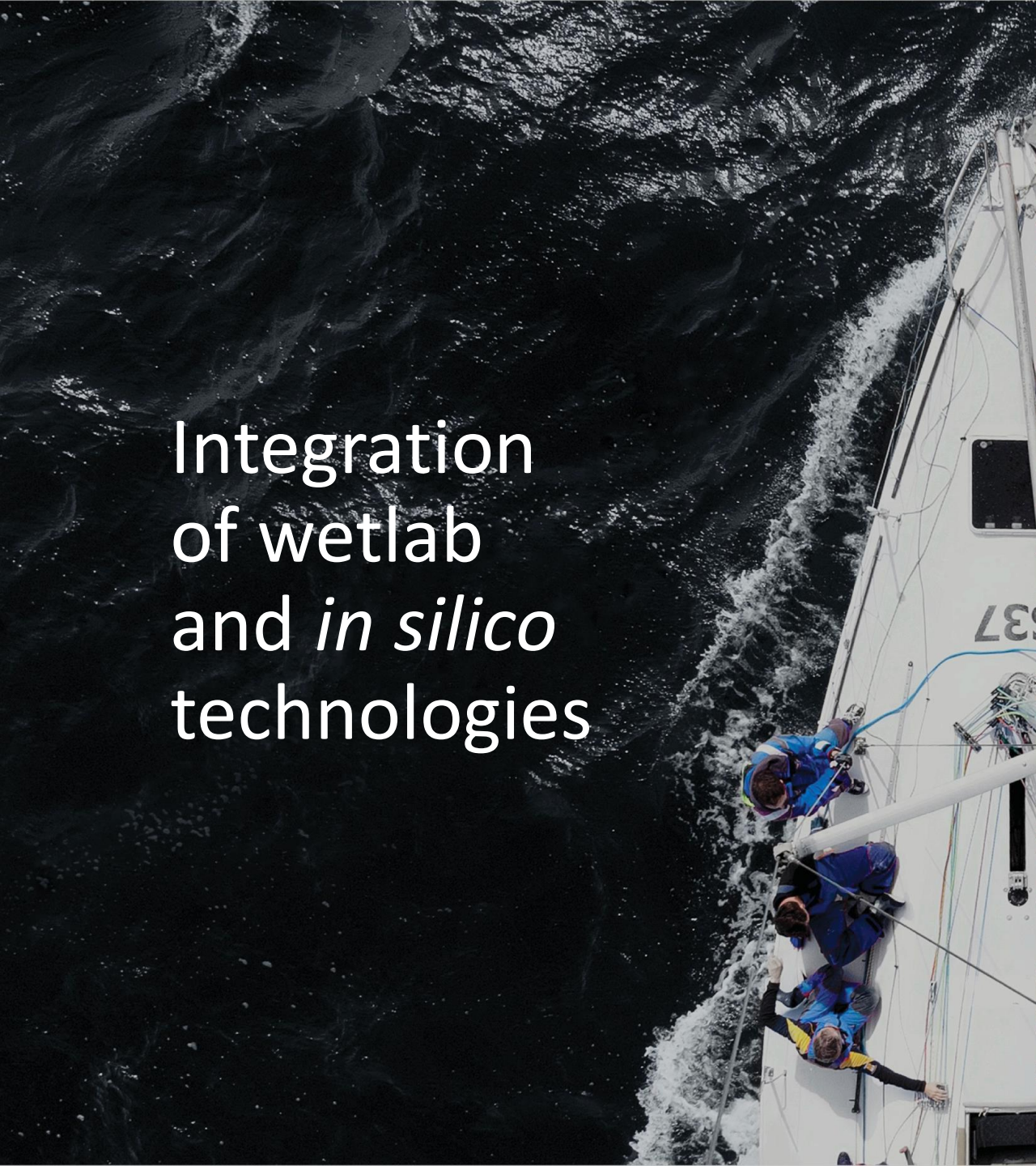
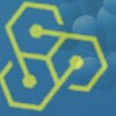




Integration of wetlab and *in silico* technologies





EXPERIENCE ^{is} IPA

95% of top 20
pharma as clients

#1 globally
ranked antibody
discovery CRO

End-to-end

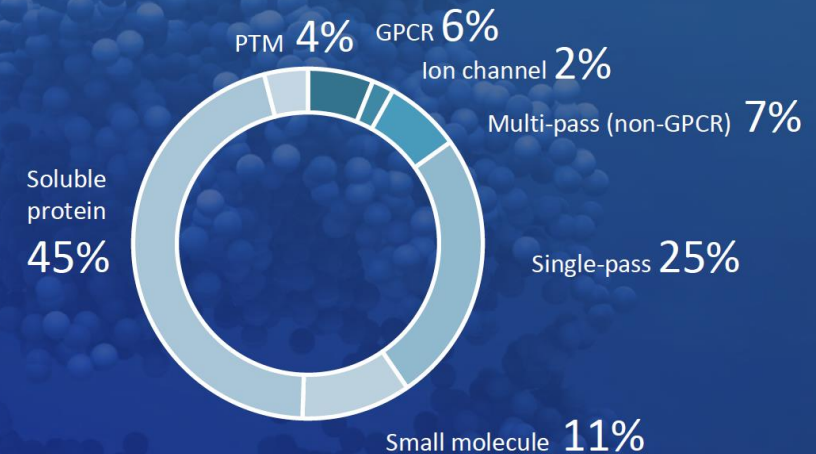
Total number of
monoclonal antibody
programs

