



Antibody Drug Design by Artificial
Intelligence



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MABSilico: Rational antibody design assisted by artificial intelligence

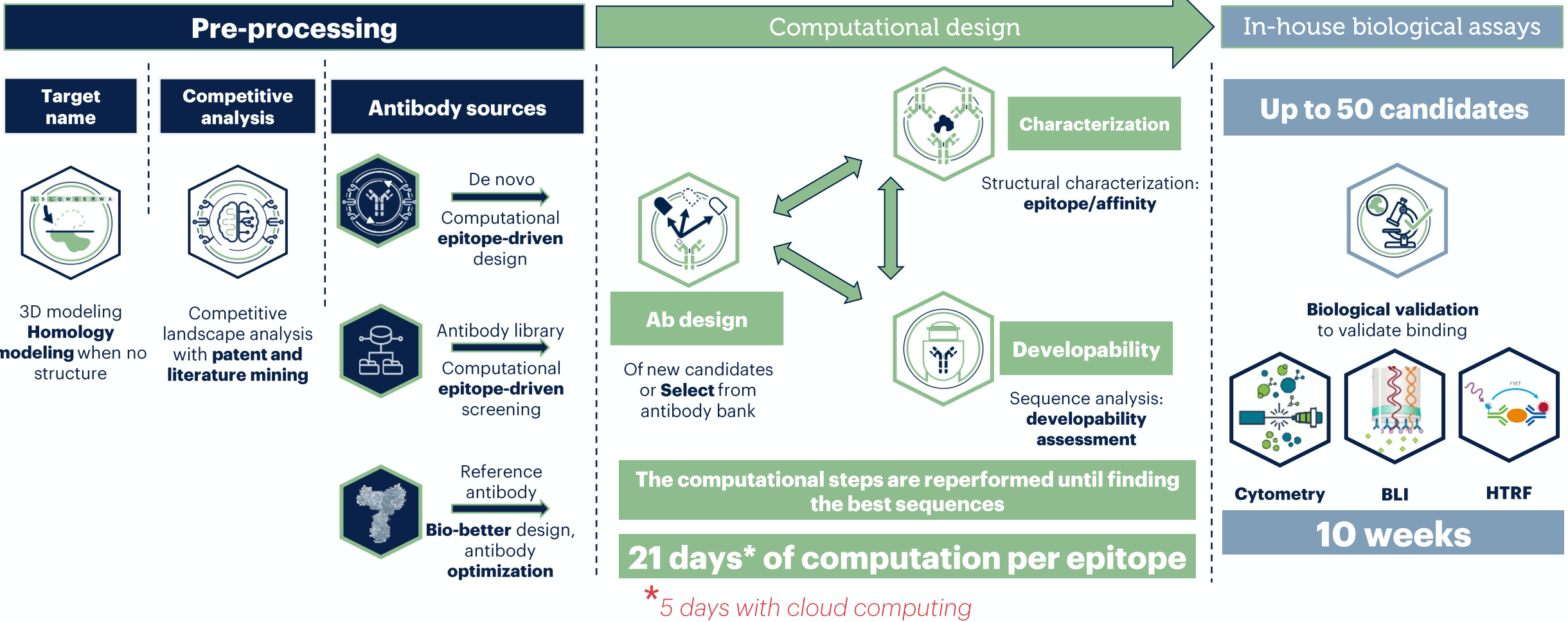
Multi-parametric approach against a selected epitope to anticipate bio-activity



- Combination of algorithms & computational solutions for design & optimization (Graph, NN, LLM,...)
- Unique structure-based, epitope-driven & multi-parametric approach
- Fail fast strategy: 21 days* of computation to test candidates



An end-to-end computational workflow for the best candidates in days



Design on predefined epitope with multiparametric assessment including affinity, cross-reactivity, aggregation, variants and isoforms



Epitope – Paratope Mapping



Computational epitope mapping

Requirements:

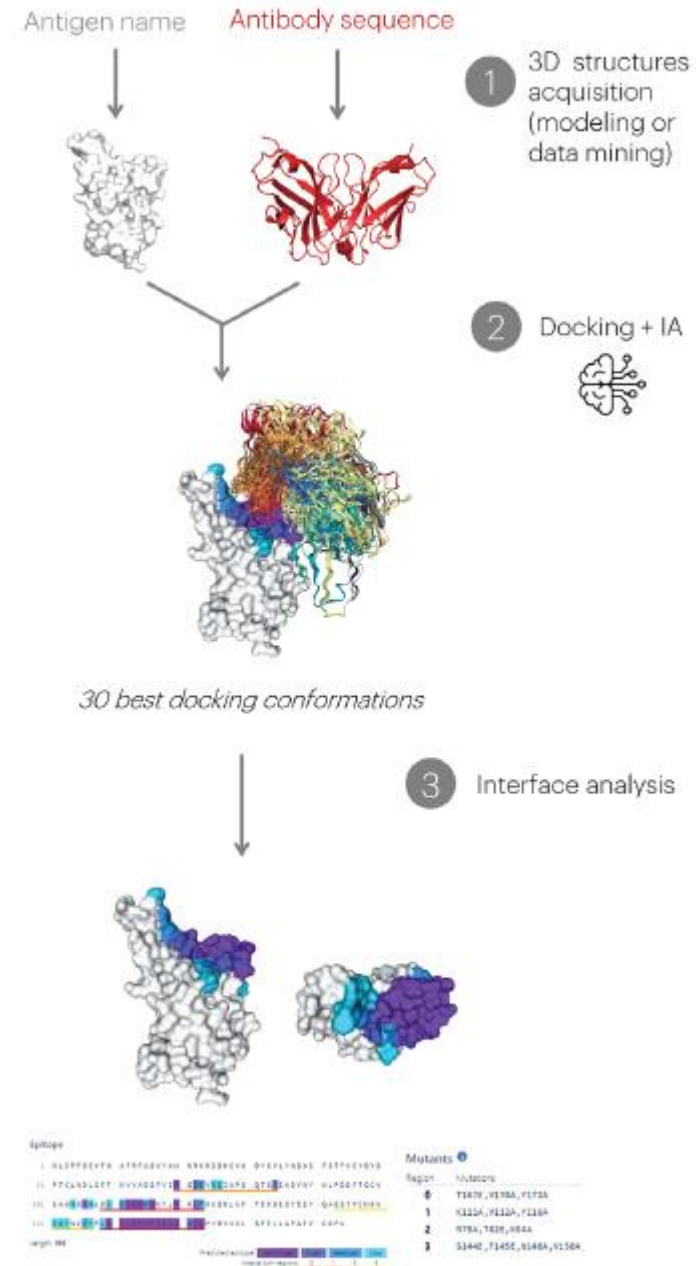
- Antibody sequence, antigen (Uniprot number)

Output:

- 3D models of antigen & antibody
- Epitope & paratope information
- Binding models
- Mutations for bio validation

Application:

- Characterization: epitope mapping
- Screening: epitope driven selection/binning
- Optimization: variant/isoform/antigen mutations



Predicted epitope residues, and proposed validating mutations



MAbTope



Examples of fast and high-throughput unbiased computational antibody characterization (epitope mapping)

