Editorial: Next-Generation Sequencing of Human Antibody Repertoires for Exploring B-cell Landscape, Antibody Discovery and Vaccine Development

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Editorial on the Research Topic

Next-Generation Sequencing of Human Antibody Repertoires for Exploring B-cell Landscape, Antibody Discovery and Vaccine Development

The next-generation sequencing (NGS) analysis of human antibody repertoires has enabled a heightened appreciation and comprehensive characterization of the B-cell receptor (BCR) landscape at an unprecedented resolution (1–4). This advance has expanded our insights and lent itself to numerous applications, including the following: NGS coupled with bioinformatics has enhanced phage biopanning of complex antibody libraries and facilitated the antibody discovery process (5); NGS analysis when coupled with large-scale computational structural modeling has revealed sequence and structural correlates between naive and antigen-experienced antibody repertoires (6); and in recent years, NGS-aided study of the antibodyome of HIV-1-infected individuals has increased our understanding of antibody responses and aided the design of antibody lineage-based immunogens that could, in principle, activate naive precursor B cells to give rise to broadly-reactive neutralizing clones (7, 8). Thus, generally speaking, NGS of human antibody repertoires holds great promise for antibody discovery (9) and vaccine development (10, 11). This editorial introduces 17 high-quality research papers published in the Research Topic which summarize recent developments and applications within the context of NGS analysis of human antibody repertoires, through a combination of Original Research, Methodology, and Review articles.

The topic contains seven Original Research articles. These articles span a wide variety of topics. These studies illustrate means by which to harness the power of NGS for antibody discovery, B-cell immunogenetics, and the evolution of affinity maturation, as well as the investigation of antibody lineages in HIV-1/SIV infections. Hong et al. used cord blood samples from 10 newborn babies and peripheral blood from 33 healthy adults to perform an in-depth analysis of human neonatal and adult IgM heavy chain repertoires. Their comparative study revealed unexpectedly high levels of similarity between the neonatal and adult repertoires although antibody repertoire of healthy adults was more diverse than that of neonates. These results are helpful in understanding the antibody development and diversity in newborn babies and adults. Kirik et al. used NGS to analyze human bone marrow B cells to elucidate how different mutational paths are traversed by antibody lineages stemming from different germline gene origins both in
showed that many different heavy-chain
successfully developed, using
present a method that
and
Vergani et al. serves as a useful protocol for Ig-seq where every IGHV-D-J
Wendel et al. used three
on a topic of bulk B-
by only certain unique V-D-J rearrangements and V
rearrangements, but that specific target binding is achieved
that the same CDR-H3 can be generated by many different
rearrangements, but that specific target binding is achieved
by only certain unique V-D-J rearrangements and V
CDR-H3 loops, using previously published algorithms, for
thousands of homology models of antibodies derived from
the NGS data to find if affinity maturation reduces their
conformational flexibility or not. They also used a total of
922 antibody crystal structures from the Protein Data
Bank (12) and performed temperature factor analysis and
molecular dynamic simulation to assess the flexibility. By
using different computational approaches, they came with
a conclusion that there is no significant difference between
antibody CDR-H3 loop flexibility in repertoires of naïve and
mature antibodies. However, they also noted inconsistent results
across those methods for some antibodies. They concluded
that further experimental methods, for example, hydrogen
deuterium exchange mass spectrometry and more accurate
modeling or structure determination of antibodies would resolve
the inconsistencies. VanDuijn et al. profiled the immune
repertoire of rats after immunization with purified antigens
using NGS and proteomics. The data obtained from different
analysis methods and experimental platforms demonstrate that
the immunoglobulin repertoires of immunized animals have
overlapping and converging features; however, the quantitative
differences between the immune repertoires obtained using
proteomic and NGS methods that might relate to differences
between the biological niches could not be correlated in
this study. With further improvement on the proteomic and
NGS immune profiling approaches, their method may enable
more interesting applications in biotechnology and clinical
diagnostics. Then, He et al. and Han et al. combined the
biopanning of scFv phage-displayed antibody libraries and 900
bp long-reads, enabling VH/VL paired NGS analysis. He et al.
identified broadly neutralizing antibody intermediates from a
HIV-1 patient, particularly PGT124 sub-lineage, possessing
an invariable CDR-H3 loop and multiple library-derived
intermediates, which might serve as a promising template for
B-cell lineage vaccine design targeting. Han et al. also showed
how they used long-read NGS combined with scFv phage
display libraries for identifying SIV gp140-specific antibodies
and analyzing their clonotypes and lineages correlating to
neutralization activity.