>3,000

Total number of
monoclonal antibody
programs since 2020

>300

Target Category
Breakdown

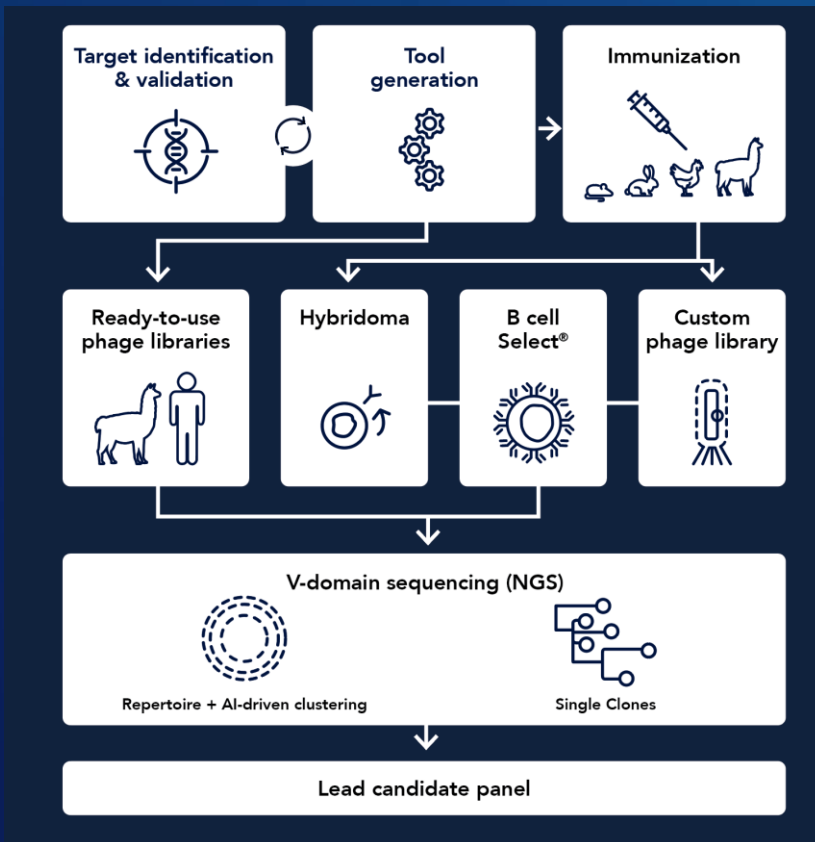


Full continuum of end-to-end services

Synergistic fusion of *in vitro*, *in vivo*, and *in silico*

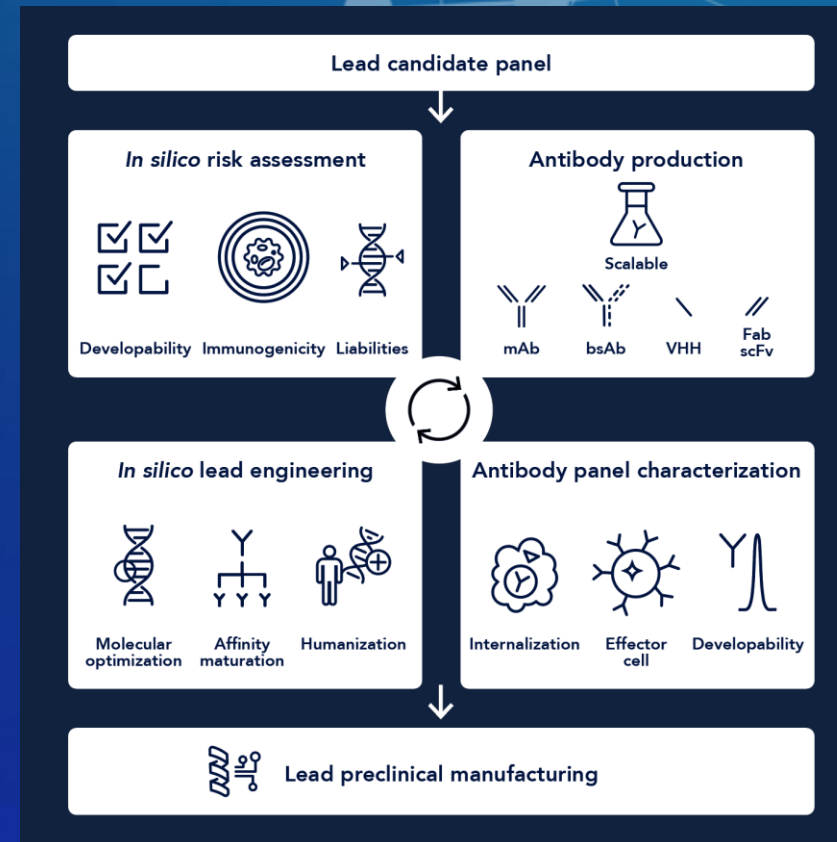
Discovery

Focused on diversity



Development

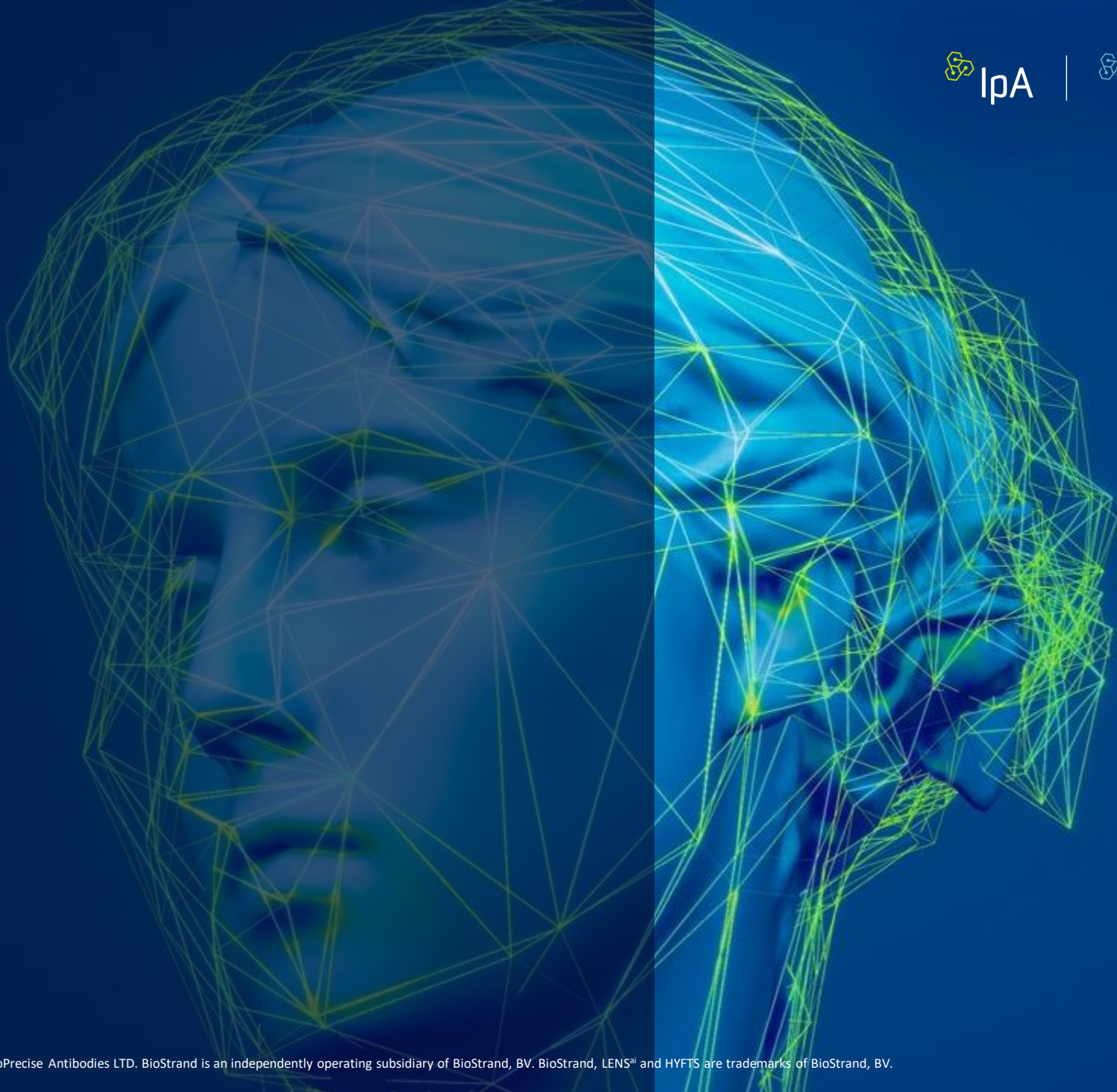
Focused on down-selection & de-risking



Powered by customization and expertise

Target Validation

Antigen and indication using RAG



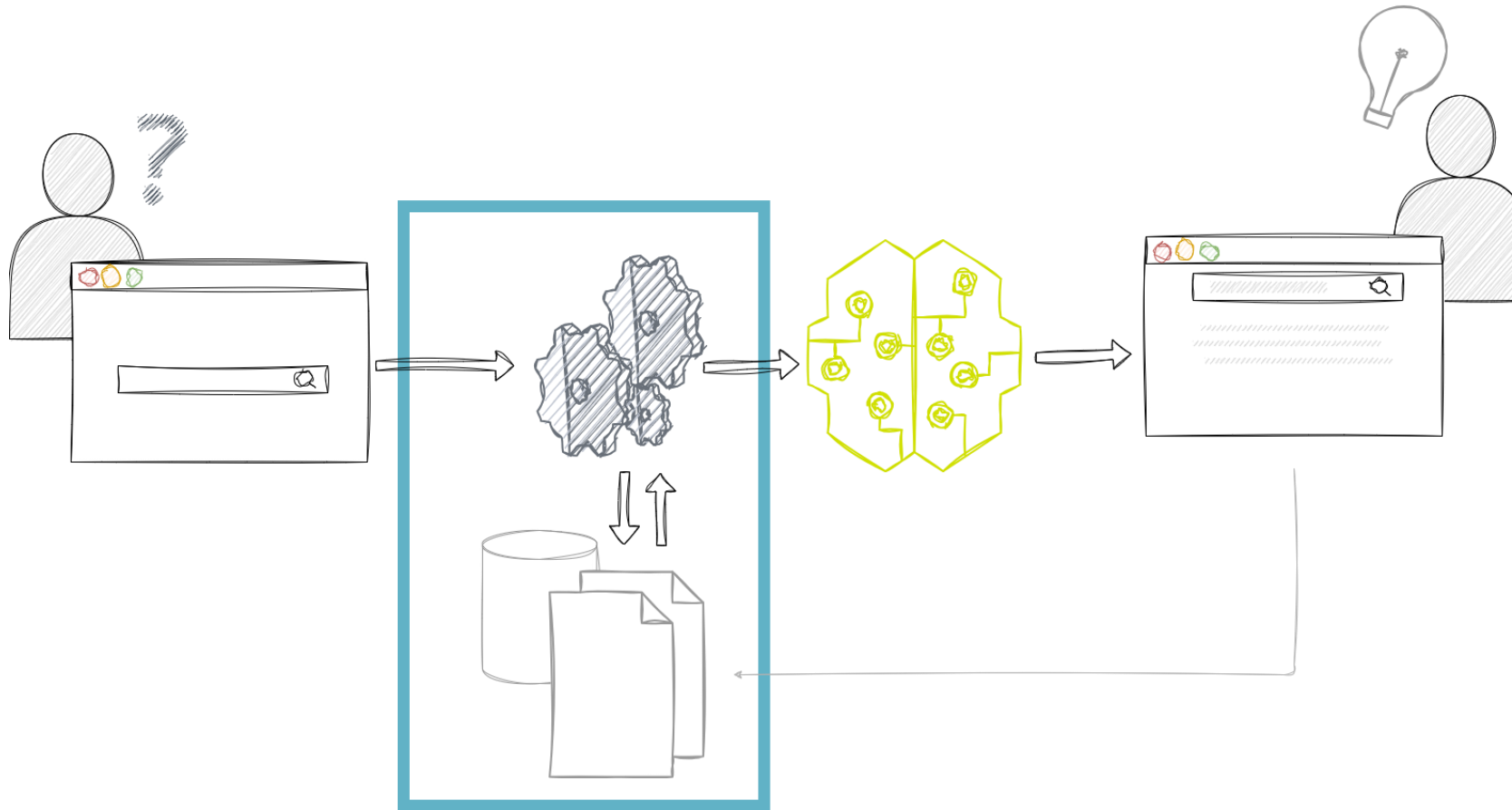
Retrieval Augmented Generation (RAG)