	Dupilumab / IL4R α	OSE-127 / IL-7R α	Eculizumab / C5	OSE-230 / ChemR23	TNB-738 / CD38
context	<ul style="list-style-type: none"> The Dupilumab (DUPIXENT[®]) is targeting the IL4Rα and is FDA-approved for Eczema, Atopic dermatitis, Severe forms of severe asthma. Epitope was not known until 2020 	<ul style="list-style-type: none"> New Ab targeting the IL-7Rα to prevent the expansion of pathogenic memory immune cells and chronic autoimmune attacks. 	<ul style="list-style-type: none"> Eculizumab targets the complement C5 and is indicated in nocturnal paroxysmic hemoglobinuria (NPH) and in atypical hemolytic and uremic syndromes (aHUS). The epitope was only partially solved and did not explain the biological observations (absence of interspecies crossreactivity) 	<ul style="list-style-type: none"> New Ab targeting ChemR23 (GPCR) which is overexpressed at the inflamed site of IBD, Arthritis, CLE, ANCA vasculitis, Asthma, Sepsis, COPD, ARDS, CHP, COVID-19 New concept in the management of severe & chronic inflammation 	<ul style="list-style-type: none"> New biparatopic Ab targeting CD38, constituted of 2 moieties: F11A and F12A CD38 is an enzyme highly and uniformly expressed on multiple myeloma (MM) cells, but not normal lymphoid and myeloid cells. It catalyses synthesis of nicotinamide and cyclic ADP-ribose (second messengers) from NAD⁺ (nicotinamide adenine dinucleotide)
MAbTope prediction				 X-ray	1 target, 2 Ab: 2 epitopes
Wet-lab	Experimentally validated residues (MabTope cytometry) vs Crystallography (PDB: 6wgl)	Peptide array vs HDX	Experimentally validated residues (peptide array) vs HDX vs Crystal. (pdb 5i5k)	Experimentally validated peptide (ELISA)	Experimentally validated residues (MabTope cytometry) vs Crystallography (PDB: 7vke) known competing Ab: Isatuximab (PDB: 4cmh)
	 <i>Tahir et al., 2021</i>	 <i>Lyssia et al., 2018</i>	 <i>Brachet et al., 2017</i>	 <i>Trilleaud et al., 2021</i>	 <i>Ugamraj et al., 2022</i>



Multiparametric Optimization



Computational affinity modeling

Requirements:

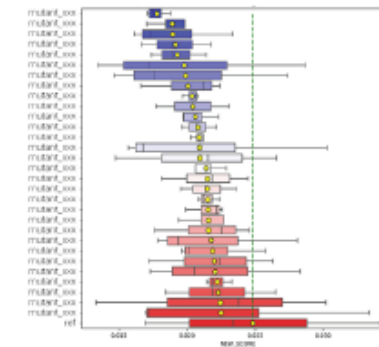
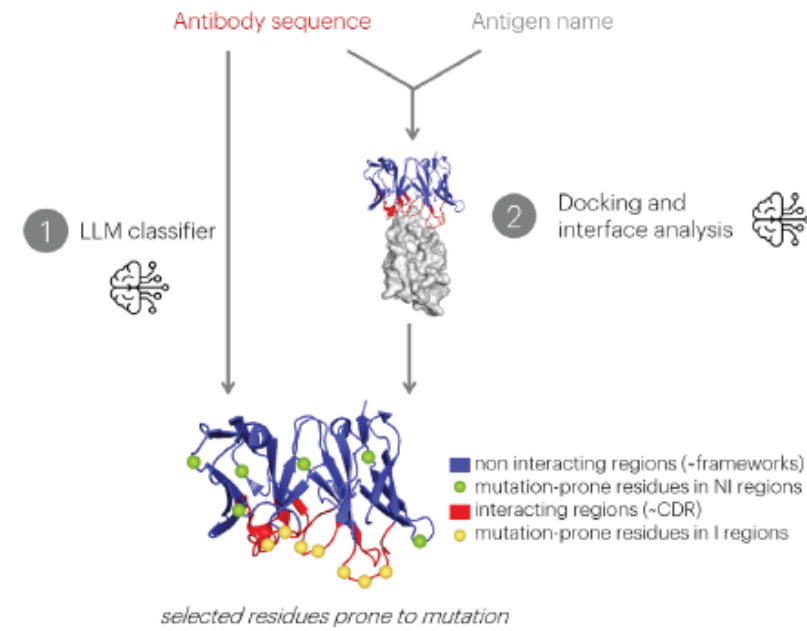
- Antibody sequence, antigen structure, epitope

Output:

- Affinity range
- dG estimation

Application:

- Characterization: affinity range
- Screening: antibody ranking
- Optimization: affinity maturation
- Design: epitope & affinity driven



MAbAffinity



Computational optimization of a chicken anti-FSH mAb

FSH

- FSH: dimeric glycoprotein hormone (α and β subunits)
- Regulates follicular development and spermatogenesis
- FSH glycosylation variants which are marker of fertility and reproductive status (premenopausal)

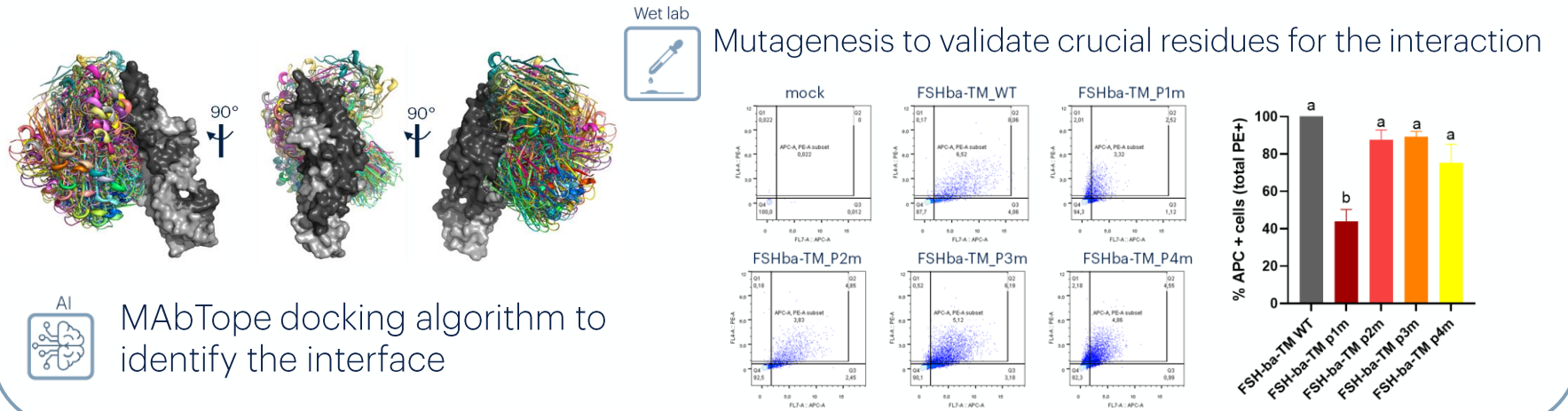
Leads

- Starting with epitope mapping of the chicken anti-FSH Y88
- 1000 mutants tested in silico (including single mutants, combinations and MD)
- **20 best sequences produced**

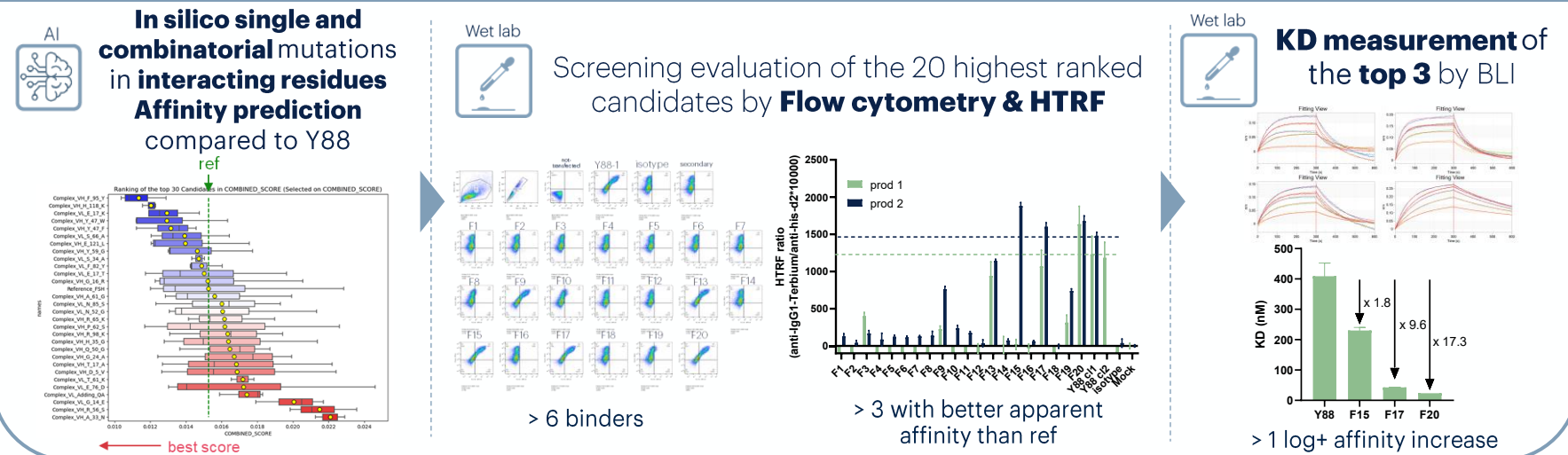
Conclusions

- ~50% of binders
- All had good production yields
- **3 sequences with improved affinity and 2 with 1 log increase in affinity**

