OmniAb®

ANTIBODY DISCOVERY POWERED BY OMNIAB

Bill Harriman, PhD
SVP Antibody Discovery
Ligand Pharmaceuticals

THE OmniAb TECHNOLOGY SUITE

COMMITMENT TO INNOVATION AND EXPANSION OF TECHNOLOGY OFFERING

OmniAb®

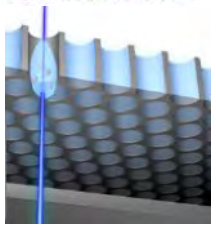
OmniRat® | OmniMouse | OmniChicken | OmniTaur™

Bispecific platforms ▸ OmniFlic | OmniClic

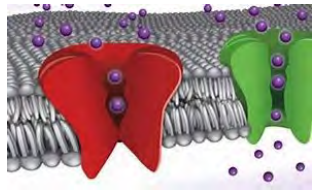
Antigen generation for challenging therapeutic targets ▸

Ab Initio Biotherapeutics

xCella BIOSCIENCES



ICAGEN ION CHANNEL TECHNOLOGY



◂ Proprietary cell lines and assays

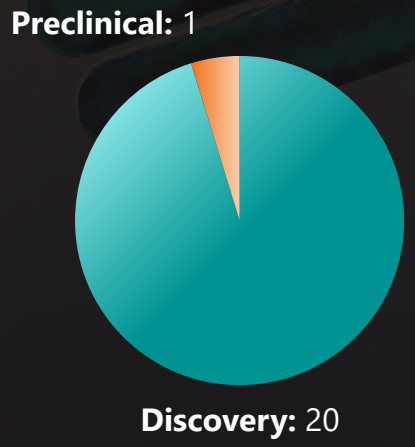
▲ Ultra-high resolution, high-speed automated Ab selection

- The only platform leveraging **four-species**
- Robust solutions for **bispecific antibodies**
- Human frameworks with **ultralong CDR-H3s**
- Industry-leading **broadest offering**
- **Proven success**

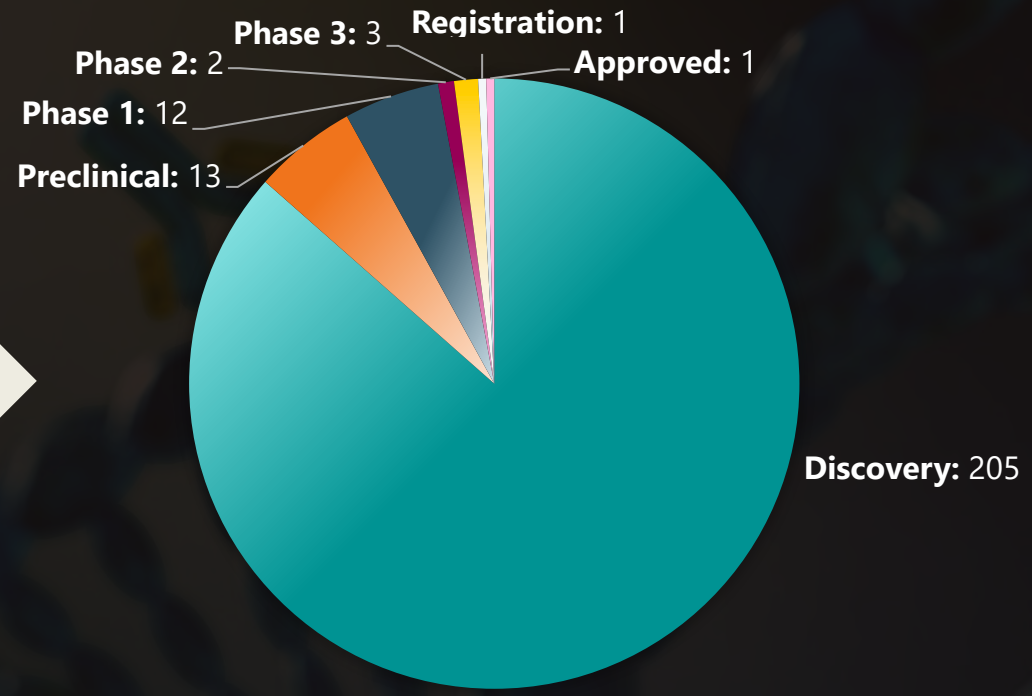
OMNIAB PARTNER PROGRAMS

PROGRESSION AND PERFORMANCE IN PROGRAMS BY STAGE OF DEVELOPMENT

2016



Today



Substantial progress in all phases, increase in discovery programs expected to **rapidly feed growth** in new clinical programs and future approvals

OmniAb

Rodent Platforms

Rodent Platform Development

Knock-out of rat Ig genes

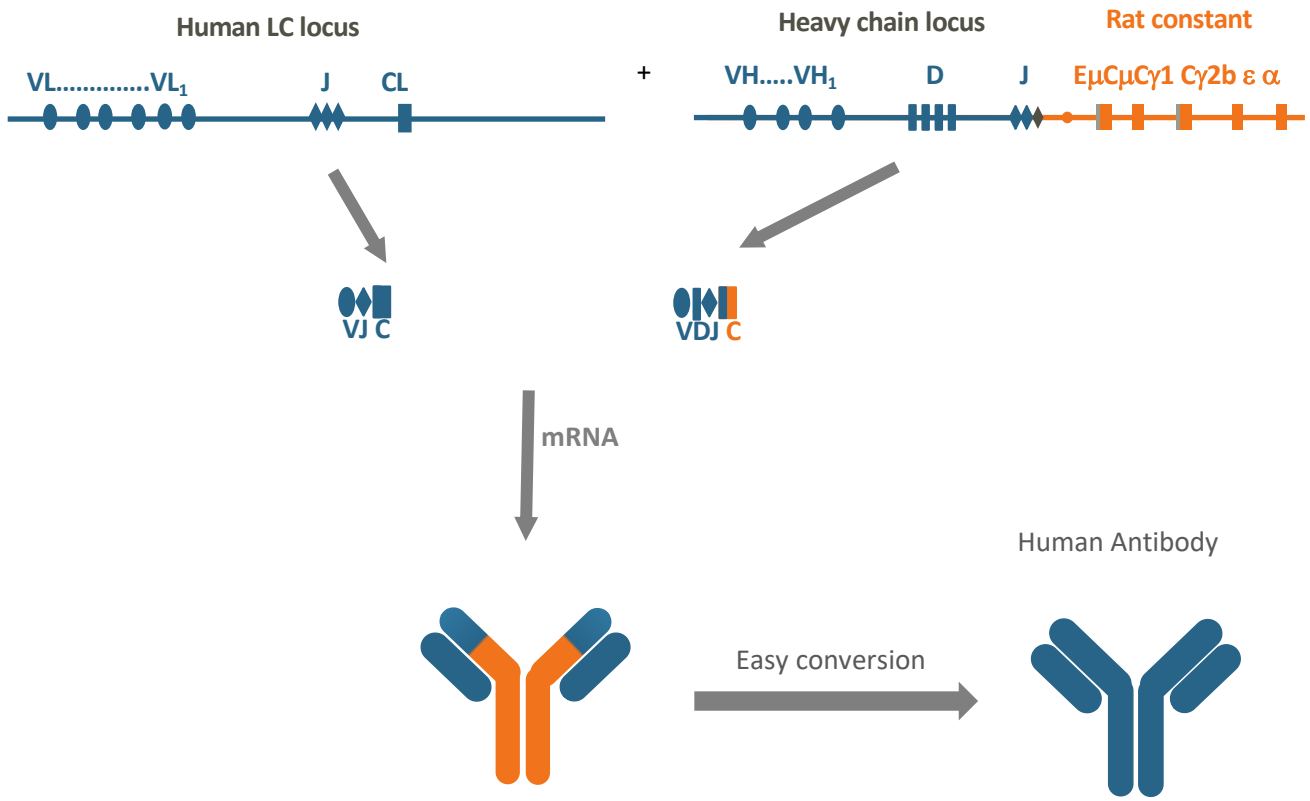
- Heavy chain J-locus
- Light chain Cκ
- Light chain Cλ

Knock-out of mouse Ig genes

- Heavy chain J-locus
- Light chain Cκ

Recombinant Ig loci in OmniRat and OmniMouse

- Fully human kappa light chain
- Fully human lambda light chain
- Human/rat heavy chain
- Random integration



Geurts et al. Science 2009
Ménoret et al. Eur J Immunol 2010
Osborn et al. J. Immunol. 2013