Improve the lookup process when selecting antigen and indication

Understanding

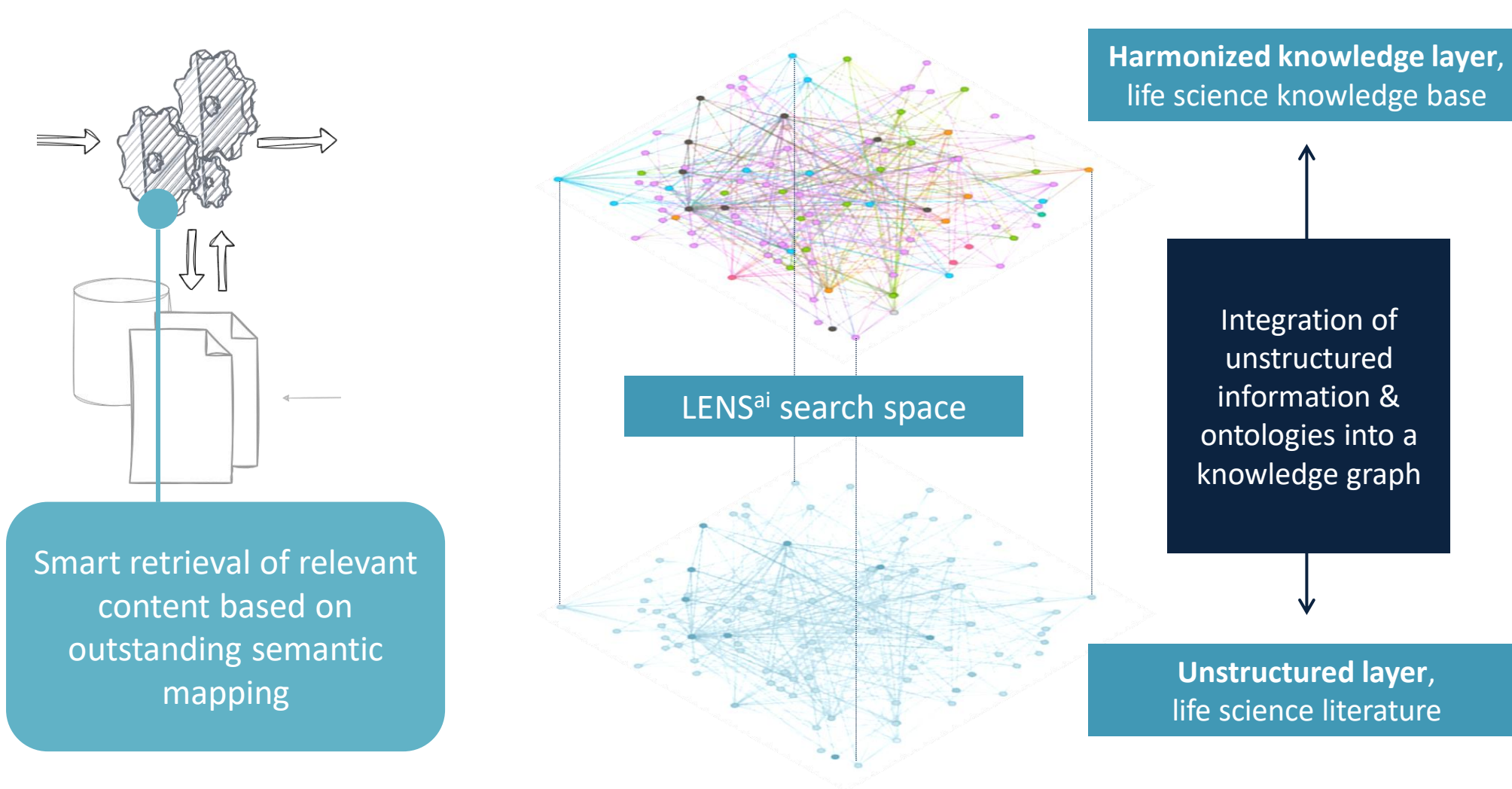
Retrieval

Answer generation



Smart retrieval of relevant content

Querying a harmonized life science knowledge layer



Correct indexation of knowledge

Through a semantic first approach



Improve Search

Query:

Accurate semantic breakdown to improve retrieval of specific and relevant documents

Dictionary - Ontology

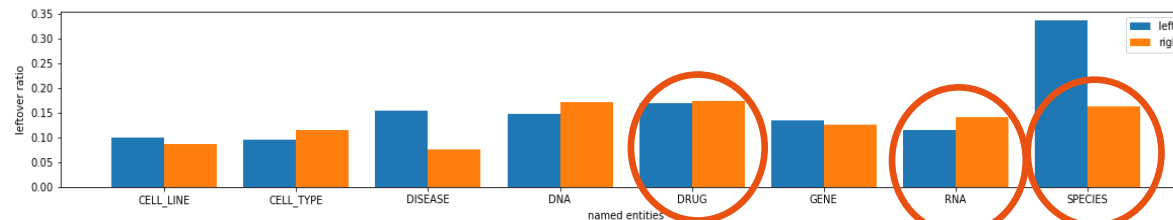
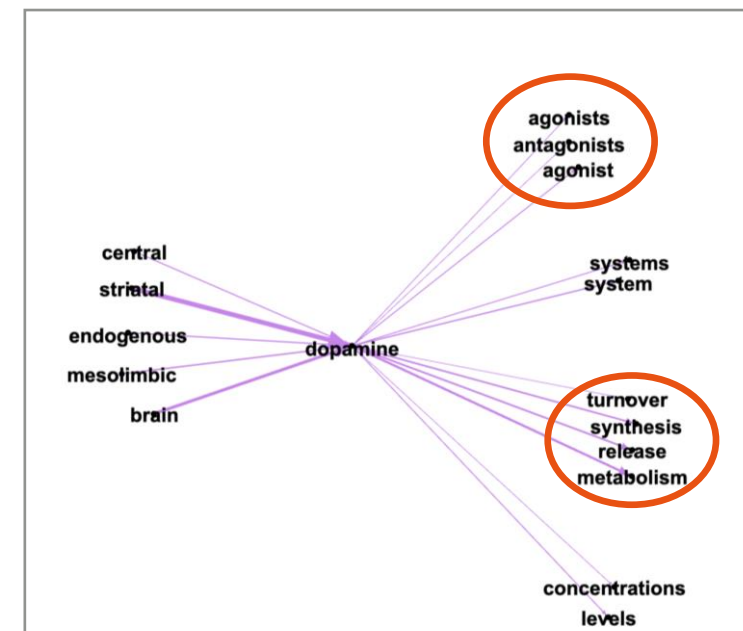
"Dopamine"
(Small molecule)

"Dopamine receptor"
(Drug Target)

"Dopamine receptor antagonist"
(Chemical drug)

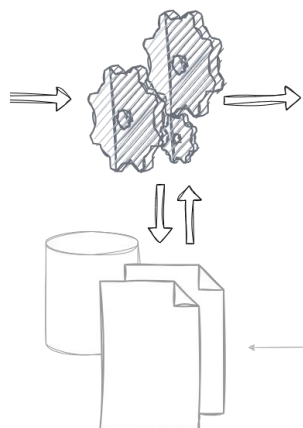
"Dopamine receptor gene"
(Gene, molecular sequence)

"Dopamine receptor gene mutation"
(Physiological process)

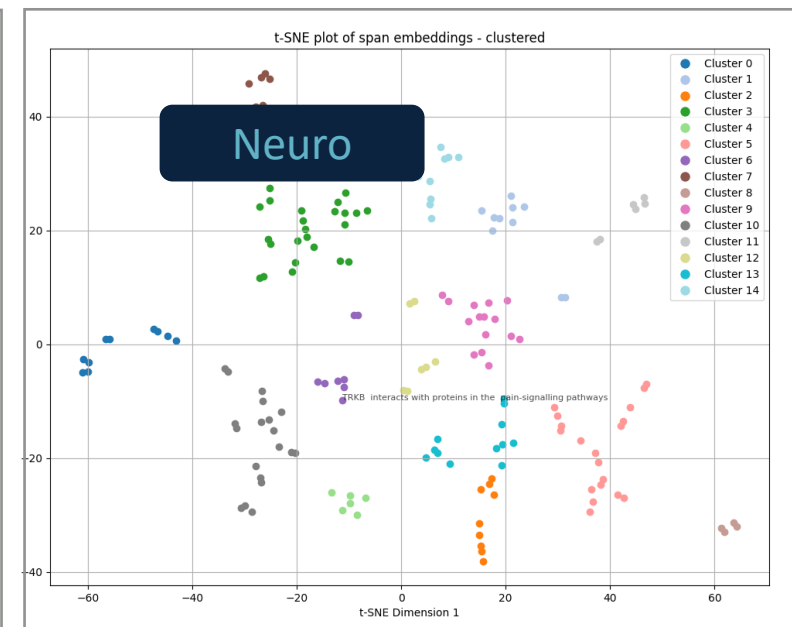
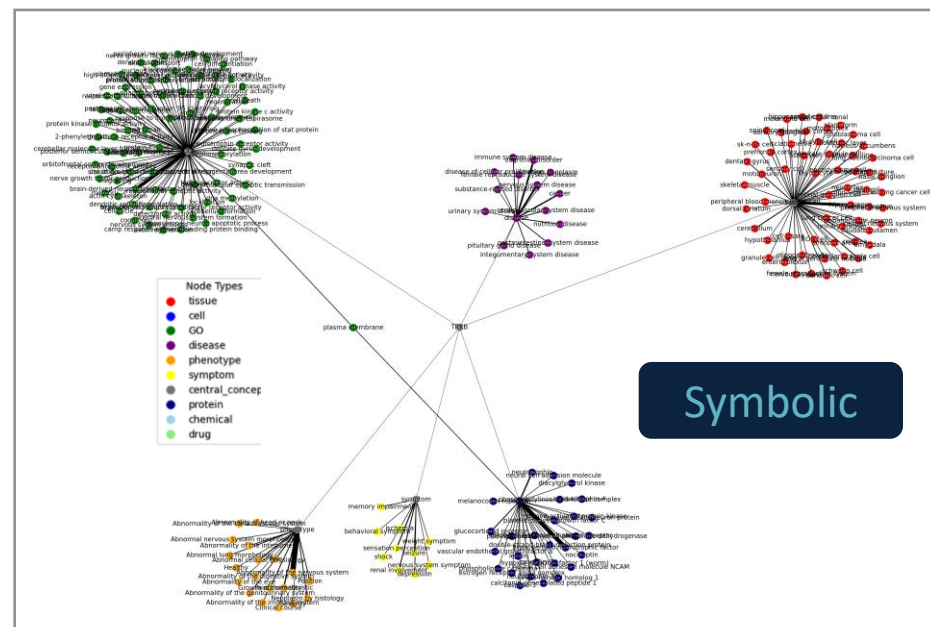


