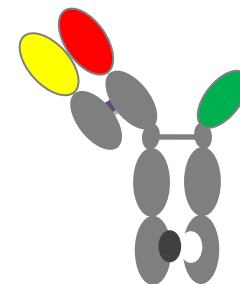
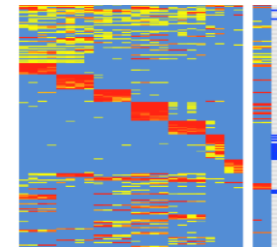




Winning the numbers game: novel multi-specific therapeutics from a diverse collection of human domain antibodies

**Shelley Force Aldred, Ph.D.
VP Pre-clinical Development**

- **Proprietary transgenic rat platforms for antibody discovery**
 - UniRat and OmniFlic
- **High-throughput sequence-based discovery engine**
 - Next-gen sequencing and bioinformatics
- **Multi-specific therapeutic antibody products**
 - Internal programs in oncology and infectious disease
- **Antibody discovery partnerships**



Primary goals:

1. Start with a large number of antibodies to ensure finding the best clinical candidate
2. Seek diversity of epitopes, affinities, and function

Outline:

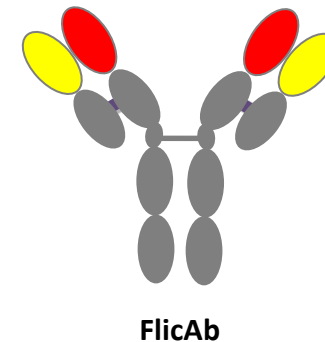
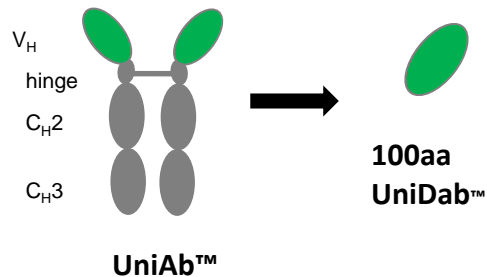
- Human Ig transgenic rats for antibody discovery
- High-throughput sequence-based discovery engine
- Modular bispecific platform



Fully human VH,
Heavy chain antibody (UniAb)
or domain antibody (UniDab)