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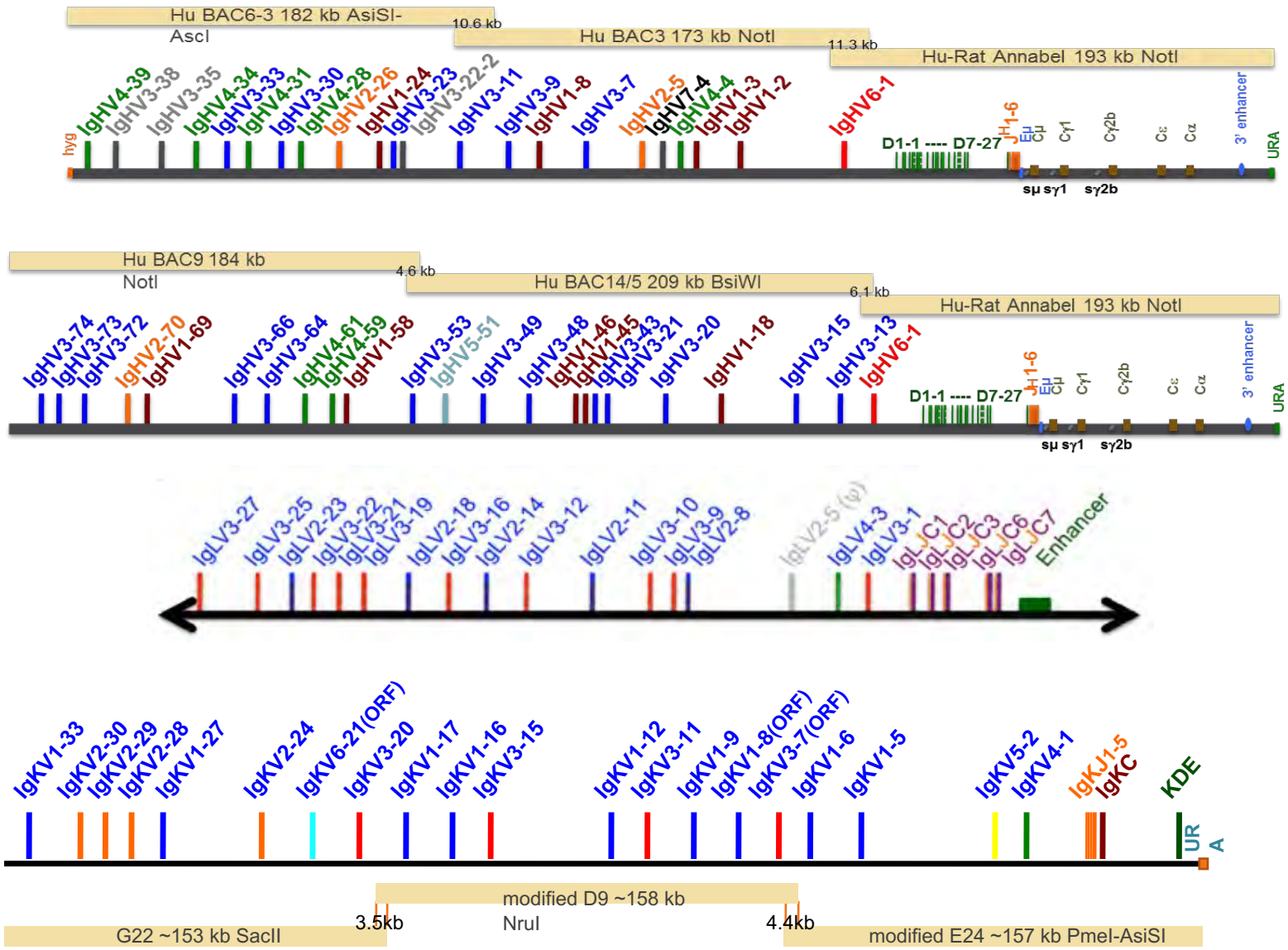
Transgenes in OmniRat and OmniMouse



HC (44 V_H, 100%)

LC (15 V_L, >60%)

KC (20 V_K, >80%)

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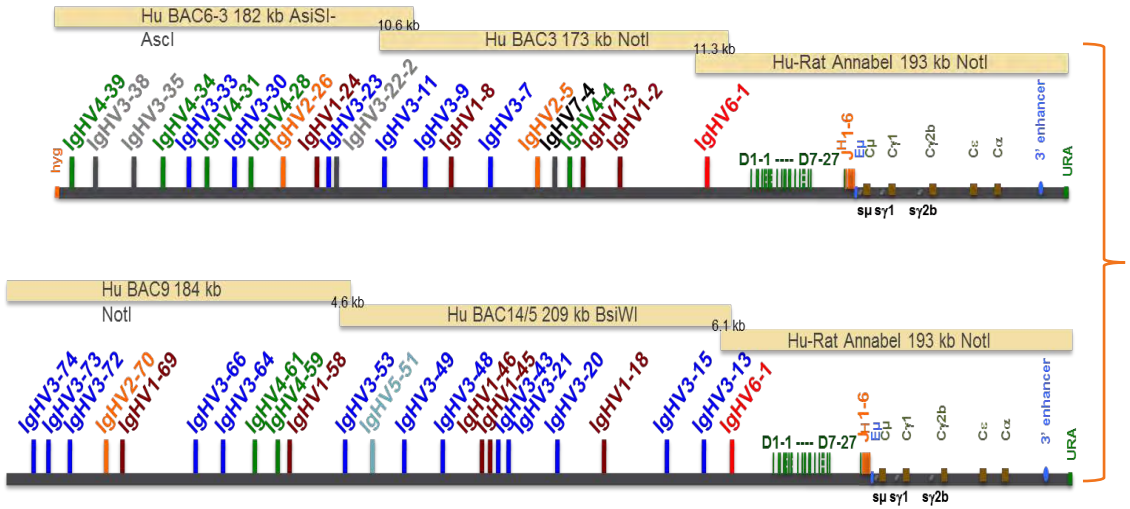
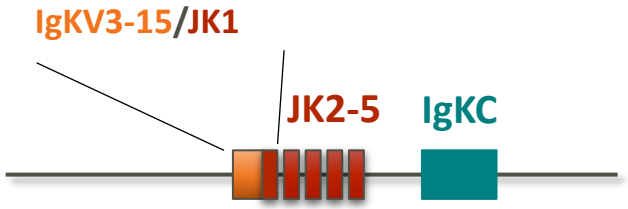
OmniFlic for Easier Bispecific Antibody Production

COMMON LIGHT CHAIN SOLVES THE LIGHT CHAIN PAIRING CHALLENGE



HC (44 VH)



LC (1 VK)

Rearranged human κ L-chain expressed with any (human) IgH locus

Monospecific IgG

Bispecific IgG

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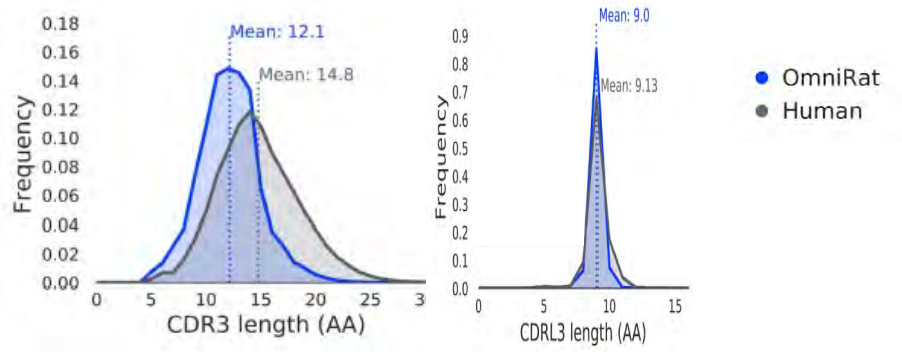
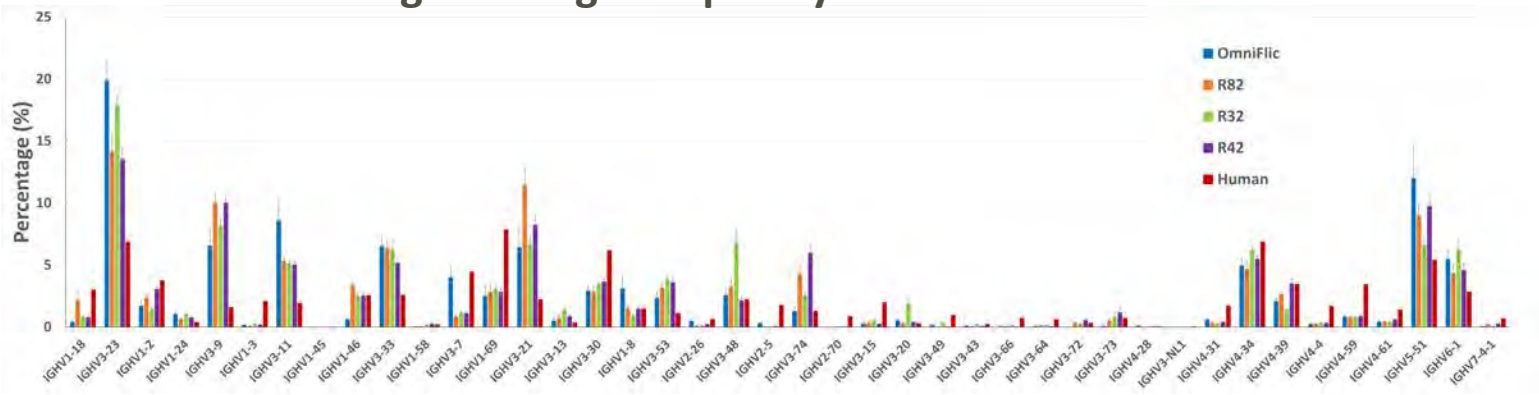
Evidence of Recombination and Somatic Hypermutation

CDR-H3 length distribution in naïve rats

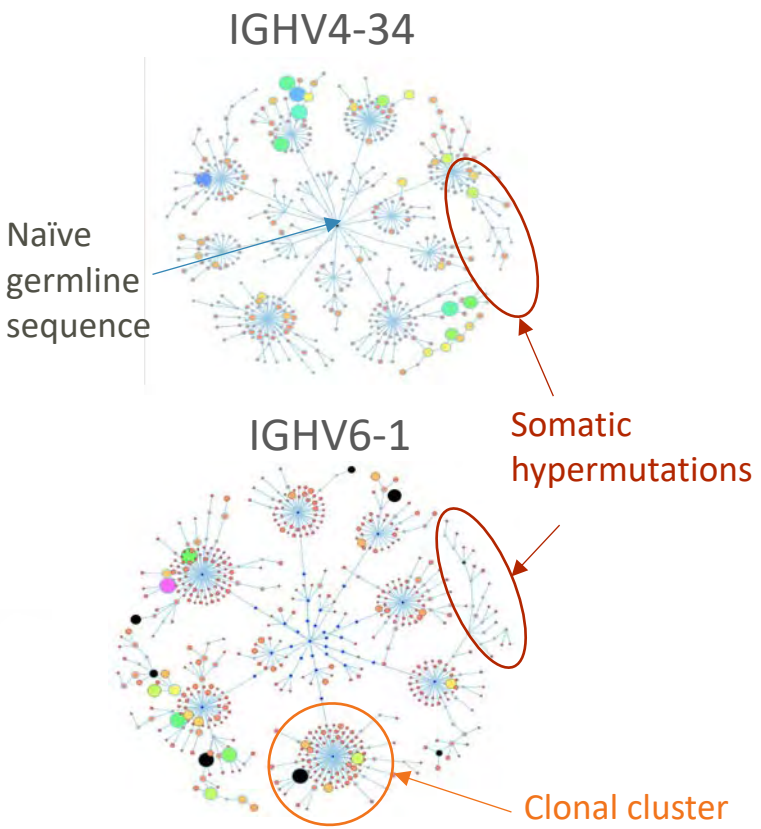


(Joyce, Science Rep 2020)

