Title: Looking for Therapeutic Antibodies in Next Generation Sequencing Repositories.

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Abstract: Recently it has become possible to query the great diversity of natural antibody repertoires using Next Generation Sequencing (NGS). These methods are capable of producing millions of sequences in a single experiment. Here we compare Clinical Stage Therapeutic antibodies to the ~1b sequences from 60 independent sequencing studies in the Observed Antibody Space Database. Of the 242 post Phase I antibodies, we find 16 with sequence identity matches of 95% or better for both heavy and light chains. There are also 54 perfect matches to therapeutic CDR-H3 regions in the NGS outputs, suggesting a nontrivial amount of convergence between naturally observed sequences and those developed artificially. This has potential implications for both the discovery of antibody therapeutics and the legal protection of commercial antibodies.

Introduction

Antibodies are proteins in jawed vertebrates that recognize noxious molecules (antigens) for elimination. An organism expresses millions of diverse antibodies to increase the chances that some of them will be able to bind the foreign antigen, initiating the adaptive immune response. This great diversity can now be queried using Next Generation Sequencing (NGS) of B-cell receptor repertoires, enabling rapid collection of millions of antibody sequences from any given individual [1–3].

The sequence of a protein, such as an antibody, is one of the chief vehicles to characterize the molecule in the patent claim[4]. Natural sequences however cannot be patented in the USA[5]. The seminal rulings in the Mayo and Prometheus cases set the precedent to reject patent claims to naturally occurring DNA sequences and it was subsequently extended to include all products of nature[6,7]. The large numbers of antibody sequences now becoming available in the public domain raise the possibility of natural sequences being found that are identical to commercial sequences[5].

This is especially pertinent in the face of large-scale organized efforts to make naturally sourced antibody NGS data[8] and analytics[9,10] more accessible[11]. Specifically, we recently created the Observed Antibody Space (OAS) database that curates the NGS antibody data from public archives and makes them available for easy processing[12]. OAS currently holds ~1b (~960m heavy chain and ~60m light chain) sequences from 60 independent studies. The datasets cover multiple organisms (human, mouse, rabbit, camel etc.), individuals, immune states (non-immunized, immunized etc.) and include the deep sequencing of the totality of adaptive repertoires of mice[13] (246m sequences) and humans[3] (318m sequences). Here we quantify how close a sequence match to current Clinical Stage Therapeutic (CST) antibody sequences we can find in OAS.

Results

We used a set of 242 CST antibody sequences[14]. These are all sequences that have passed Phase I of clinical trials. We separately aligned the CST variable regions (VH or VL), combination of the three Complementarity Determining Regions (CDRs) from VH or VL and CDR-H3s to all the sequences in OAS (see methods). We performed the search across all organisms, individuals and immune states to be comprehensive and to reflect the myriad antibody types (humanized, fully human, chimeric or mouse[15]). The individual identities of the CSTs with respect to the best match from OAS are given in Figure 1 and Table 1 and their distributions are plotted in Figure 2. The aligned sequences are available in the Supplementary Material and on our website http://naturalantibody.com/therapeutics.

Analysis of Clinical Stage Therapeutic sequence matches to naturally sourced NGS datasets.

The best sequence identity matches of CST variable regions to naturally sourced NGS datasets in OAS are given in Figure 1A. Ninety (37.1%) CST heavy chains have matches within OAS of ≥ 90% sequence identity (seqID), with 18 (7.4%) ≥ 95% seqID. We find 158 (65.2%) therapeutic light chains with ≥ 90% seqID to an OAS sequence, with 96 (39.7%) ≥ 95% seqID, and 28 (11.5%) with 100% seqID. For 16 (6.6%) of the CSTs we find both heavy and light chain matches ≥ 95% seqID. In the most extreme case, Enfortumab, we were able to find both heavy and light chain matches of 98% seqID (the differences are H38:N-S, H88:S-Y, L37:G-S, L52:F-L where the first amino acid comes from Enfortumab and the second from an OAS sequence).

The largest discrepancy between the CSTs and any given natively-expressed antibody is typically concentrated in the CDR regions that determine antigen complementarity[16]. It remains unclear, however, the extent to which the highly mutable CDR loops of engineered therapeutics differ from those that are expressed naturally. We searched for the best CST matches to the CDR regions in OAS. The search was performed using IMGT-defined CDR triplets from the heavy or light chain, disregarding the framework region (Table 1, Figure 1B and Figure 2). We find 46 (19.0%) of CST heavy chain CDR regions to have matches to an OAS CDR region with ≥ 90% seqID, 15 (6.1%) with ≥ 95% seqID and 4 (1.6%) with 100% seqID. There were 156 (64.4%) CST light CDR regions with ≥ 90% seqID to an OAS CDR region, with 110 (45.4%) ≥ 95% seqID, and 90 (37.1%) with 100% seqID. We found perfect matches for both light and heavy chain CDRs in two CSTs, Obiltoxaximab and Zanolimumab.