Safeguard close semantic similarity to the question

Define the closest embeddings using a combined approach



Smart retrieval of relevant content based on outstanding semantic mapping

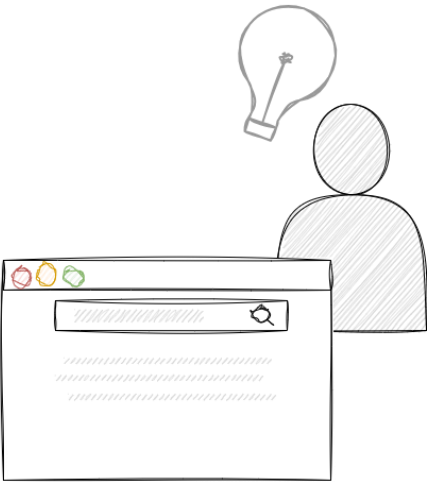


Combining formal knowledge with embeddings

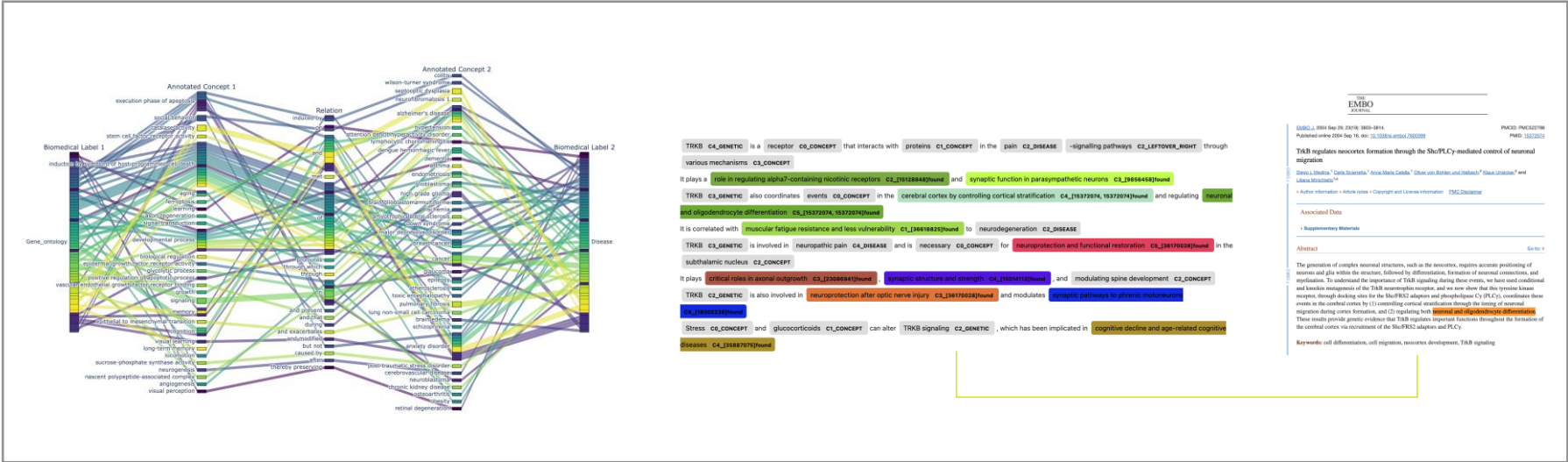
Smart retrieval of relevant content

Querying a harmonized life science knowledge layer

Linking target – protein – indication



Smart retrieval of relevant content based on outstanding semantic mapping



Answer breakdown

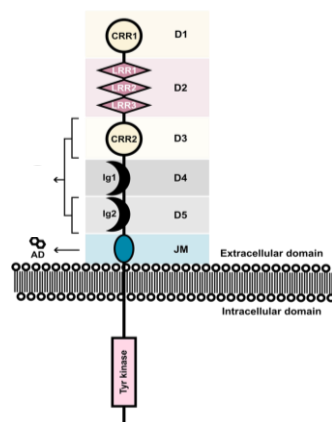
- Reference traceback on subsentence level details
- Human readable answer based massive amounts of datapoints
- Flexible integration into multiple use cases and interfaces

Building a model for your Antigen

Structural modeling of a target

Modeling complex targets: from high throughput to detailed refinements

Target is a multi-domain, heavily glycosylated protein



In general, for modelling complex targets a multi-strategy approach is required

- AlphaFold
- Template-based modeling
- Combination of multiple individual known domains
- Stability assessment

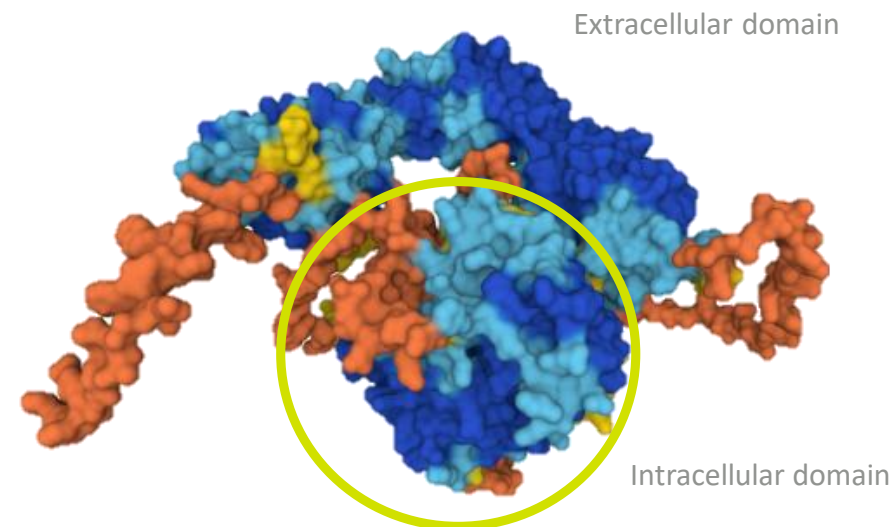
Model quality is leading

Alpha Fold

Modeling of the EC domain of target

In various regions of the protein, AlphaFold structure prediction shows low to very low model confidence.

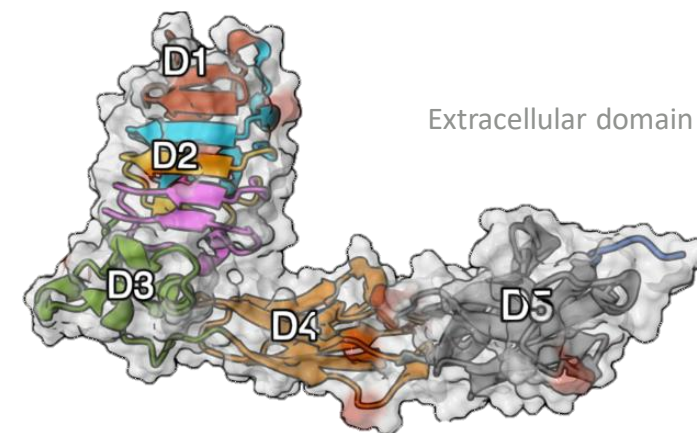
pLDDT	> 90	Very high
pLDDT	90 - 70	Confident
pLDDT	70 - 50	Low
pLDDT	< 50	Very low



Template-based

Modeling of the EC domain of target based on family member model

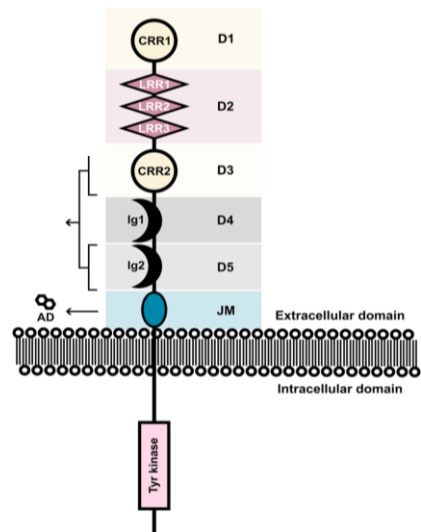
family member model (resolution X-ray diff 1.84 Å) has the largest coverage and a seq. identity of 37,8% with respect to target EC.