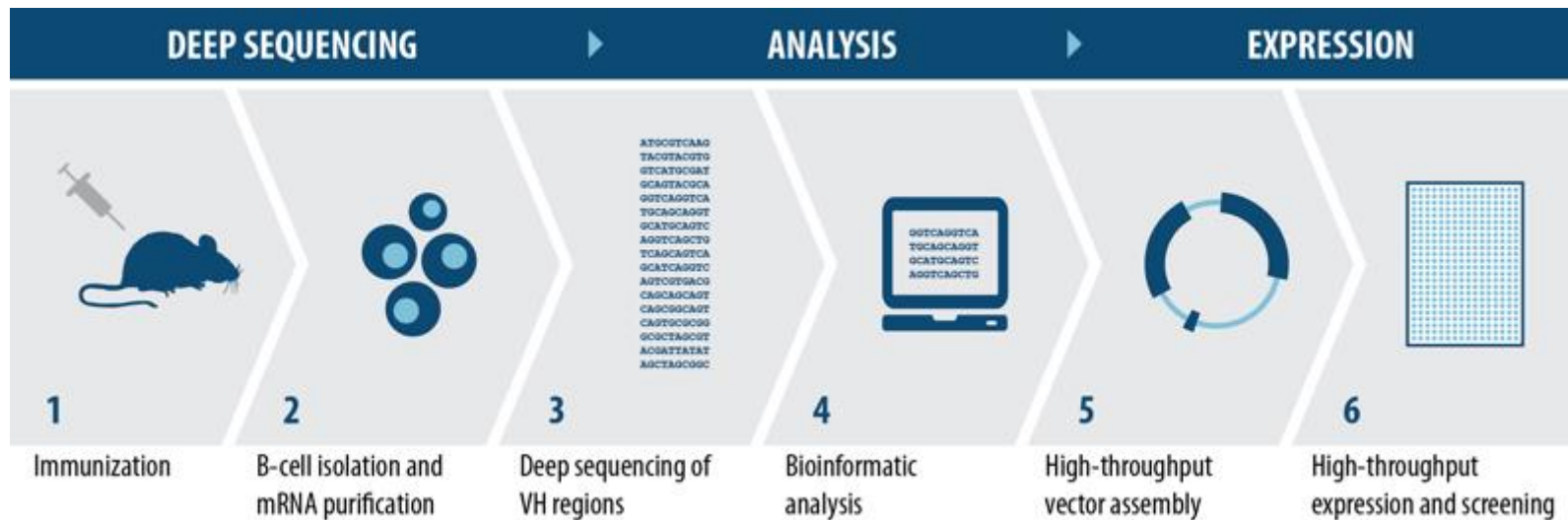


Fully human VH,
fixed light chain IgG



- Triple knock-outs for endogenous rat Ig loci
- Comprehensive human VH gene repertoire, robust heavy chain rearrangement
- Variations on traditional H:L pairing
 - UniRat: no light chain, CH1 deleted (heavy chain only antibodies)
 - OmniFlic: expresses a single rearranged human kappa light chain

- **Our platform is a unique combination of:**
 - Antibody repertoire sequencing of germinal center B-cells
 - Custom bioinformatics analysis
 - High-throughput vector assembly
 - Recombinant expression and screening



Naïve B-cells



Affinity matured B-cells

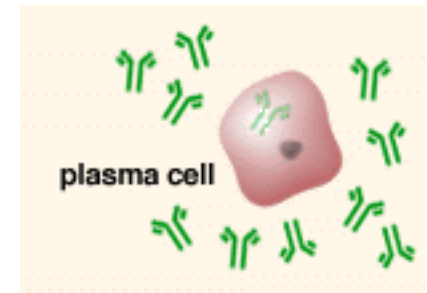
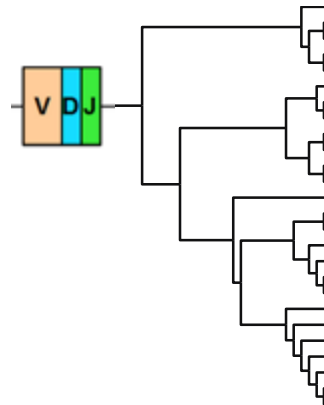
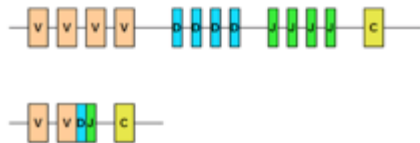


Plasma cells

Many unique VDJ rearrangements (unique CDR3s)