Of the six Complementarity Determining Regions, CDR-H3 is the most sequence and structurally diverse[17,18]. Due to its key role in binding, it is subjected to extensive antibody engineering[19,20]. We checked how likely it is to find CST-derived CDR-H3s in naturally sourced sequences. To assess this, we searched for the best CST CDR-H3 matches in OAS, regardless of the framework region and remaining CDRs (Table 1, Figure 2). Of our 242 CST CDR-H3s, we found 54 perfect matches in OAS. The perfect matches tended to be for shorter CDR-H3s, however some longer loops with perfect matches were also found (see Supplementary Section 1). Twenty-nine perfect matches were found in the recent deep sequencing dataset of Briney et al. (2019)[3], suggesting that a single comprehensive NGS study can cover a significant amount of CDR-H3 diversity. Forty-seven perfect matches were found in OAS datasets other than that of Briney et al. (2019), showing that certain artificial CDR-H3 sequences can be independently observed in naturally sourced NGS. Twenty-two CDR-H3 matches were found in both Briney et al. data and other OAS datasets. These 22 shared sequences come from 9 humanized and 13 fully human CSTs. The 54 perfect CDR-H3 matches were distributed among all antibody types,

with 23 humanized, 22 fully human, 8 chimeric and 1 mouse (21.9%, 22.0%, 22.8% and 50.0% of each category, respectively). These results show that, despite the large theoretical sequence space accessible to the CDR-H3 region[3], therapeutically-exploitable CDR-H3 loops are found in just ~960m heavy chain sequences from 60 NGS studies (see Supplementary Section 2). This convergence, coupled with the fact that CDR-H3 loops often mediate antibody specificity[21] and binding affinity, could suggest intrinsically driven biases in antigen recognition[22], independent of artificial discovery methods.

Stratifying the best CST matches in OAS by antibody type.

The quality of the variable region match we could find for any given CST sequence appears to be highly dependent on the discovery platform/antibody type. Figure 3 suggests that antibodies produced via more artificial protocols such as humanization have lower variable region sequence identities to sequences in OAS from those of fully human molecules. For the majority of the fully human sequences we find matches of 90% seqID or better whereas matches to the majority of humanized molecules fall below 90% seqID (Figure 3). Chimeric antibodies appear to have seqID values intermediate between the two classes (Figure 3).

The CST antibody type also reflects the organism that produced the best NGS seqID match. Of the 100 fully human CSTs, the 90 (90.0%) most similar heavy chains, 100 (100.0%) most similar light chains, and 55 (55.0%) most similar CDR-H3 loops come from human-sourced NGS. Of the 105 humanized antibodies, 82 (78.0 %) of heavy chains, and 79 (75.2%) of light chains found closest matches in human-sourced NGS, while 71 (67.6%) of the best CDR-H3s matches were identified in mouse-sourced NGS. This further reflects the dominance of CDR-H3 in binding, as therapeutic companies tend to graft this loop from binding mouse antibodies to transfer specificity and binding affinity. It also suggests that data-mining a dataset such as OAS could provide a more accurate measure of antibody 'humanness' than our current metrics[23,24].

Discussion

Our results demonstrate that despite the theoretically large diversity allowed to antibodies[3,25], there exists a nontrivial convergence between artificially developed CSTs and naturally sourced NGS sequences. The closest NGS matches to CSTs were sourced from 48 of the 60 (80.0%) independent datasets available in OAS indicating that finding a close match to at least one CST is likely in most NGS datasets.

It was previously suggested that such an overlap could cause issues in claiming patents on therapeutic antibodies[5]. Until a legal opinion on the subject is available, it will remain unclear if NGS data poses potential problems for the patentability of monoclonal antibodies. Firstly, sequence is one of the main ways to characterize a molecule in a patent claim but by itself it does not offer information about its cognate antigen and therapeutic action. Such information however is crucial in patent application to demonstrate novelty of the invention[4]. NGS studies produce copious amounts of sequences but they do not alone relate them to any target molecule. Secondly, the antibody variable region is a product of two polypeptide chains (heavy and light) and its function is intimately related to this combination. Currently the majority of available NGS datasets report heavy and light chains separately. Thirdly, NGS outputs are known to have high error rates[26] and lastly, it is unclear how close a sequence-identity match to a publicly available sequence or its portion (such as CDR-H3) would cause issues in establishing the inventiveness of a sequence. For instance, there exist only four pairs of CSTs with heavy chain sequence identities of more than 94% (see supplementary section 3). In three of such high sequence-identity pairs, both sequences come from the same company and the

fourth is the original patent-expired antibody and its derivative. This is compared to 18 therapeutic heavy chains with matches to OAS better than 95%.

In light of ongoing efforts to further consolidate antibody NGS data and make it more accessible, it follows that finding therapeutic candidate sequences in published NGS datasets will become easier[11,27].

Methods.

We used the Observed Antibody Space database as the source of NGS sequences. Since its first release, the database has been expanded by four more datasets, most notably the recent deep sequencing of human antibody repertoire by Briney et al. 2019[3]. We employed the processed consensus sequences from Briney et al., removing any sequences with stop codons as these were deemed unproductive.

