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Meeting Report on MAbSilico's AI-Assisted Antibody Design Platform

AvATher Working Group | 30 April 2026 | 17:00-19:00

A. Context:

Respiratory viruses remain a major public health threat, responsible for substantial morbidity, mortality, and health-system burden worldwide. Beyond seasonal epidemics, the continued risk of emerging and re-emerging respiratory viruses, including zoonotic spillover events and rapidly evolving viral variants, supports ongoing preparedness efforts and the evaluation of antiviral and antibody-based strategies that could complement vaccination and existing therapeutics.

Current antiviral and antibody-based approaches remain valuable but may face limitations related to viral evolution, reduced effectiveness against emerging variants, and the rapid emergence of escape mutations. Accordingly, the AvATher Working Group of ANRS-MIE continues to identify, assess, and prioritize innovative therapeutics, as well as technologies that could be integrated into the therapeutic arsenal against respiratory viruses. In this context, the Working Group invited MAbSilico to present its artificial intelligence-based *in silico* platform dedicated to antibody drug design, with potential applications in immune escape assessment and rapid therapeutic adaptation.

B. MAbSilico technology

- ***AI-assisted multi-parametric antibody design[1-2]***

MAbSilico has developed an artificial intelligence-assisted, structure-based and epitope-driven platform for therapeutic antibody design. The company reported experience in more than 100 computational projects across several therapeutic areas, including infectious diseases, immuno-oncology, oncology and bacterial resistance. Its platform has contributed to the design or characterization of antibodies directed against targets such as CD38, IGF1R and CD19, as well as to work on the COVEPIT vaccine.

The platform does not rely only on the linear amino-acid sequence of the antigenic target but uses its three-dimensional structure to identify epitopes of interest and guide antibody candidate selection. It then involves a combination of algorithms and computational solutions to evaluate and optimize candidates across multiple parameters, including binding

[1] Bourquard T, Musnier A, Puard V, Tahir S, Ayoub MA, Jullian Y, Boulo T, Gallay N, Watier H, Bruneau G, Reiter E, Crépieux P, Poupon A. MAbTope: A Method for Improved Epitope Mapping. J Immunol. 2018 Nov 15;201(10):3096-3105. doi: 10.4049/jimmunol.1701722.
[2] Tahir S, Bourquard T, Musnier A, Jullian Y, Corde Y, Omahdi Z, Mathias L, Reiter E, Crépieux P, Bruneau G, Poupon A. Accurate determination of epitope for antibodies with unknown 3D structures. MAbs. 2021 Jan-Dec;13(1):1961349. doi: 10.1080/19420862.2021.1961349.

affinity, epitope stability, specificity, developability, risk of off-target binding and candidate stability. The objective is therefore not simply to identify the strongest binder, but to prioritize candidates with the best overall profile, balancing efficacy, specificity, safety-related risks and downstream developability.

MAbSilico's internal workflow is designed as an end-to-end computational pipeline, from target preprocessing to biological validation of selected candidates. The process begins with structural modeling of the therapeutic target, based either on available experimental structures or on homology/3D modeling when no structure is available. This is complemented by competitive landscape analysis, including literature and patent mining, to integrate existing knowledge on known antigens and antibodies. Depending on the project, candidate antibodies may then be generated *de novo*, selected from antibody libraries, or optimized from reference antibodies to develop bio-better candidates.

The computational design phase evaluates candidates through structural characterization, affinity prediction, cross-reactivity assessment, variant/isoform analysis and developability profiling. The pipeline is iterative, with computational steps repeated until suitable candidates are identified, generally within approximately 21 days of computation, or potentially around five days using cloud computing. Up to 50 candidates can then be advanced to in-house biological assays, including cytometry, HTRF and BLI, to experimentally validate binding and support the validity of the parameters predicted by algorithms.

A core component of the platform is a computational epitope-paratope mapping, which aims to predict where and how a given antibody binds to an antigen. This module starts with the antigen name or identifier and the antibody sequence, generates three-dimensional models of both partners when needed, and performs docking simulations under geometric and physicochemical constraints. By exploring many possible antibody-antigen conformations, the platform identifies the most probable binding interfaces and estimates the contribution of individual antigen residues to the interaction. The output includes predicted epitope and paratope information, binding models and proposed mutations for biological validation. This module can support antibody characterization, epitope-driven screening or binning, and optimization against variants, isoforms or antigen mutations.