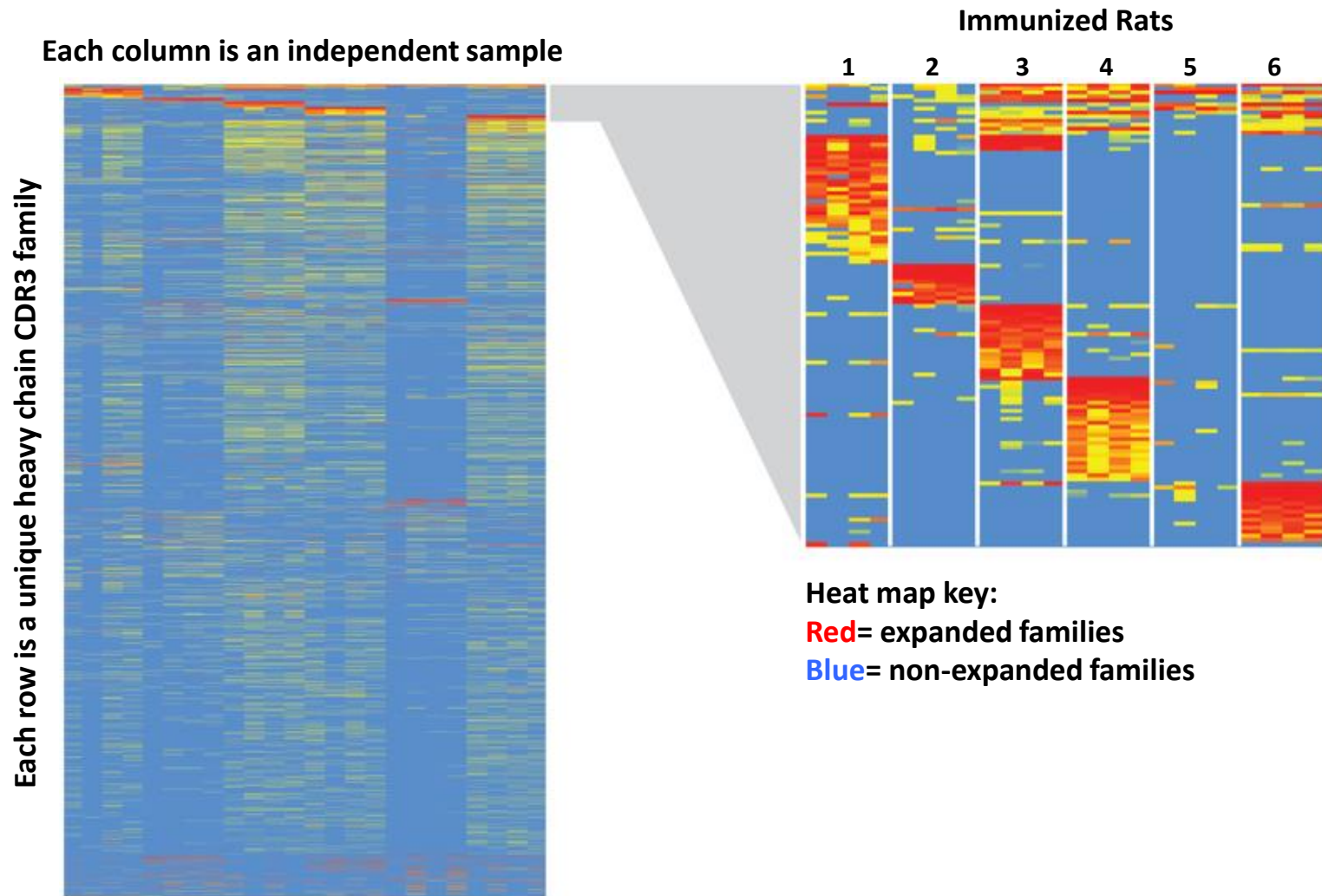
SHM and expansion of antigen-specific CDR3 lineages in GCs

High-expression of antigen-specific sequences

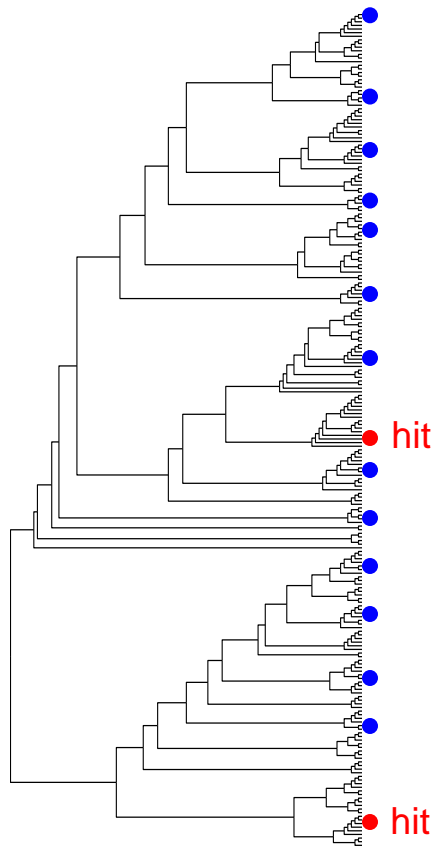


~100 CDR3 families * ~300 members per family
= ~30,000 unique ag-specific seqs in germinal centers of animal
(highly expressed members of large sequence lineages)