We used the 242 antibodies from Raybould et al.[14] as the source of Clinical Stage Therapeutic (CST) antibodies. We numbered the CST sequences according to the IMGT[28] scheme using ANARCI[29]. The CST sequences were classified into four groups, based on their International Nonproprietary Names[15,30]. Sequences with names containing ‘-xizumab’, ‘-ximab’ or ‘-monab’ were labeled as ‘chimeric’. Sequences not matching this criterion but containing ‘-zumab’ in their name were classified as ‘humanized’. Sequences that contained only ‘-umab’ in their name were labeled as ‘fully human’. Two mouse antibodies (Abagovomab and Racotumomab), were labeled as ’mouse’.

We separately aligned the heavy chain, light chain, the combination of the three heavy or light chains IMGT-defined CDRs and the IMGT-defined CDR-H3 of CSTs to each of the sequences in OAS[12]. We note a match if an IMGT position in a 'query' CST is also found in a 'template' sequence from OAS, and they have the same amino acid residue. For the full sequence alignments, the number of matches is divided by the length of the query and by the length of the template, producing two sequence identities. The final sequence identity is the average between these two. Calculating the sequence identity in this way prevents the scenario when one sequence is a substring of another, creating an artificially high sequence identity with a large length discrepancy. The CDR alignments were performed when the IMGT-defined loop lengths matched. The aligned sequences are available in the supplementary section 4 and through an interactive version of Figure 1 and Table 1 accessible at http://naturalantibody.com/therapeutics.

Disclosure Statement.

The authors report no conflict of interest

References

1. Miho E, Yermanos A, Weber CR, Berger CT, Reddy ST, Greiff V. **Computational Strategies for Dissecting the High-Dimensional Complexity of Adaptive Immune Repertoires**. Front. Immunol. 2018; 9:224; PMID: 29515569; http://dx.doi.org/ 10.3389/fimmu.2018.00224
2. Georgiou G, Ippolito GC, Beausang J, Busse CE, Wardemann H, Quake SR. **The promise and challenge of high-throughput sequencing of the antibody repertoire.** Nat. Biotechnol. 2014; 32(2):158-68; PMID: 24441474; http://dx.doi.org/10.1038/nbt.2782
3. Briney B, Inderbitzin A, Joyce C, Burton DR. **Commonality despite exceptional diversity in the baseline human antibody repertoire.** Nature 2019; PMID: 30664748; http://dx.doi.org/ 10.1038/s41586-019-0879-y
4. Germinario C, Bertoli S, Rampinelli P, Cini M. **Patentability of antibodies for therapeutic use in Europe.** Nat. Biotechnol. 2018; 36(5):402-405; PMID: 29734309; http://dx.doi.org/ 10.1038/nbt.4134
5. Ponraj P. **Next-generation sequencing may challenge antibody patent claims.** Nature 2018; 557(7704):166; PMID: 29743696; http://dx.doi.org/10.1038/d41586-018-05065-5
6. Harrison C. **Patent watch.** Nat. Rev. Drug Discov. 2012; 11:344–345; http://dx.doi.org/ 10.1038/nrd3735
7. Harrison C. **Isolated DNA patent ban creates muddy waters for biomarkers and natural products.** Nat. Rev. Drug Discov. 2013; 12(8):570-1; PMID: 23903213; http://dx.doi.org/ 10.1038/nrd4084
8. Cowell LG. **VDJServer: A Cloud-Based Analysis Portal and Data Commons for Immune Repertoire Sequences and Rearrangements.** Front. Immunol. 2018; 9:976; PMID: 29867956; http://dx.doi.org/10.3389/fimmu.2018.00976
9. Krawczyk K, Kelm S, Kovaltsuk A, Galson JD, Kelly D, Trück J, Regep C, Leem J, Wong WK, Nowak J, et al. **Structurally mapping antibody repertoires.** Front. Immunol. 2018; 9:1698; PMID: 30083160; http://dx.doi.org/10.3389/fimmu.2018.01698
10. López-Santibáñez-Jácome L, Avendaño-Vázquez SE, Flores-Jasso CF. **The pipeline repertoire of Ig-Seq analysis.** PeerJ 2018; http://dx.doi.org/ 10.7287/peerj.preprints.27444v1
11. Rubelt F, Busse CE, Bukhari SAC, Bürckert JP, Mariotti-Ferrandiz E, Cowell LG, Watson CT, Marthandan N, Faison WJ, Hershberg U, et al. **Adaptive Immune Receptor Repertoire Community recommendations for sharing immune-repertoire sequencing data.** Nat. Immunol. 2017; 18(12):1274-1278; PMID: 29144493; http://dx.doi.org/10.1038/ni.3873
12. Kovaltsuk A, Leem J, Kelm S, Snowden J, Deane CM, Krawczyk K. **Observed Antibody Space: A Resource for Data Mining Next-Generation Sequencing of Antibody Repertoires.** J. Immunol. 2018; 201(8):2502-2509; PMID: 30217829; http://dx.doi.org/ 10.4049/jimmunol.1800708
13. Greiff V, Menzel U, Miho E, Weber C, Riedel R, Cook S, Valai A, Lopes T, Radbruch A, Winkler TH, et al. **Systems Analysis Reveals High Genetic and Antigen-Driven Predetermination of Antibody Repertoires throughout B Cell Development.** Cell Rep. 2017; 19(7):1467-1478; PMID: 28514665; http://dx.doi.org/10.1016/j.celrep.2017.04.054
14. Raybould MIJ, Marks C, Krawczyk K, Taddese B, Nowak J, Lewis AP, Bujotzek A, Shi J,

