OmniAb Technology Suite

Expanding our **best-in-class** status with innovation and new technology offerings

Naturally optimized human antibodies

OmniRat

OmniMouse

OmniChicken

Bispecific platforms

OmniFlic

OmniClic

Recent technology additions

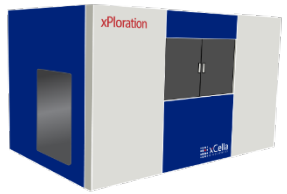
Ab Initio

Antigen generation for challenging therapeutic targets

Taurus BIOSCIENCES

OmniTaur

xCella BIOSCIENCES



- The only **four species platform**
- High demand for **bispecific antibodies**
- Industry-first **ultralong CDR-H3s**
- Industry-leading **broadest offer**
- **Proven success**

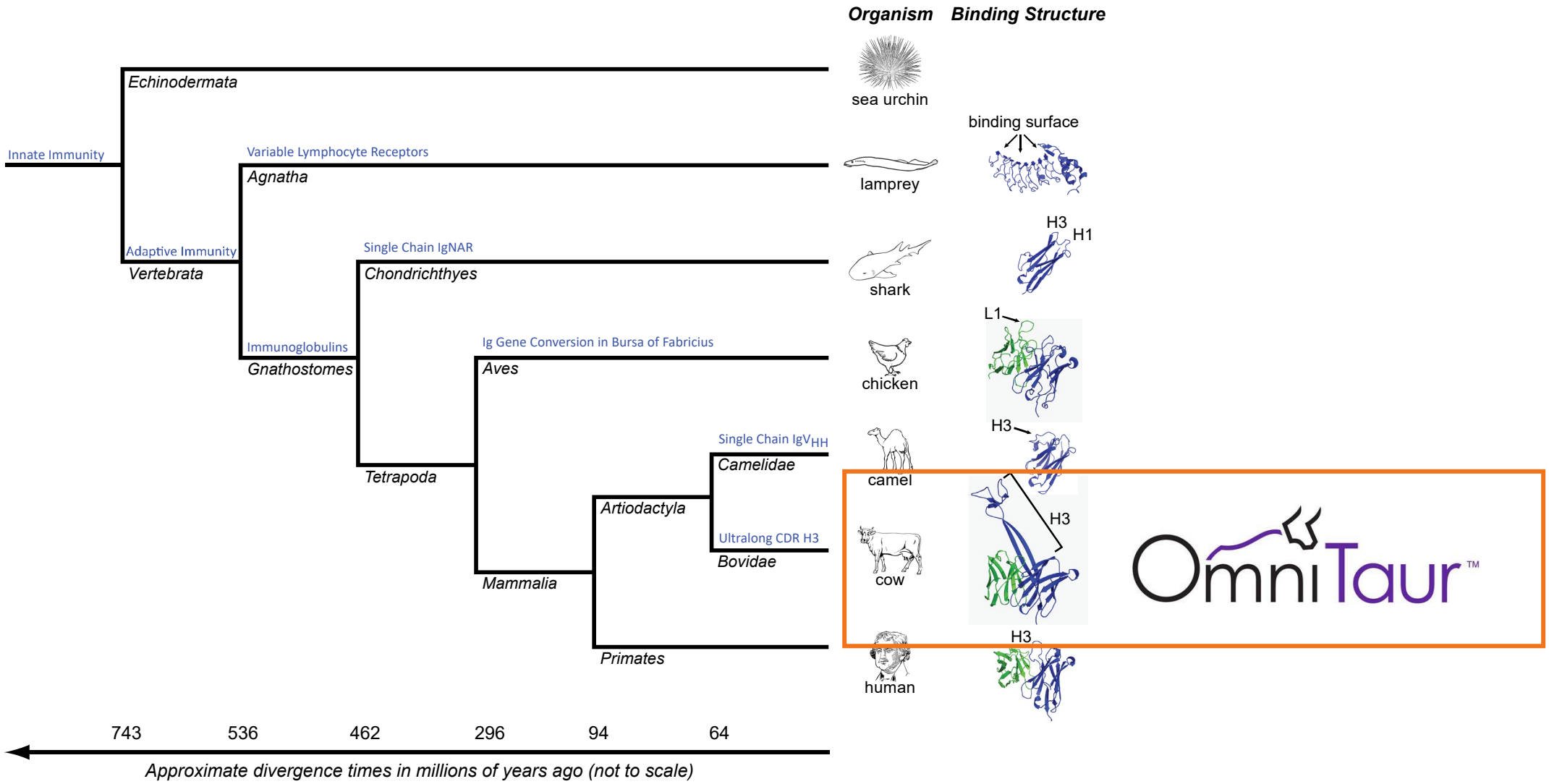
OmniTaur™: Ultralong CDR3 Cow Antibodies for Challenging Targets

Vaughn V. Smider M.D., Ph.D.

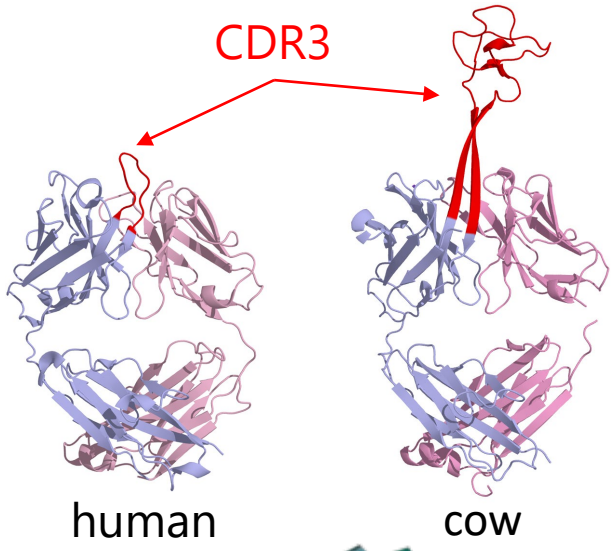
OmniTaur™

October 29, 2020

Novel antibody paratopes have evolved in different species



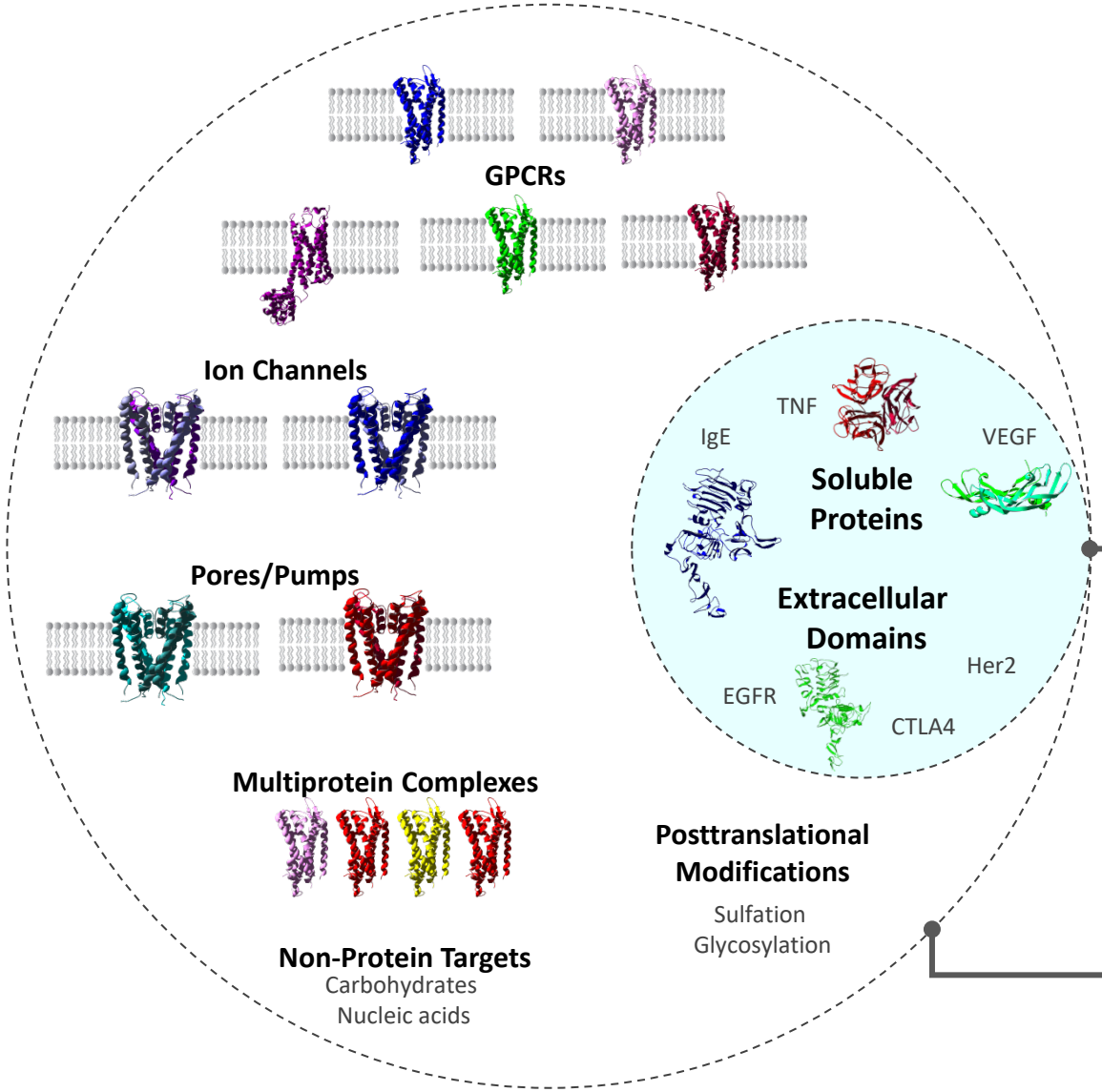
Unique cow antibody structures enable binding to challenging targets