Antibody repertoire lineage rank analysis

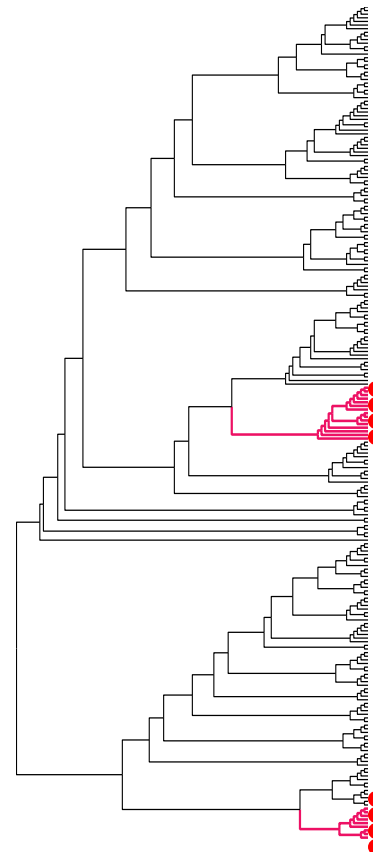


- **Primary screen:** diverse CDR3 sequence families (ELISA, affinity, functional)
- **Secondary screen:** complete lineages of primary hits (affinity, functional)



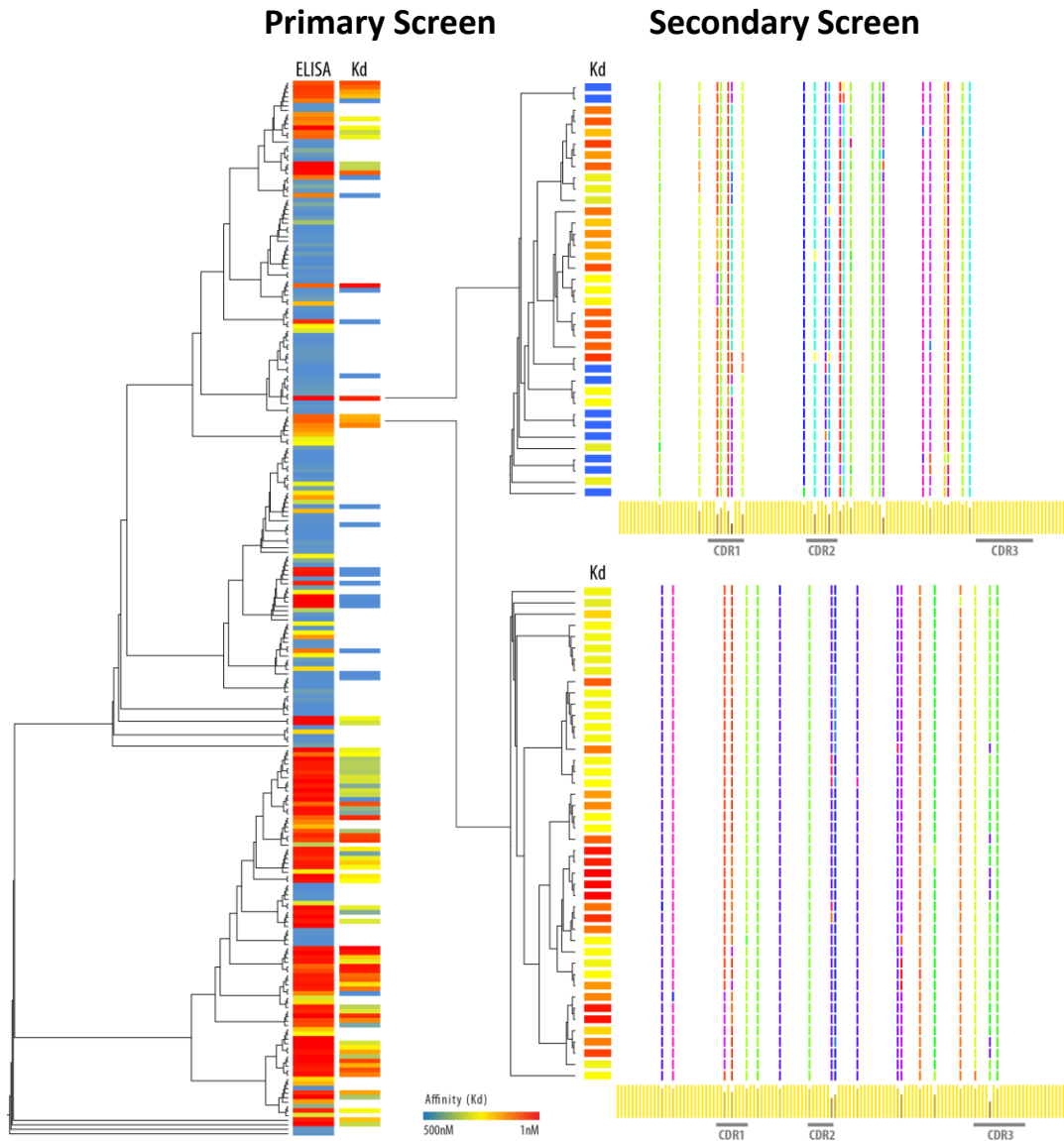
Primary
Screen:
300-400
diverse
CDR3
sequences