Computational epitope mapping and wet-lab validations



AI driven affinity maturation





Developability Assessment



Computational developability

Requirements:

- Antibody sequence

Output:

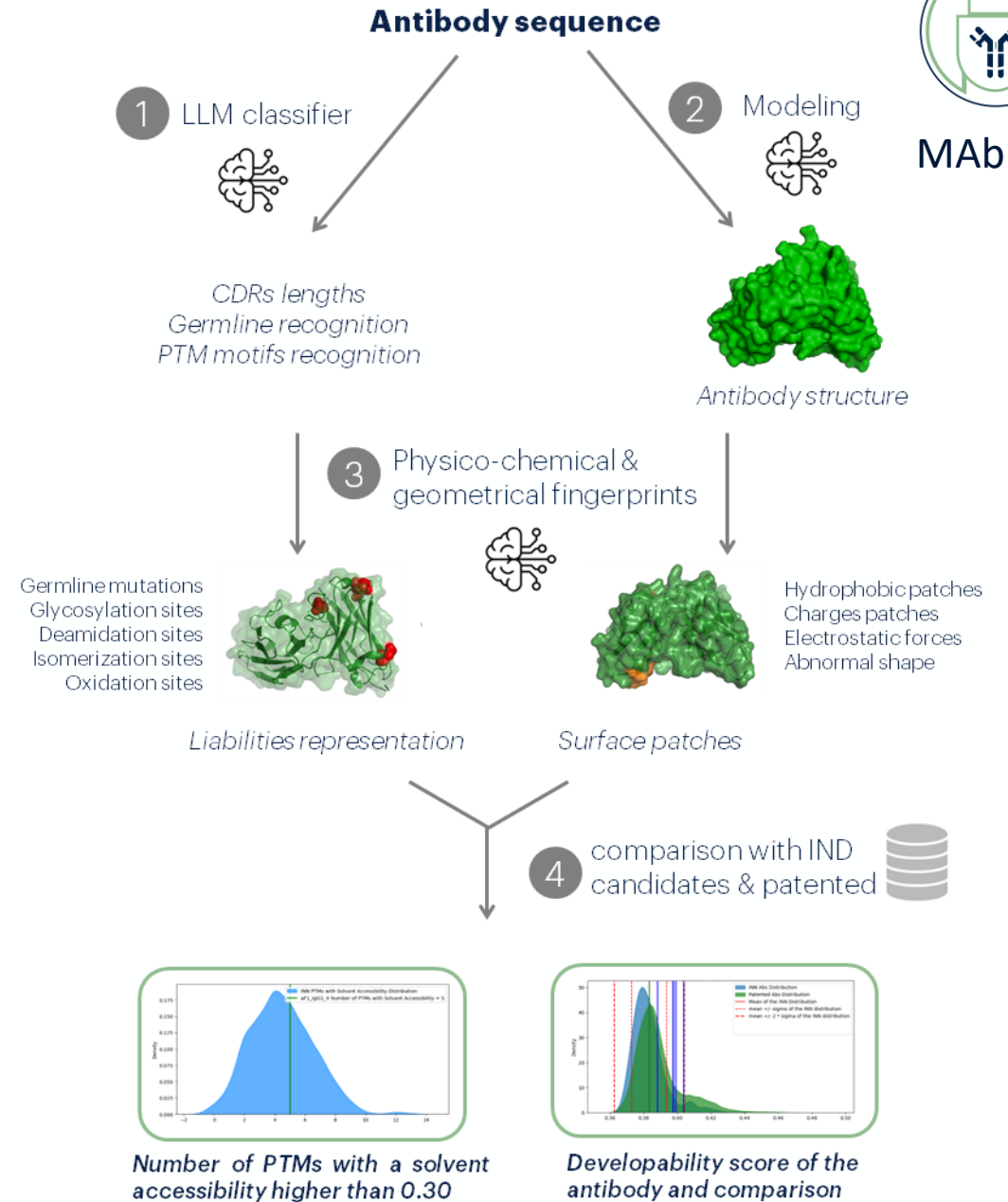
- Linear analysis:
 - CDRs lengths & Germline
 - PTM assessment
- Structural analysis:
 - Aggregation assessment
 - Off-target risk

Application:

- Characterization: developability
- Screening: selection criteria
- Optimization: improve developability

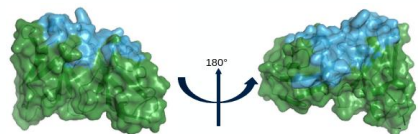
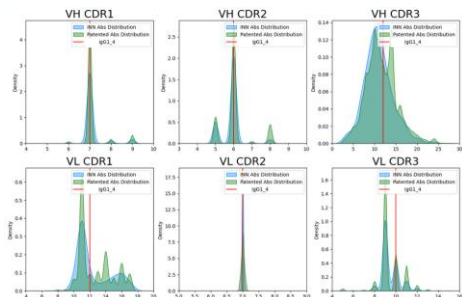


MABDev





CDRs length Analysis & comparison with INN mAbs



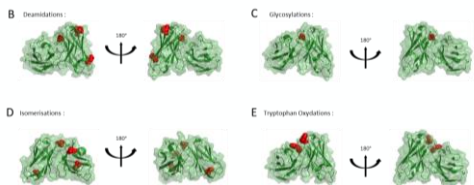
3D representation of antibody paratope. The CDRs are colored in blue, frameworks in green.

CDRs length analysis. CDRs lengths (red lines) were compared with the distribution of the CDRs length collected from antibodies which were patented (referred as “Patented Ab distribution”, in green) or reached clinical/preclinical trials (referred as “INN Abs Distribution”, in blue).

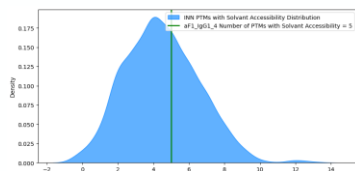
Comparison with the closest germline

Part	V-gene germline	J-gene germline	Species
VH	IGHV3-23*04	IGHJ2*01	Human
VL	IGKV3-20*01	IGKJ1*01	Human

PTMs evaluation & comparison with INN mAbs

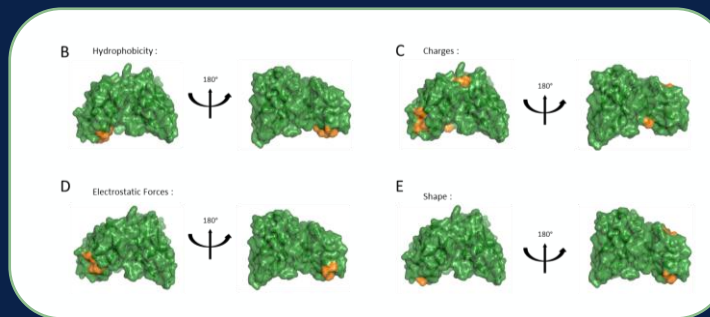


PTMs motifs identification and representation. Five PTM motifs are searched: deamidation, isomerization, glycosylation, methionine oxidation and tryptophan oxidation.



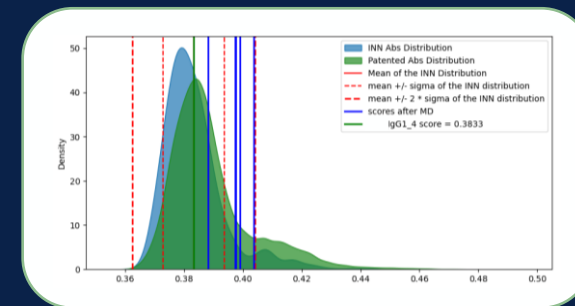
Number of PTMs with a solvent accessibility higher than 0.30 compared with the INN antibodies.