Technical landscape for NGS analysis of human antibodies
has changed tremendously and will continue toward the
improvement of methods, immunoinformatics and data analysis
tools. In this respect, we have four exciting articles devoted to
methods/protocols. Hemadou et al. successfully developed, using
the PacBio RS II system, and generated long reads (>800 bp)
covering full length scFvs following in vivo panning in an animal
model of atherosclerosis. They tested its performance by tracking
and analysis of known, identical and related scFv-phage clone P3.
Rosenfeld et al. and Vergani et al. present on a topic of bulk B-
cells which provides a way for computationally assessing B-cell
clonal size and a library preparation method for NGS to capture
an exhaustive full-length repertoire for nearly every sampled B-
cell to be sequenced respectively. Rosenfeld et al. used three
different measures of B cell clone size: copy numbers, instances
and unique sequences, and then showed how these measures can
be used to rank clones, analyze their diversity, and study their
distribution within and between individuals. Overall, this method
showed how different clone size measures can be used to study
the clonal landscape in bulk B cell immune repertoire profiling
data. On the other hand, the methodology as adopted by Vergani
et al. serves as a useful protocol for Ig- seq where every IGHV-D-J
rearrangement in the starting B-cell populations can be detected.
Finally, advancements in NGS and error corrections have enabled
antibody repertoire sequencing with single mutation precision
but still compromising with sequencing accuracy. This opens the
possibility for undocumented novel germline alleles. To address
on this important issue, Wendel et al. present a method that
can be quickly and easily applied to any antibody repertoire
data set to mitigate the effects of germline mismatches on
SHM patterns.

Next, we provide five excellent reviews in the Research Topic,
starting with a review by Chaudhary and Wesemann, which
provides a sound introduction to practical steps involved in
the process of immune repertoire profiling including sample
preparation, platforms available for NGS, sequencing data
processing and annotations, and fundamental measurable
features of the immune repertoire such as V/D/J gene-segment
frequencies, CDR-H3 diversity and physicochemical properties,
and immunoglobulin somatic hypermutation (SHM). They also
highlight additional analyses using the NGS-derived repertoire
data: isotype analysis, which offers insights into the effector
biology mediated by heavy chain constant regions, such as
complement fixation or binding to Fc receptors; clonal lineage
analysis, which is used to trace clonal evolution of HIV-1
broadly neutralizing antibodies; and B-cell network analysis
that can link mature antibody sequences to their germline
precursor sequences. Extrapolation of these procedures for
analyzing paired VH/VL repertoires was also discussed. The
readers attracted to this review article will likely appreciate the
detailed description of statistical tools and their features that
can be used for analysis and interpretation of NGS big data sets,
along with a comprehensive list of software tools available for
sequence error correction, annotation, and evaluation of B cell
repertoires. This is followed by a review in which Miho et al.
discuss four computational strategies: (i) measuring immune
repertoire diversity, (ii) clustering and network approaches to
resolve the sequence similarity architecture, (iii) phylogenetic methods to retrace antigen-driven evolution, and (iv) machine learning methods to dissect naïve and antigen-driven repertoire convergence. Furthermore, they summarize outstanding questions in computational immunology and propose new directions for systems immunology by possibly linking NGS-based potential metrics with computational discovery of immunotherapeutics, vaccines, and immunodiagnostics. These two reviews are followed by a mini-review article by Rouet et al., which specifically addresses the strategies for NGS of phage- and other antibody-display libraries, and list NGS platforms and analysis tools. This review also touches briefly on bioinformatic tools and applications to design validation with analyses of naïve antibody libraries, affinity maturation and epitope mapping with specific examples from literature. After these three reviews, our Research Topic addresses a challenging question of how B-cell receptor repertoire sequencing can potentially be enriched when coupled with structural antibody data, as described in the review by Kovaltsuk et al.. This review covers the basic principles about structural architecture of IgG, repertoire sequencing technologies and antibody structural properties. Further, they highlight on computational approaches and tools that leverage antibody structure information and provide a generalized workflow of antibody modeling. Overall, the authors illustrate how these two data types—NGS DNA sequences (i.e., BCR-seq) and atomic structures, that can enrich one another and yield potential for advancing our knowledge of the immune system and improving antibody engineering and developability. Along this line of work, Mishra and Mariuzza review the structural basis of antibody affinity maturation from NGS data. Interestingly, they looked at the studies of antibody affinity maturation prior to and after NGS. They further emphasized how important the NGS is for the reconstruction of antibody clonal lineages in immune responses to viral pathogens, such as HIV-1. They discussed in detail about various mechanisms of paratope preorganization, rigidification, reorientation, and indels as described for many antibodies. Overall, this review provides a more holistic perspective to structural basis of antibody affinity maturation from the point of next-generation sequencing.

To finish this topic, we aptly include a perspective article on reproducibility and reuse of adaptive immune receptor repertoire data. We are delighted to have included an excellent contribution from the Adaptive Immune Receptor Repertoire (AIRR) community (Breden et al.), which provides an overview of the founding principles and presents the progress it has made to develop and promote standards and recommendations for best practices and data-sharing protocols. In conclusion, NGS combined with innovative single-B-cell technologies has the potential to yield millions of native human antibody sequences and some of them that could match with therapeutic antibodies (13, 14). This suggests a possible implication for data mining in the NGS repositories for discovering therapeutic antibody candidates in future. Also, large-scale NGS analysis of individual antibodyome will lead to improved insights into overall diversity of the human antibody repertoire and B cell immunogenetics (15–17).

AUTHOR CONTRIBUTIONS

PP wrote the manuscript. All authors contributed to this work and approved the final version of the manuscript.

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The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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