Wang et.al. (2013) Cell 153: 1379-1393

- **Novel cow antibody structure**
  - Could enable targeting crevices, pores, channels, or other epitopes that "regular" antibodies cannot; two approaches:
    1. Cow immunization to select novel structures
    2. Knob engineering with bioactive peptides
- **Fully humanized cow scaffold**
  - Enables therapeutic use
  - Human IgG constant region
  - CDR3 region de-immunized
  - Novel intellectual property
- **Basic science from The Scripps Research Institute and Applied Biomedical Science Institute**
- **Major peer reviewed publications include:**
  - Wang et.al. (2013) *Cell* 153: 1379-1393
  - Stanfield et.al. (2016) *Science Immunol* 1: aaf7962
  - Sok et.al. (2017) *Nature* 548: 108-111
  - Stanfield et.al. (2020) *Science Advances* 6: eaba0468

Expanding target and epitope space: a fraction of potential targets are addressed by current modalities

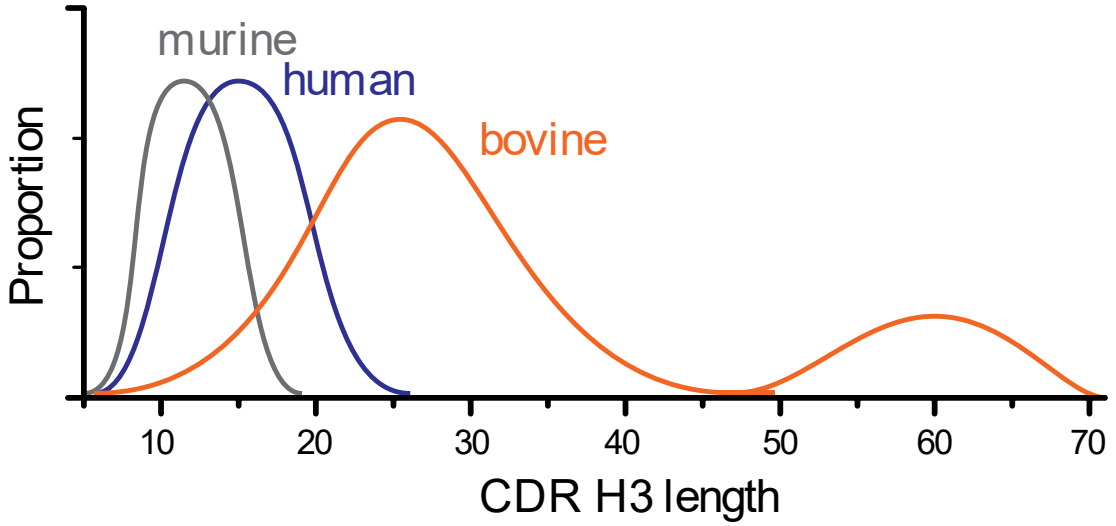


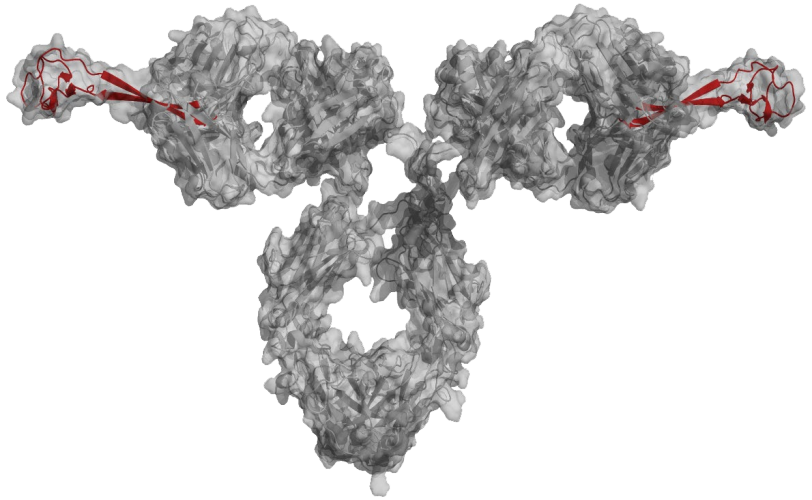
Current Antibody Discovery

OmniTaur™

Cow antibody scaffold uniquely suited for cryptic or membrane targets

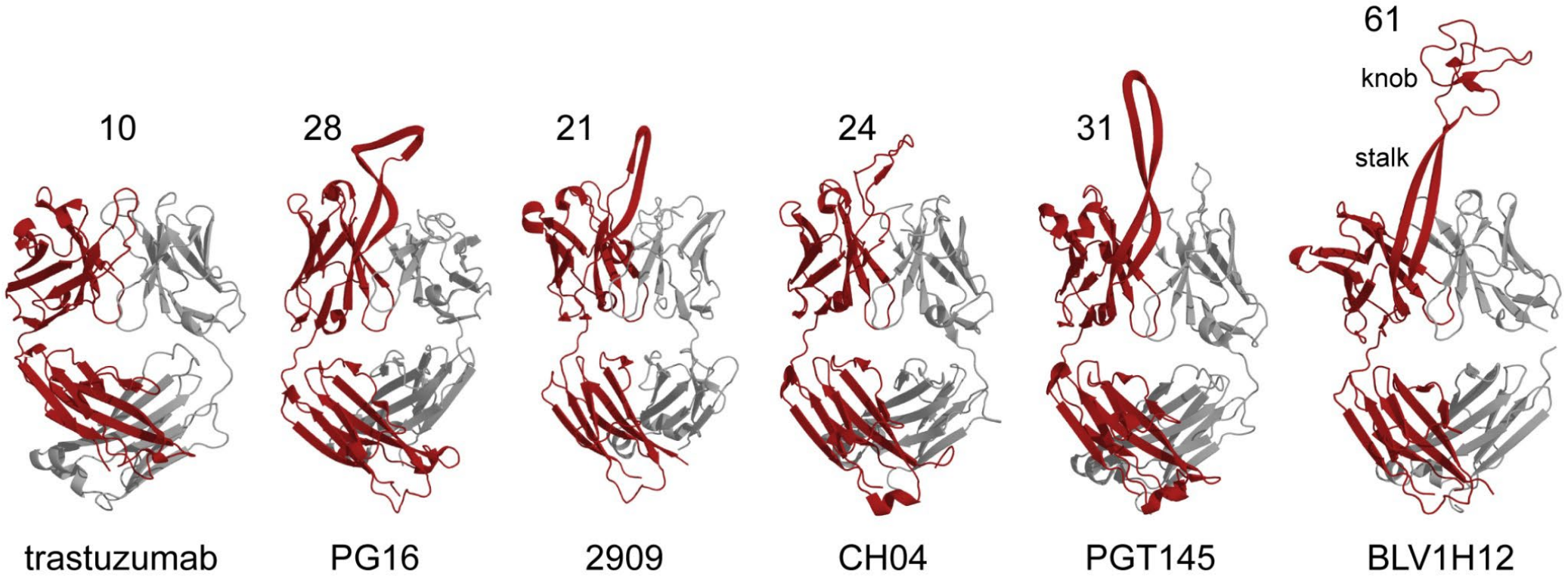
Why cow antibodies?