Epitope prediction of a target

Excellent target models used for downstream epitope prediction

Target is a multi-domain, heavily glycosylated protein



Multiple strategies used

- B-cell epitope prediction tools
- Lookup of known epitopes

Epitope prediction

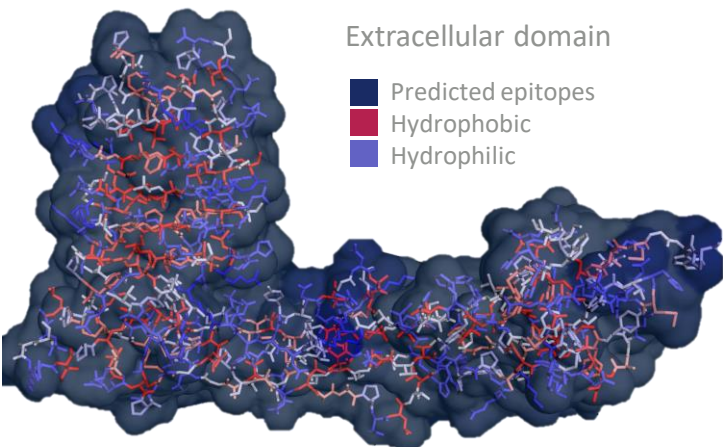
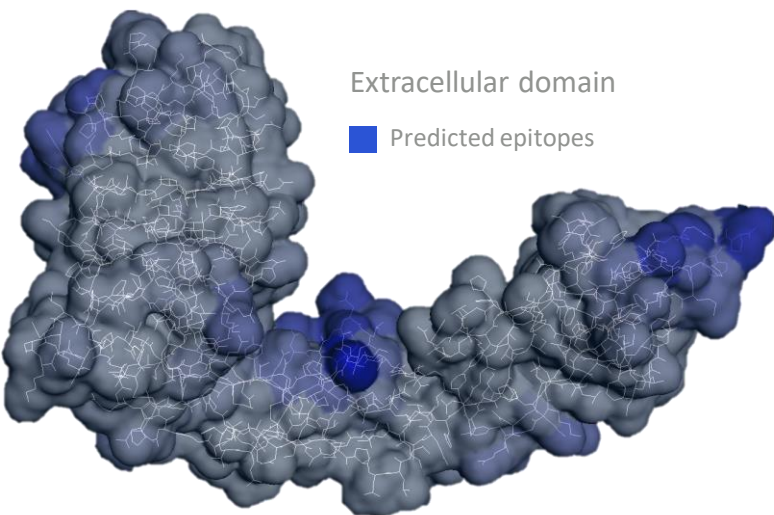
Using our target model as an input

Using AI based epitope prediction tools, we define potential binding areas on the antigen. We combine predicted epitopes with known epitopes in our final model.

Multi parameter view

Driven by sequence analysis

Overlaying various protein characteristics, we can further break down the epitope's profile. For example, hydrophobicity, surface accessibility,....



Discover Antibodies for your Antigen



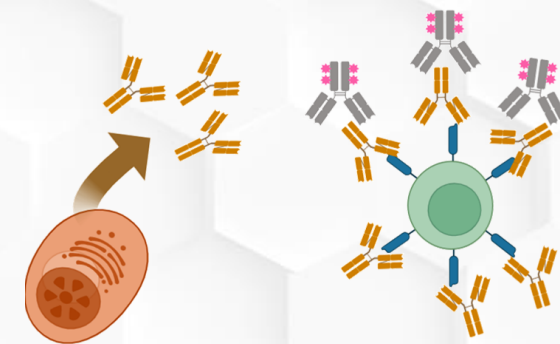
Flexible, high-throughput plasma B cell selection workflow

Plasma B cells: The opportunity to directly select B cells based on function

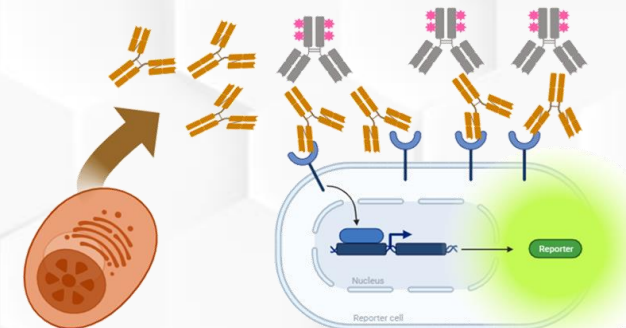
- **High-throughput** single plasma B cell isolation, up to 1 million wells/day
- Identification of antibodies that
 - **Bind** to (cell-expressed) target
 - Induce **functional** effects like receptor activation
- Integrated fluorescent microscope for **automated** hit-detection and isolation
- **Species and tissue agnostic** technology

Assay principle

Antibody binding



Target activation upon antibody binding



Repertoire sequencing and AI-driven hit prediction



IpA



BioStrand
a subsidiary of IPA

Species agnostic repertoire sequencing

Increase your lead candidate panel through the combination of our data driven discovery platforms and NGS repertoire sequencing



Human



Chicken



Rodent



Camelid



Rabbit



LLM driven functional clone prediction to select optimal leads



Repertoire analysis

High-throughput early-stage risk assessment

Increase your lead candidate panel

Example: Phage selection + screening

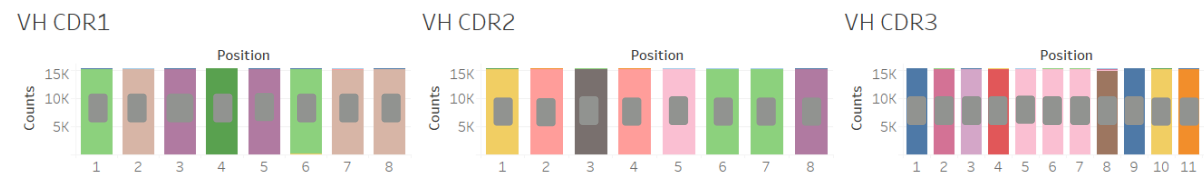
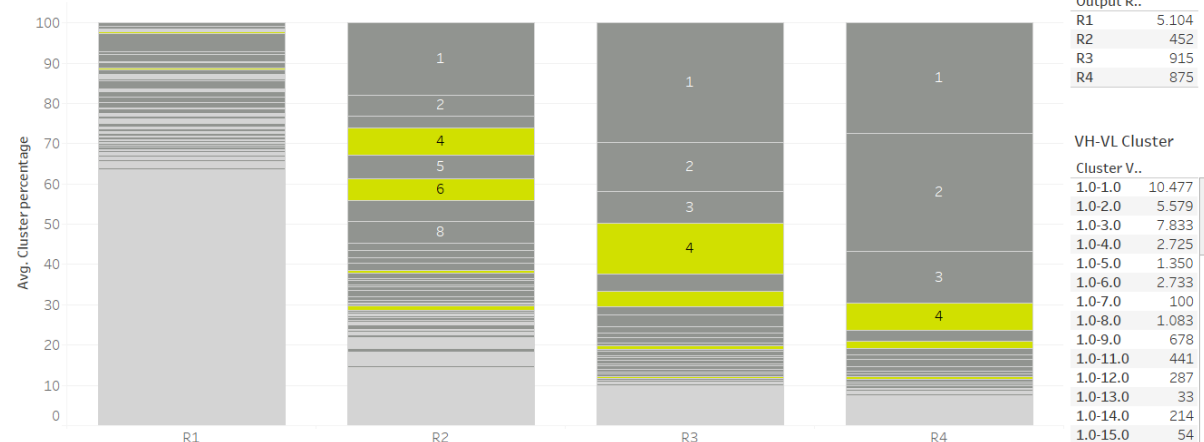
- Multiple phage selections against **recombinant** target
- Monoclonal screening on **recombinant + cell-expressed** target
- Monoclonal sequencing of **cell-reactive** clones

In-silico Repertoire screening

- Identify sequence liabilities, Immunogenic sequences,...
- AI driven Functional Clone selection

NGS Analysis

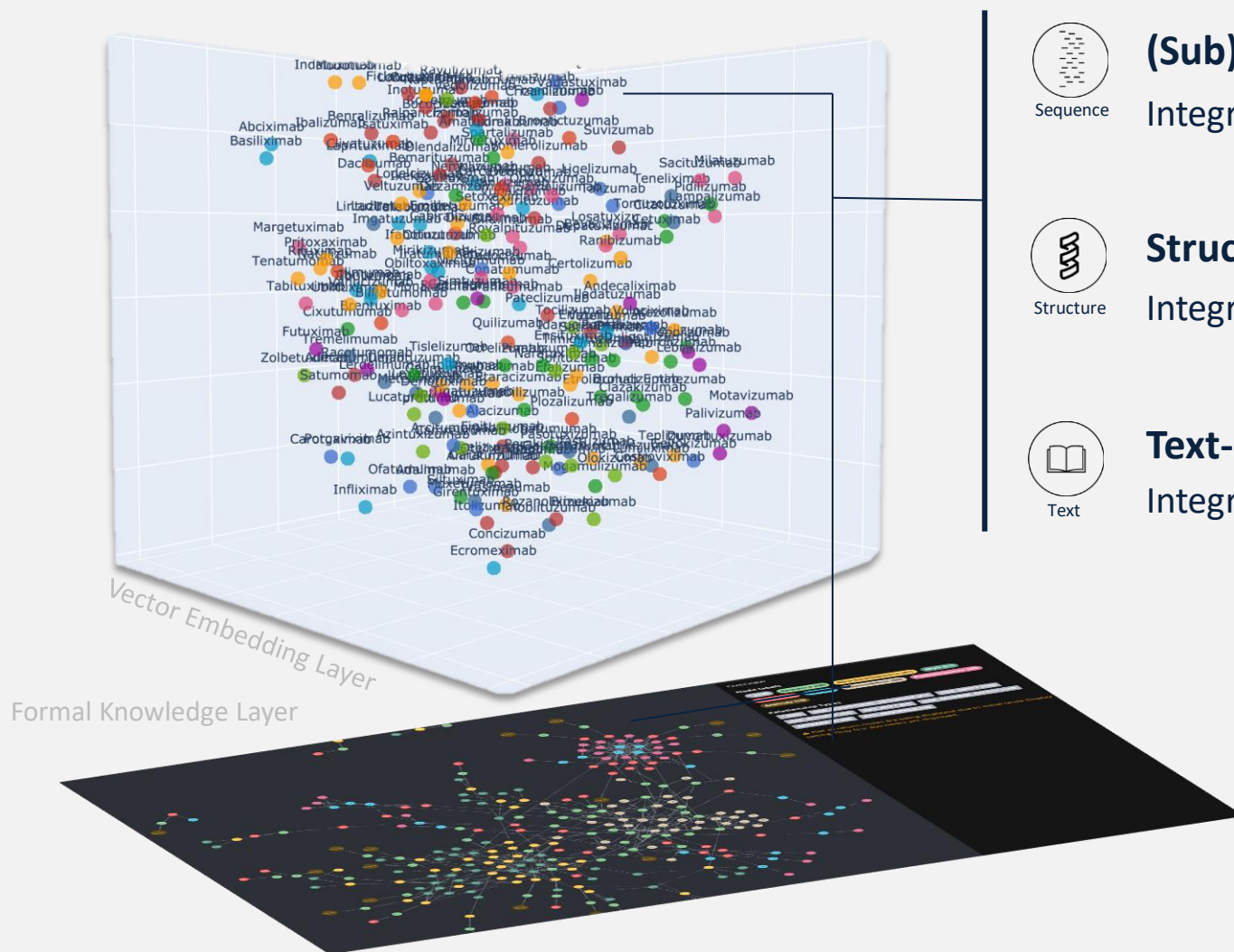
Strategy PS2B



- Clusters identified per panning
- Stacked bar graphs show frequency of VH-CDR3 clusters per round
- Sequences obtained with monoclonal sequencing are highlighted in yellow

