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ENEA
Agenzia nazionale per le nuove tecnologie,
l'energia e lo sviluppo economico sostenibile

AN *IN-SILICO* DRIVE-THROUGH FOR mAbs DISCOVERY

Valerio Chiarini, Simone Giusepponi, Caterina Arcangeli, Sara Marchio, Nicolò Colistra, Paolo Roberto Saraceni, Fabiana Ferrara, Silvia Serrao, Emanuela D'acunto, Manuela Cappelletti, Roberto Arriga, Shaila Sellathurai, Mariateresa Mancuso & Giuseppe Roscilli

CONFERENCE
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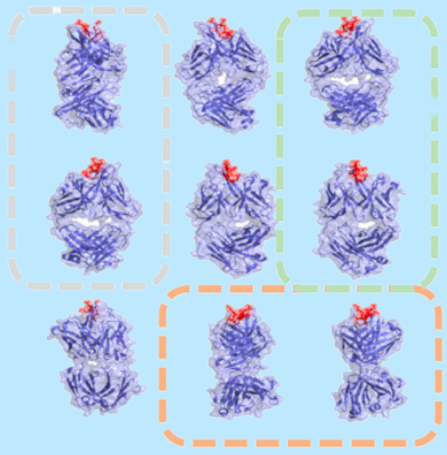
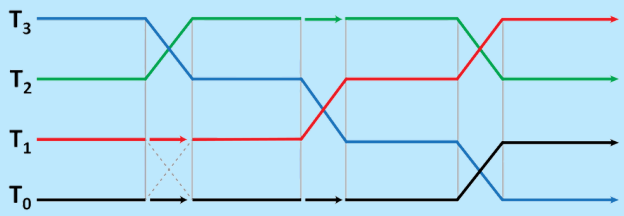
Italiadomani PIANO NAZIONALE DI RIPRESA E RESILIENZA
ROME TECHNOPOLE INNOVATION ECOSYSTEM

