Patents

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Redefining antibody patent protection using paratope mapping and CDR-scanning

Patent protection for therapeutic monoclonal antibodies requires a fundamental shift in strategy following *Amgen v. Sanofi*, which invalidated broad functional claims for antibody genera in the USA.

Antibody therapeutics, like small-molecule drugs, undergo extensive research and development before reaching the market, so inventors understandably seek robust patent protection for their intellectual property (IP). The most straightforward method of patenting small-molecule or large-molecule drugs is to claim their exact chemical structures or amino acid sequences. However, the effectiveness of this narrow approach is limited because minor structural modifications can often be made while maintaining the drug's mechanism of action and therapeutic effects, leaving the IP easy to evade by making only a few modifications. For small molecules, the standard patent strategy is to claim the scaffold structure of the parent compound 'species' in addition to a 'genus' of related structures that are defined by their shared characteristics and that retain the effects of the parent molecule. We propose that antibodies can be similarly protected using structure-based genus claims around an antibody's target-binding residues, the 'paratope'.

Both small-molecule drugs and antibodies are protected using utility patents that claim composition of matter or methods of use. To be allowed, a patent application must accurately enable the invention and provide a written description. Enablement means that the invention is described in sufficient detail that a person with ordinary skill in the art can "make or use" the claimed invention, while written description requires disclosing a detailed description and examples that demonstrate possession of the actual invention at the time of filing[1].

Antibody genus patents were historically allowed with broad claims that described antibody function, reflecting the limited scientific techniques available to define antibody sequence and structure at the time monoclonal antibodies (mAbs) were first isolated. Antibody functional claims typically involved the ability to bind a specific protein target (an 'antigen') or a distinct set of amino acids within the antigen (the 'epitope') (Fig. 1). By claiming any antibody that bound the antigen or epitope, these patents claimed perhaps millions of possible antibody compositions that the inventor did not actually possess. This strategy is no longer viable in the USA following the landmark 2023 case *Amgen v. Sanofi*, where the Supreme Court unanimously ruled that patent claims covering a genus of functionally defined PCSK9-inhibiting mAbs were invalid[2].

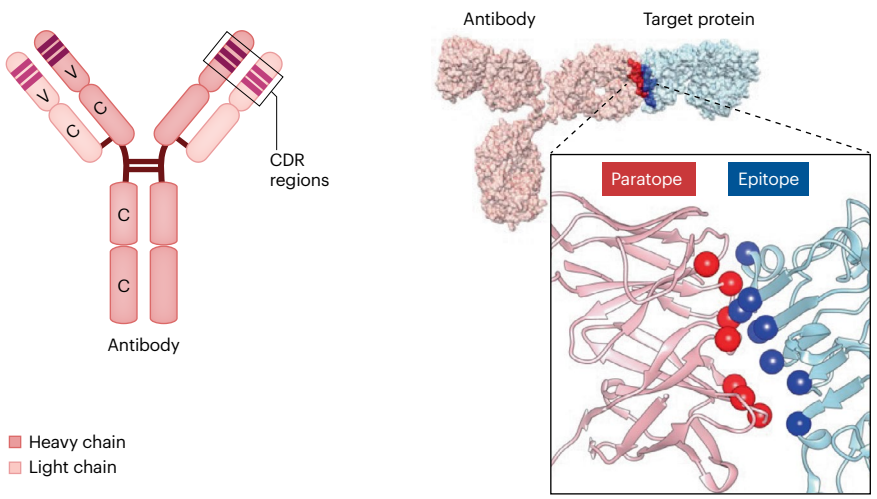


Fig. 1 | Illustration of antibody CDRs, paratopes and epitopes. Human antibodies comprised two protein chains, heavy and light. Each antibody possesses six complementarity-determining regions (CDRs), three in the heavy chain variable region and three in the light chain variable region, that define the specificity of antigen binding. Specific amino acids in the CDRs — the paratope — make contact with specific amino acids on the target antigen — the epitope. These paratope residues define the physical binding points of the antibody, forming astructural feature that defines the specificity of each antibody. Paratope residues and permissible CDR substitutions cannot be identified or predicted solely from an antibody's sequence and must be determined experimentally. V, variable region; C, constant region.

In January 2024, the US Patent and Trademark Office (USPTO) issued guidance for patent examiners to assess compliance with enablement requirements[3]. Although these and other guidelines clarify the requirements for an antibody invention, they do not prescribe any technical approaches for achieving enablement and written description. This has provoked concern that perhaps there is "no way to describe genus claims to antibodies that satisfy the court's current tests"[4].