Deane CM. **Five computational developability guidelines for therapeutic antibody profiling.** Proc. Natl. Acad. Sci. USA 2019; 116(10):4025-4030; PMID: 30765520; http://dx.doi.org/ 10.1073/pnas.1810576116

15. Jain T, Sun T, Durand S, Hall A, Houston NR, Nett JH, Sharkey B, Bobrowicz B, Caffry I, Yu Y, et al. **Biophysical properties of the clinical-stage antibody landscape.** Proc. Natl. Acad. Sci. USA 2017; 114(5):944-949; PMID: 28096333; http://dx.doi.org/10.1073/pnas.1616408114
16. Sela-Culang I, Kunik V, Ofran Y. **The structural basis of antibody-antigen recognition.** Front. Immunol. 2013; 4:302; PMID: 24115948; http://dx.doi.org/10.3389/fimmu.2013.00302
17. MacCallum RM, Martin AC, Thornton JM. **Antibody-antigen interactions: contact analysis and binding site topography.** J Mol Biol 1996; 262(5):732-45; PMID: 8876650; http://dx.doi.org/10.1006/jmbi.1996.0548
18. Krawczyk K, Dunbar J, Deane CM. **Computational Tools for Aiding Rational Antibody Design.** Methods in molecular biology (Clifton, N.J.) 2017; 1529:399-416; PMID: 27914064; http://dx.doi.org/0.1007/978-1-4939-6637-0_21
19. Knappik A, Ge L, Honegger A, Pack P, Fischer M, Wellnhofer G, Hoess A, Wölle J, Plückthun A, Virnekäs B. **Fully synthetic human combinatorial antibody libraries (HuCAL) based on modular consensus frameworks and CDRs randomized with trinucleotides.** J. Mol. Biol. 2000; 296(1):57-86; PMID: 10656818; http://dx.doi.org/ 10.1006/jmbi.1999.3444
20. De Kruif J, Boel E, Logtenberg T. **Selection and application of human single chain Fv antibody fragments from a semi-synthetic phage antibody display library with designed CDR3 regions.** J. Mol. Biol. 1995; 248(1):97-105; PMID: 7731047; http://dx.doi.org/ 10.1006/jmbi.1995.0204
21. Tsuchiya Y, Mizuguchi K. **The diversity of H3 loops determines the antigen-binding tendencies of antibody CDR loops.** Protein. Sci. 2016; 25(4):815-25; PMID: 26749247; http://dx.doi.org/10.1002/pro.2874
22. Morea V, Tramontano A, Rustici M, Chothia C, Lesk AM. **Conformations of the third hypervariable region in the VH domain of immunoglobulins.** J. Mol. Biol. 1998; 275(2):269-94; PMID: 9466909; http://dx.doi.org/10.1006/jmbi.1997.1442
23. Abhinandan KR, Martin ACR. **Analyzing the "Degree of Humanness" of Antibody Sequences.** J. Mol. Biol. 2007; 369(3):852-62; PMID: 17442342; http://dx.doi.org/ 10.1016/j.jmb.2007.02.100
24. Choi Y, Hua C, Sentman CL, Ackerman ME, Bailey-Kellogg C. **Antibody humanization by structure-based computational protein design.** MAbs 2015; 7(6):1045-57; PMID: 26252731; http://dx.doi.org/10.1080/19420862.2015.1076600
25. Glanville J, Zhai W, Berka J, Telman D, Huerta G, Mehta GR, Ni I, Mei L, Sundar PD, Day GMR, et al. **Precise determination of the diversity of a combinatorial antibody library gives insight into the human immunoglobulin repertoire.** Proc. Natl. Acad. Sci. USA 2009; 106(48):20216-21; PMID: 19875695; http://dx.doi.org/10.1073/pnas.0909775106
26. Kovaltsuk A, Krawczyk K, Kelm S, Snowden J, Deane CM. **Filtering Next-Generation Sequencing of the Ig Gene Repertoire Data Using Antibody Structural Information.** J. Immunol. 2018; 201(12):3694-3704; PMID: 30397033; http://dx.doi.org/

