbs Have High Affinity

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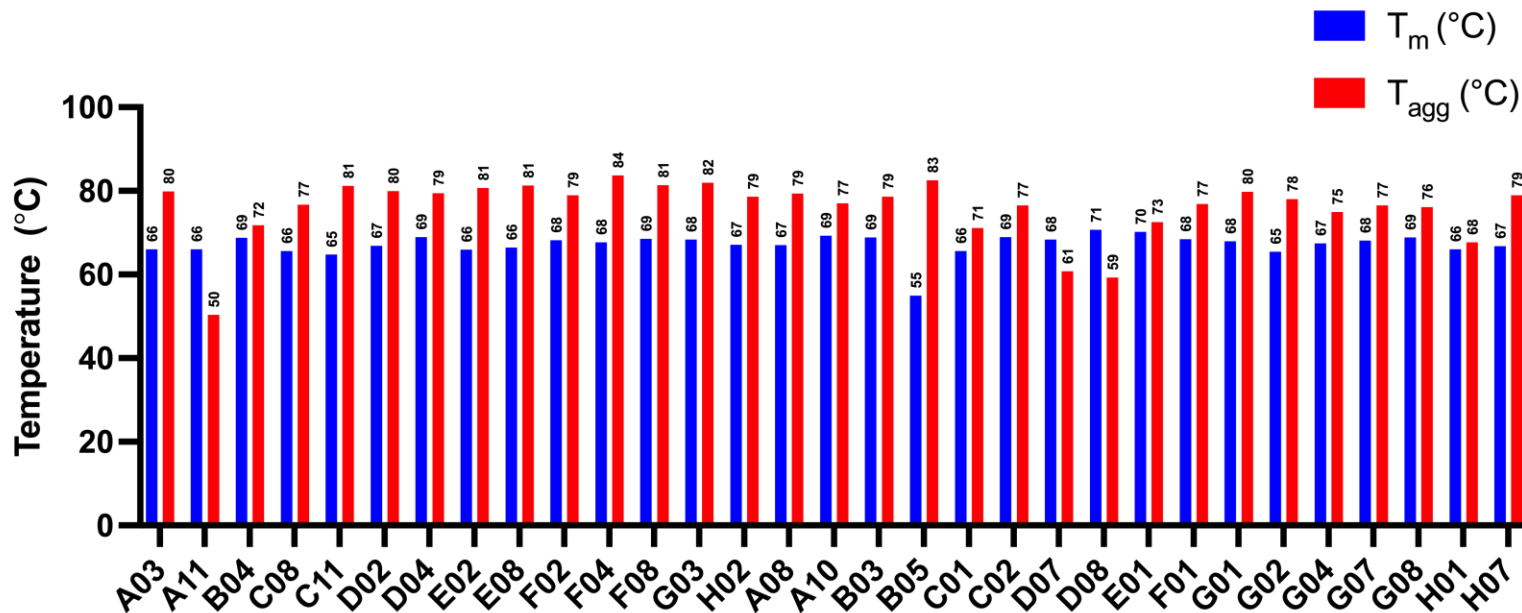
Preliminary Binning Results on NKp46



OmniAb™ has unique epitope coverage against NKp46

Developability Assessment

PHYSICAL PROPERTY CHARACTERIZATION OF NKp46 sdABs PANEL



Ideal:

$T_m > 60^\circ\text{C}$

$T_{agg} > 60^\circ\text{C}$

Our sdAbs:

