We live in an era of rapidly advancing computing capacity and algorithmic sophistication. “Big data” and “artificial intelligence” find progressively wider use in all spheres of human activity, including healthcare. A diverse array of computational technologies is being applied with increasing frequency to antibody drug research and development (R&D). Their successful applications are met with great interest due to the potential for accelerating and streamlining the antibody R&D process. While this excitement is very likely justified in the long term, it is less likely that the transition from the first use to routine practice will escape challenges that other new technologies had experienced before they began to blossom. This transition typically requires many cycles of iterative learning that rely on the deconstruction of the technology to understand its pitfalls and define vectors for optimization. The study by Vásquez et al. identifies a key obstacle to such learning: the lack of transparency regarding methodology in computational antibody design reports, which has the potential to mislead the community efforts through the steps of the design cycle. Regrettably, the authors have chosen not to provide them as the online Supplementary Materials. This omission made the analysis of the progression from the template sequences to final antibodies very difficult. Nonetheless, we found the results reported by Tharakaraman et al. to be thought-provoking.

It is well established that the majority of de novo antibody binding specificities are mediated by CDR-H3 loops, which are highly heterogeneous in sequence and structure, as this is needed to bind myriad foreign antigens.13 This heterogeneity in length and sequence makes the CDR-H3 loop very challenging to model. These loops generally do not conform strictly to canonical structural classes and are often poorly resolved in crystal structures.14 As a result, to the best of our knowledge, in silico-designed antibodies have generally been derived from the insertions of known binding peptides into antibody scaffolds15 or the complementarity-engineering of previously described whole antibody sequences towards epitopes of interest.16 In both cases, initial engineering is typically augmented by the modulation of sequence in other loops in the antibody binding interface to improve binding affinity, often via display technologies.17,18

Each of the design approaches described above is a process heavily influenced by in silico design, but still relies on substantial in vitro efforts to finally arrive at a desirable product. In contrast, the reports from Tharakaraman et al. suggested that they had successfully overcome these historical challenges and had derived de novo antibodies with novel binding capacity, using predominantly in silico methods. The paper by Vásquez et al., published in this issue of mAbs, offers an alternative explanation on the origin of these novel antibodies. They draw a convincing link between in silico designed antibodies by Tharakaraman et al. and closely related previously
disclosed sequences of broadly neutralizing influenza- and Zika-targeting antibodies. The lineages traced by Vásquez et al. are plausible and are much more compatible with our understanding of the current state of the art in antibody design.

It is difficult to reconcile these two different accounts for the origins of the antibodies disclosed by Tharakaraman et al. One potential explanation could be the “black-box” nature of the computational algorithm employed by Tharakaraman et al., which could have been substantially more knowledge-based than the authors appreciated and misled them into erroneously reporting the design templates in their manuscripts. It is impossible to conclude this definitively without analyzing the evolution of the sequence space through the steps of the design cycle for both antibodies.

The more profound question that Vásquez et al. paper raise is the extent of the responsibility that both authors and reviewers need to take for understanding how the sophisticated computational methods work in novel manuscripts produced in this field. We would pose the following questions to the antibody/protein engineering community at large: Is it enough for authors to generate experimental data that suggest success, but not to report their methods in detail? Should we accept that computational methods are becoming so advanced that it is impractical for a human being to deconstruct their outputs without slowing down progress in the design field to the point of inefficiency, or should we strive to understand the “nuts-and-bolts” of the successful solutions? We believe that, in the area of in silico antibody drug design, extra care is needed in assessing the true nature of new drug discovery technologies, and of the potential drug candidates they generate, before their advancement. In the case of the Tharakaraman et al. manuscripts, considerable effort and scrutiny were required by Vásquez et al. to establish the plausible origins of the binding domains of the antibodies that neutralize H7N9 flu strain and Zika virus in a manner consistent with our understanding of state of the art. We strongly believe that this level of scrutiny by the scientific community is necessary to drive further evolution of de novo antibody drug design techniques.

To further illustrate the challenges in this field, we would like to remind readers of some historical examples. Every new antibody engineering technique had required years of optimization before robust, reliable processes were attained. The antibody engineering field has learned multiple painful and costly lessons from early experiences with mouse monoclonal antibodies that were immunogenic in man, antibody humanization techniques that led to the loss of affinity where iterative protein engineering is needed to restore function, polyreactivity problems with early phage-display derived antibodies that limited their developability, and side effect-potentiating polyspecificity in monoclonal antibodies derived directly from immunized mice. It is difficult to believe that huge leaps forward in de novo antibody design that will de-risk drug discovery could be achieved without iterative learning on how to address such issues.

The factors outlined above are critical concerns if the de novo generation of antibodies by in silico design is to enter challenging ‘real world’ applications. Indeed, the antibodies described by Tharakaraman et al. are desirable as they potently neutralize viral proteins, suggesting they will find practical utility not only in research settings but also as therapeutics. Therefore, these antibodies need to possess many fundamental developability attributes, including stability, solubility, manufacturability, favorable pharmacokinetic characteristics, and, importantly, the specificity of target binding. The studies required to access these characteristics were beyond the scope of work of the published reports, but they are undoubtedly needed before the advancement of antibodies targeting H7N9 flu strain and Zika virus into the clinical studies. If antibodies are ever to be truly designed fully in silico, it is essential that they are optimized for all characteristics of a successful antibody drug and not only for high complementarity to their target antigen of interest. Development of computational methods that can accurately predict antibody drug properties will require an integrative community effort that can be only achieved upon robust disclosure of the methods used to optimize a certain antibody property. The failure to do so will delay the emergence of robust methods for in silico antibody drug design. The real-world issues in that we highlight here, combined with the concerns raised by Vásquez et al., suggest that much more work is needed to realize the bold vision of delivering in silico designed antibody therapies to patients in need.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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