10.4049/jimmunol.1800669
27. Breden F, Luning Prak ET, Peters B, Rubelt F, Schramm CA, Busse CE, Vander Heiden JA, Christley S, Bukhari SAC, Thorogood A, et al. **Reproducibility and Reuse of Adaptive Immune Receptor Repertoire Data.** Front. Immunol. 2017; 8:1418; PMID: 29163494; http://dx.doi.org/10.3389/fimmu.2017.01418
28. Lefranc M, Pommié C, Ruiz M, Giudicelli V, Foulquier E, Truong L, Thouvenin-Contet V, Lefranc G. **IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains.** Dev. Comp. Immunol. 2003; 27(1):55-77; PMID: 12477501; http://dx.doi.org/10.1016/S0145-305X(02)00039-3
29. Dunbar J, Deane CM. **ANARCI: Antigen receptor numbering and receptor classification.** Bioinformatics 2015; 32(2):298-300; PMID: 26424857; http://dx.doi.org/10.1093/bioinformatics/btv552
30. Jones TD, Carter PJ, Plückthun A, Vásquez M, Holgate RGE, Hötzel I, Popplewell AG, Parren PWHI, Enzelberger M, Rademaker HJ, et al. **The INNs and outs of antibody nonproprietary names.** MAbs 2016; 8(1):1-9; PMID: 26716992; http://dx.doi.org/10.1080/19420862.2015.1114320

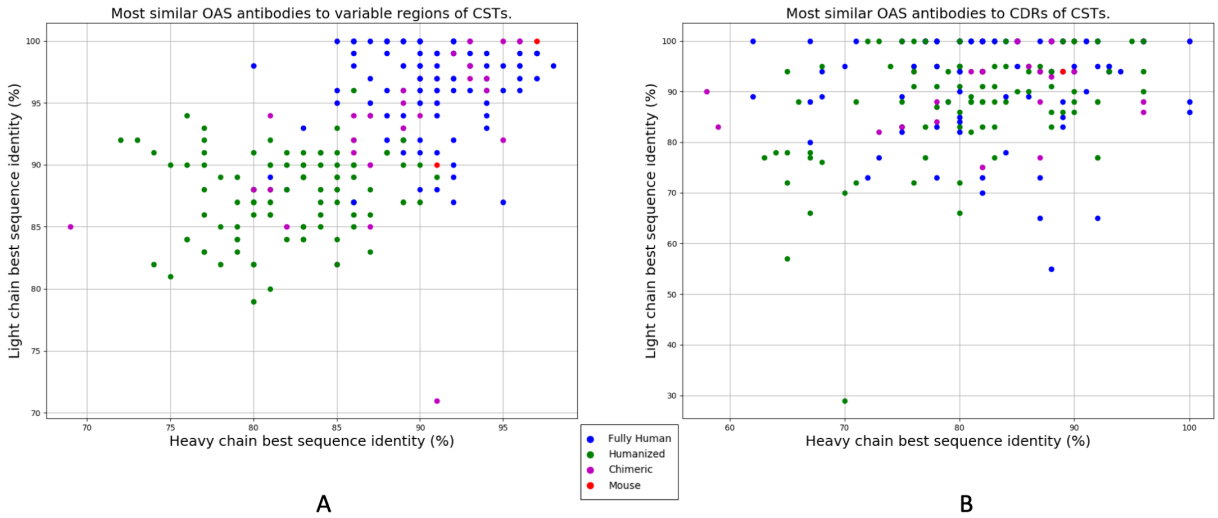


Figure 1. Best sequence identity matches to Clinical Stage Therapeutics (CST) in naturally sourced NGS datasets. A) Heavy and light chain variable regions of 242 CST sequences from Raybould et al.[14] aligned to variable region sequences in OAS[12]. **B)** Heavy and light chain IMGT CDR regions of 242 CSTs aligned to IMGT CDR regions in OAS. Fully human sequences are denoted by blue dots, humanized by green and chimeric by magenta. The two mouse sequences are shown in red. Interactive versions of these charts are available at http://naturalantibody.com/therapeutics.