THE PIPELINE

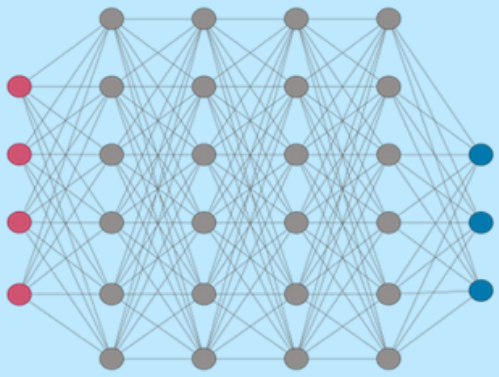


De-novo design or proprietary based Ab optimization

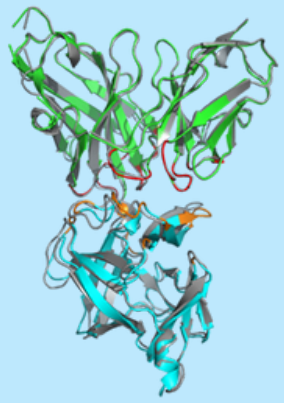


Exahustive Ab conformational sampling with Replica-Exchange-MD

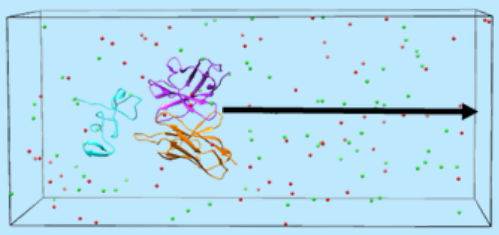
CRESCO6



Deep Learning selection of binding confermer



Ab-antigen docking



Binding-force profiling by steered MD

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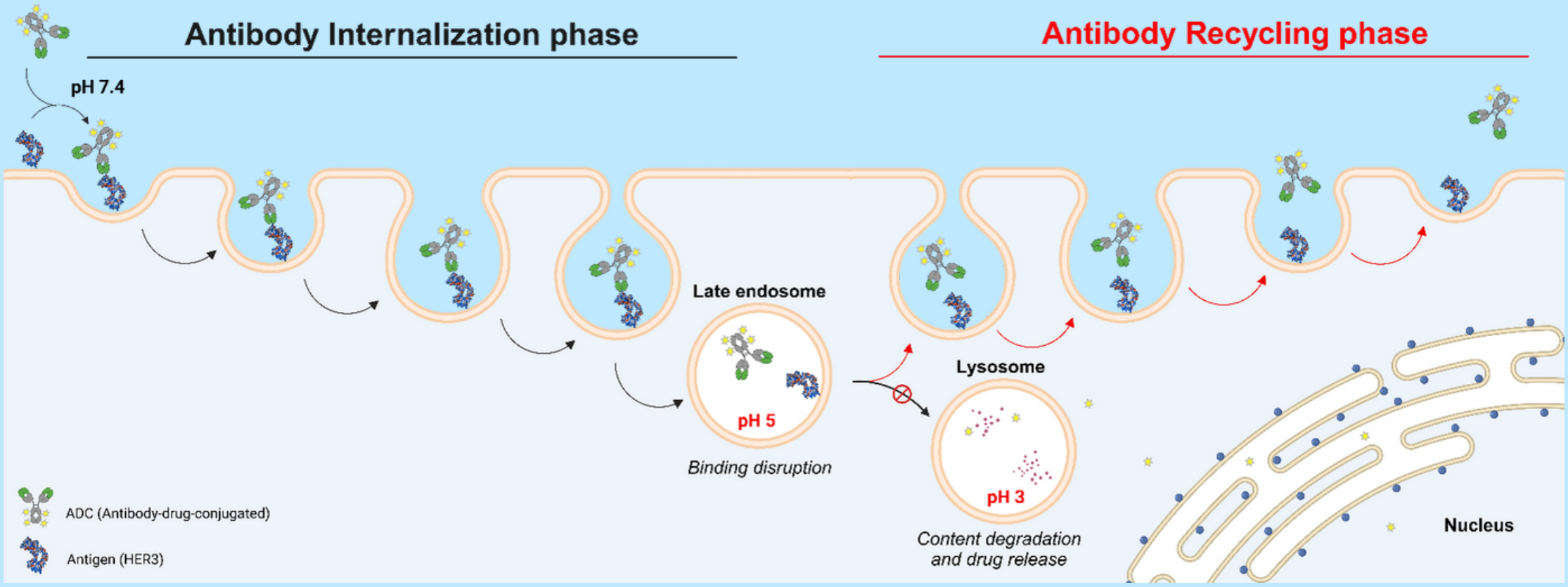
THE CHALLENGE

- Monoclonal antibodies (mAbs) have **irreversibly revolutionized** current **medicine**.
- Although extremely efficient, **identification of mAbs** candidates to enter clinical trials **remains challenging.**
- With a landscape of **>10^13 possible variants** **experimental studies** are both time and cost prohibitive.
- Modellization of **molecular interactions on High Performance Computing (HPC**) clusters offers the chance to address both problems and narrow down the plethora of ideal candidates to be experimentally validated.