Neuro symbolic integration to identify functional clones

Integration down to Sub-sequence level



Sequence

(Sub)sequence-based insight

Integrated sequence knowledge base and sub-sequence features



Structure

Structure-based insight

Integrated structural models and Protein language models



Text

Text-based insight

Integrated functional data extracted from documents

Leveraging integration

Optimized extraction of leads from repertoires to improve diversity and total number of suitable candidates

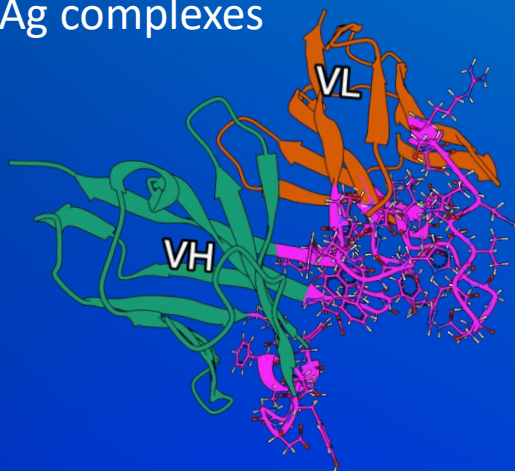
In silico prediction of epitope bins

Validation using a complex multidomain target

Next to target modeling, all antibody structures are modeled with high variable loop accuracy

Our proprietary *in silico* epitope binning algorithm considers:

- Antibody sequential and structural profiling
- Docking, accounting for steric hindrance and glycosylation sites
- Atomic interactions of Ab-Ag complexes



The result of the *in silico* meta-clustering approach

Clusters are the 'bins' predicted in silico and indicated by colors: 6 clusters are defined epitope bins are the bins determined by wet-lab assays: in total 9 bins, also counting the sub-bins



Validation of *In-silico* prediction of epitope bins

Methodology

The wet lab validation data:

	Ab1	Ab2	Ab3	Ab4	Ab5	Ab6	Ab7	Ab8	Ab9	Ab10	Ab11	Ab12	Ab13	Ab14	Ab15	Ab16	Ab17	Ab18	Ab19	Ab20	Ab21	Ab22	Ab23	Ab24	Ab25	Ab26	Ab27	Ab28	Ab29	bins	
Ab1	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab2	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab3	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab4	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab5	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab6	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab7	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab8	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab9	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab10	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1a	
Ab11	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	pb	pb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab12	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	pb	pb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab13	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	pb	pb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab14	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	pb	pb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab15	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	pb	pb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab16	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	pb	nb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab17	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab18	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	b	nb	nb	nb	nb	nb	nb	-	-	-	-	-	1b	
Ab19	nb	nb	nb	nb	nb	nb	nb	nb	pb	pb	pb	pb	pb	pb	pb	b	b	b	b	b	b	b	nb	nb	nb	-	-	-	-	-	2a
Ab20	nb	nb	nb	nb	nb	nb	nb	nb	pb	pb	pb	pb	pb	pb	pb	b	b	b	b	b	b	b	nb	nb	nb	-	-	-	-	-	2a
Ab21	nb	nb	nb	nb	nb	nb	nb	nb	pb	pb	nb	nb	nb	pb	nb	nb	nb	nb	b	b	b	b	nb	nb	nb	-	-	-	-	-	2b
Ab22	nb	nb	nb	nb	nb	nb	nb	nb	nb	nb	nb	nb	nb	pb	nb	nb	nb	nb	pb	nb	nb	nb	nb	b	nb	nb	-	-	-	-	5
Ab23	nb	nb	nb	nb	nb	nb	nb	nb	pb	nb	nb	nb	nb	pb	nb	nb	nb	nb	nb	nb	nb	nb	nb	b	nb	-	-	-	-	-	6
Ab24	nb	nb	nb	nb	nb	nb	nb	nb	pb	pb	nb	nb	nb	pb	nb	nb	nb	nb	pb	pb	pb	nb	nb	nb	b	b	pb	b	b	nb	3a
Ab25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	nb	b	nb	b	b	nb	3b	
Ab26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	b	b	b	b	nb	3a	
Ab27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	nb	pb	nb	b	b	nb	3b	
Ab28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	nb	pb	nb	pb	b	nb	3b	
Ab29	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	nb	nb	nb	nb	nb	b	7	

Validation method:

The clusters determined by *In silico* prediction were compared with the bins, including the sub-bins as separate entities, defined via *in vitro* competition assays.

Analysis:

An inter-annotator agreement analysis (Cohen's Kappa Test) was performed using a majority consensus label mapping.

Landis, J.R.; Koch, G.G. (1977). "The measurement of observer agreement for categorical data". *Biometrics*. **33** (1): 159–174. doi:10.2307/2529310. JSTOR 2529310. PMID 843571

The validated result

Near perfect agreement

Label mapping	κ
Cluster ids → bin labels	0.925
Bin labels → cluster ids	0.842

Cluster id = the cluster number assigned to a cluster for the *in silico* method
Bin label = the bin number assigned to a bin for the wet lab method

Value reference

The value of κ ranges between -1 and 1

< 0.2: no agreement, typical values for random annotations

> 0.8: Near perfect agreement

Conclusion

- Very good agreement between the *in vitro* epitope binning and the *in silico* results.
- LENS^{ai} epitope binning can reproduce with high confidence the outcome of *in vitro* competition assays.

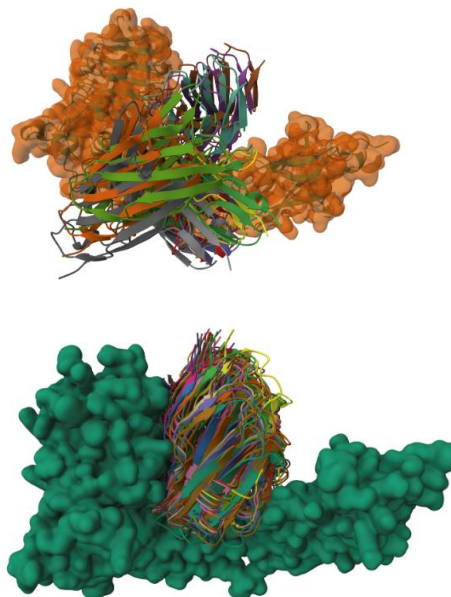
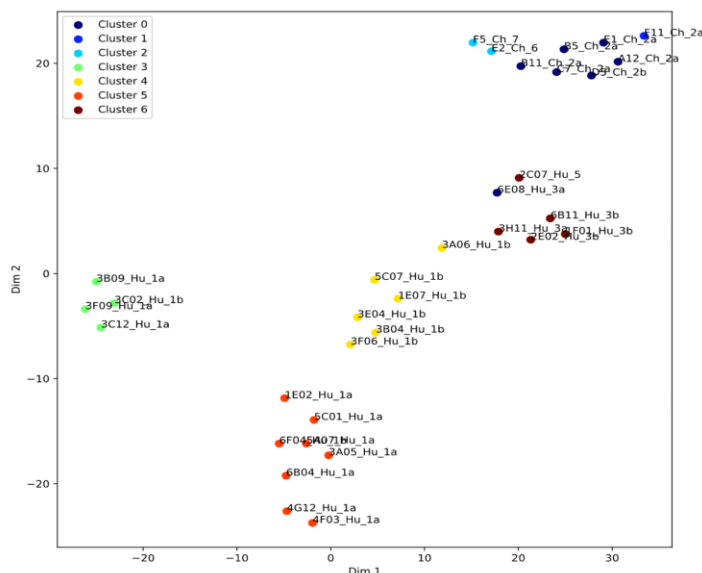
The difference in binning results between *in silico* and *in vitro* methods:

- The difference in accounting for glycosylation: full homogeneous glycosylation *in silico* versus more heterogeneity *in vitro*
- *In vitro* bins are the result of interpretation, the boundaries of bins can be difficult to determine
- Wet-lab assays used both monomeric and dimeric protein, while *in silico* binning was performed with monomeric protein only
- Steric hindrance is considered *in silico* and *in vitro* but methodology differs
- Binding strength of Abs influences *in silico* clustering

In silico epitope-paratope mapping & optimization

Full *in silico* workflow to predict epitopes and optimize affinity of your leads

In silico workflow to identify epitope bins and perform epitope mapping.



Multi-feature-based epitope mapping:

Based on Syntactical -, structural profiling and, atomic interactions to enable Affinity Propagation clustering.