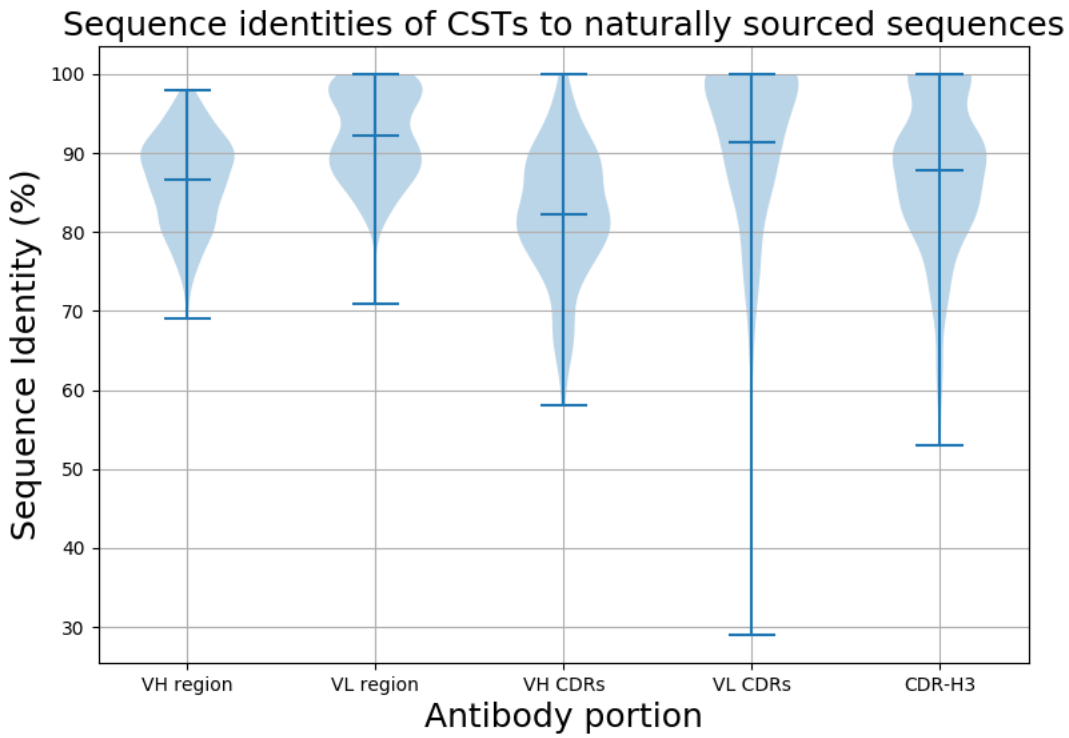
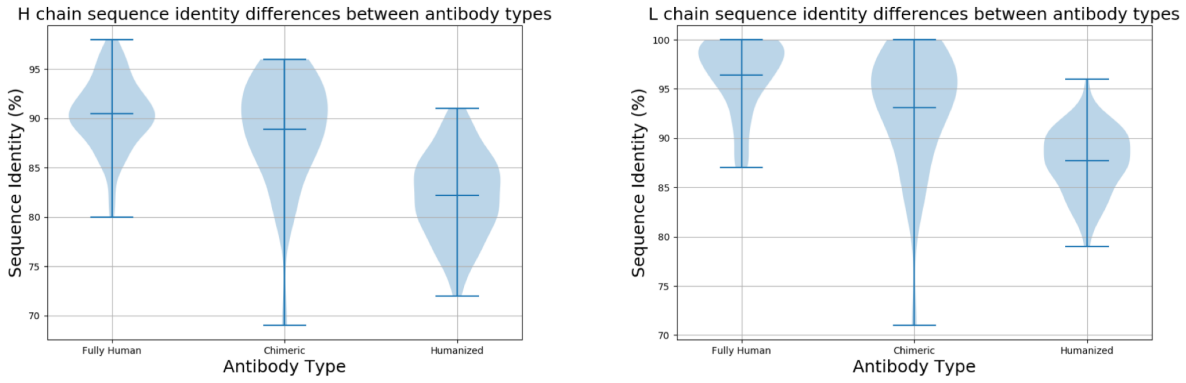


Figure 2. Distribution of sequence identity matches of Clinical Stage Therapeutics (CSTs) to naturally-sourced NGS. The violin plots show the distribution of sequence identities of the variable heavy (VH) and light (VL) chains, heavy and light CDR regions and CDR-H3 of CSTs to best matches in OAS.



A B

Figure 3. Sequence identity matches of Clinical Stage Therapeutic (CST) variable regions to naturally sourced NGS datasets stratified by CST antibody type. CST **A)** heavy chain and **B)** light chain identities to NGS sequences in OAS stratified by Fully Human, Chimeric and Humanized antibody types. The two mouse molecules were omitted as too small a sample.

Table 1. Best sequence identities of Clinical Stage Therapeutic (CST) antibodies to sequences found in public NGS repositories. Sequence identities are given for the best alignment of a sequence from a public repository to a CST heavy or light chain variable region, heavy or light CDR region or CDR-H3 alone (IMGT-defined). The CSTs are identified by their names in the leftmost column. The entries are sorted from top to bottom by the highest heavy chain identity. An interactive version of this table together with aligned sequences are available at http://naturalantibody.com/therapeutics.

CST Name	Best Heavy Chain Identity (%)	Best Light Identity (%)	Best Heavy CDRs Identity (%)	Best Light CDRs Identity (%)	Best CDR-H3 Identity (%)
Enfortumab	98	98	96	100	100
Racotumomab	97	100	90	100	92
Tabalumab	97	99	96	100	100
Emapalumab	97	99	93	95	87
Tremelimumab	97	97	94	94	88
Ascrinvacumab	96	100	96	100	100
Derlotuximab	96	100	89	100	92
Zolbetuximab	96	100	88	100	81
Ganitumab	96	99	92	100	91
Rilotumumab	96	98	93	94	100
Durvalumab	96	98	90	94	92
Patritumab	96	97	92	95	90
Brazikumab	96	96	90	95	94
Carotuximab	95	100	85	100	77
Varlilumab	95	98	89	100	91
Brodalumab	95	96	88	100	100
Futuximab	95	92	87	88	81
Ramucirumab	95	87	100	88	100
Zanolimumab	94	99	100	100	100
Foravirumab	94	98	89	100	100
Dusigitumab	94	97	100	86	100
Rituximab	94	97	90	94	85
Muromonab	94	97	82	100	83
Ublituximab	94	96	96	88	100
Dectrekumab	94	96	93	95	100
Necitumumab	94	95	93	94	92
Cixutumumab	94	94	89	85	82
Fasinumab	94	93	89	88	83
Sifalimumab	93	100	88	100	100
Modotuximab	93	100	82	100	91