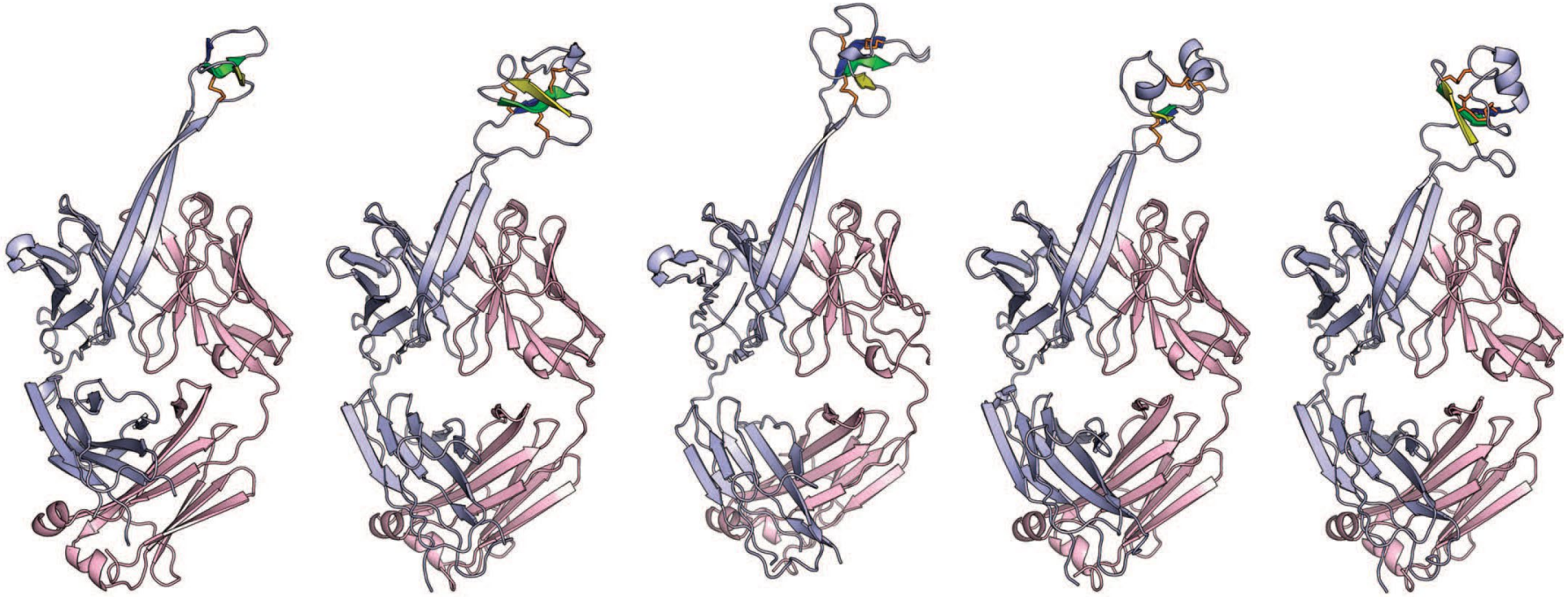


- The *widest* range of CDR3 length of any species
  - the longest CDR3s known (10% of the repertoire between 40-70 residues - ‘ultralong’)
  - enhanced structural diversity
  - protruding structures for binding challenging epitopes like crevices, pores, channels, etc.
- Standardized discovery and humanization techniques
- Robust expression in CHO, HEK

Cow antibodies have the longest CDR H3s



Five structures reveal conserved and diverse features of ultralong CDR H3s



Length:	44	63	61	56	61
Cys:	2	8	6	6	6
Pattern:	1-2	1-4, 2-7, 3-8, 5-6	1-4, 2-6, 3-5	1-3, 2-4, 5-6	1-4, 2-5, 3-6

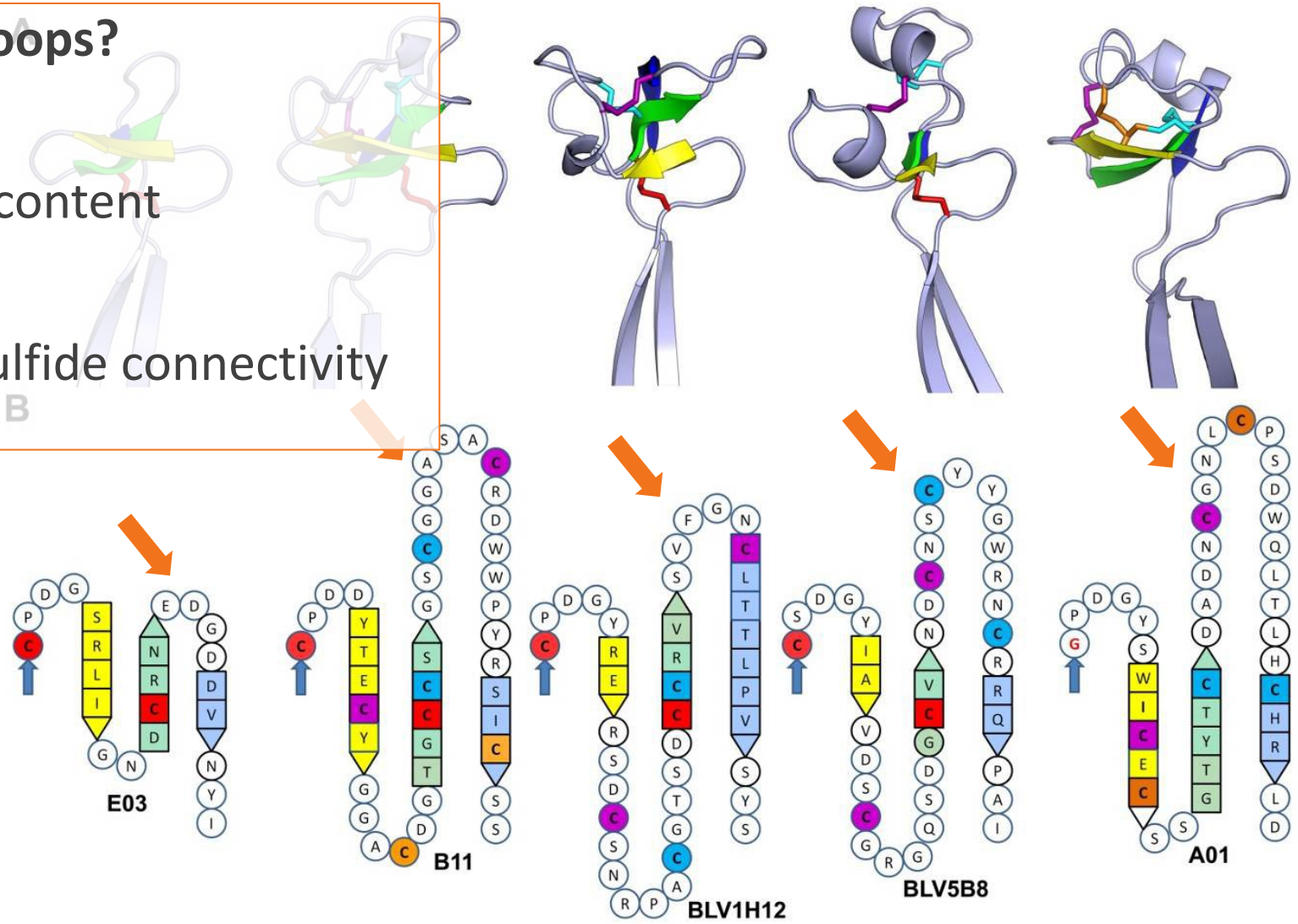
Stanfield, et.al. (2016) *Science Immunology*: 1(1)

A conserved 3-strand core forms a scaffold for two highly diverse loops and disulfide

“CDR-like” loops?