Guided by
lineage rank
analysis



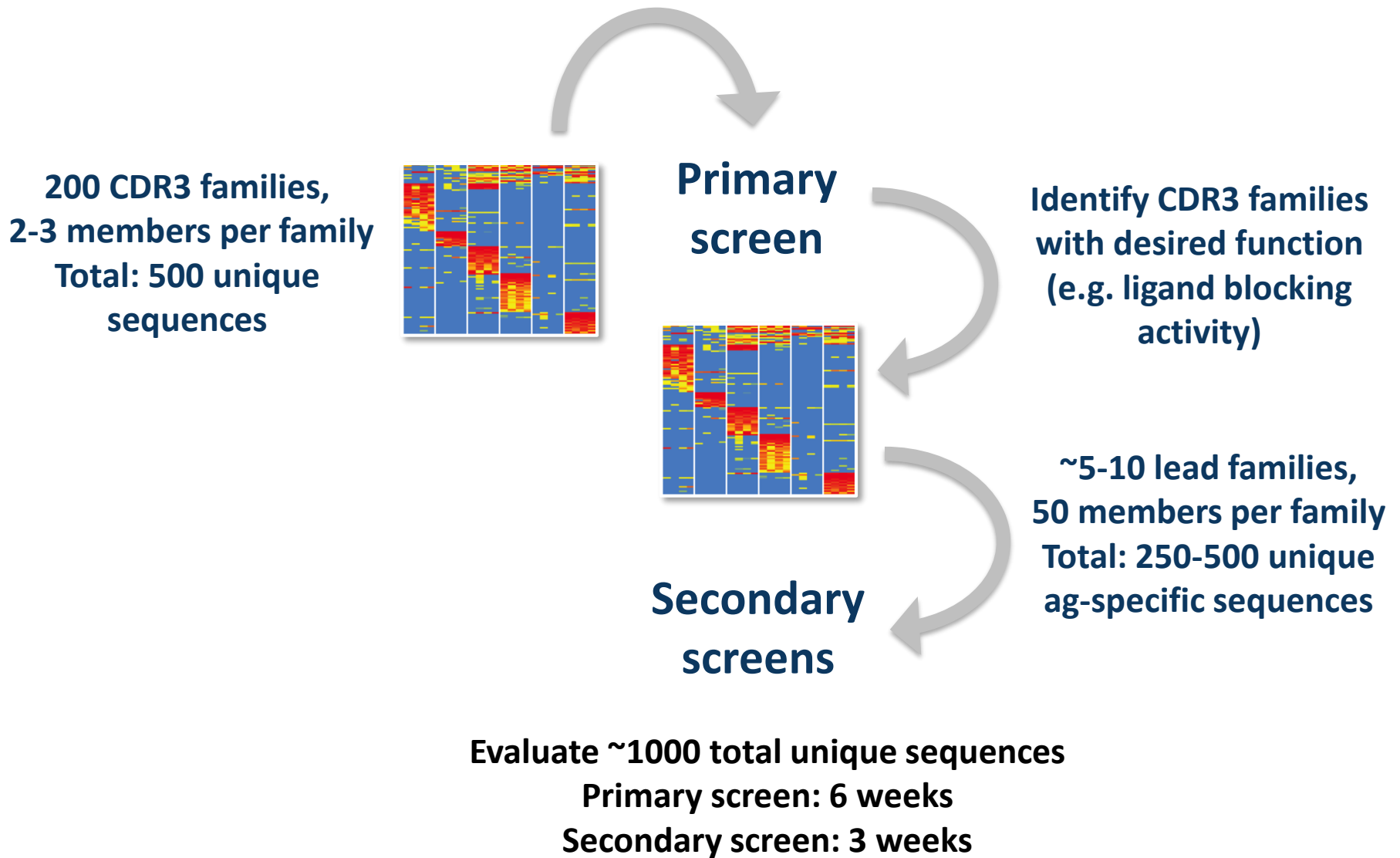
Secondary
Screen:
50-300
unique
sequences
per lineage