Developability evaluation & comparison with INN mAbs

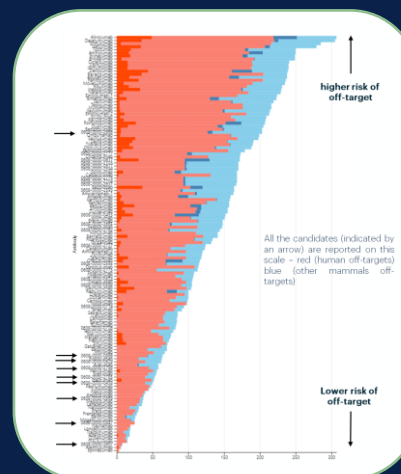


Analysis of the surface physico-chemical parameters. Surface hydrophobicity, electrostatic forces, charges and shape were computed.

Developability score of the antibody and comparison with INN and patented antibodies. The INN antibodies distribution is represented by the blue curve, the patented antibodies distribution is represented by the green curve. The Antibody score is shown by the green line. Five score values obtained for the antibody after Molecular Dynamic are shown by the blue lines. The red dashed lines show the INN distribution mean \pm 1 or 2 standard deviation(s).



Off-Target evaluation & comparison with INN mAbs



Comparison of potential off-targets (~35000 candidates and corresponding antigens) of lead candidates against approved antibodies and their corresponding adverse effects. Overall NN candidates are good candidates with limited number of off-targets (including human and other mammals off-targets)



Antibody design & Combining in vitro workflows and AI

- Use patients' immune repertoire as antibody library combined with epitope-driven selection
- De novo design by phage display screening, computational epitope driven selection and optimization
- De novo design by computational library screening with epitope and affinity selection

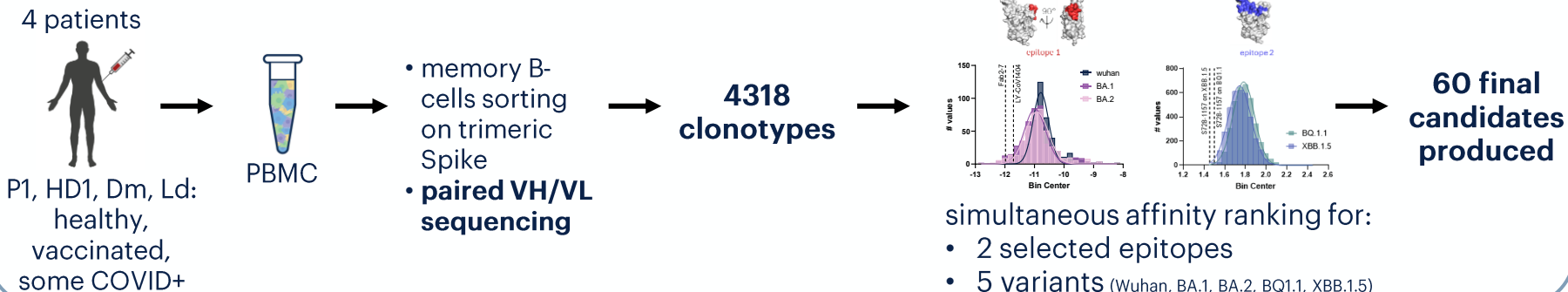


Use patients' immune repertoire as antibody library combined with epitope-driven selection anti-SARS-CoV-2

Context

- Cross-neutralizing IgG isolated from patients as starting Ab
- in silico finding of new sequences in **immune repertoires isolated of 4 patients (vaccinated, and Covid+ or Covid-)**

Humabdiag platform: from patients to effective antibodies



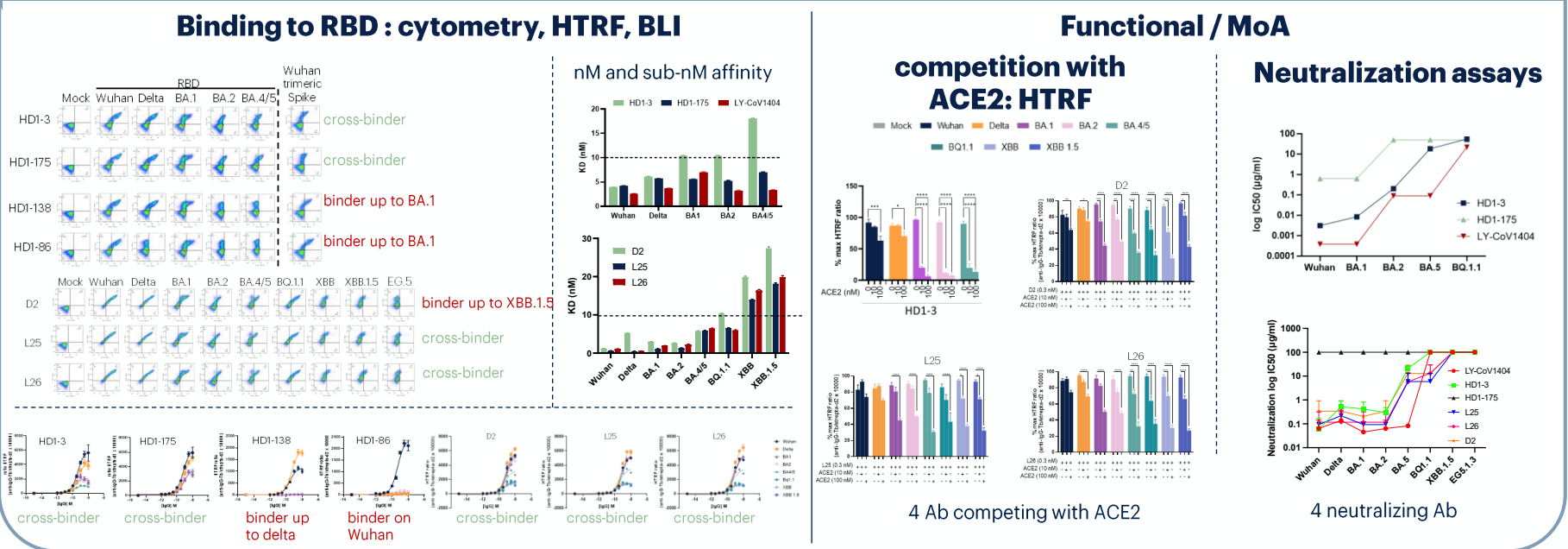
Candidates

- 4318 clonotypes evaluated
- 60 candidates produced as IgG
- 20 binding antibodies
- 7 strong binders
- 5 cross binders with nM or sub-nM affinity
- 4 neutralizing antibody

Biological validations of candidates using on RBD proteins & virus

Conclusions

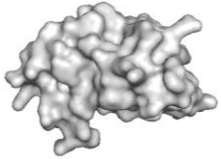
- Potential therapeutic cross-neutralizing mAb
- Ab discovery platform unique in the world combining patients' samples combined and AI to find and design Ab