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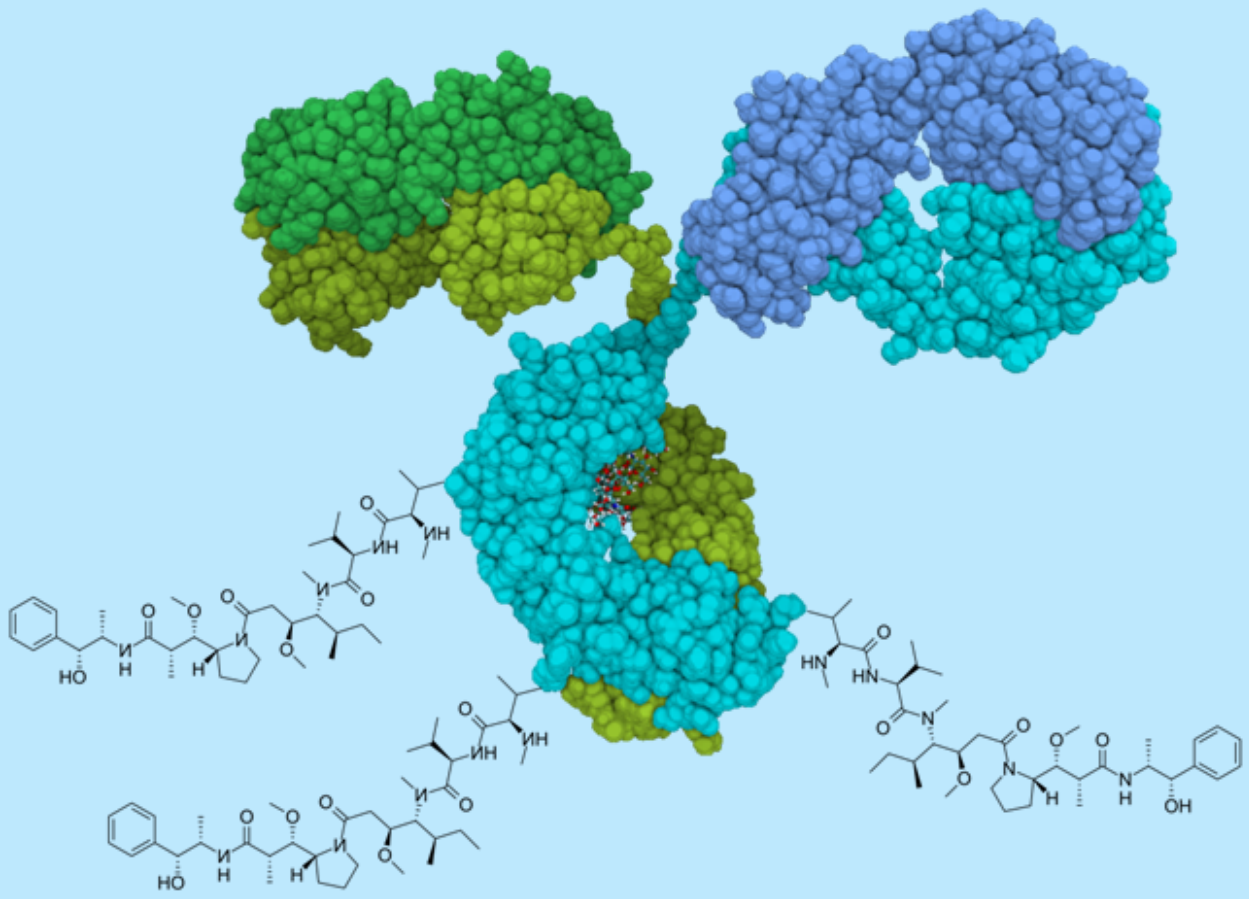
THE IDEAL ANTIBODY-DRUG-CONJUGATED (ADC) CANDIDATE



- Monospecificity
- High-affinity
- High-productivity
- Low immunogenicity
- High payload content
- Low self-aggregation

Differential binding mode at different pH to promote Ab recycling and prevent its sequestration.