VH gene usage frequency in immunized rats



Clonal cluster analysis in immunized rats



OmniAb®

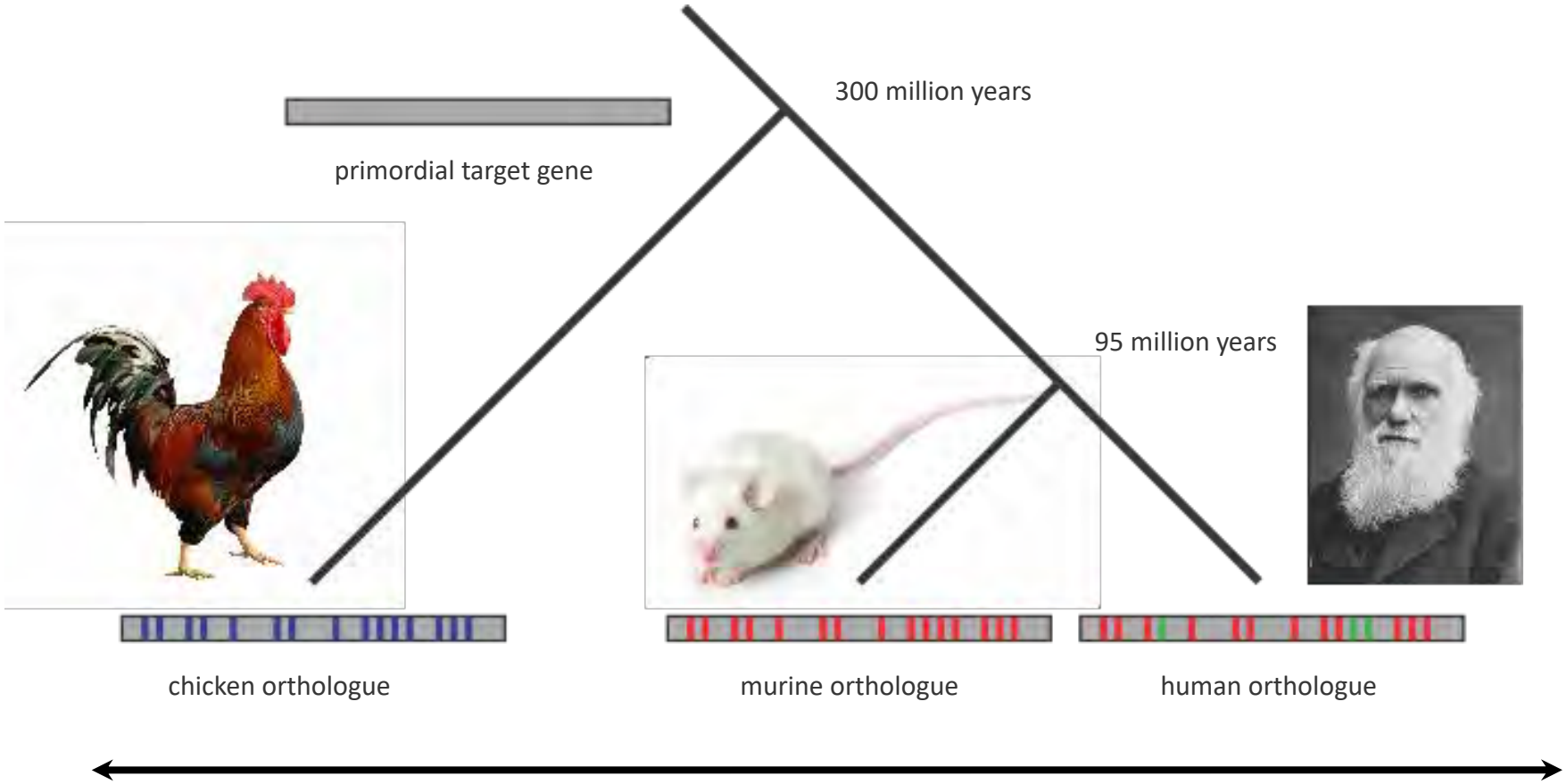
OmniRat/Flic And OmniMouse

- Functional recombinant immunoglobulin loci
  - Normal B cell development
  - Productive rearrangement of all functional human genes
  - Normal human frequency of V-, D-, J-gene usage
  - Similar human CDR3 length distribution
- Normal hypermutation and affinity maturation
- High expression of human antibodies
- Increased sequence diversity via
  - Mixed genetic background
  - Choice of lines with different light chain isotype choices

	OmniRat	OmniMouse	OmniFlic
Genetic background	Sprague Dawley/ Brown Norway/ Lewis	B6.SJL (mixed with other coming soon)	Sprague Dawley/ Brown Norway/ Lewis
Lines	• Kappa/Lambda • Kappa • Lambda	• Kappa/Lambda • Kappa • Lambda	Fixed KC

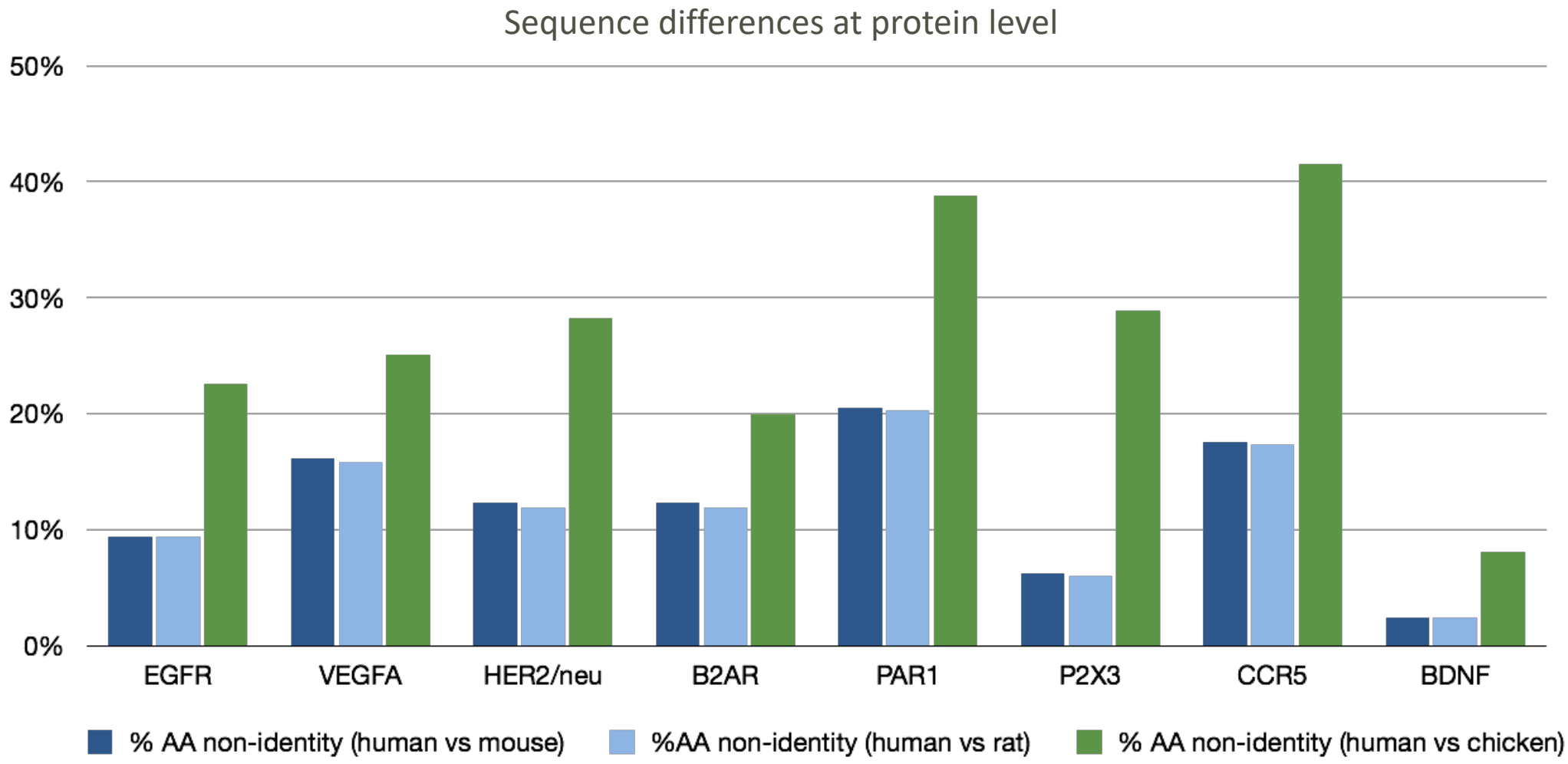
Chicken Platforms

Powered By Evolution



Greater evolutionary distance yields greater immunogenicity and more antibody diversity