Includes rare
sequences in
lineages of
interest



Each row is a unique VH expressed as a UniAb

- **Primary screen**
 - Apply high-throughput primary screen assays (expression, binding, function)
 - Identify families with preferred functional activity
- **Secondary screen**
 - Identify family members with higher affinity and fewer sequence liabilities



ADVANTAGES

- Comprehensive analysis of the full B cell repertoire
 - No fusion, panning, or selection
- Efficient and effective
 - >10,000 total antibodies screened, >2,500 unique binders identified for 18 diverse targets
- Sequence + function database
 - >25,000 functional data points across thousands of unique binding sequences

ADVANTAGES

- Comprehensive analysis of the full B cell repertoire
 - No fusion, panning, selection, etc.
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OUTPUT

- Large collection of binding domains
 - Many antigen targets (effector cells, tumor-specific, IO)
 - Diverse binding domain choices for each antigen (varying affinity, epitope, functional effects, and developability profiles)
 - Mono- or multi-valent binding domain arms

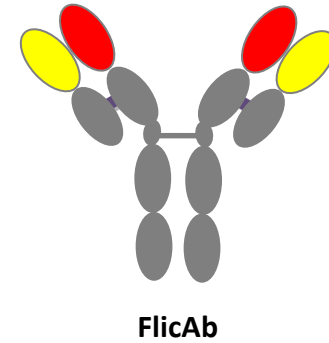
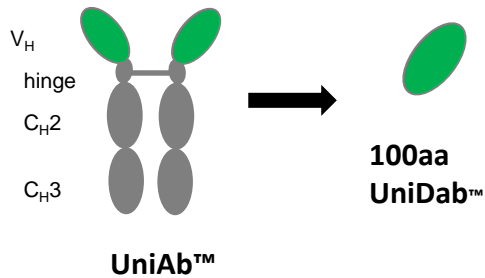
Modular bispecific platform



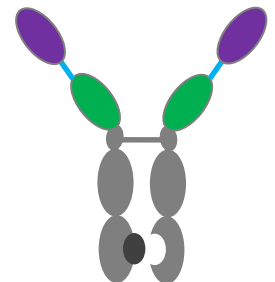
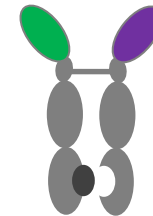
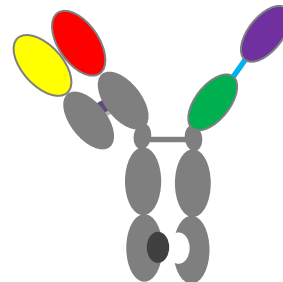
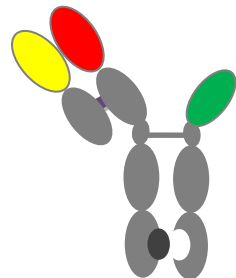
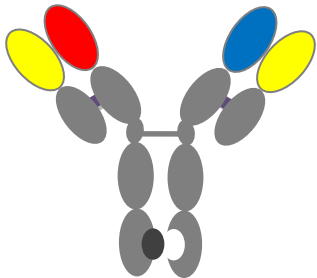
Fully human VH,
Heavy chain antibody (UniAb)
or domain antibody (UniDab)