Diversity in:

- Sequence content
- Length
- Shape/disulfide connectivity



Ultralong CDR H3 sequences are enormously diverse

	V_H	N(?)	D_H	J_H	(L)
V_H Germ	CTTVHQ				
D_H2 Germ			SCPDGYSYGYGCGYGYGCSGYDCYGYGGYGGYGGYGYSSYSYSYTYEY		
J_H1 Germ				YVDAW	
BLV1H12	CTSVHQ	ETKKYQ	SCPDGYRERSDCSNRPACGTSDCCRVSVFGNCLTTLPVSYSYTYNYEW	HVDVW	61
BLV5B8	CTTVHQ	ETRKT	CSDGYIAVDSCGRGQSDGCVNDCNSCYYGWRNCRRQPAIHSYEF	HVDAW	56
(12 cys)	CSPVHQ	EIRK	CCPAGCQCGRSCGACCGCAGDEFCGINVYGYVTCGGYRTCSCIDTYDF	YVDAW	59
(10)	CTTVHQ	KTKK	LCPNGRTCGCGCDCGSGCCTSYCDSFGCWGGRDTFGSSCTSATYTYEW	GVDAW	59
(10)	CATVHQ	HTNKK	RCPDGYEFSAGCCCGEGCSGSDCCCNSRLRCSWYEIYCSVSPSDTYEF	HVDAW	60
(8)	CSTVHQ	KTRTTQGN	TCPDGYTLKDDCPRCRGGCDGYDCCWGDACRSSGLCWGHNPLVTETYTYEF	YIDAW	66
(8)	CTTVHQ	ETHKR	CPDGYTYGYYCGYACTCSGDECYRYDYCAAYGSLGCCTNDHTYTYEF	HVDSW	59
(6)	CTAVYQ	QTRK	SCPDGYRSGNDCSSACSCSNYECYRYGSYGSNGKCGYDAHAYTYTYEI	HIDAW	59
(6)	CGAVHQ	KTAR	SCPNIYSTYYGGRSGSVGCSAYDCENCCTYDGMGRYSVSTCSGSVIYEF	YVDTW	60
(6)	CATKKQ	I	CCPDDSSLEVACSHGAGCSGCVGYTGGTWGTLSDYFHGKYTCTYTYEH	NVDAW	56
(5)	CTIVHQ	QTTK	RCPDDDNYPYWCSVANGGGSDACYGCSGRSSDTFWRCSTVRYRYTYEW	HVDAW	59
(6)	CATVHQ	LTRA	HCPDDYSYLYTSRWDCASCDDGCYAARDWRGCFDCESSKTSVSYIYEH	HVNAW	59
(8)	CATVHQ	RTEK	SCSAGHIDGVQCCCSGVACDGAGCVRGCSYGTDGWYGWCNRYSYTITYEF	YVTAW	61
(4)	CTTVHQ	RTKR	SCPDDYTYTYTCVSESDHQAERGCYGPGGYGWCDWTGSTTVSREGERNNYEF	HIDAW	63
(6)	CTTVHQ	ITHK	ECPDGYSDGCTCTRSWYYSGWNCYPGEVCWSRGGCGISGVTYSDTYEF	YIDAW	59
(8)	CGTVHQ	HTTTKN	TCPDGYTFRAGCCCSSGCISCDSSICDNTSPSWFCSRTSPTYTYTYEF	YITAW	61
(6)	CATVHQ	KTLEK	TCPDGYAYGDTDNGHCSAYDCWRMGTYCTEDMYGCSCYSGTTTYEW	YVEAW	58
(6)	CATVHQ	EVQKK	TCPDGYAHLGFCNDDDGRLGSACCSGGAFGSDGDTDCHCYSDSYNYEN	HVDEW	60
(6)	CSTVHQ	KTQR	SCPDGYRTGYGCDDGSCCSGSNCYSYLSRINRGTCRTKITTYEH	HIDAW	55
(7)	CTTVHQ	ETKTRS	TCPDGYGCTVGCYYGTYSCSGSDCTCSRIRRVYGATGGLSICTSTHTYEW	HVDTW	63
(4)	CTTVHQ	RTTTER	SCPEGYNWRYGCDGWVRGCSDACWTGDTDGARGEYGGDGSVRTSYEW	YADAW	60
(6)	CTTVHQ	KTQR	TCPDGWTDIWDCCRKSTCSGSDCPTNDDCRLIFPYAWSTTYLYTYEH	HVDTW	58

Wang et.al. (2013) *Cell* 153: 1379-1393

Ligand

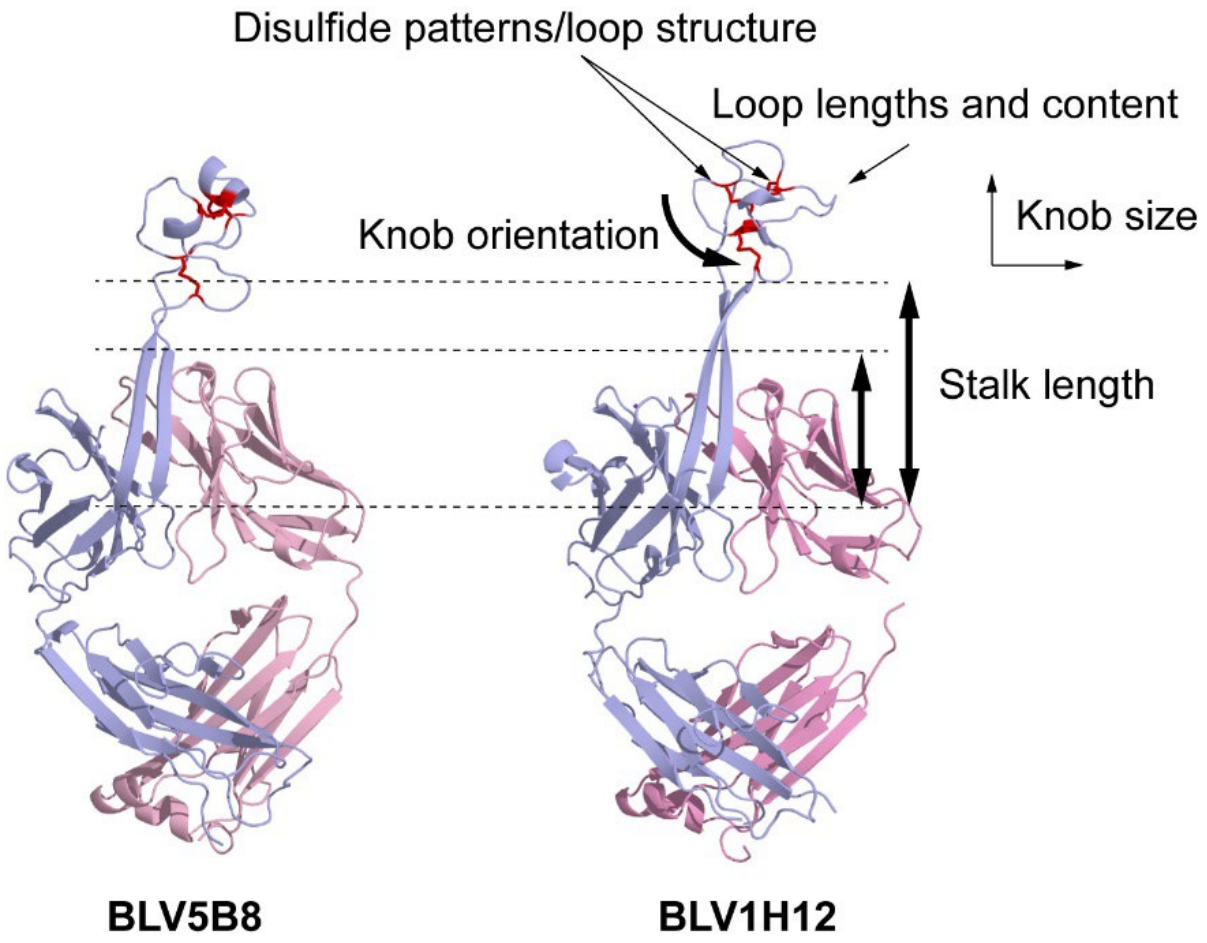
Loops within ultralong CDR H3s may be CDRs themselves

CDR = Complementarity Determining Region

CDR Loops

CDR Loops?

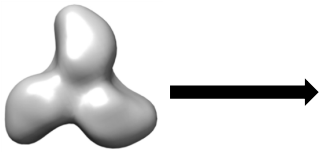
Cow antibodies have unique structural diversity



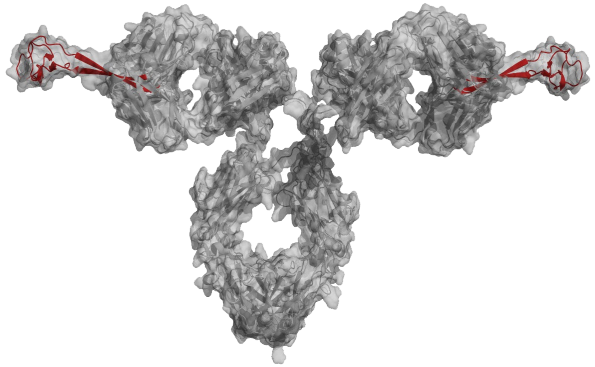
Stanfield, et al. (2017) *Adv Immunol*, 137: 135
Wang et.al. (2013) *Cell* 153: 1379-1393

OmniTaur discovery platforms

- Immunization
  - Single-cell VH and VL cloning, expression
  - Phage display



antigen



Monoclonal antibody discovery

- Customized “knob” engineering (libraries, bioactive peptides, etc.)