Orthologue Comparison



average Δ
≈ 2-3x

Chicken orthologues are always more divergent from human than those from mammalian species

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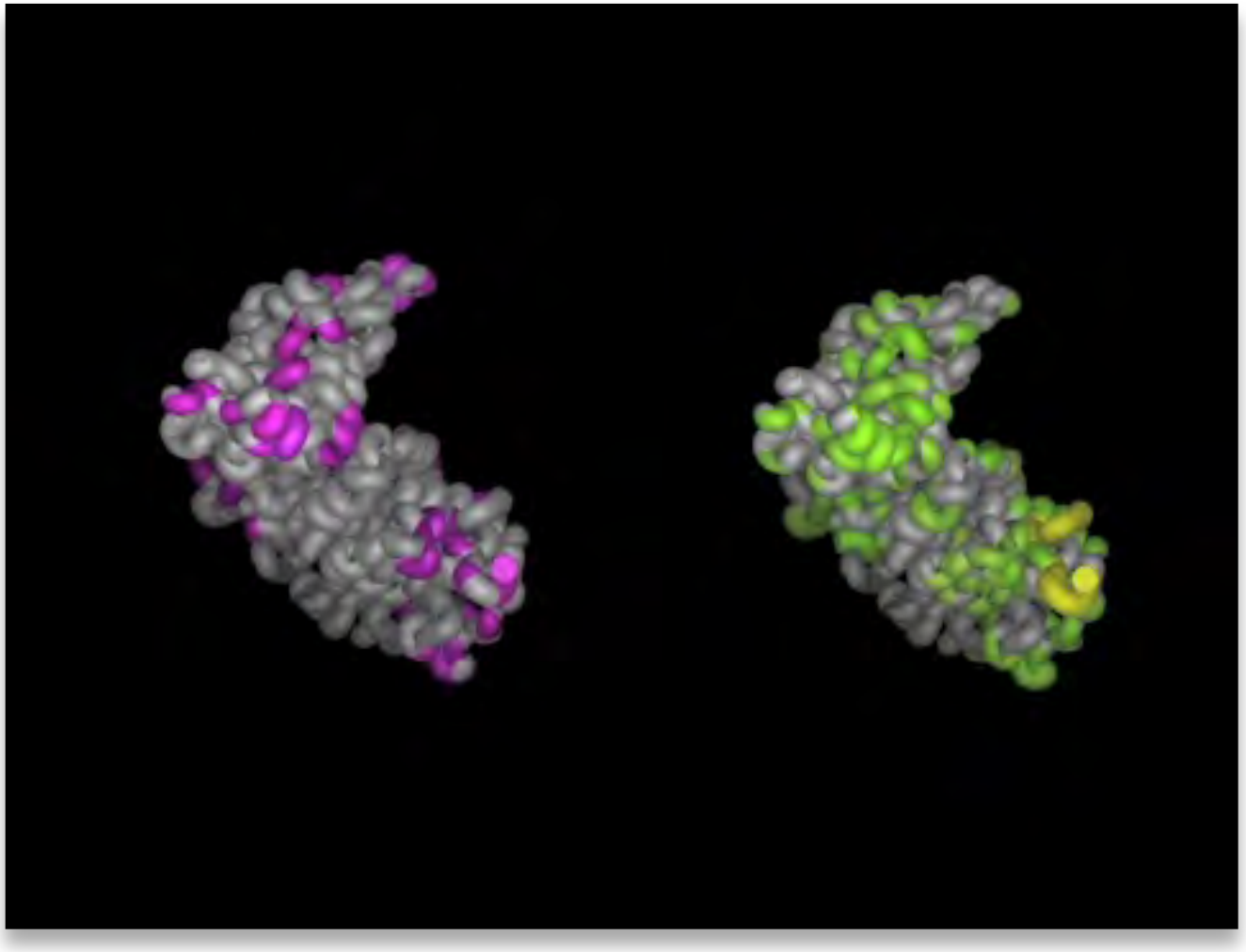
HER2 Orthologues

human vs mouse
(differences in pink)

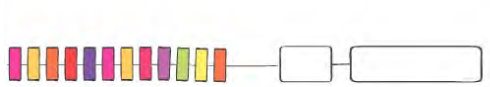


human vs chicken
(differences in green)

Engineering of Ig Loci

ADAPTATION TO CHICKEN GENE CONVERSION PROCESS

Gene conversion

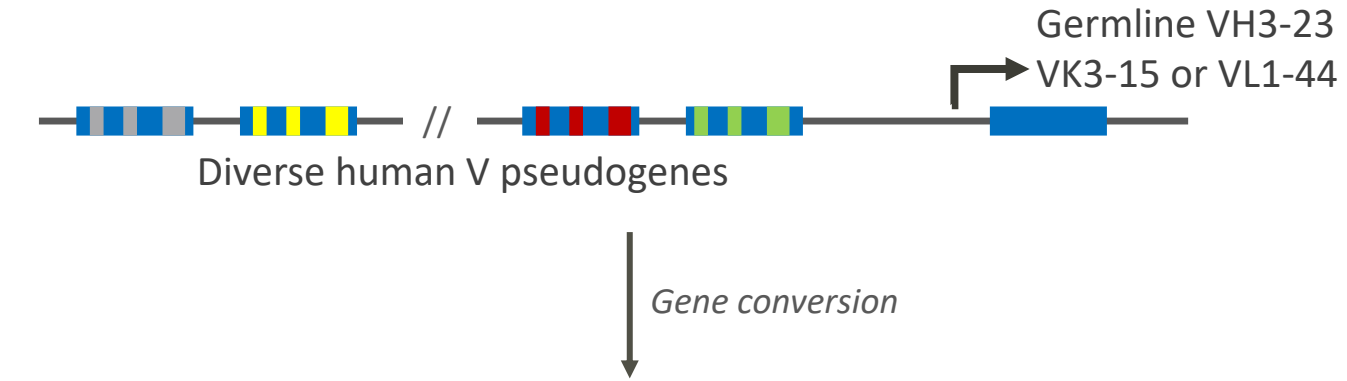


for animation go to:
https://www.omniab.com/technology/omnichicken-omniclic

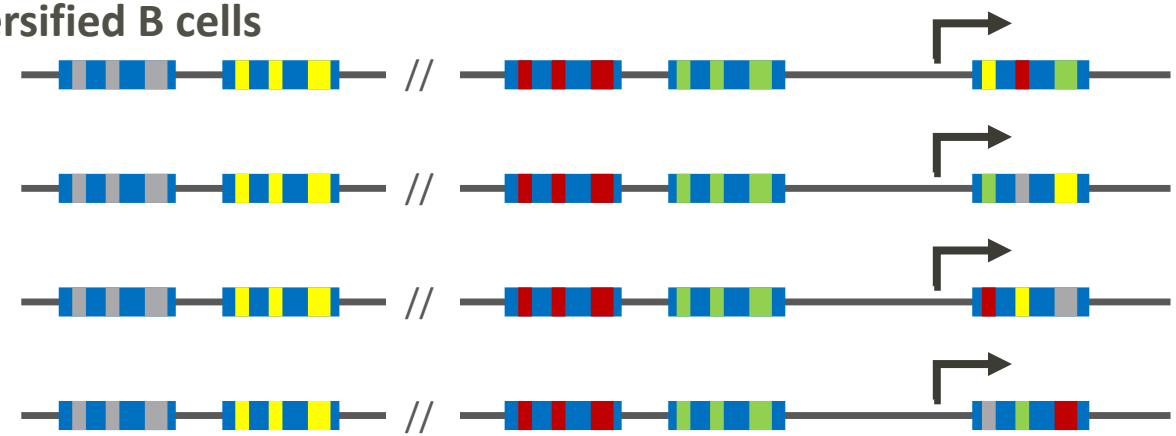
Human V's selected for:

- High expression level, stability, ubiquity
- High sequence diversity in CDRs
- Low sequence diversity in FWs

Engineered locus



Diversified B cells



OmniAb

OmniClic™: Tg Chickens with Common Light Chain

Engineered for Bispecific Antibody Discovery and Development

COMMON LIGHT CHAIN BASED UPON HUMAN VK3-15 SCAFFOLD

- Active V gene fully germline
- Pseudogenes also germline with no CDR sequence diversity