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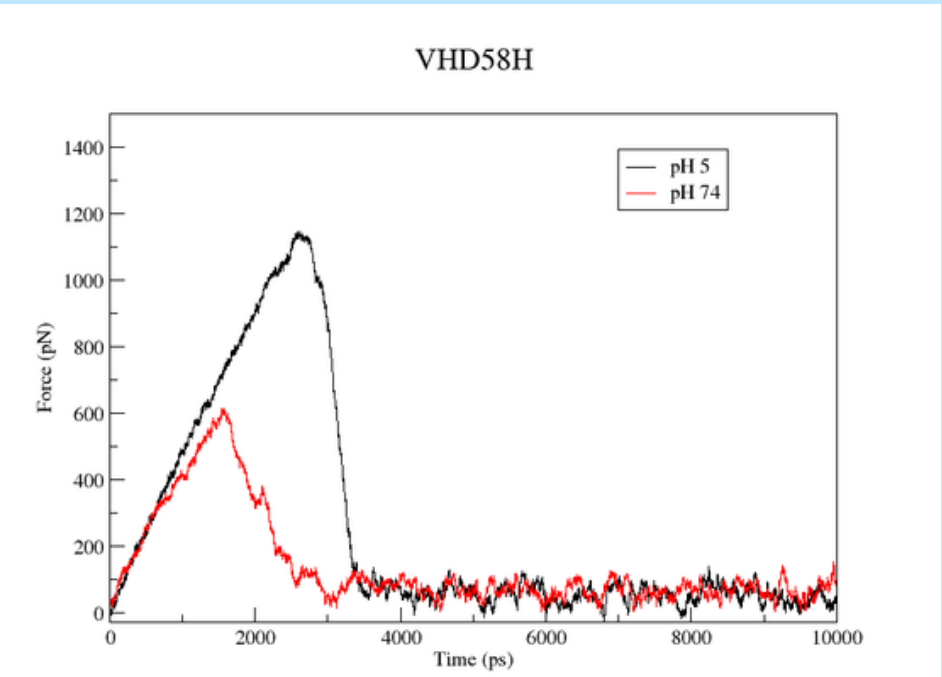
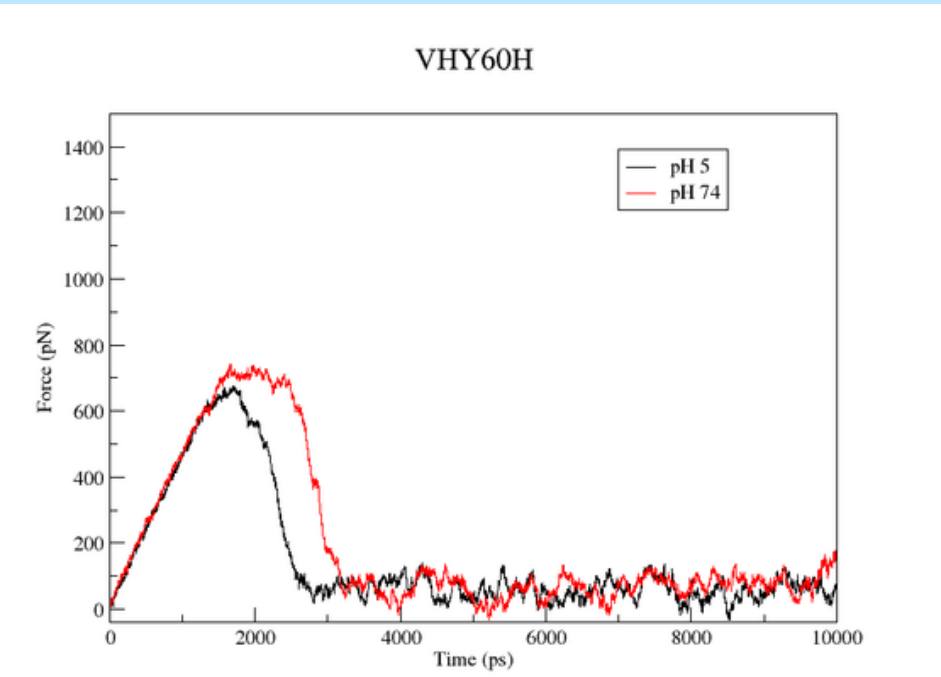
RESULTS





In-silico analisys revealed pH-dependent conditional binding profiles for several mutants. Some show slower dissociation at acid pH (5.8H), other slower at phisiological pH (6.0H). Such behavior translates to better performance in antibody recycling and targeting the oncologic microenvironment.

OUTLOOKS

- In-vitro validation of found mutants by Bio-Layer-Interferometry (OCTET).
- Design de-novo Ab against selected epitopes
- Consolidation of AI infrastructures for Ab generation based on existing candidates.

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•Chowdhury R, Allan MF, Maranas CD. OptMAVEn-2.0: De novo Design of Variable Antibody Regions against Targeted Antigen Epitopes. Antibodies (Basel). 2018 Jun 30;7(3):23. doi: 10.3390/antib7030023. PMID: 31544875; PMCID: PMC6640672.

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