Golimumab	93	99	88	94	94
Brentuximab	93	98	96	100	100
Suvratoxumab	93	98	87	94	87
Zalutumumab	93	98	85	100	88
Bavituximab	93	98	82	94	92
Basiliximab	93	97	88	93	90
Radretumab	93	96	80	84	100
Ofatumumab	92	100	90	100	93
Bezlotoxumab	92	100	89	100	91
Daratumumab	92	100	83	100	86
Inclacumab	92	100	75	100	88
Siltuximab	92	99	89	100	91
Canakinumab	92	99	85	100	100
Lirilumab	92	99	84	100	87
Abrilumab	92	97	85	100	90
Tisotumab	92	97	81	100	81
Indusatumab	92	96	82	100	84
Carlumab	92	92	82	70	83
Tovetumab	92	90	86	89	92
Utomilumab	92	89	88	55	100
Tesidolumab	92	87	92	65	100
Glembatumumab	91	99	92	100	100
Ipilimumab	91	99	88	100	90
Iratumumab	91	98	85	100	100
Cetuximab	91	97	82	94	92
Burosumab	91	97	80	94	90
Anifrolumab	91	96	84	89	90
Pritoxaximab	91	96	80	100	80
Seribantumab	91	95	78	95	83
Girentuximab	91	95	78	88	91
Guselkumab	91	94	80	82	90
Lenzilumab	91	91	78	83	83
Abagovomab	91	90	89	94	100
Domagrozumab	91	89	92	100	88
Briakinumab	91	88	87	65	75
Otelixizumab	91	71	82	75	83
Intetumumab	90	100	85	100	91
Icrucumab	90	100	82	100	78
Foralumab	90	100	81	100	90

Fulranumab	90	100	78	100	93
Aducanumab	90	100	78	100	88
Sarilumab	90	99	88	100	100
Bleselumab	90	98	80	100	84
Tezepelumab	90	98	80	100	80
Opicinumab	90	98	77	100	90
Panitumumab	90	97	89	94	90
Tomuzotuximab	90	97	82	94	92
Timolumab	90	97	80	100	100
Adalimumab	90	97	80	94	71
Figitumumab	90	96	91	100	88
Evolocumab	90	96	91	90	100
Berlimatoxumab	90	95	89	83	90
Tralokinumab	90	95	80	85	80
Ensituximab	90	94	81	94	85
Anetumab	90	92	82	73	84
Setrusumab	90	91	84	78	90
Itolizumab	90	90	82	88	83
Ianalumab	90	88	78	73	71
Elotuzumab	90	87	96	100	100
Emibetuzumab	90	87	87	94	100
Evinacumab	89	100	91	100	94
Eldelumab	89	100	81	100	94
Nivolumab	89	100	77	100	100
Avelumab	89	100	75	100	84
Denosumab	89	98	87	100	80
Atidortoxumab	89	98	67	88	83
Setoxaximab	89	96	85	100	91
Drozitumab	89	96	80	90	85
Indatuximab	89	95	87	94	100
Tarextumab	89	94	75	89	75
Amatuximab	89	93	82	94	100
Infliximab	89	93	75	83	90
Lorvatuzumab	89	92	88	86	100
Bimagrumab	89	92	87	73	100
Solanezumab	89	92	80	91	100
Mavrilimumab	89	91	72	73	61
Camrelizumab	89	90	92	88	100
Tigatuzumab	89	87	89	100	83

Anrukinzumab	89	87	85	90	91
Urelumab	88	100	80	100	86
Secukinumab	88	100	80	100	80
Olaratumab	88	100	77	100	78
Erenumab	88	99	71	100	82
Alirocumab	88	96	85	95	90
Gantenerumab	88	94	68	89	63
Orticumab	88	92	73	77	78
Crenezumab	88	91	95	100	100
Concizumab	88	91	80	95	85
Bapineuzumab	88	91	75	100	83
Actoxumab	87	100	83	100	86
Dupilumab	87	97	76	95	72
Rafivirumab	87	95	75	83	70
Margetuximab	87	94	82	94	84
Trevogrumab	87	94	79	88	69
Dinutuximab	87	90	86	95	83
Mirvetuximab	87	90	77	100	90
Olendalizumab	87	88	75	100	92
Quilizumab	87	86	88	91	100
Obiltoxaximab	87	85	100	100	100
Lampalizumab	87	83	79	94	75
Pamrevlumab	86	100	82	100	92
Fletikumab	86	100	80	100	85
Lanadelumab	86	100	67	100	73
Ustekinumab	86	99	78	100	83
Teprotumumab	86	98	85	100	90
Refanezumab	86	96	80	100	73
Galiximab	86	94	58	90	63
Coltuximab	86	92	96	86	100
Ibalizumab	86	92	87	95	80
Isatuximab	86	91	89	94	92
Otlertuzumab	86	90	92	77	88
Rovalpituzumab	86	90	88	94	90
Landogrozumab	86	89	81	89	100
Daclizumab	86	87	92	88	100
Etaracizumab	86	87	84	88	90
Enokizumab	86	87	80	72	86
Robatumumab	86	87	77	100	91