PAIRED WITH PROVEN VH3-23 HEAVY CHAIN

- Almost all mAb diversity occurs in VH, and in CDRs

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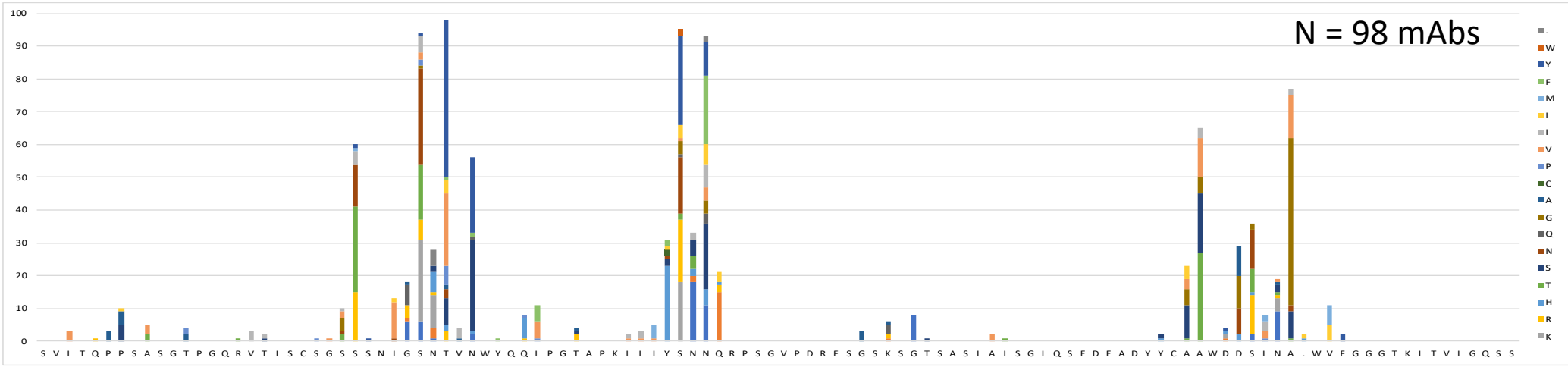
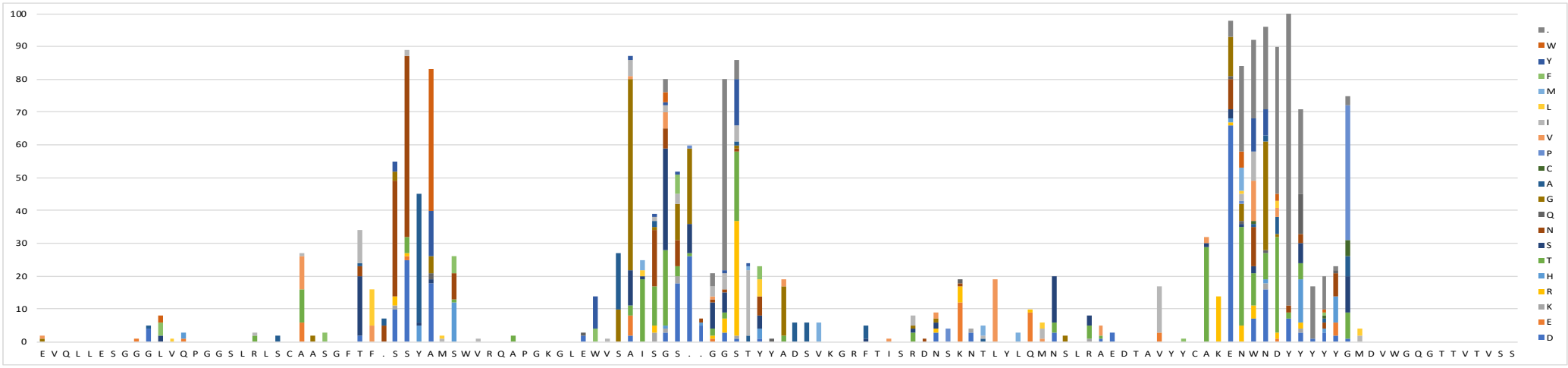
Sequence Diversity of PGRN mAbs from OmniChicken

VL



VH



Diversity is principally focused in the CDR regions of human VH and VL;
a result of both transgene design and cellular selection

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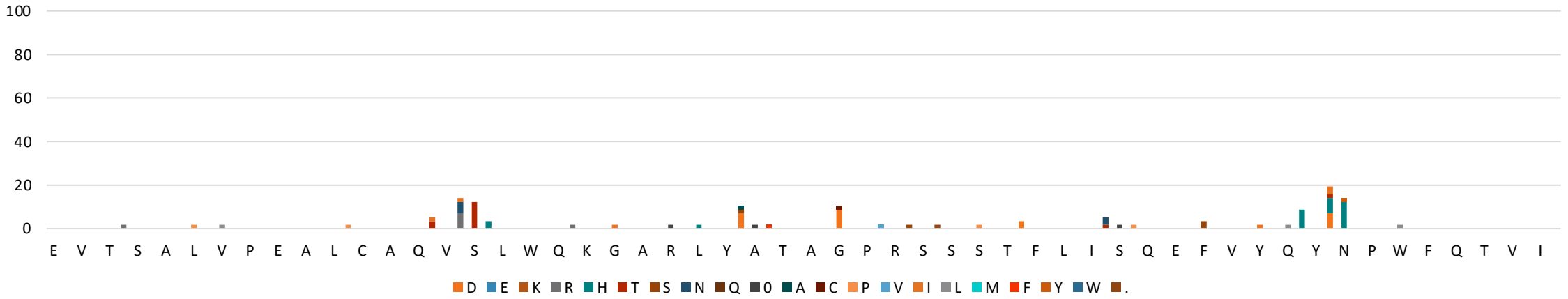
Sequence Diversity of PGRN mAbs from OmniClic

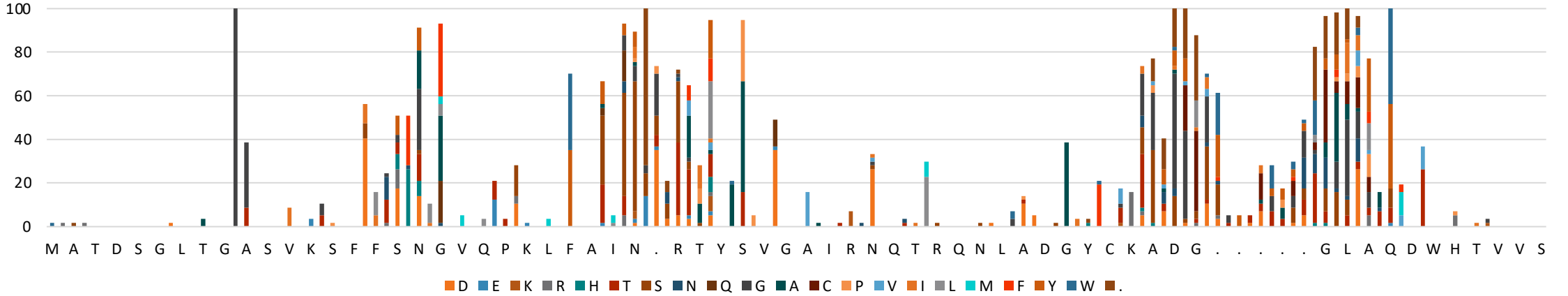
42518, CmLC4/IgL KO

VL



N = 57 mAbs

VH



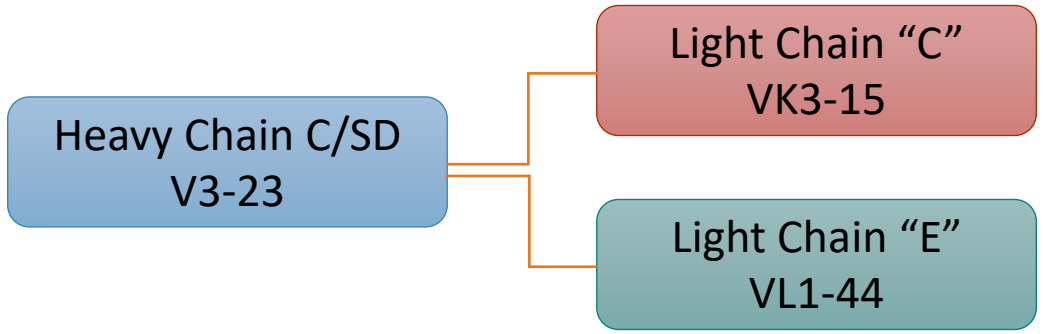
Diversity is focused to CDRs of VH; very little mutation seen in VL

OmniAb®

Conclusions

- OmniChickens retain the antigen recognition capabilities of wild-type chickens, including response to conserved antigens, unique epitope coverage, and species cross-reactivity *(Ching et al, mAbs, 2017)*
- OmniChickens generate high affinity and high specificity antibodies through CDR focused diversification of transgenes that are designed upon a single-family human antibody scaffold (VH3/VK3) *(Leighton et al, Front. Immunol., 2018)*
- High affinity antibodies covering diverse epitopes can be obtained from OmniChickens with either kappa or lambda light chains. *(Ching et al, PLOS One, 2020)*
- OmniClic offers the ability to derive antibodies that focus sequence diversity almost entirely on the VH domain, leaving the VL essentially germline. *(Ching et al, mAbs 2021)*

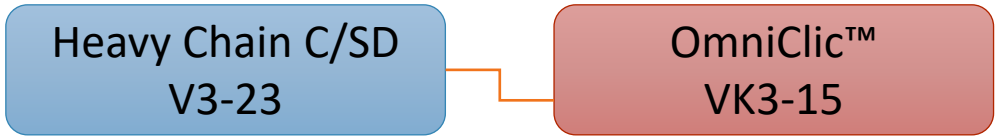
OmniChicken Platforms



OmniChicken
naturally optimized human antibodies®

Conventional HxL antibodies

Choice of light chain



OmniClic
naturally optimized human antibodies™

Common LC antibodies

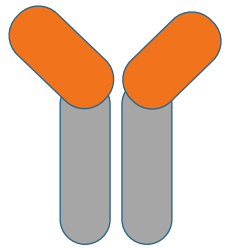
For bispecific applications

Novel Scaffolds

OmniDab: Transgenic chickens expressing heavy chain-only antibodies

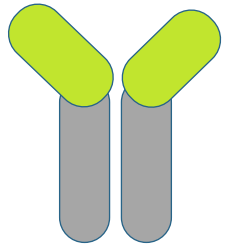
HCO STRATEGY USING TRUNCATED LIGHT CHAIN (TLC)

tLC transgene



Chicken VH sdAb
(hu Fc)