Cow antibodies with ultralong CDR3s can target the challenging antigen, HIV gp120

LETTER

doi:10.1038/nature23301

Rapid elicitation of broadly neutralizing antibodies to HIV by immunization in cows

Devin Sok[1,2,3,4]*, Khoa M. Le[1,2,3,4]*, Melissa L. Vadnais[5], Karen L. Saye-Francisco[1,2,3], Joseph G. Jardine[1,2,3], Jonathan L. Torres[6], Zachary T. Berndsen[6], Leopold Kong[6], Robyn Stanfield[6], Jennifer Ruiz[1,2,3,4], Alejandra Ramos[1,2,3,4], Chi-Hui Liang[1,2,3], Patricia L. Chen[7], Michael F. Criscitiello[7], Waithaka Mwangi[8], Ian A. Wilson[2,3,6], Andrew B. Ward[2,3,6], Vaughn V. Smider[5] & Dennis R. Burton[1,2,3,9]

Sok et.al. (2017) *Nature* 548: 108-111

Can cows develop broadly neutralizing antibodies against HIV?

HIV gp120
(BG505 Env)

→

→ **Neutralizing Antibodies?**

Serum Neutralization Breadth Against Multiple HIV-1 strains

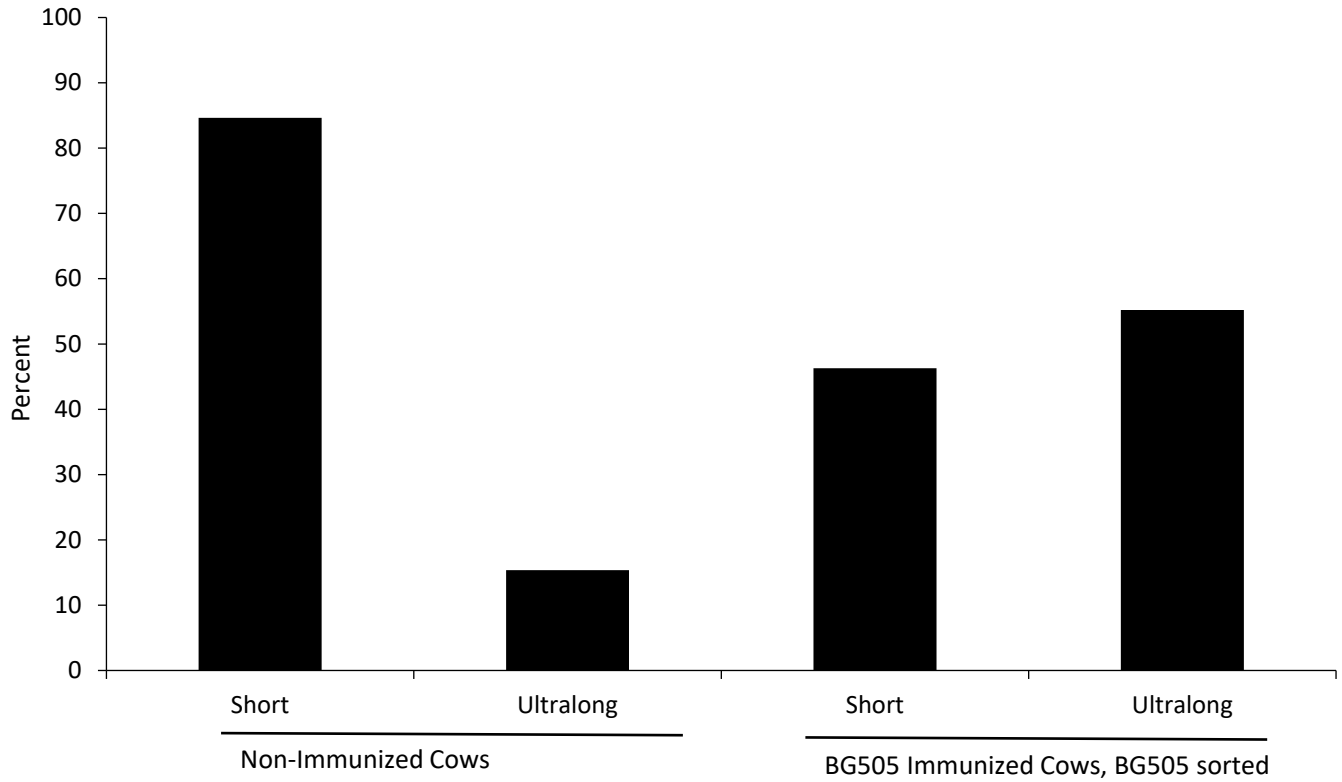
		Percent breadth				Median ID_{50}			
Clade	n	D42	D77	D238	D381	D42	D77	D238	D381
A	10	60%	90%	100%	100%	265	389	5796	5635
B	23		70%	100%	100%		47	192	233
C	30	13%	93%	97%	97%	63	148	791	600
D	2		100%	100%	100%		32	162	263
G	7	14%	43%	71%	86%	38	25	1144	342
AC	5	80%	100%	100%	100%	44	163	1539	1742
AE	16	6%	44%	75%	88%	116	68	897	469
AG	7	43%	86%	86%	86%	25	94	942	1004
BC	10	20%	100%	100%	100%	114	261	993	1101
CD	5	20%	80%	80%	100%	25	112	504	253
ACD	2	50%	100%	100%	100%	25	88	9873	12181
	117	20%	79%	92%	96%	62	108	671	595

Percent neutralization				
0	25%	50%	75%	100%

Neutralization ID_{50} (1/dilution)				
0	100	500	1000	5000

Sok, D. et al. *Nature* (2017) 548: 108

Ultralong CDR H3s were selected

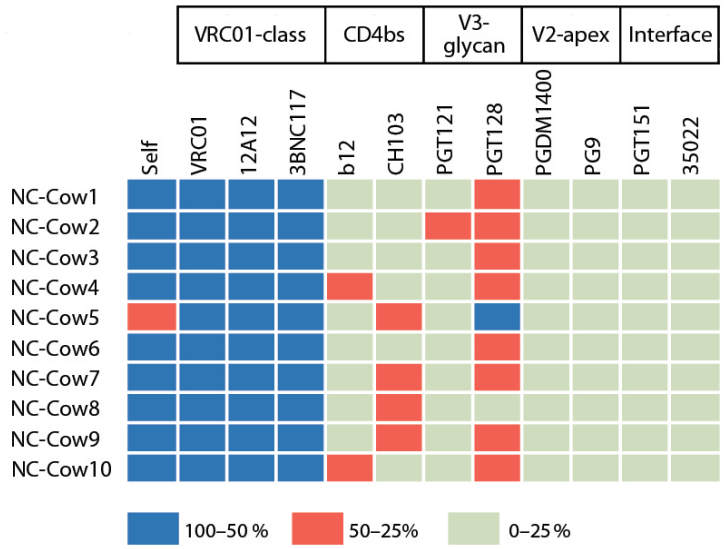


Monoclonal antibodies utilize ultralong CDR H3s

	V	N	D	J	L	# Cys
Germline	CTTVHQ		SCPDGYSYGYGCGYGYGCSGYDCYGYGGYGGYGGYGYSSYSYSYTYEY	YVDAWGQGLLVTVSS		
NC-Cow1	CITAHQ	KTNKK	ECPEDYTYNPRCPQQYGWSDCDCMGDRFGGYCRQDGCSNYIHRSTYEW	YVSAWGQGLLVTVSS	60	6
NC-Cow2	CGTVHQ	KTQRKP	ICPDGYSDDSTLRYYSRCSDRDCWRCTGTTYYDTCQCGTYTWIDTHEL	HVDAWGQGLLVTVSS	61	6
NC-Cow3	CGTVHQ	RTHRKQ	NCPGGYSDDNALRYRSRCDDRDCWRCTGTTYYDTCQCASYFYTDTYEF	YVDAWGQGLLVTVSS	61	6
NC-Cow4	CGTVHQ	RTQPKQ	TCPNGYSDDSALRYYSRCSDRDCWRCTGTTYYDTCQCSSYTYIHTYEL	YVDAWGQGLLVTVSS	61	6
NC-Cow5	CGTVHQ	RTQPKQ	TCPNGYSDDSALRYYSRCSDRDCWRCTGTTYYDTCQCSSYTYIHTYEL	YVDAWGQGLLVTVSS	61	6
NC-Cow6	CGTVHQ	RTQPKQ	TCPNGYSDDSALRYYSRCSDRDCWRCTGTTYYDTCQCSSYTYIHTYEL	YVDAWGQGLLVTVSS	61	6
NC-Cow7	CTTVHQ	KAYKK	VCPDDYSSNPDCVRLYGWSHCDCMRDSFGGWCRADGCSSTVEIGPYEW	YVNAWGQGLLVTVSS	60	6
NC-Cow8	CTTVYQ	KTTKK	DCPEYYTYNPDCARRYGWSDCECMADKFGGYCRHDGCATNTVRSTYEW	HLDAWGQGLLVTVSS	60	6
NC-Cow9	CTTVYQ	KTTKK	DCPEYYTYNPDCARRYGWSDCECMADKFGGYCRHDGCATNTVRSTYEW	HLDAWGQGLLVTVSS	60	6
NC-Cow10	CTTVHQ	KTNEK	DCPEYYSYNPDCPRRYGWSNCDCMADKFGGWCRHDGCSDYADMTTDEW	YVDAWGQGLLVTVSS	60	6
		100	B2	101		