Once the probable binding interface has been identified, the platform can also support affinity modeling and antibody maturation. Rather than relying only on generic tools such as large language models or AlphaFold 3, which may be poorly suited to antibody-antigen interactions, MAbSilico evaluates the geometry and physicochemical properties of the interface to estimate interaction strength. The approach considers all amino acids contributing to the interface, including residues that may indirectly affect scaffold rigidity and affinity, and uses this information to identify regions where mutations could increase or decrease binding. This supports targeted antibody optimization after epitope-paratope mapping.

- ***Real-world applications[3,4]***

MAbSilico presented several examples illustrating how its AI-based *in silico* epitope-mapping approach can be used to predict antibody-binding regions and support antibody candidate selection or optimization. In case studies involving antibodies such as dupilumab/IL-4Rα and eculizumab/C5, the predicted binding regions, including conformational epitopes, were subsequently compared with experimental data generated using methods such as crystallography, peptide arrays, HDX, ELISA and cytometry. These examples were presented as evidence that computational predictions can help guide and accelerate experimental characterization, rather than replace it. According to MAbSilico, these *in silico* predictions can be generated rapidly, potentially within minutes for epitope mapping, whereas full experimental characterization may take several months, thereby supporting faster and more cost-effective prioritization of candidates for biological validation. Moreover, they worked on more than 100 projects for startup and pharma clients (based in Europe and USA), academic groups and governmental agencies, to either characterize or engineer new candidates against more than 50 different targets.

- ***MAbSilico antiviral platform: patient-derived antibody discovery and in silico selection***

The antiviral platform combines patient immune repertoires, *in vitro* workflows and AI-based computational selection to identify antibodies against viral targets. In the SARS-CoV-2 example, PBMCs from infected patients (CHU Tours) were used to isolate antigen-specific B cells, followed by single-cell sequencing to reconstruct paired heavy- and light-chain antibody repertoires (clonotypes). MAbSilico then applied epitope-driven and multiparametric *in silico* screening to assess binding against selected Spike epitopes and across evolving variants. This enabled the evaluation of several thousand clonotype sequences and docking poses, leading to the prioritization of top candidates based on predicted affinity and cross-reactivity. Selected antibodies were then produced and validated experimentally using binding assays such as cytometry, BLI, HTRF and ELISA, followed by in vitro neutralization and in vivo assessment by partner laboratories. The approach demonstrated the potential to rapidly identify cross-binding and cross-neutralizing candidates from a limited number of patients, while also highlighting that some biological effects, such as neutralization potentiation, still require experimental validation.

C. Discussion:

- ***Could the MAbSilico platform be applied to influenza, particularly to support the identification or optimization of broadly neutralizing monoclonal antibodies***

[3] Tahir S, Bourquard T, Musnier A, Jullian Y, Corde Y, Omahdi Z, Mathias L, Reiter E, Crépieux P, Bruneau G, Poupon A. Accurate determination of epitope for antibodies with unknown 3D structures. MAbs. 2021 Jan-Dec;13(1):1961349. doi: 10.1080/19420862.2021.
[4] Brachet G, Bourquard T, Gallay N, Reiter E, Gouilleux-Gruart V, Poupon A, Watier H. Eculizumab epitope on complement C5: Progress towards a better understanding of the mechanism of action. Mol Immunol. 2016 Sep;77:126-31. doi: 10.1016/j.molimm.2016.07.016.

targeting conserved regions of hemagglutinin (e.g., the stalk region) and demonstrating the ability to retain activity against circulating variants?

The platform has already been applied to influenza hemagglutinin through an industrial collaboration, with the objective of identifying conserved epitopes of interest and assessing whether candidate antibodies maintain binding despite antigenic variation. This work has particularly focused on the hemagglutinin stalk region, which is considered the most relevant target for broadly neutralizing antibodies. Beyond prospective discovery, the approach may also support retrospective re-screening of existing antibody candidates using *in silico* methods, including integration of geographically stratified viral sequence data to identify candidates with broader or region-specific relevance. While this would not necessarily require retraining the core model, more targeted influenza-specific modeling could be developed if needed to improve prediction accuracy while maintaining robustness across circulating variants.