tLC transgene +
VHH transgene

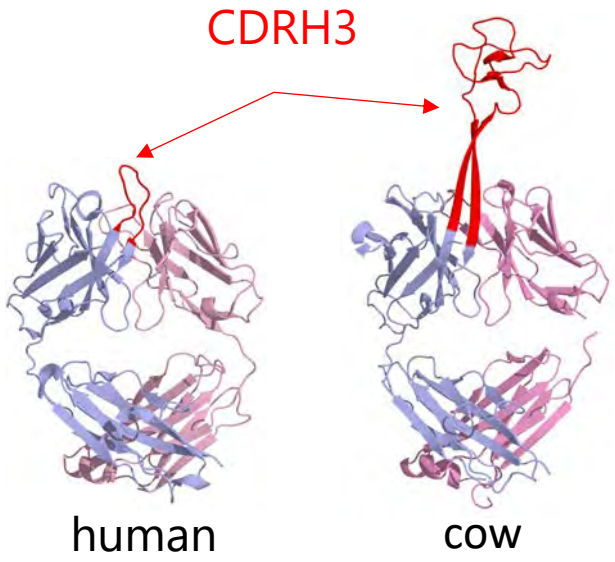


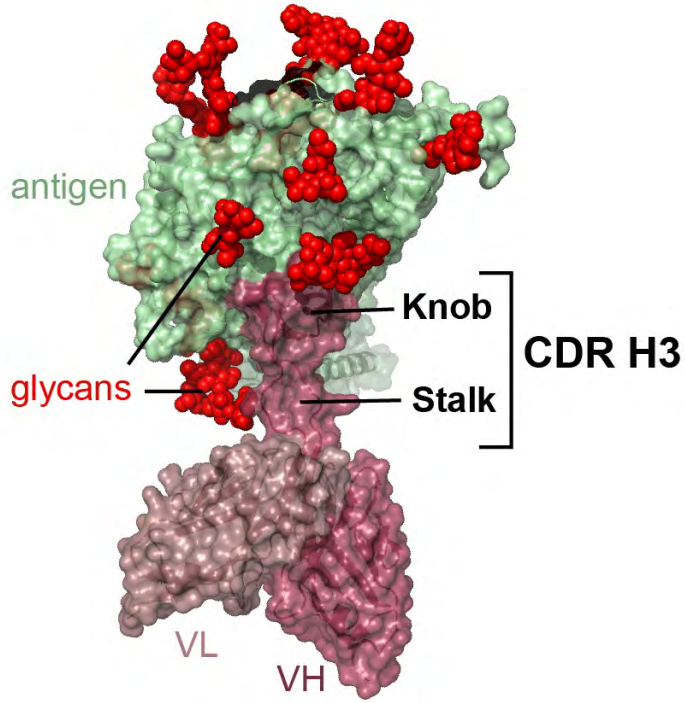
human VHH sdAb
(hu Fc)

- *Normal chicken heavy chain can express as VH alone*
- *VHH transgene in development*

OmniTaur: ultralong CDRH3s create novel binding domains

UNIQUE STRUCTURAL FEATURES OF ULTRALONG H3 ANTIBODIES



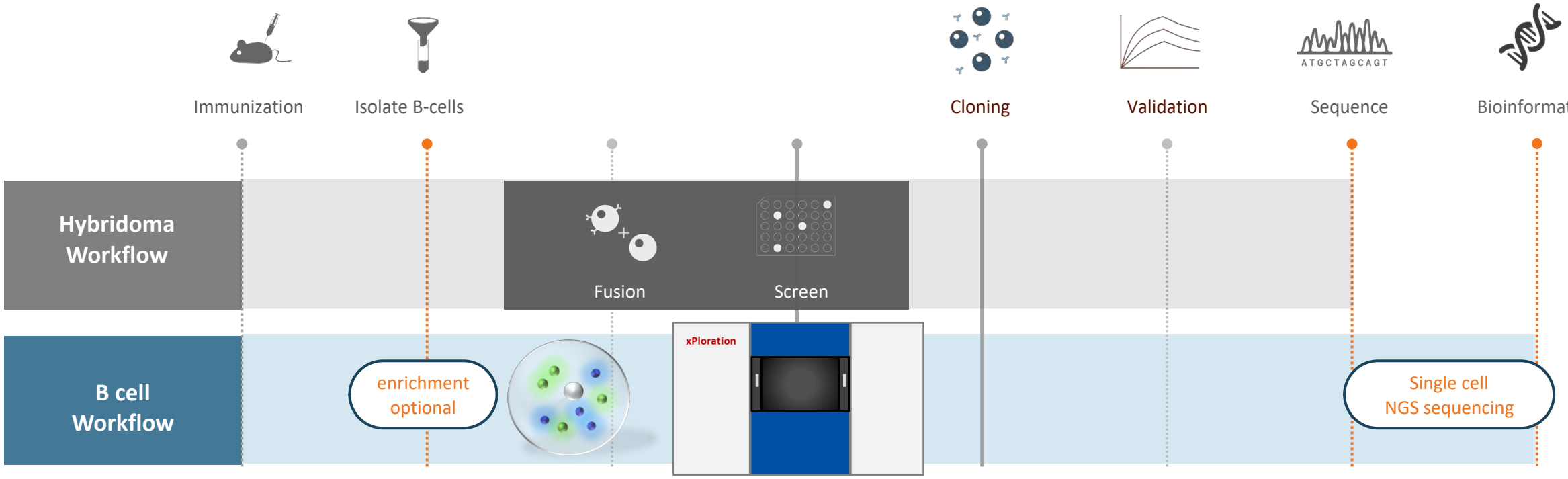


- *Novel structure may enable targeting epitopes unreachable by standard antibodies*
- *Long H3 domains can be expressed on human VH framework, or alone as ~5kD Picobodies™*

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

Screening Technologies

B cell screening



- **Bypass diversity and time bottleneck** of traditional hybridoma workflows
- Ligand offers two powerful single B-cell screening technologies: the **GEM assay and xPloration®**
- These two technologies enable **screening against difficult targets**: GPCRs, ion channels and surface antigens

B cell screening provides **greater depth of data** and **more shots on goal for antibody discovery**

OmniAb®

Screening for mAbs Using GEMs

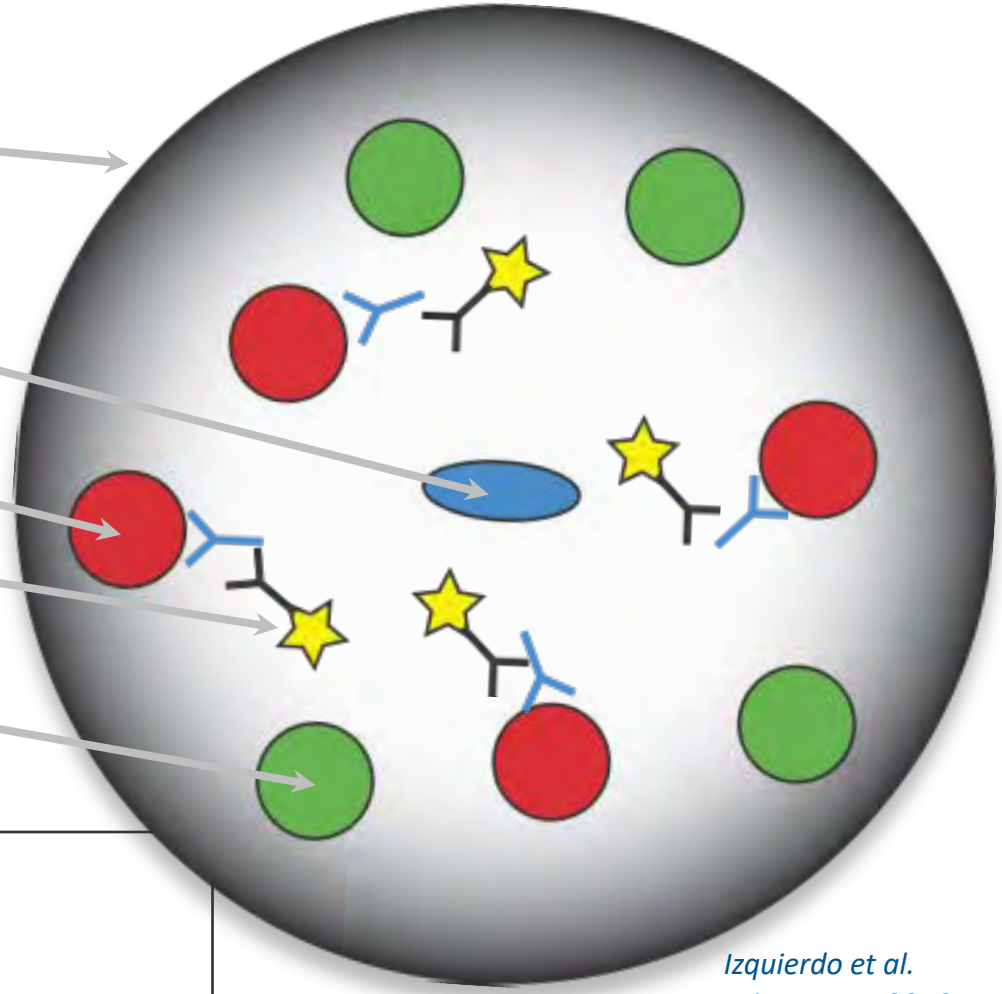
Capsule
(gel microdrop)

B Cell

Reporter Bead 1
(coated with target protein)

Detected Signal

Reporter Bead 2
(control protein)