NC-Cow1

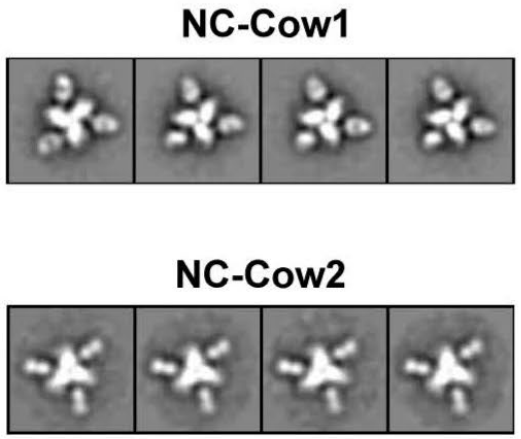
Clade	n	% Breadth	Median IC_{50}
A	10	100%	0.021
B	23	83%	0.151
C	30	67%	0.021
D	2	50%	0.007
G	7	57%	0.019
AC	5	40%	0.077
AE	16	75%	0.009
AG	7	43%	0.015
BC	10	80%	0.019
CD	5	60%	0.253
ACD	2	100%	0.057
	117	72%	0.028

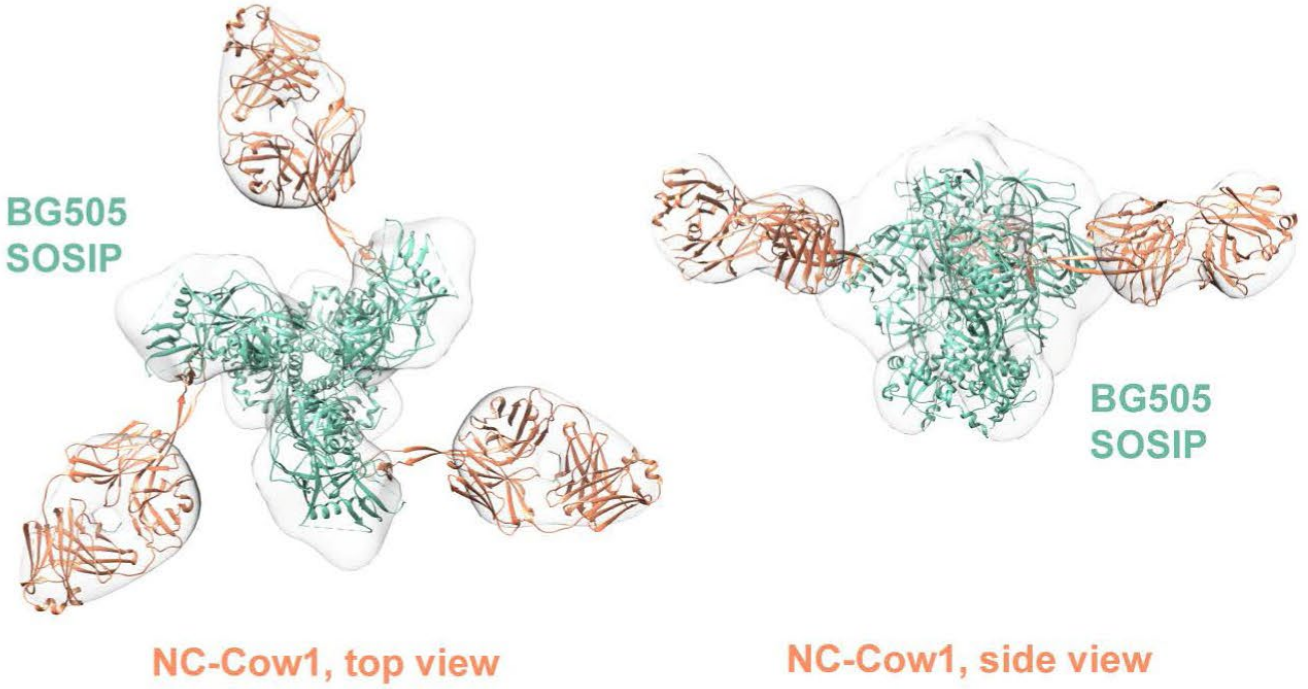


Sok, D. et al. *Nature* (2017) 548: 108

Ligand

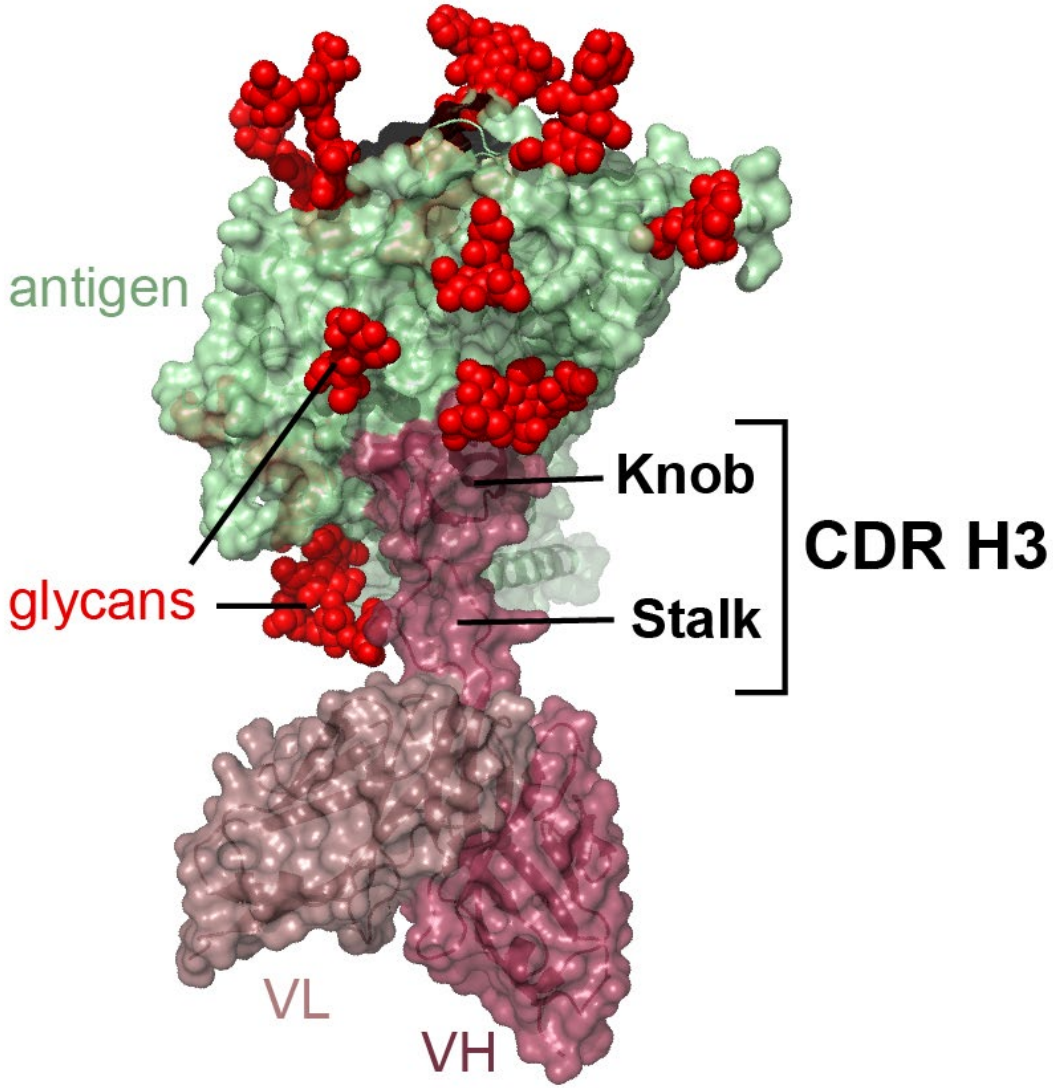
NC-Cow1 binds the CD4 binding site





Sok, D. et al. *Nature* (2017) 548: 108

NC-Cow1 Ultralong CDR H3 Binds the Recessed CD4 Epitope on HIV Env

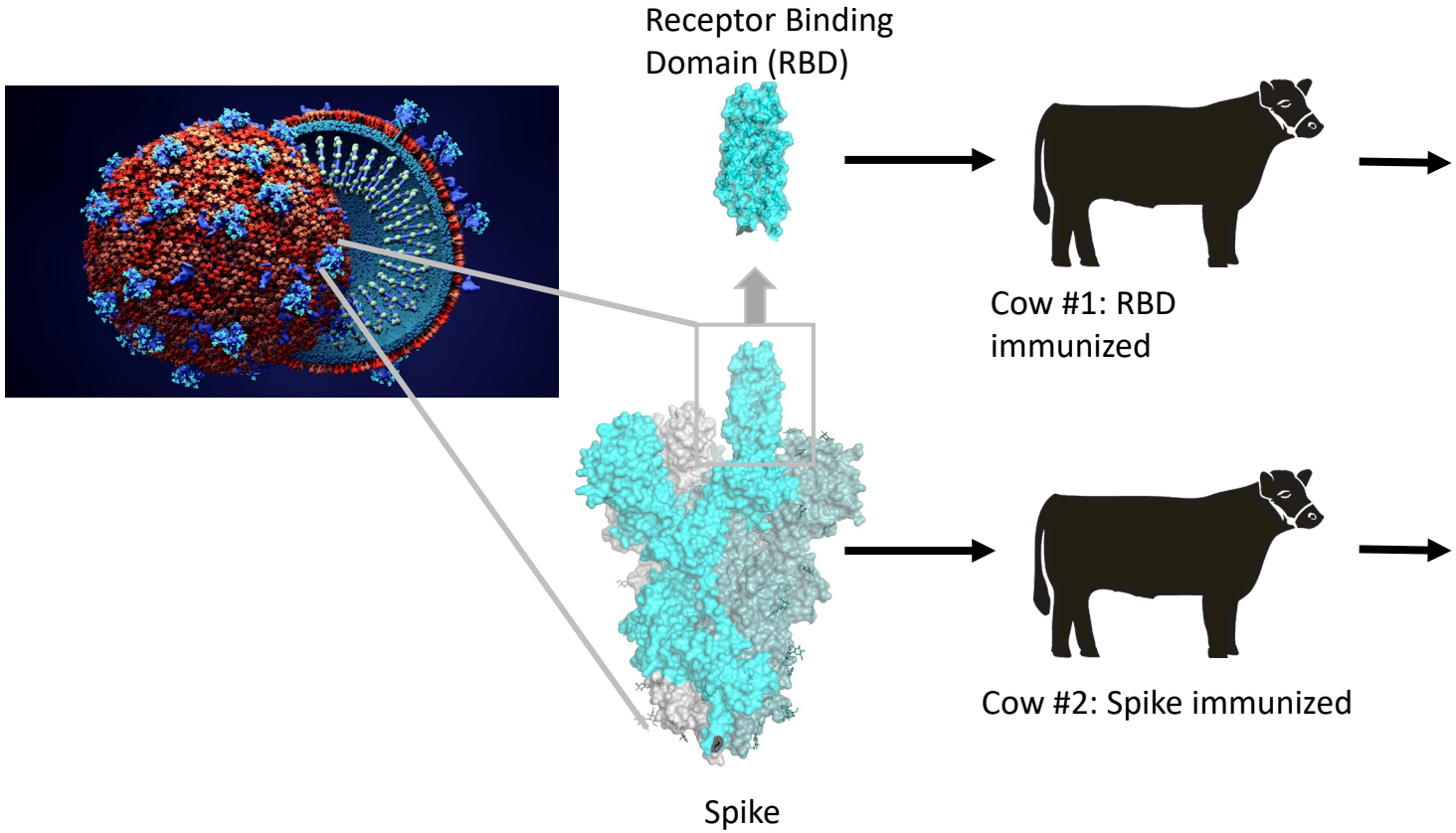


Stanfield, et.al. *Sci Adv* (2020) 6(20): eaba0468.

Cow antibodies with ultralong CDR H3s have very high affinity

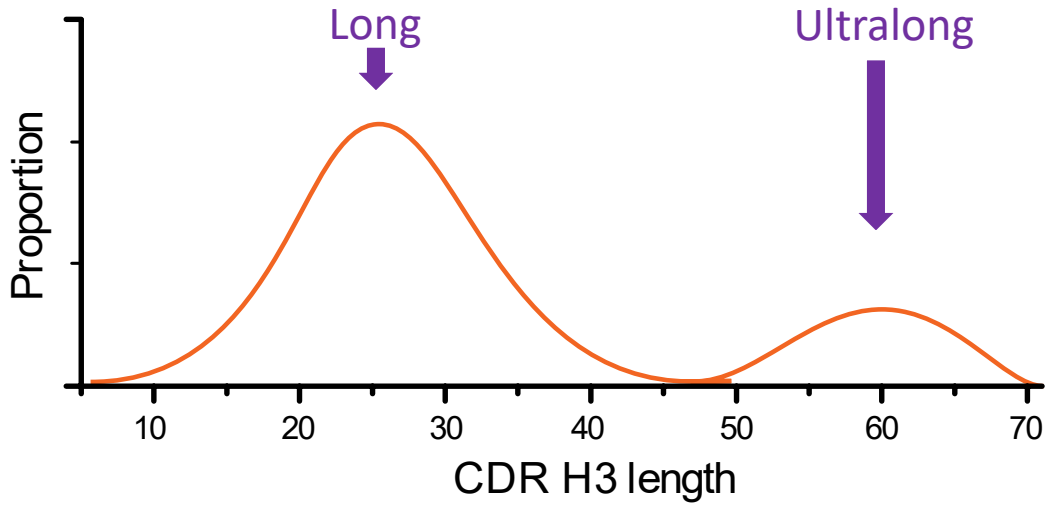