- ***Could the MAbSilico platform be used to anticipate resistance to monoclonal antibodies in RSV, for example by predicting which mutations within antibody-targeted epitopes are most likely to reduce binding or lead to immune escape?***

Yes. The platform could be used to assess the resistance potential of RSV monoclonal antibodies by performing in silico epitope-wide mutational scanning to evaluate which substitutions are most likely to impair antibody binding. Rather than relying solely on static structural prediction, this approach integrates mutational profiling with molecular dynamics to assess the impact of amino acid substitutions on antibody-antigen interactions in a more realistic structural context. This allows identification of mutations that may reduce binding affinity or compromise antibody efficacy, while also distinguishing potentially meaningful escape mutations from structurally neutral variation.

- ***Given the short window of efficacy observed for monoclonal antibodies against rapidly evolving viruses such as SARS-CoV-2, could the MAbSilico platform still support the timely development and deployment of updated monoclonal antibodies, or is this approach better suited to more genetically stable viruses?***

The approach remains feasible, but its utility depends strongly on the evolutionary dynamics of the target virus. For relatively stable viruses, or viruses with conserved antigenic regions, this strategy is particularly well suited and may support durable monoclonal antibody development. For rapidly evolving viruses such as SARS-CoV-2, the value of the MAbSilico platform lies less in predicting future variants with certainty than in enabling rapid risk assessment and therapeutic triage as viral evolution occurs. In practice, existing antibodies can be rapidly reassessed *in silico* against newly emerging variants within hours to estimate the risk of escape and determine whether currently available candidates remain viable. If mutations fall outside the targeted epitope, immediate risk may be limited; conversely, even a single mutation within a critical epitope may be sufficient to abolish antibody activity. In such cases, the platform can support rapid re-screening of broader existing antibody repertoires, including external candidates already developed by third parties, to identify alternative monoclonal antibodies that may retain cross-neutralizing activity and can be

rapidly prioritized for experimental validation. In this context, the platform functions less as a deterministic predictive tool than as a pragmatic surveillance and response system to support rapid therapeutic adaptation.

- ***The MAbSilico platform appears to rely on a structural 3D approach, identifying how an antibody may bind to an existing epitope. How does this approach compare with alternative strategies that design or engineer new binding sites* de novo*, for example to generate antibodies against targets such as influenza hemagglutinin or Clostridium difficile toxin B? What are the main advantages and limitations of these different approaches****?***

De novo antibody-design approaches based on diffusion algorithms are scientifically attractive but currently remain limited, particularly for antibody-antigen interactions. These methods attempt to generate new structures from noise and progressively refine them toward a desired binding solution. However, their current performance for antibodies remains low, with reported precision rates around 3-5%. One major limitation is that predicting the interaction between two proteins is much more difficult than modeling a single protein, because antibody-antigen binding depends on relatively unstable and context-dependent interfaces. Robust docking and molecular dynamics therefore remain critical.

Some *de novo* approaches, including Rosetta-type models, also require a known structural anchor or constrained system to improve performance. In addition, candidates generated in published studies may still show relatively modest affinity, raising questions about their immediate clinical relevance. Some approaches also rely on VHH/nanobody formats, which may carry development and immunogenicity risks, and some industrial actors appear to be reconsidering their use.

By contrast, MAbSilico's approach focuses less on creating antibodies entirely *de novo* but more on screening and prioritizing candidates from very large antibody libraries against a defined epitope. For example, the platform can screen naïve libraries containing up to 10^{12} sequences and prioritize the most promising candidates based on predicted affinity at a given antibody-antigen interface. Because the platform is designed to evaluate binding affinity more consistently, this strategy may translate better into experimental validation than purely *de novo* generation approaches.

- ***Could the MAbSilico platform support the creation of a fully in silico "pre-positioned" library of plausible antigenic variants and corresponding antibody predictions, in order to anticipate emerging viral mutations and rapidly identify the monoclonal antibodies most likely to remain effective in a future alert scenario****?*

Such an approach is feasible and far from unrealistic. The MAbSilico platform could in principle support the creation of a fully *in silico* pre-positioned library of plausible antigenic variants and corresponding antibody predictions. In practice, this is computationally tractable for limited mutational scenarios (e.g., one to two mutations) but becomes substantially more resource-intensive as epitope diversity increases. The company noted that access to high-performance computing infrastructure (e.g., Adastra, Jean Zay) now

makes this type of large-scale in silico exploration technically achievable. While such an approach would still require additional refinement steps, including molecular dynamics, to ensure robustness, it is feasible provided that the search space and number of candidate antibodies are clearly defined and kept within manageable limits.