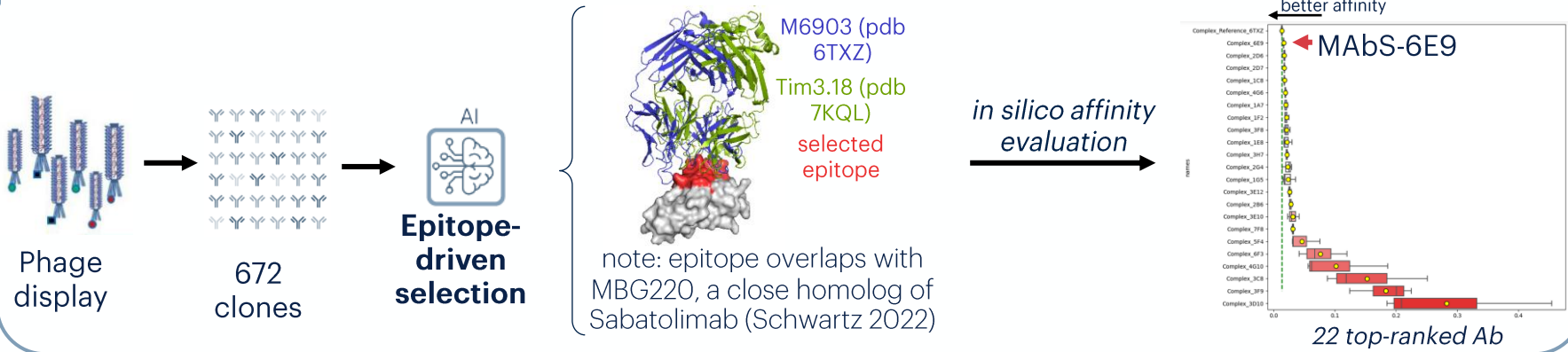
De novo design with phage display & computational epitope driven selection of anti-TIM3

TIM3



- Cell surface receptor
- Implicated in modulating innate and adaptive immune responses.
- T-cell checkpoint inhibitor

Computational epitope driven selection and optimization



Leads

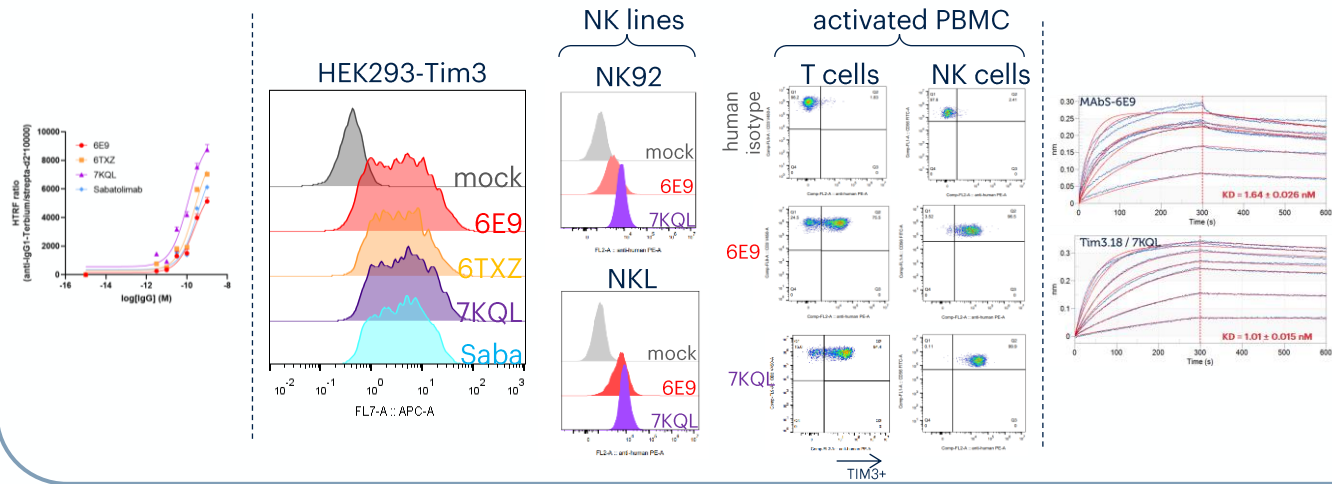
- Original: M6903 (6TXZ) and Tim3.18 (7KQL)
- **New: 1 antibody + genus**

New anti-TIM3 with binding properties comparable to SoTA

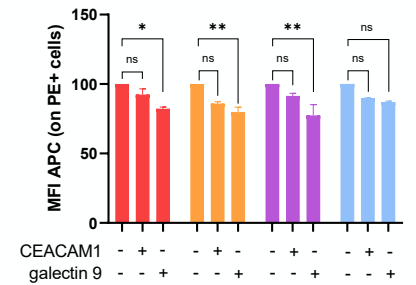
Conclusions

- Binder with same properties as references
- Could have less adverse effects

Binding : HTRF, cytometry, BLI



Competition with ligands: cytometry



Functional: ongoing



De novo design with phage display & computational epitope driven selection of anti-CD36

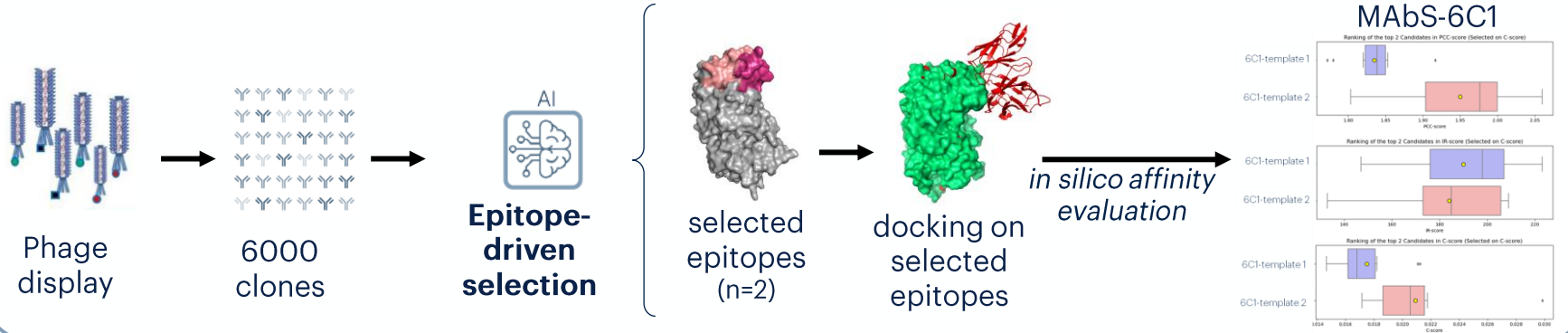
CD36



• Multifunctional glycoprotein

- Cell membrane
- Major target for cancer, such as atherosclerosis, non-alcoholic fatty liver disease, and diabetes

Computational epitope driven selection and optimization



Leads

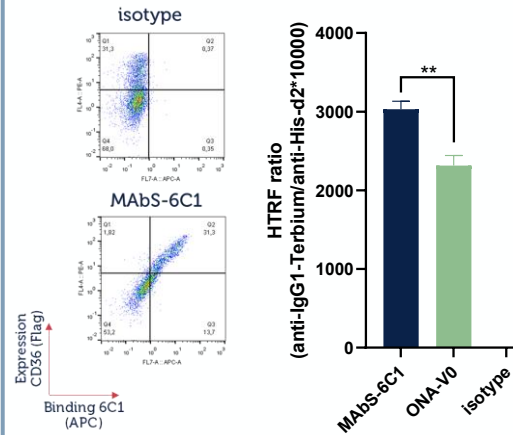
- ONA-0 epitope
- **New: 1 antibody + genus**

Conclusions

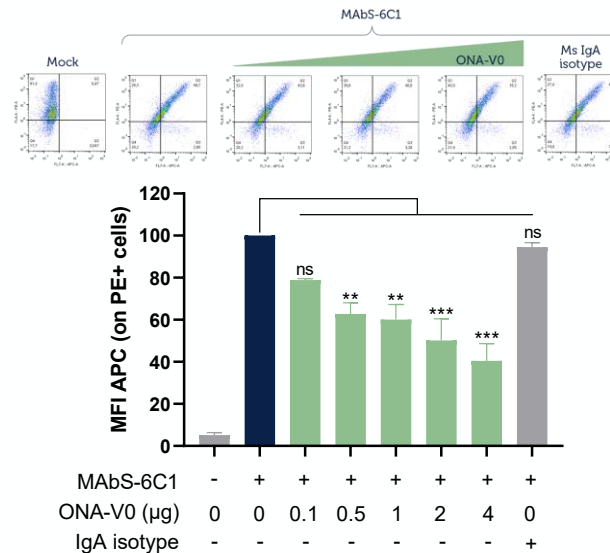
- one antibody with overlapping epitope with ONA-V0
- seem to display better binding properties and functionality