IgG	K_D (M)	k_a (1/Ms)	k_d (1/s)
NC-Cow-1	4.198×10^{-12}	5.592×10^{5}	2.347×10^{-6}
P1F1	4.640×10^{-11}	6.508×10^{6}	3.020×10^{-4}
P3H4	1.237×10^{-10}	1.315×10^{6}	1.626×10^{-4}
P4F8	9.987×10^{-12}	2.459×10^{6}	2.456×10^{-5}
P4G8	1.345×10^{-11}	1.829×10^{6}	2.460×10^{-5}

Cow anti-coronavirus SARS-CoV-2 antibodies

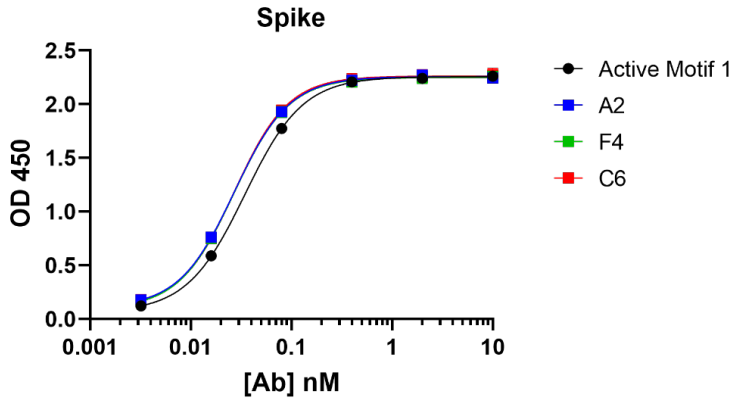


Two human "common cold" coronaviruses evolved after species transfer from cow (BCoV) to humans

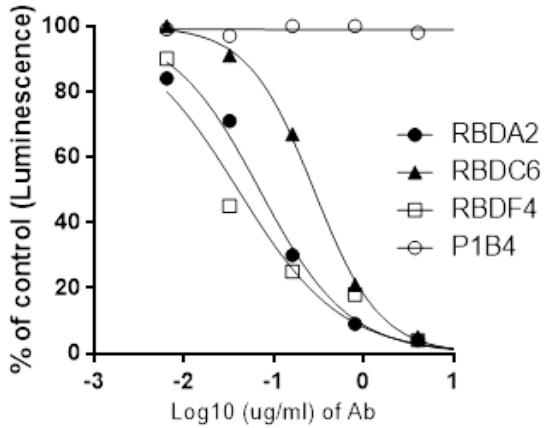
Cow anti-SARS-CoV-2 antibody discovery



Binding



Pseudovirus Neutralization



Ligand

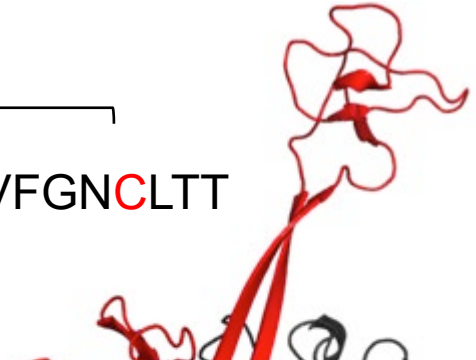
Natural peptides that inhibit ion channels are similar to cow antibody “knob” domains