Tislelizumab	86	86	88	83	91
Lacnotuzumab	86	85	88	94	90
Panobacumab	85	100	84	100	80
Fezakinumab	85	96	70	95	71
Fresolimumab	85	95	62	89	84
Romosozumab	85	93	84	100	81
Dalotuzumab	85	91	80	100	90
Imgatuzumab	85	90	68	76	92
Bococizumab	85	89	77	83	81
Atezolizumab	85	89	77	77	90
Visilizumab	85	88	89	100	100
Lodelcizumab	85	88	70	70	90
Lintuzumab	85	87	96	100	100
Bimekizumab	85	84	67	66	66
Veltuzumab	85	82	90	94	92
Rozanolixizumab	85	82	73	82	80
Codrituzumab	84	91	83	91	87
Plozalizumab	84	91	73	100	87
Simtuzumab	84	90	92	100	100
Mogamulizumab	84	88	67	78	75
Tildrakizumab	84	87	92	100	100
Gevokizumab	84	86	79	88	75
Sacituzumab	84	85	96	94	100
Gedivumab	83	93	67	80	55
Obinutuzumab	83	91	78	100	83
Ozanezumab	83	90	90	100	83
Ixekizumab	83	90	78	91	75
Abituzumab	83	89	85	100	90
Trastuzumab	83	89	82	94	84
Etrolizumab	83	89	76	72	100
Ponezumab	83	89	64	78	77
Matuzumab	83	85	83	88	92
Motavizumab	83	85	75	88	83
Inebilizumab	83	84	90	90	92
Lifastuzumab	83	84	65	78	76
Tanezumab	82	91	80	83	86
Olokizumab	82	90	65	72	81
Ocrelizumab	82	88	93	94	93
Sirukumab	82	88	75	82	83

Andecaliximab	82	85	87	77	100
Palivizumab	82	84	86	94	100
Lumiliximab	81	94	59	83	88
Tocilizumab	81	92	82	100	83
Galcanezumab	81	90	75	83	83
Duligotuzumab	81	90	63	77	78
Roledumab	81	89	68	94	73
Vadastuximab	81	88	88	100	100
Vedolizumab	81	88	86	95	85
Mirikizumab	81	88	83	77	87
Natalizumab	81	87	90	100	100
Eculizumab	81	87	83	100	86
Pinatuzumab	81	86	89	86	100
Ficlatuzumab	81	86	81	88	90
Eptinezumab	81	80	70	29	100
Belimumab	80	98	62	100	62
Crizanlizumab	80	91	90	86	93
Depatuxizumab	80	88	76	94	88
Pertuzumab	80	88	75	83	91
Ligelizumab	80	88	71	88	81
Blosozumab	80	88	66	88	81
Ravulizumab	80	87	77	100	86
Fremanezumab	80	87	67	77	53
Clazakizumab	80	87	65	57	78
Pembrolizumab	80	86	86	90	84
Inotuzumab	80	82	80	95	100
Pidilizumab	80	82	76	94	90
Vatelizumab	80	79	82	88	92
Benralizumab	79	89	83	83	71
Certolizumab	79	87	81	100	100
Lebrikizumab	79	85	74	95	91
Epratuzumab	79	84	84	95	88
Satralizumab	79	84	71	72	83
Risankizumab	79	83	82	83	84
Reslizumab	78	89	92	77	100
Onartuzumab	78	85	78	87	75
Farletuzumab	78	82	96	90	100
Bevacizumab	77	93	90	88	93
Vonlerolizumab	77	92	65	94	80

Idarucizumab	77	91	83	95	87
Polatuzumab	77	90	80	95	80
Rontalizumab	77	88	76	95	90
Parsatuzumab	77	86	81	82	93
Gemtuzumab	77	83	80	86	88
Spartalizumab	77	83	76	91	90
Efalizumab	76	94	83	100	85
Alemtuzumab	76	90	80	66	91
Dacetuzumab	76	84	82	91	85
Tregalizumab	76	84	72	100	93
Omalizumab	75	90	76	100	71
Nimotuzumab	75	81	68	95	62
Pateclizumab	74	91	81	88	81
Teplizumab	74	82	82	100	83
Ranibizumab	73	92	81	88	93
Mepolizumab	72	92	78	95	84
Ontuxizumab	69	85	78	84	82