New anti-CD36 competing with ONA-V0

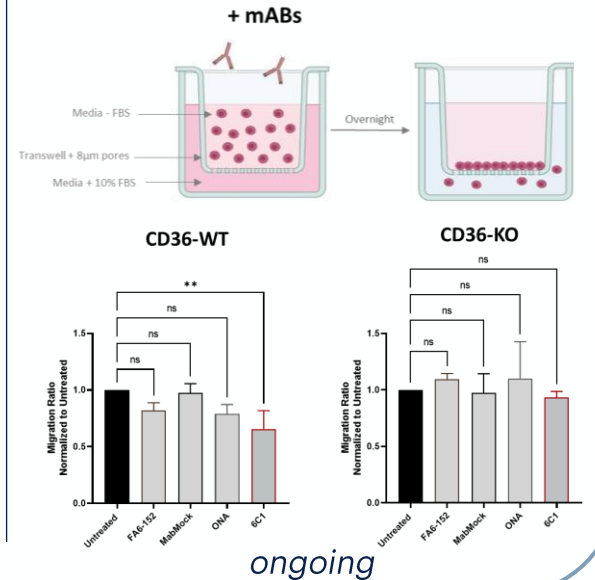
Binding : cytometry, HTRF



Competition (cytometry)



Functional assay (migration assay)





De novo design by computational library screening with epitope and affinity selection against TIGIT

TIGIT

- T-cell immunoreceptor with Ig and ITIM domains
- Immune check-point

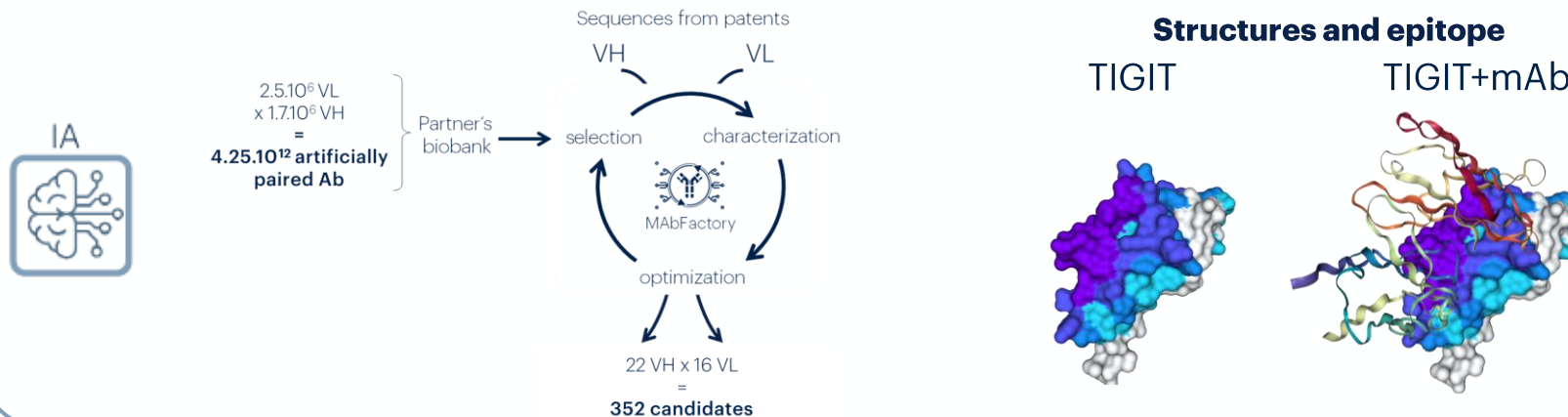
Leads

- starting from epitope of anti-TIGIT Ab disclosed in patents
- starting with **4.25.10¹² artificially paired Ab** (2.5.10⁶ VL x 1.7.10⁶ VH)
- **New: 352 sequences** (22 VH & 16 VL), **94% being binders**

Conclusions

- Selection of binders from very large biobank in days
- Predicted affinities validated by biological assays
- Computational design **in 21 days**

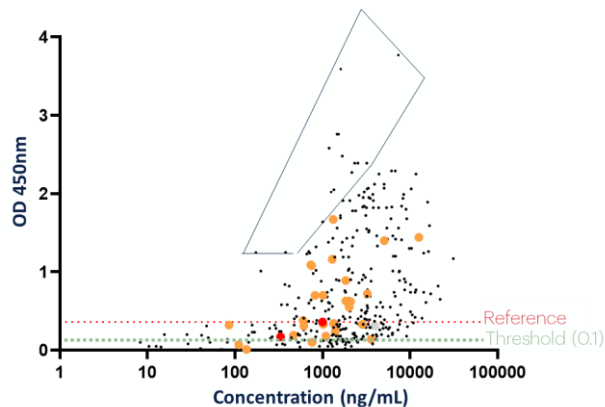
Antibodies designed using MAbFactory



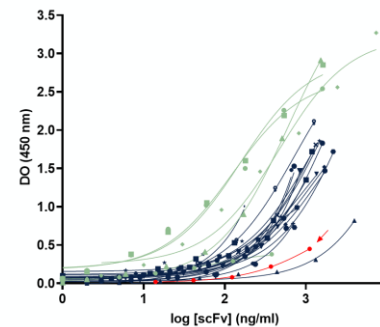
in vitro validation of the new leads



ELISA binding assay from CHO supernatants of the 352 candidates



ELISA binding assays



scFv	EC50 (ng/ml)	scFv	EC50 (ng/ml)
reference	8515	VH7/VL4	1143
VH1/VL4	2016	VH7/VL6	4189
VH1/VL12	22750	VH7/VL7	1078
VH2/VL4	1851	VH8/VL1	800
VH3/VL4	2003	VH8/VL4	1525
VH4/VL7	1338	VH9/VL4	2187
VH5/VL4	188	VH10/VL4	1072
VH5/VL7	392	VH11/VL4	1970
VH5/VL8	1019	VH12/VL4	191
VH6/VL4	399	VH12/VL7	699
VH7/VL1	761	VH20/VL12	386

94% binders (DO>0.1)
53% strong binders



TSLP

- Thymic stromal lymphopoietin
- Alarmin that induces pre-B cell differentiation and proliferation
- Upregulated in inflammatory disorders

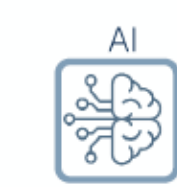
Leads

- Starting from the Tezepelumab
- 2000+ mutants tested in silico (including single and mutant combinations)
- **New: 60 sequences**

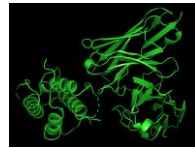
Conclusions

- 50% of sequences in +/- 1 log affinity range
- All passed developability tests
- **3 sequences with equivalent characteristics and 1 potentially superior than reference**

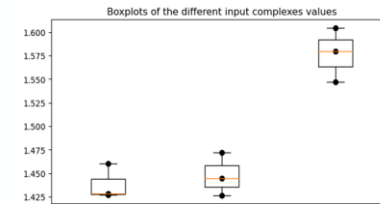
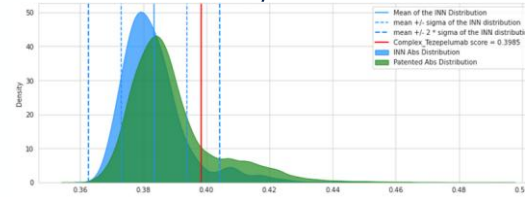
Antibodies designed using MAbFactory