GEMs With Bead Based-Reporters

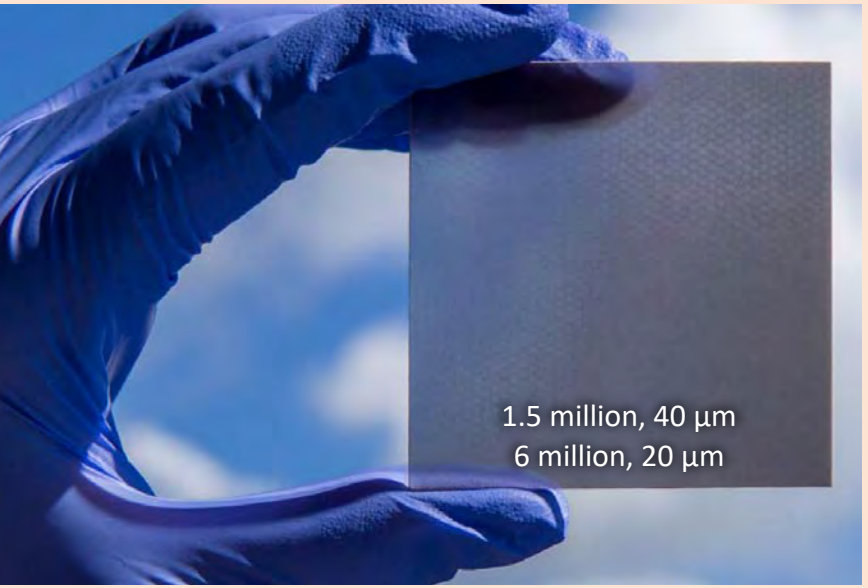
- fluorescent beads are coated with antigens
- bound antibody is detected by fluorescent polyclonal antibody
- antigen specificity is determined by colocalization of signal with alternative bead types

Izquierdo et al. Microscopy, 2016, 1-12

OmniAb®

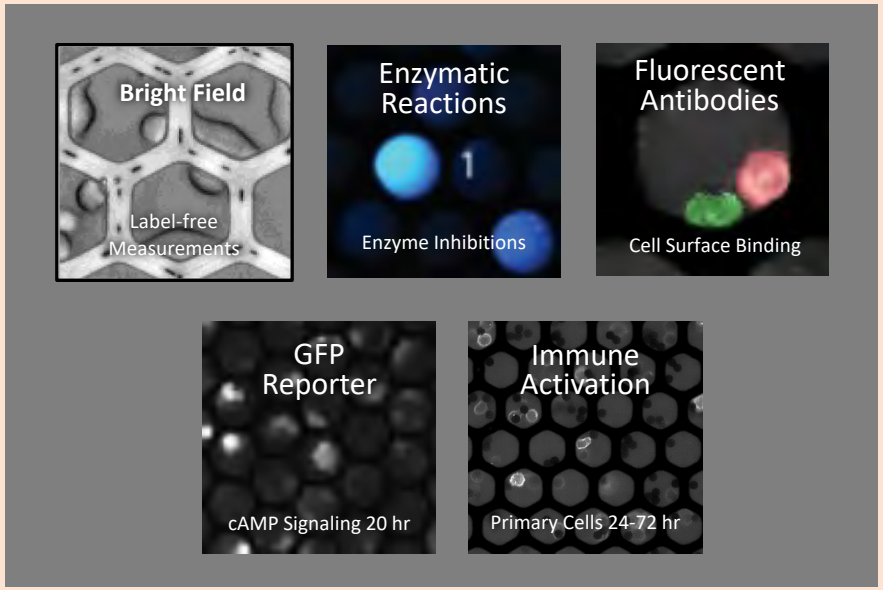
xPloration® Core components

1 | Loading



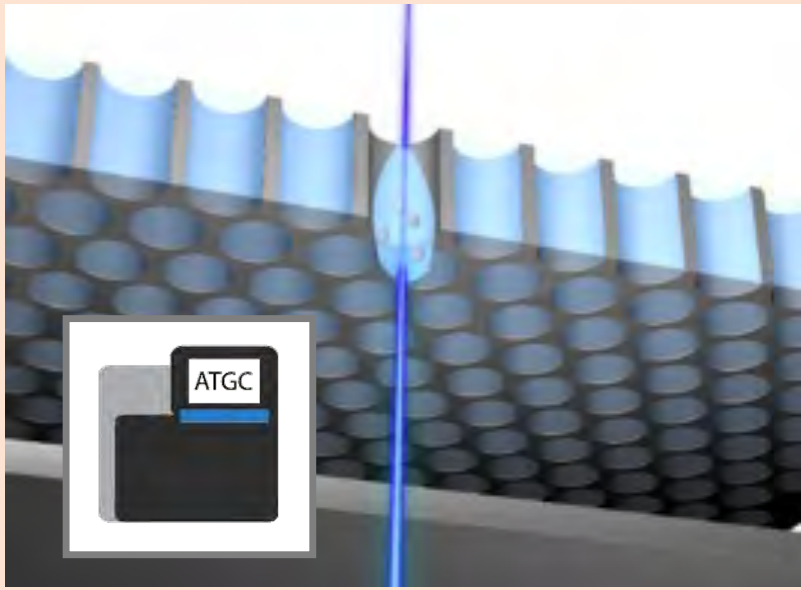
- Unique through-hole format: no bottom
- ~1 cell/µPore
- Compatible with bacteria, yeast, and animal cells
- Established workflows for chicken, rat, mouse antibody secreting cells

2 | Imaging & Functional Assay



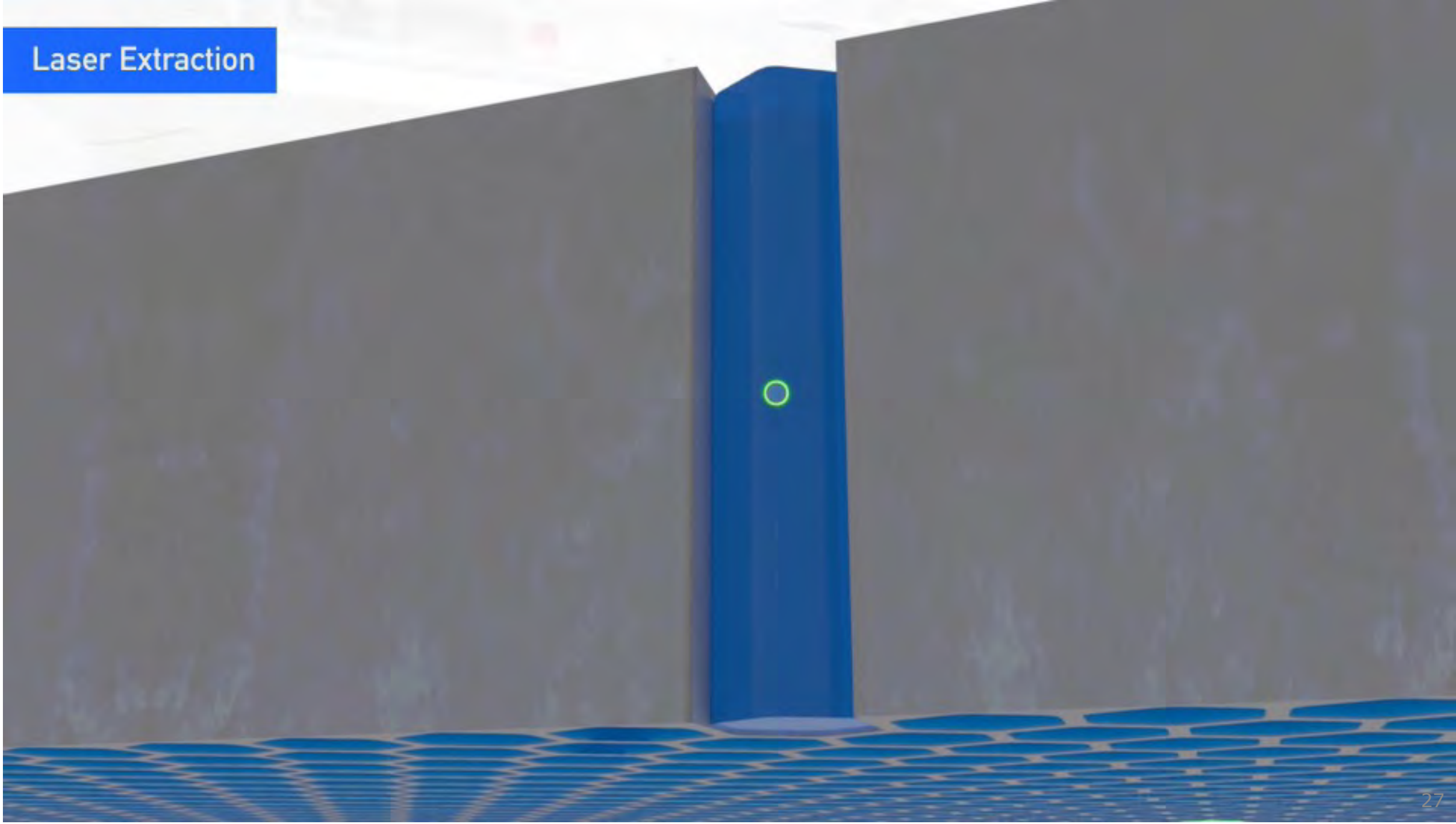
- Flexible assays
- Dynamic time-scale
  - Repeated imaging

3 | Recovery & Single Cell NGS



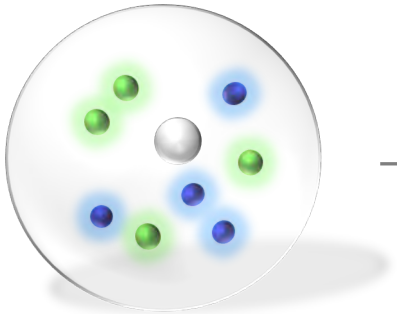
- Precise laser-based recovery
- 1 cell/sec (single cell mode)
  - Single cell barcoding
- 500 cells/sec (bulk mode)

OmniAb®


Laser Extraction

xPloration deep dives

Goal: *Apply deep screening to find a more diverse panel of functional antibodies*