Shk peptide

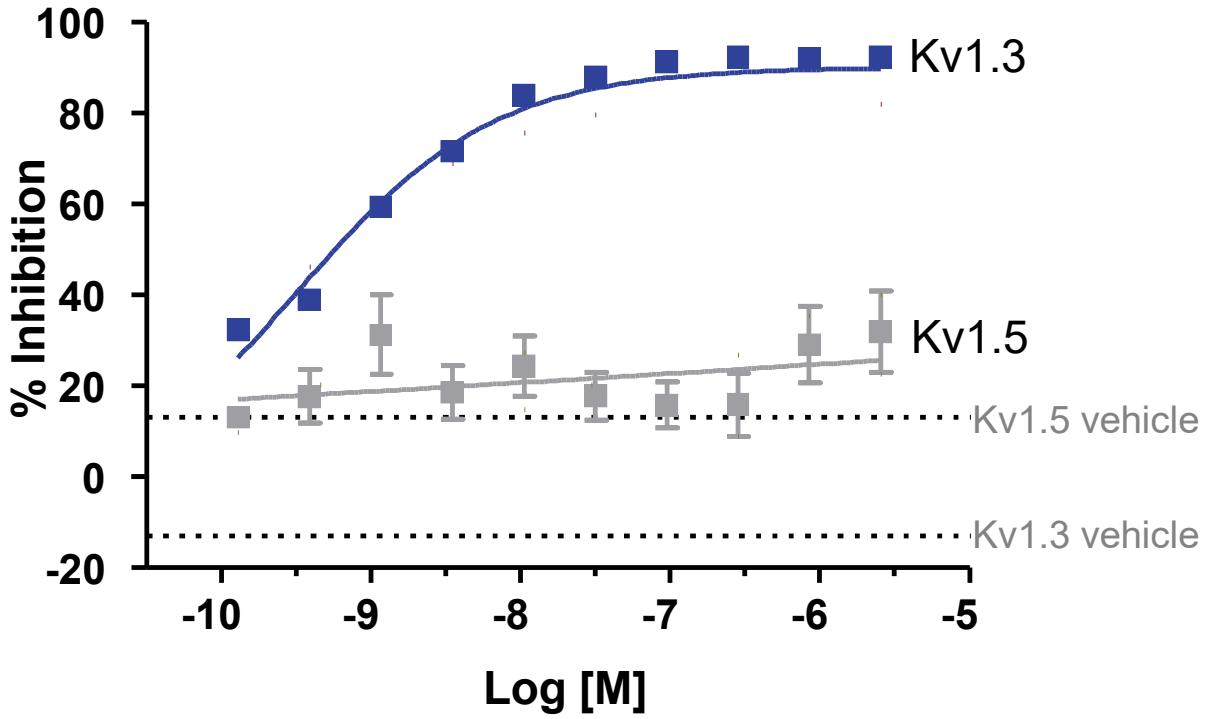
RSCIDTIPKSRCTAFQCKHSMKYRLSFCRKTCGTC

Cow antibody “knob”

SCPDGYRERSDCSNRPACGTSDCCRVSVFGNCLTT

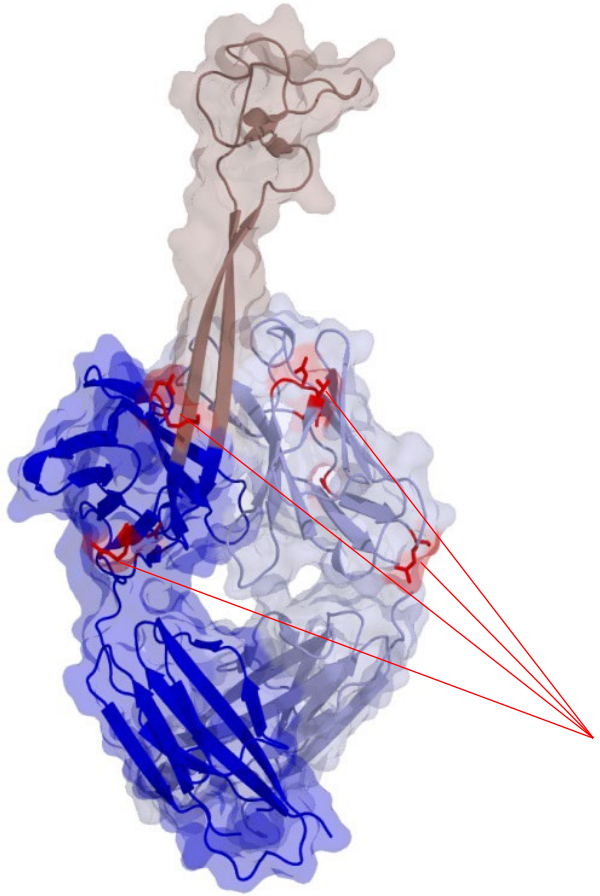


An engineered cow antibody specifically inhibits the ion channel Kv1.3



Electrophysiology, IC_{50} ~ 140-310 pM

Cow antibody humanized scaffold



- 95% identical to human germline outside CDR H3 (heavy chain)
- 90% identical to human germline (light chain)

Red = stabilizing cow residues

Blue = human

OmniTaur Intellectual Property

- 22 granted or issued patents internationally
- Broad coverage of ultralong CDR H3 antibody compositions and sequences
- Key compositions and motifs enabling humanized scaffolds
- Internal Patents acquired from Taurus Biosciences and the Scripps Research Institute
- 12 pending patents

OmniTaur™

Summary

- OmniTaur is a cutting-edge antibody platform based on the novel long CDR H3 structure of humanized cow antibodies
  - Challenging targets/epitopes
- Discovery can occur through immunization and
  - Single-cell PCR of VH and VL, expression, and screening
  - Phage Display
- The knob domain is independently folding and similar in size and shape to ion channel-inhibiting bioactive peptides (*e.g.* venoms, toxins)
  - "Knobs" can be replaced by bioactive peptides and retain ion channel inhibiting properties

OmniAb® Platform

Single license provides access to full suite of discovery technologies

- **Ab Initio Antigen** – proprietary methods for purifying multi-Tm and other difficult proteins for immunization and screening
- **OmniRat®, OmniMouse®, and OmniChicken®** – 3 different species engineered to generate novel fully human antibodies
- **OmniFlic® and OmniClic™** – engineered rat and chicken for fully human bispecific antibodies
- **OmniTaur™** – cow-inspired ultralong H3 antibodies with humanized framework
- **xPloration® and GEM** – robust single B cell screening technologies to enable deep searches into immune repertoires to identify unique antibodies with special properties

OmniAb®

Naturally Optimized Human Antibodies®

OmniAb partners enjoy evergreen access to the most comprehensive and cutting-edge suite of antibody discovery technologies available

Acknowledgements

Smider Lab / ABS Institute

Current

Riqui Huang

Jeremy Haakenson

Gabrielle Warner

Duncan McGregor

Abigail Kelley

Biura Markanian

Gorune Gorolian

Recent

Melissa Vadnais

Jason Higa

Erik Wold

Wenyong Tong

Veronica Verplancken

Applied Biomedical Science Institute

Taurus BIOSCIENCES

Ligand®

Funding: NIH, DoD, American Cancer Society, USDA

Collaborators

Scripps

Dennis Burton

Devin Sok

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Karen Saye-Francisco

Joseph Jardine

Jennifer Ruiz

Alejandro Ramos

Chi-Hui Lang

Ian Wilson

Robyn Stanfield

Damien Eckiert

Wenli Yu

Leopold Kong

Andrew Ward

Jonathan Torres

Ali Torkamani

Peter Schultz

Feng Wang

Texas A&M

Michael Criscitiello

Thad Deiss

Patricia Chen

Kansas State University

Waithaka Mwangi

K.C. Cheong

Fabrus/Sevion

Helen Mao

Miguel de los Rios

Cory Bentley

Omar Bazirgan

Jacek Ostrowski

Evan Holmes

Thank you!

OmniTaur™