- ***Could the MAbSilico platform be used prospectively in influenza to map the probability of immune escape and identify mutations most likely to compromise the effectiveness of seasonal vaccine strains once the strains and epitopes have been selected by the WHO****?*

This is one of the relevant prospective applications of the platform. Beyond building a library of antibodies, a more informative approach would be to assess whether a given antibody can recognize a broad library of antigenic variants. Applied to influenza, this would allow prospective evaluation of how mutations introduced into selected epitopes may affect antibody recognition and whether they are likely to induce partial or complete loss of binding. In practice, this could support mapping of immune escape risk across WHO-selected seasonal strains and help characterize the breadth of antibody activity against evolving antigenic variants. More broadly, the platform could also support structure-informed analysis of human antibody repertoires at the paratope level, which may provide a more relevant framework than conventional sequence-based repertoire analyses for identifying broadly reactive antibody profiles. Over time, this could improve prospective assessment of antibody breadth, cross-reactivity, and escape susceptibility across antigenically evolving respiratory viruses.

D. AvAThер Working Group's overall assessment of MAbSilico technology

- **Strategic Value and Preparedness Potential**: The platform presents a technically credible and potentially high-value approach for strengthening preparedness against rapidly evolving viral threats. Its added value lies in the possibility of scaling simulation capacity both on the antigenic target side and through the creation of pre-positioned antibody libraries with prior characterization of cross-reactive activity. Conceptually, this could support a more proactive preparedness framework by enabling rapid *in silico* assessment of emerging variants and facilitating earlier identification of candidate antibodies with likely retained activity.

- **Uncertainly and Risks:** The group noted that predictive modelling of viral evolution remains inherently uncertain, particularly for viruses such as influenza, where emergence may involve complex reassortment or recombination events rather than predictable stepwise mutations. As a result, *in silico* approaches may support risk estimation and prioritization but cannot reliably anticipate all biologically viable or clinically relevant future variants. The group also noted that overly reactive or poorly targeted use of monoclonal antibodies may contribute to selective pressure and escape mutants, reinforcing the need for broader cross-neutralizing strategies and proactive preparedness approaches. In addition, the group emphasized that rapid *in silico* identification of candidate antibodies would not, by itself, be sufficient to ensure

timely availability during an outbreak, as downstream steps such as experimental validation, manufacturing, regulatory pathways and deployment would also need to be anticipated and accelerated.

E. Strategic recommendations for the consolidation and integration of the MAbSilico platform into preparedness frameworks:

• **Institutional sustainability:** The platform was considered scientifically promising and strategically relevant for epidemic preparedness; however, it was noted that there is an absence of a solid long-term contractual and institutional framework between MAbSilico and public academic actors and public health institutions. The group therefore highlighted the need to establish clearer legal, contractual, and institutional structures to ensure that France can sustainably benefit from this strategically valuable platform and preserve national sovereignty over such capabilities. In this context, the group suggested that national public health actors, such as ANRS-MIE and/or the DGS, may have a role to play in the long-term strategic anchoring of this initiative.

• **Strategic value for national preparedness:** The group considered that the platform could represent a potentially valuable national asset for preparedness against emerging infectious diseases, particularly through its capacity to support rapid *in silico* assessment of antibody breadth and variant escape risk.

• **Exploration of proactive preparedness approaches despite uncertainties:** Although the feasibility and operational relevance of a fully proactive preparedness framework based on large-scale *in silico* anticipatory approaches remain uncertain and subject to debate, the group considered that such approaches should not be dismissed prematurely. **The group recommended further discussion with MAbSilico to clarify whether such proactive approaches are technically feasible, strategically meaningful, and primarily limited by resources and prioritization, or whether they remain largely theoretical at this stage.** Even partial implementation could provide added value in the context of preparedness for emerging infectious diseases and rapid response planning.

• **Integration into rapid response pathways:** The group emphasized that, if the platform were to be considered for outbreak response, it should be integrated into a broader operational pathway including access to early patient samples, antigen production, virology and molecular biology capacity, experimental validation, manufacturing readiness and adapted regulatory mechanisms. In particular, the group noted that rapid antibody identification would only be useful if subsequent development and access pathways could also be shortened, for example through pre-established processes or mock-up-type regulatory approaches where appropriate.

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