Capabilities for every challenge

Targets can be challenging proteins or occur in a challenging environment. Our *in silico* workflow is made to match your challenge:

- *pH – specificity*
- *Complex proteins, including multimers*
- *Glycans*

Affinity optimization

Optimize affinity with molecular dynamics workflows and generative AI to optimize your lead molecule.

- *pH-dependent specificity*
- *Epitope specificity*
- *Binding affinity*

Engineering lead candidates: Immunogenicity Screening

Immunogenicity Screening

High-throughput early-stage risk assessment

High-throughput immunogenicity analysis

Early screening of libraries and proteins

Comparison and selection of molecule formats

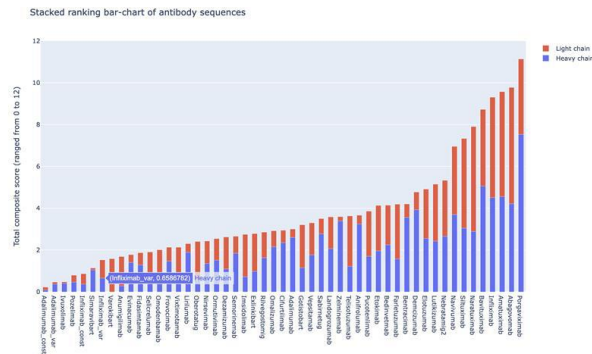
Guided re-engineering

Industry leading Data package to optimize candidate selection stages and lead selection

Integrates easily with developability screening.

Detailed reporting

- Massive data package made transparent and instantly usable



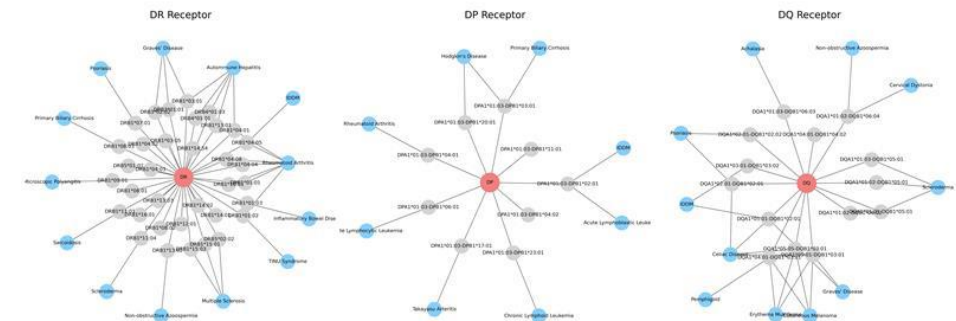
In-depth immunogenic profiling

Built for insight

- Detailed linkage between clone and target
- Geno- and phenotype binding distribution mapped to target indication profile

Connecting target, lead and clinical events

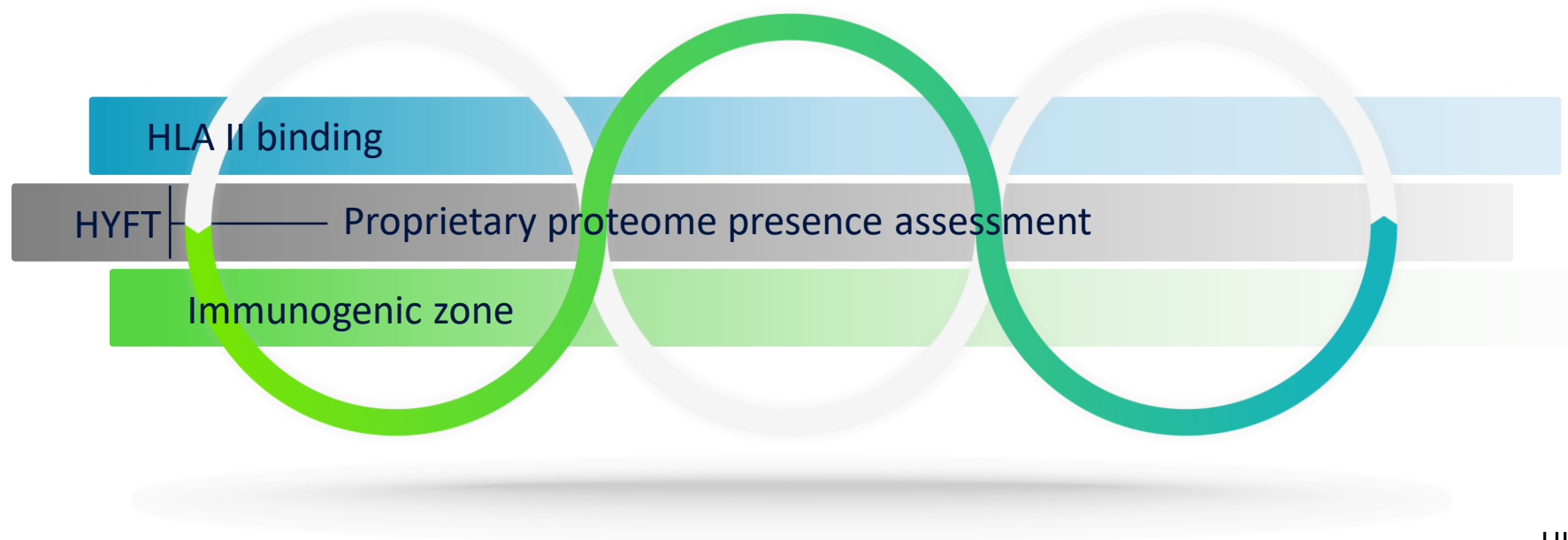
- MHCII allele Phenotypes and genotypes associated with clinical events



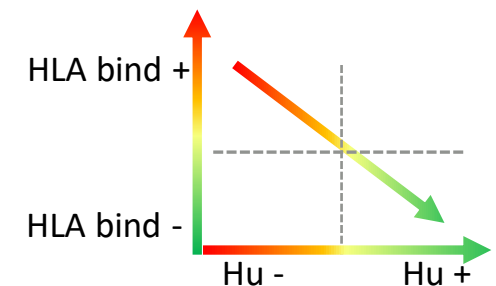
Defining immunogenic zones in sequences

Combine HLA II binding + peptide presence in human proteome

Immunogenicity calculation combines HLA II binding and human proteome presence using BioStrand's proprietary HYFT[®] technology



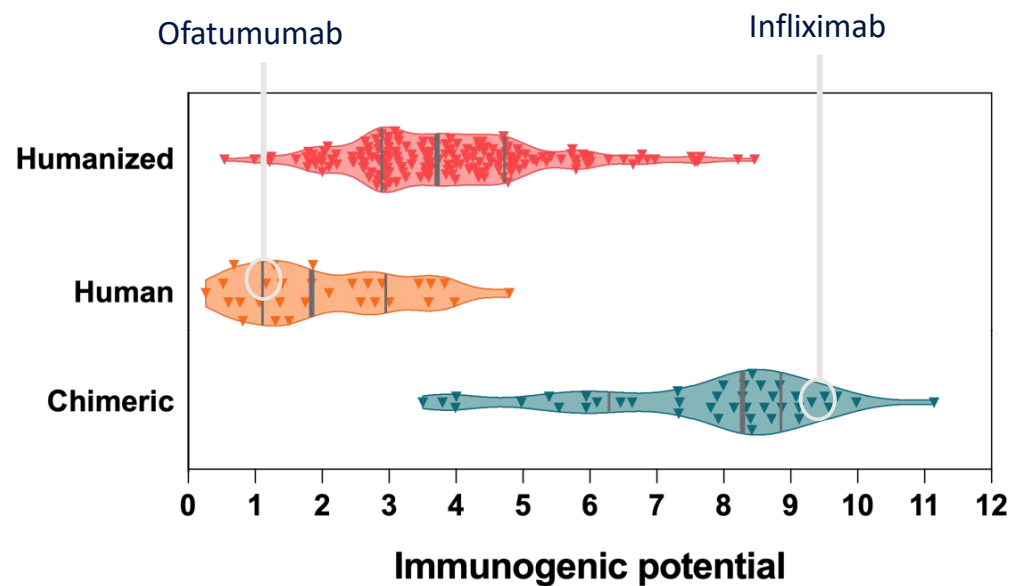
HLA II binding + no human presence:
increases immunogenicity score -> immunogenic hot spot - danger zone



Immunogenicity screening: Composite scoring

How immunogenic are YOUR (newly discovered) antibodies?

Reference your antibodies against a database of all therapeutic antibodies (>2.000)



- Early candidate selection or post humanization
- Target specific geno- & phenotyping

Immunogenicity composite scores of antibodies in the therapeutic structural Ab database (n ≈ 2000):

- Parsed based on Nomenclature (n ≈ 260)
- Statistical significance:
 - Significant difference between all means based on Kruskal-Wallis analysis [P-value: <0,0001]
 - Significant, Bonferonni corrected, difference between individual groups and Human (control group) based on Mann-Whitney [P-value: 0,0002 and better]

Infliximab VH (1)



Infliximab VL (1)



Adalimumab VH (2)



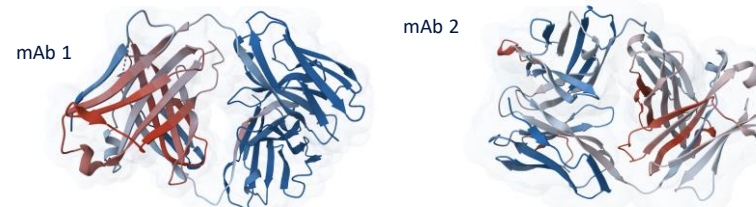
Adalimumab VL (2)



Immunogenic zones per sequence.