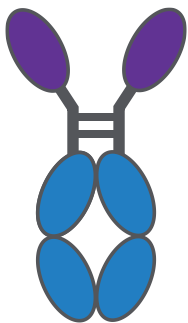
$T_m > 65^\circ\text{C}$

$T_{agg} > T_m$

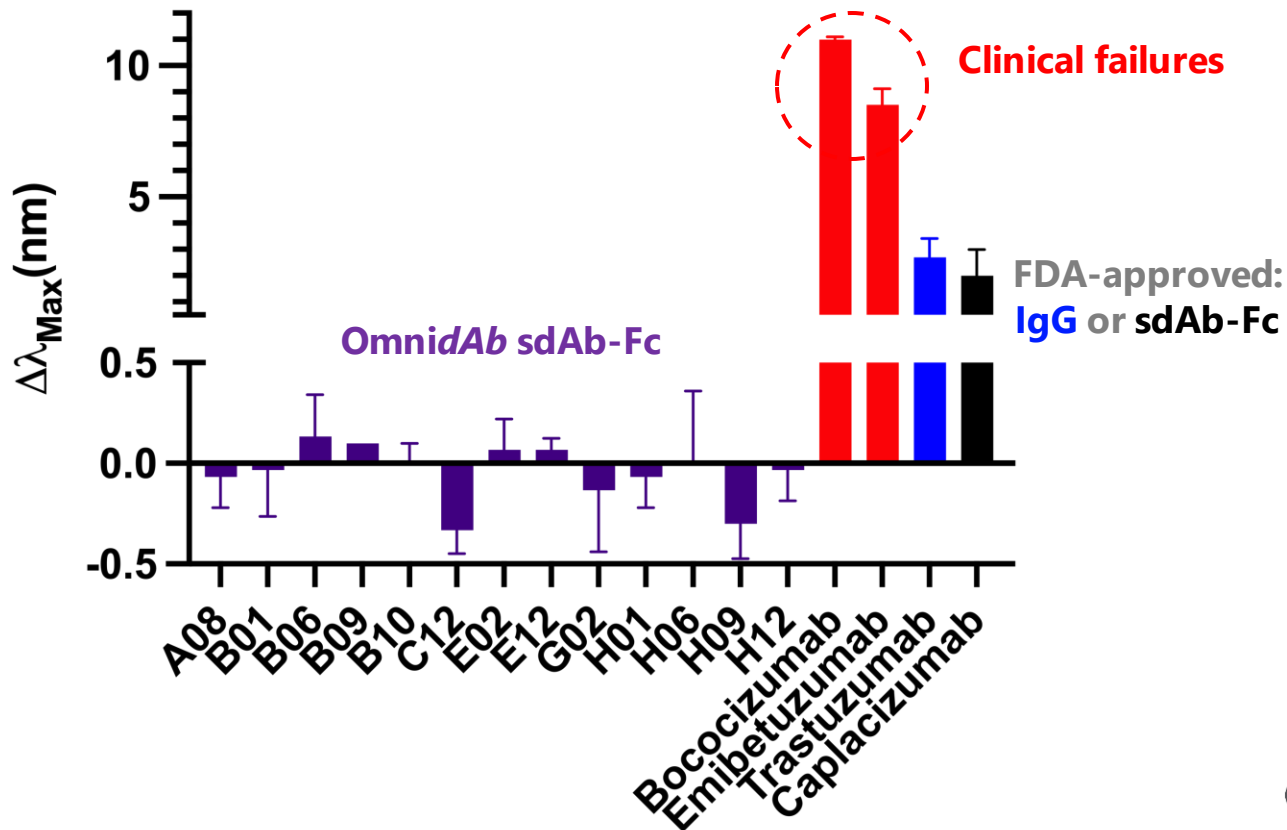
OmniAb™ clones meet "clinical grade" developability criteria