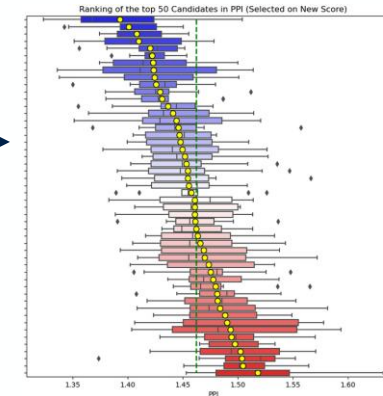
Reference analysis



TSLP-Tezepelumab

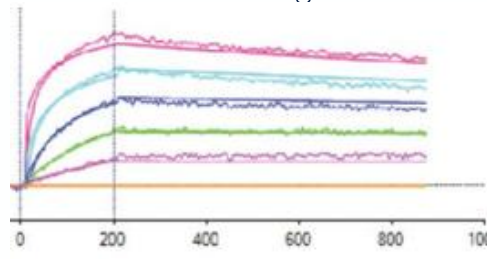


Multiparametric ranking of candidate sequences

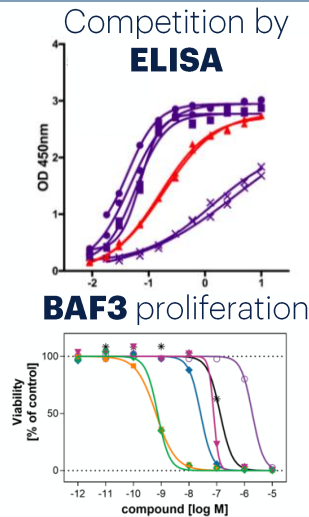


60 Ab with a relevant profile identified in silico

in vitro validation of the new leads



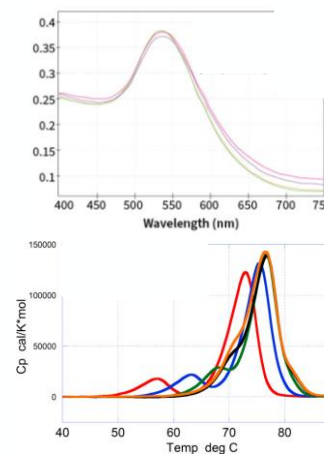
SPR affinity measurement on human and cyno target



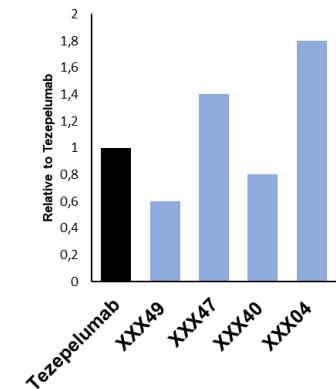
Competition by ELISA

BAF3 proliferation

AC-SINS, BVP and Tm



CCL17/TARC release from human PBMCs





Design of bispecific bio-better derived from Penpulimab (PD-1) and Bevacizumab (VEGF)

Bispe. PD1 x VEGF

- Ivonescimab from SUMMIT
- Lots of traction around this combination
- Program partnered with the biotech company NAYA

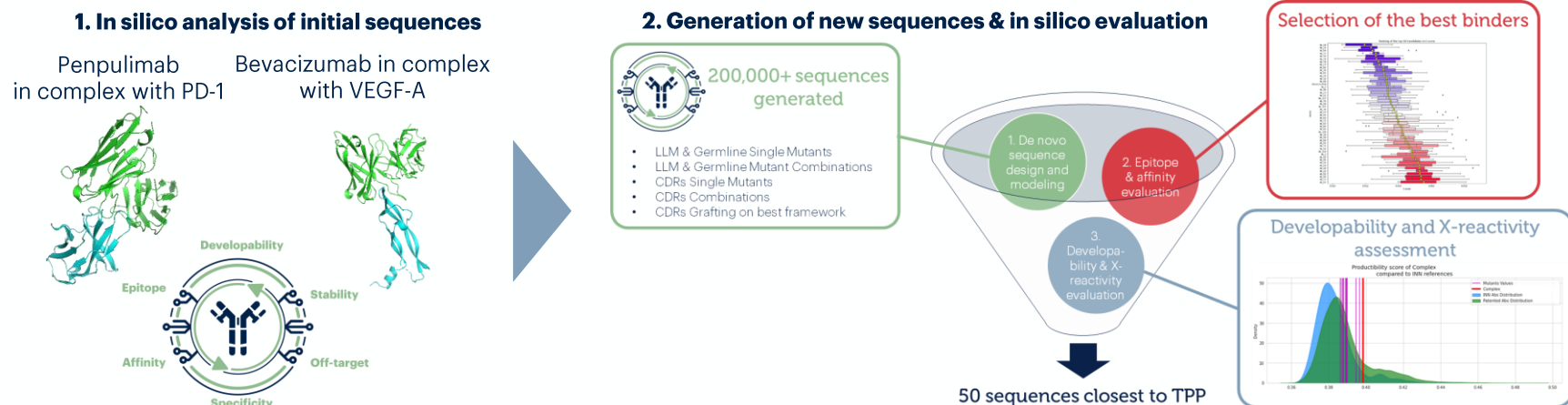
Leads

- Starting from the Penpulimab (PD-1) and Bevacizumab (VEGF)
- 200 000+ in silico mutants
- **New: 50 sequences for each arm & selected the best ones for bispecific as DVD format**

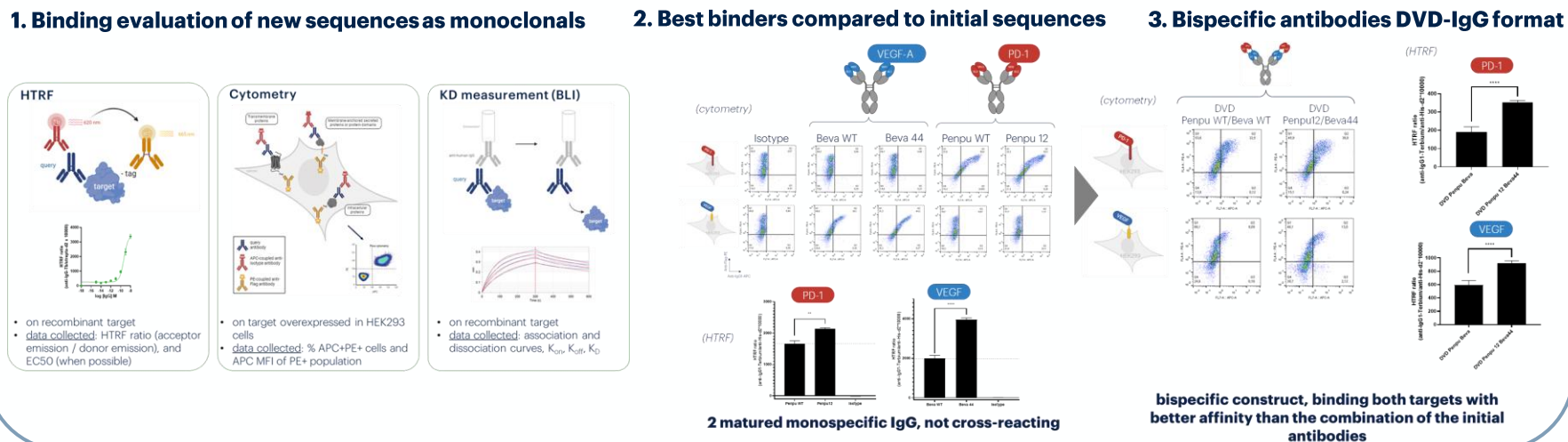
Conclusions

- Sequence homology far enough from initial sequences
- Improved properties for affinity and developability
- **New bispecifics available for bio activity evaluation**

AI-design of new sequences from validated and approved antibodies



in vitro validation of the new leads from mono to bispecific





MABFactory: data intelligence for antibody discovery

- Curated database available through software (MS Azure)
- Proprietary database of 99529 antibodies (91371 binding units) for 6473 targets:
 - 1344 human targets with at least one binding unit (i.e. antibody or antibody-like)
 - 3817 patents analyzed and curated, including:
 - 48312 affinity data covering 21925 binding units
 - 12445 epitope data covering 9306 binding units
 - 5906 binding units with cross-specificity data
 - 33914 EC50 or IC50 measures

The screenshot displays the Azure Marketplace page for MABFactory. The header includes the Microsoft logo and 'Azure Marketplace'. The product name 'mabfactory-mabsilico' is prominently displayed with a 'Save to my list' option. Below the name, there are tabs for 'Overview', 'Plans', and 'Ratings + reviews'. The main content area describes MABFactory as a unique software and database for antibody and CAR-T discovery, highlighting its ability to provide easy and fast access to a comprehensive range of antibody-related data and tools. A video player is embedded in the center, showing a preview of the software interface. On the left side, there are links for 'Contact Me', 'Categories', 'Support', and 'Legal'. The bottom of the page lists several key features of the software.