Normalized score showing immunogenicity hotspots by combining HYFT Universal Fingerprint proteome screening and HLA II binding scores.

: Blue = 0 = low immunogenic potential
: Red = 100 = highest immunogenic potential
: innovations based on IMGT numbering



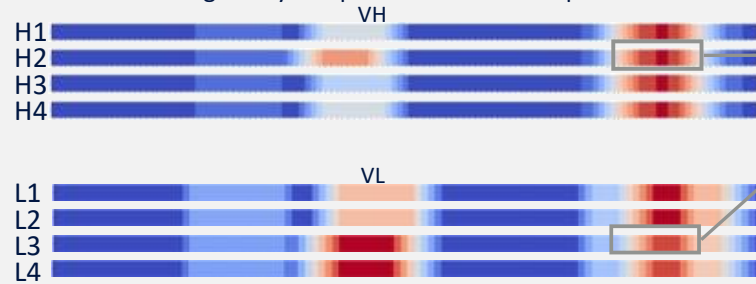
Immunogenicity screening: Contextualization

In-depth insight to guide your clinical strategy

Connecting target-specific knowledge to lead specific MHCII binding and clinical events

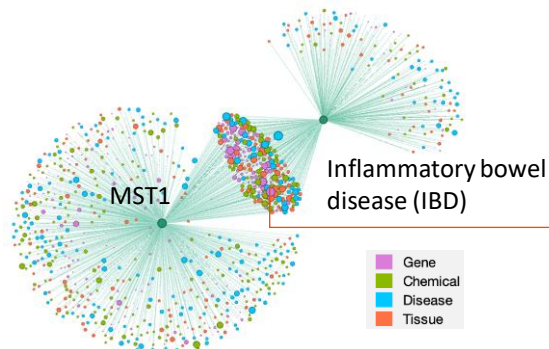
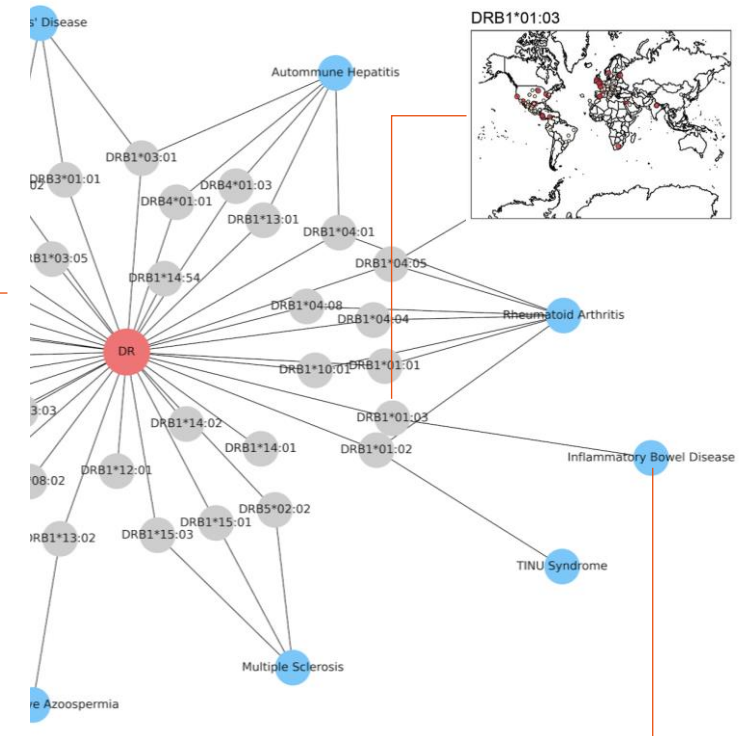
Hypothetical MST1 Binding Antibodies

Immunogenicity composite score heat map



Immunogenic hotspots
 Binding the **DRB1*01:03** MHCII allele
 Antibodies associated to **MST1**

DR Receptor



MST1 – Is linked to - Crohn's disease (IBD)

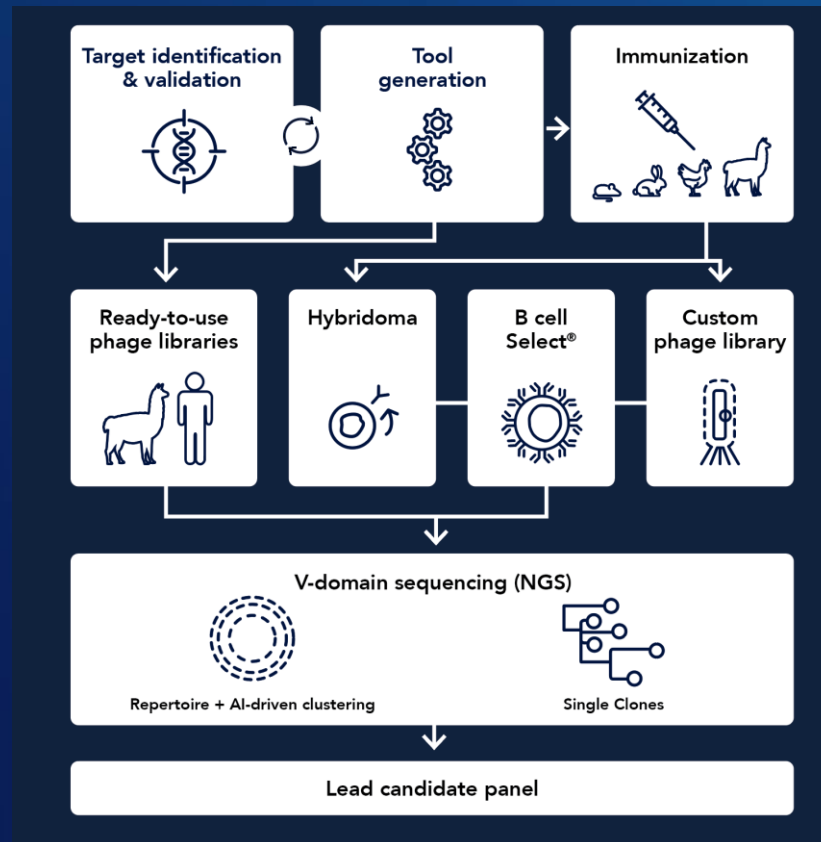
of IBD may result in part from genetic abnormalities that regulate epithelial barrier function and innate and adaptive immune responses. Crohn's disease shows strong association with CARD15, ATG15L1, and IRGM, which are involved in the innate immunity. In the adaptive immune response, IL23R, MST1, IL12B, and STAT3 polymorphisms are associated with Crohn's disease and ulcerative colitis. Current pharmacologic treatment of IBD, including 5-aminosalicylate, steroids, and immunomodulator therapy, are mainly aimed at suppressing inflammation non-specifically, except biologic therapies such as anti-tumor necrosis factor

Full continuum of end-to-end services

Synergistic fusion of *in vitro*, *in vivo*, and *in silico*

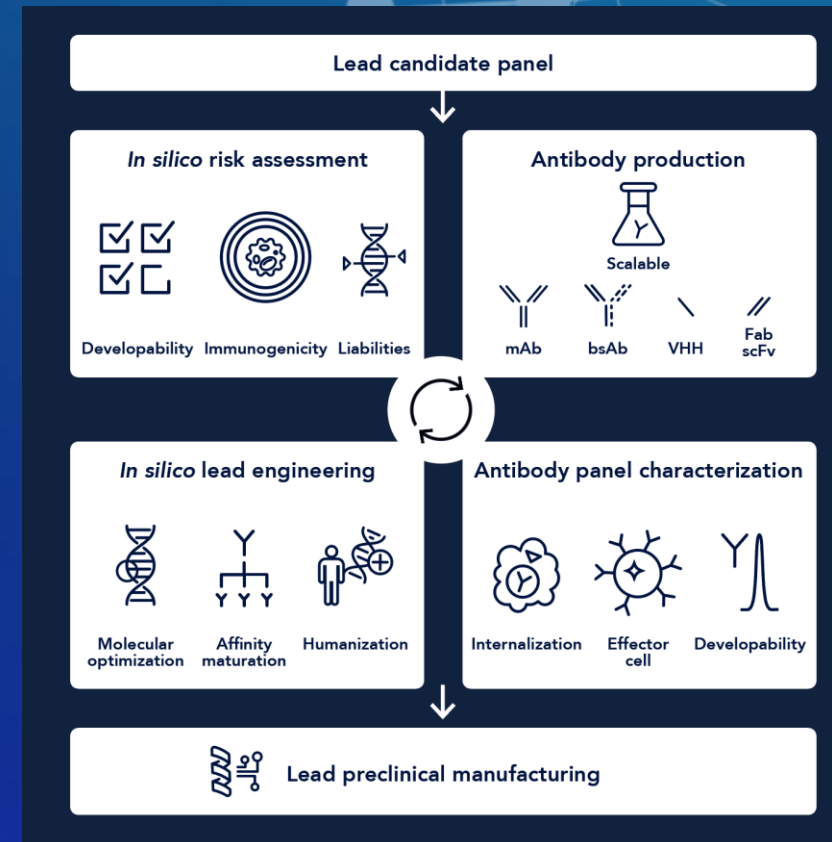
Discovery

Focused on diversity



Development

Focused on down-selection & de-risking



Powered by customization and expertise



LENS^{ai} Integrated Intelligence Technology

End-to-(no) end

Our mission is to provide a HUB of the most advanced intelligence and technology to treat diseases, bar none.



Engineered for the race
and the shared pursuit
of clinical success



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