OmnidAb™ sdAbs Show No Self-Association

AC-SINS CHARACTERIZATION OF PGRN sdABs PANEL



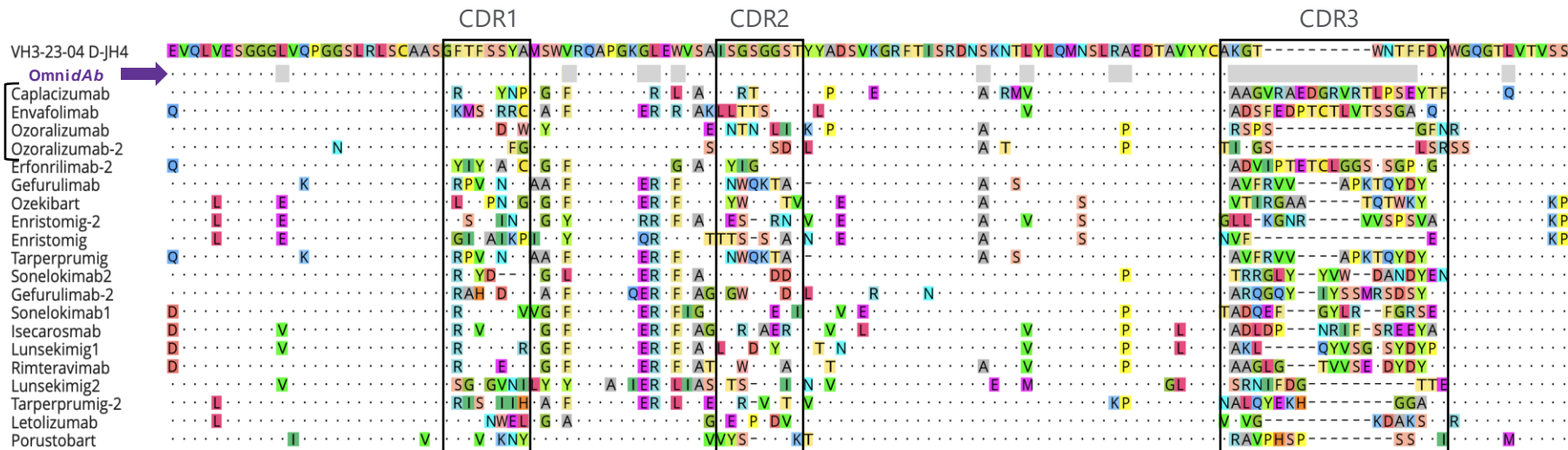
Format: sdAb-huFc



Sequence of Non-Germline Framework Positions

POTENTIAL FOR IMMUNOGENICITY

OmniAb vs.
other clinical-stage molecules:



*OmniAb*TM is predicted to have low immunogenicity

Omni^dAb™

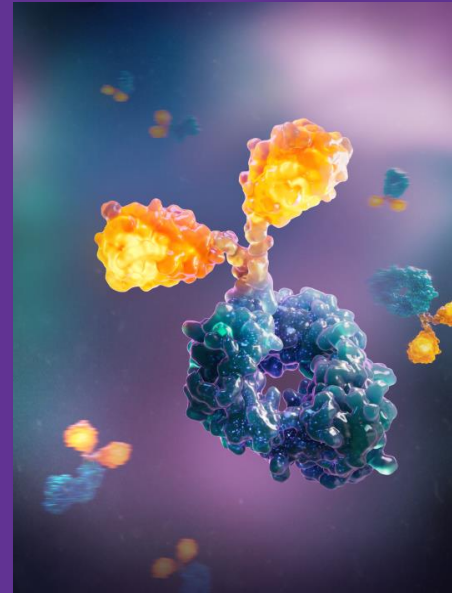
Omni^dAb™ transgenic chickens:

Express an optimized single domain human framework
-no non-canonical cysteines

Produce robust titers upon immunization and develop functionally diverse repertoires of sdAb sequences

Generate high-affinity, antigen-specific mAbs that target various epitopes

Exhibit favorable developability and high expression in mammalian cells



Acknowledgements to the OmniAb Team:



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Ellen Collarini



Darlene Pedersen



Robyn Cotter



Dev Srivastava



Sam Zeng



Gerry Sann Rivera



Yulei Zhang



Swetha Garimalla



Bill Harriman

OmniAb®

THANK YOU!

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