MAbSilico in numbers



Led by an executive team with scientific background

Spin-off from CNRS and INRAe, LabEx MAbImprove

2017



Vincent Puard
CEO

Vincent holds a PhD in biology and worked in biotech and public research institutes in Europe before founding MABSilico.

Teamed up with Zakaria



Thomas Bourquard
CSO

Thomas holds a PhD in structural biology and computer sciences. He worked on implementing AI approaches in genomics, docking, immuno-oncology.

Teamed up with Raouf, Sahel, Adrien & Sylvine



Astrid Musnier
Head of Biology

Astrid holds a PhD in cellular biology. She worked on GPCRs mechanisms of action and their modulation by antibodies.

Teamed up with Mélanie & Yannick



Zakaria Omahdi
BOO

Zak holds a PhD in immunology. He worked as a biologist at MABSilico before moving to business development.

3

Wet-lab, offices & computation sites

Based in Tours (FR) and at Biolabs Paris with Golden Tickets from Novo Nordisk and Pfizer

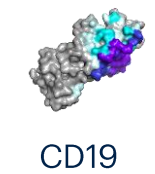
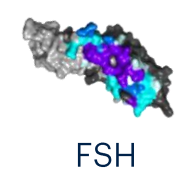
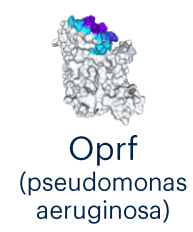
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Track record AI drug discovery

100+

Projects involving computational solutions

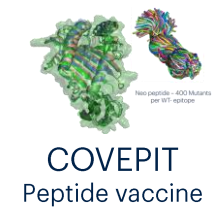
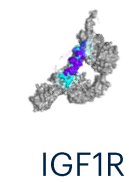
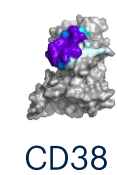
In the fields of infectious diseases, immuno-oncology, oncology, bacterial resistance



Clients' products in clinical development

MABSilico either designed or characterized the molecules

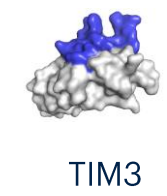
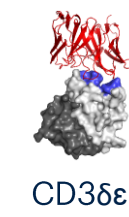
6



26

Internal discovery pipeline (mono and bispe)

Antibody computationally designed and validated with biological assays



24



AI adopters and supporters

100

Clients worldwide since creation

Based in Europe, US, and Asia, like TENEObio, SANOFI, OSE Immuno, BIOND Bio

Non confidential clients & partners

Teneobio → AMGEN OSE IMMUNO THERAPEUTICS

BIOND BIOLOGICS → sanofi VALENZABio

DJS Antibodies → abbvie IGYXOS R O-THERAPEUTICS

Tech & financial support from:

Microsoft bpi france RÉGION CENTRE VAL DE LOIRE European Commission

NVIDIA INCEPTION PROGRAM BILL & MELINDA GATES foundation novo nordisk® Pfizer


25.03.26

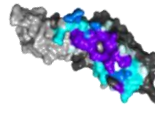
Track record AI drug discovery


100+

Projects involving computational solutions

In the fields of infectious diseases, immuno-oncology, oncology, bacterial resistance

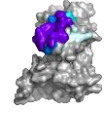
 Oprf (pseudomonas aeruginosa)

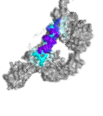
 FSH

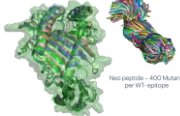
 CD19

Clients' products in clinical development

MAbSilico either designed or characterized the molecules

 CD38

 IGF1R


 COVEPIT Peptide vaccine


6

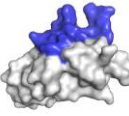
26

Internal discovery pipeline (mono and bispe)

Antibody computationally designed and validated with biological assays

 CD36

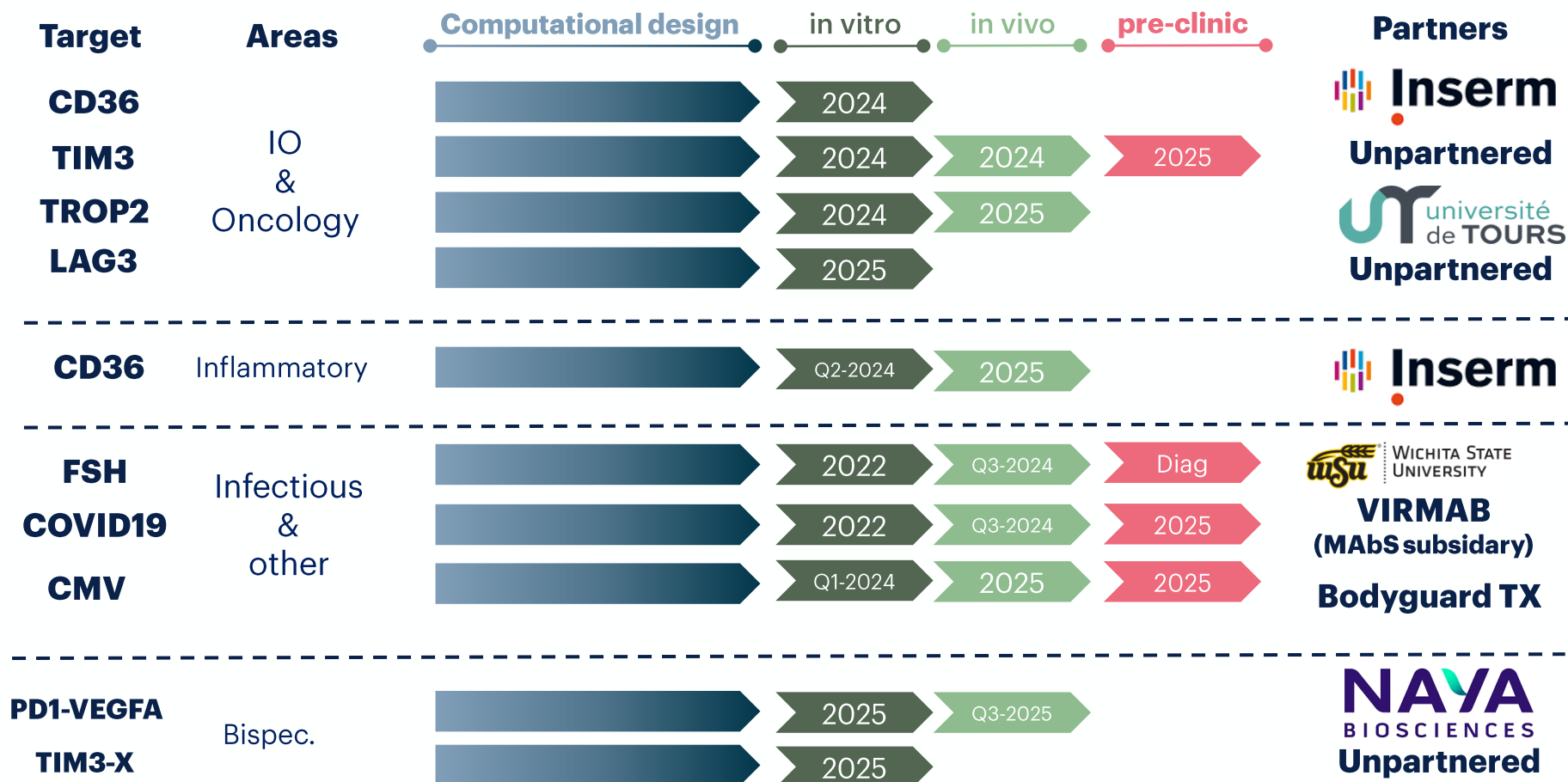
 CD3δε

 TIM3

25



MABSilico discovery pipeline (non confidential)



MAbSilico, the best TechBio for computational antibody drug design



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