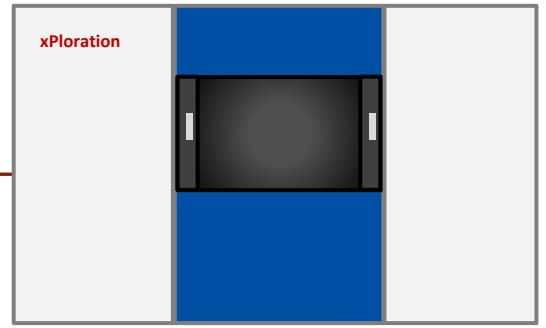


GEM

Seed sequences with functional binding data

xPloration

Large number of sequences to expand diversity



- New sequence clusters
  - Hit expansion
  - Optimization

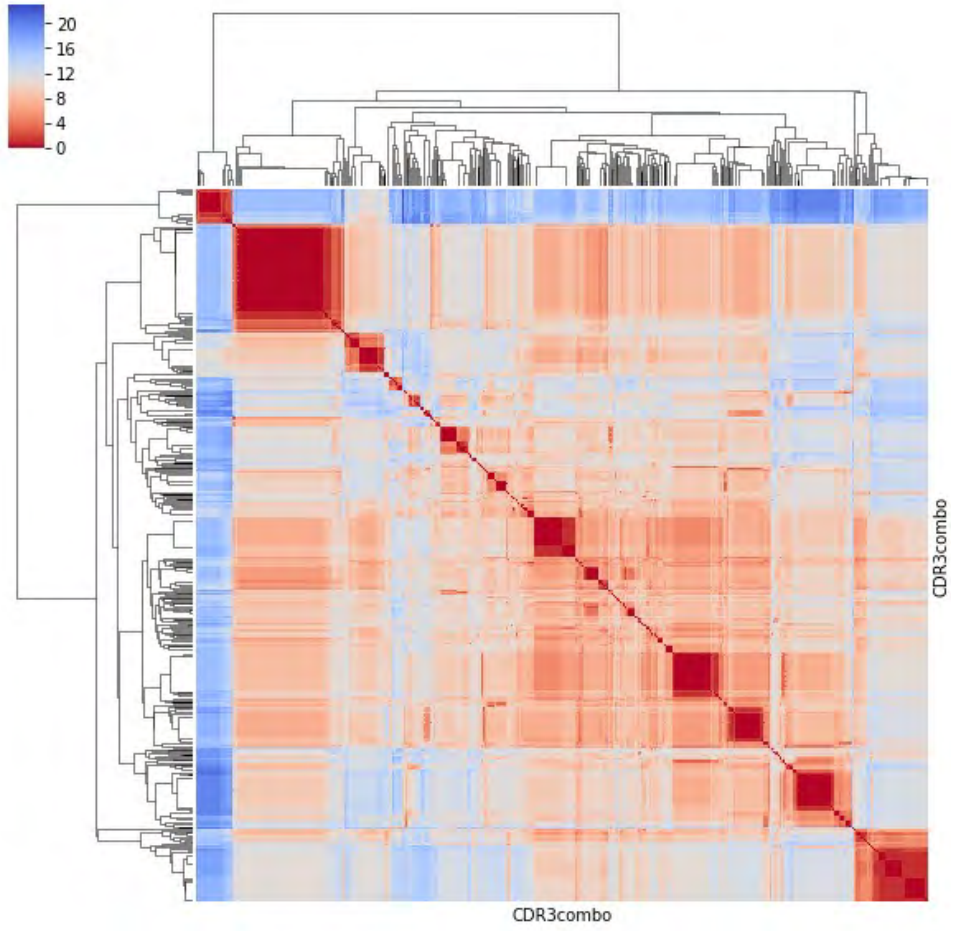
OmniAb®

Natively-paired VH and VK recovery via cell barcoding

- Post screen, isolate cells in 96 well plate
- NGS sample prep and sequencing

Recovered Cells	No.	%
Captured	760	100%
Cells with paired H & K	569	75%
Unique sequences	485	64%

Pairwise distance between each cell's concatenated HCDR3-LCDR3



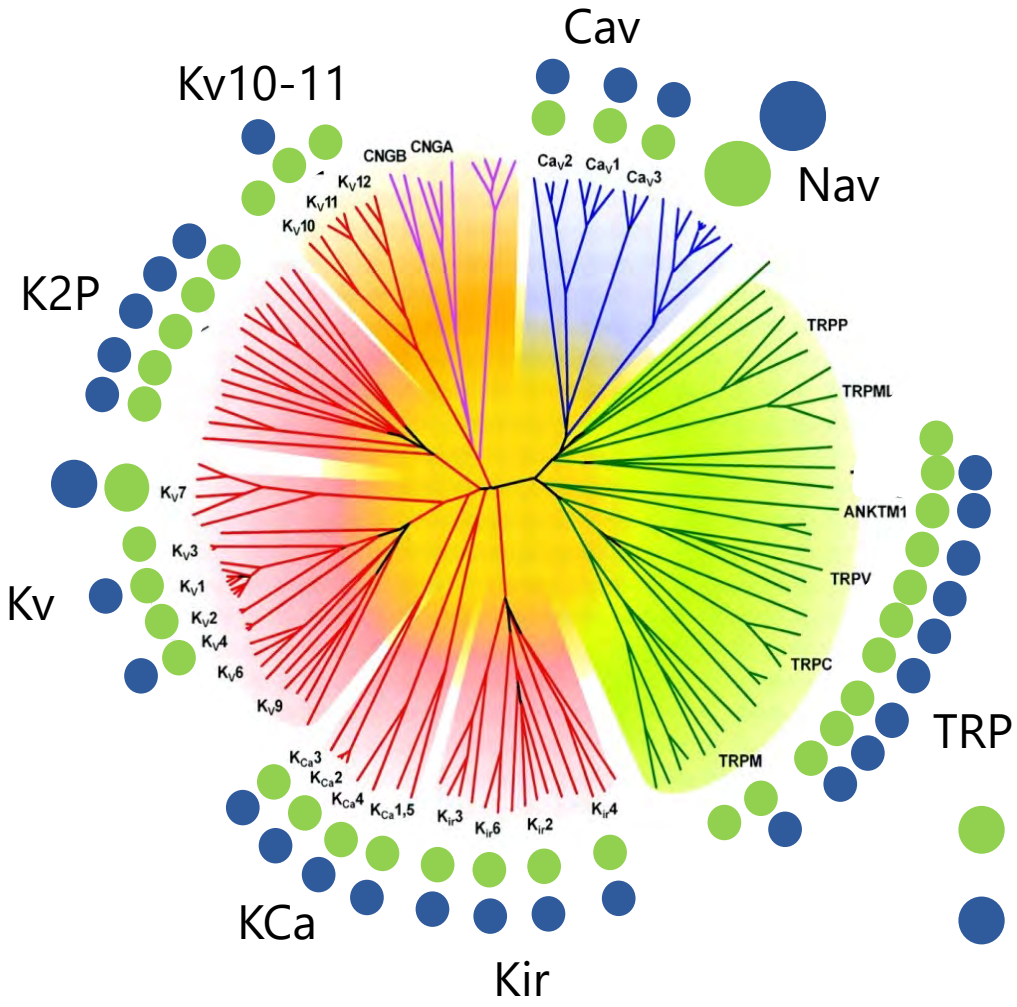
OmniAb

Icagen

Ion Channel & Transporter Technologies

ION CHANNEL & TRANSPORTERS

EXTENSIVE ION CHANNEL DRUG DISCOVERY PLATFORM



- Voltage gated ion channel drug discovery (Nav, Kv, Cav)
- Inward rectifier and two pore potassium channels
- TRP channels and second messenger gated channels (i.e. KCa1, 2 & 3.x, Kir6.x)
- Ligand gated ion channels (i.e. $GABA_A$, iGLURx)
- Aquaporins

Stable Cell Line(s)

Compound Screening Assays

ICAGEN
ION CHANNEL TECHNOLOGY

ION CHANNELS & TRANSPORTERS

EXTENSIVE BIOLOGICAL CAPABILITIES FOR ION CHANNELS AND TRANSPORTERS DEVELOPED AT ICAGEN

Proprietary cell lines can enable high speed antigen production

Cutting-edge assays can facilitate high-throughput screens in GEM and xPloration platforms

Proprietary assays leveraged for discovery and characterization of ion channels

***Best-in-class* capabilities for viable *target-to-lead* delivery for difficult and high-value ion channel targets, established in small molecules and potential in multiple formats and modalities**

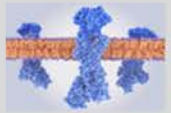
ICAGEN
ION CHANNEL TECHNOLOGY

THE OMNIAB PLATFORM

OmniAb Technologies

Create Diverse Antibody Pools

Create Diverse Pools of High-Quality Naturally Optimized Antibodies



Computational Antigen Design & Proprietary Reagents

OmniRat

OmniMouse

OmniChicken

Robust Antibodies for Any Target

OmniFlic

OmniClic

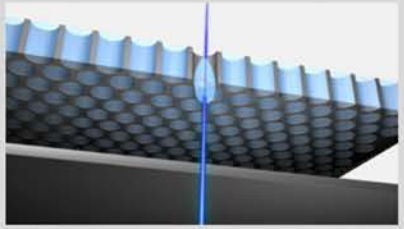
Bispecific Antibody Generation

OmniTaur™

Cow-inspired Antibodies for Difficult Targets

Screen Antibody Candidates

Screen Millions of Cells to Find Potential Therapeutic Candidates



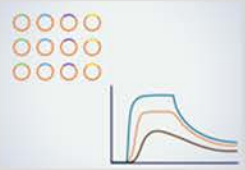
xPloration High-Throughput Single Cell Screening

Gel Encapsulated Microenvironment (GEM) Single Cell Screening

Identify the Right Antibody

Further Characterize, Select & Optimize the Right Antibody

- *Custom Bioinformatics*
- *Next Generation Sequencing (NGS) Hit Expansion*



- *Comprehensive Functional Characterization*
- *Proprietary Ion Channel Assays*

Technology offering addresses the most critical challenges of antibody discovery

OmniAb®