Fully human VH,
fixed light chain IgG

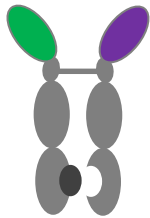


Combine for fully human
bispecific antibody proteins

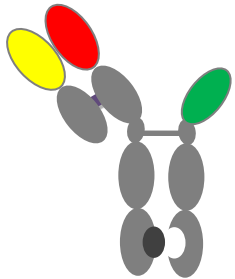


Modular bispecific platform

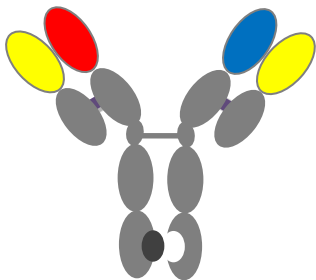
- Classic knob+hole system for easy manufacturing and purification
- Bispecific functionality and sub-nM affinity in all three forms



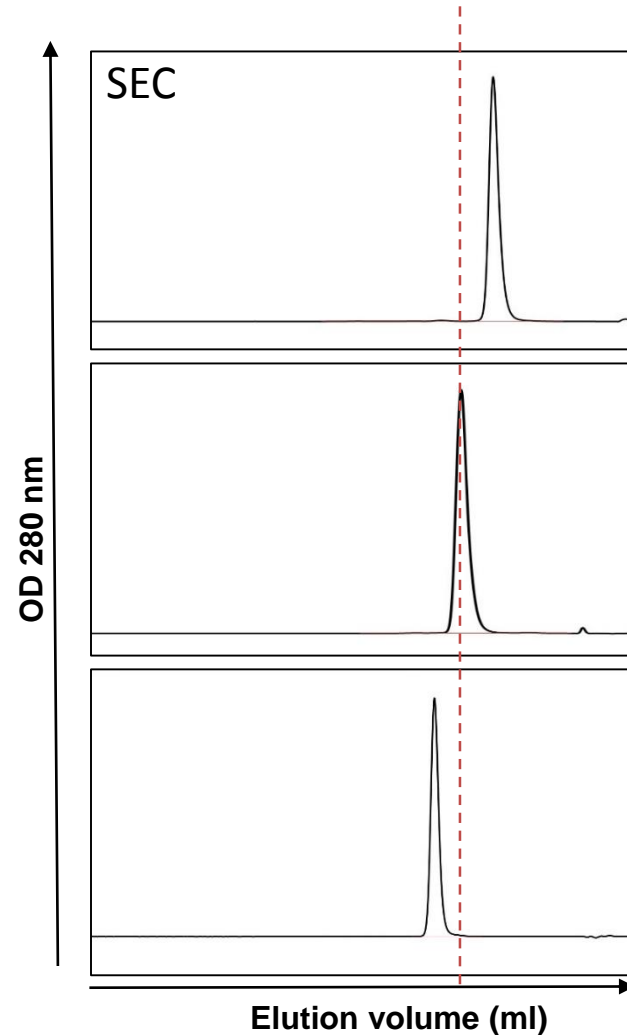
2-chain UniAb bispecific
80,000 Da



3-chain FlicAb+UniAb
bispecific
115,000 Da



4-chain FlicAb bispecific
150,000 Da



- High-throughput discovery engine generates hundreds of lead candidates for each new antigen
- In-house database relates sequence and functional analysis of thousands of recombinant antibodies
 - >25,000 functional data points from >10,000 unique antibody sequences
 - Machine learning for continued refinement of sequence-activity relationships
- UniRat and OmniFlic platforms enable mix-and-match domain strategies
- Many multi-specific antibodies are evaluated for every project

- **TeneoBio Team**

- Andrew Boudreau
- Ben Buelow
- Starlynn Clark
- Kevin Dang
- Katherine Harris
- Duy Pham
- Payal Pratap
- Ute Schellenberger
- Nathan Trinklein
- Harshad Ugamraj
- Wim van Schooten