We suggest that recent guidance, case law and technology provide a pathway to robust

patent protection using a strategy of claiming a genus of structurally related antibodies defined by a common 'paratope' (the residues of the antibody that contact the target antigen) plus all of the alternate forms of the antibody with complementarity-determining region (CDR) amino acid substitutions that permit binding. This strategy has precedence in the approach traditionally used for claiming small-molecule drugs around a core chemical scaffold with permissible R-group substitutions. Large numbers of antibody amino acid substitutions can now reasonably be created using scientific advancements that allow high-throughput cloning, sequencing and antibody testing. By formulating an antibody claim strategy around paratopes and permissible CDR substitutions, inventors can (1) construct claims around an antibody's common structural feature, (2) demonstrate both enablement and written description of the genus of antibodies in their possession, and (3) secure robust protection against potential infringement.

Table 1 | Key cases and references

Case	Issue	Summary
Amgen v. Sanofi (Supreme Court, 2023)	Lack of enablement	Functional claims for a genus of antibodies that bind PCSK9, where specifications included 26 antibodies. Invalidated as a result of lack of enablement; patents did not teach how to make the full genus of antibodies.
Baxalta v. Genentech (Federal Circuit, 2023)	Lack of enablement	Functional claims for a genus of antibodies that bind factor IX or IXa and increase procoagulant activity, where specifications included 11 antibodies. Invalidated as a result of lack of enablement, citing similarity to *Amgen v. Sanofi*.
AbbVie v. Janssen (Federal Circuit, 2023)	Lack of written description	Functional claims for a genus of antibodies that bind and inhibit interleukin-12, where specifications included almost 300 antibodies. Invalidated as a result of lack of written description, noting that antibodies were not representative of the genus.
Ex parte Chamberlain (referred to as *In re Xencor* in Federal Circuit) (USPTO Appeals Review Panel, 2024)	Lack of written description	Method of treatment (means plus function) claims for a genus of antibodies against C5. Invalidated as a result of lack of written description (albeit due to other parts of the claim).
Teva v. Lilly (Massachusetts District Court, 2023; appeal pending in Federal Circuit)	Lack of written description	Method of treatment claims designed to cover a broad genus of antibodies targeting calcitonin gene-related peptide to treat migraine. Invalidated as a result of lack of written description.

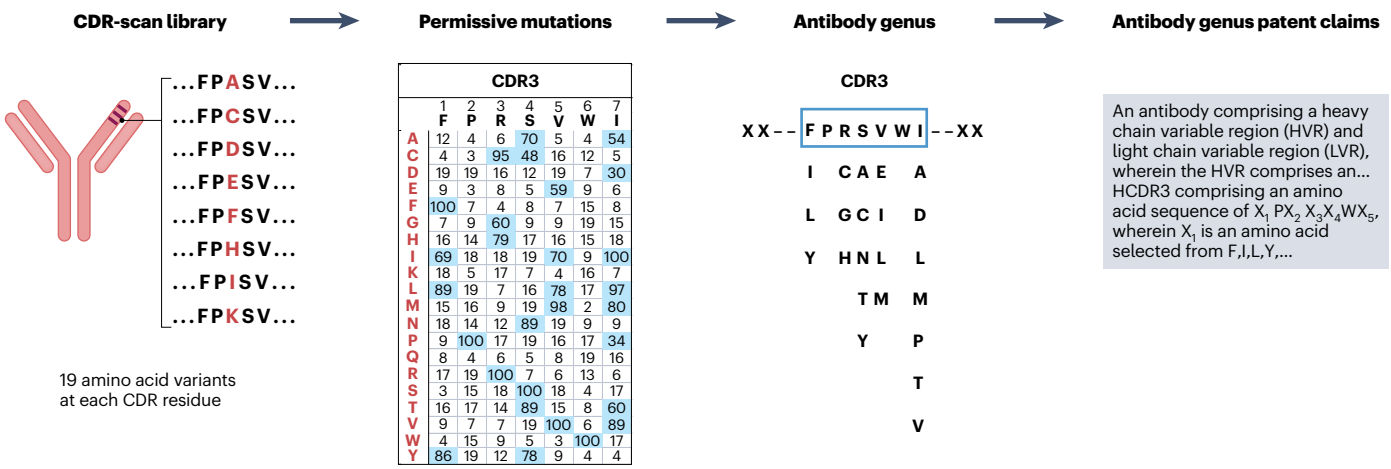
Enablement requirement for antibodies

Central to any US patent strategy is fulfillment of the enablement requirement outlined in 35 USC §112(a), which mandates that patent specifications must describe the invention, such that one skilled in the art can make and use the claimed invention. Sufficient detail must be provided so that the invention can be made and used without an "unreasonable" amount of experimentation. When mAbs were first isolated in 1975 (ref. 5), technologies to characterize antibodies by their sequence were not readily available. Inventors described and claimed antibodies using functional descriptions based on antigen binding and, later, more precisely by describing the epitope bound on the antigen[6]. This strategy could cover an almost infinite number of antibody sequences that bind a target through a multitude of different mechanisms. Despite being an apparent exception to the enablement rule, it held for decades as a result of the complexity of antibodies and limitations of technology.

The growing commercial importance of antibodies[7] coupled with scientific progress allowing antibodies to be described by sequence and structure has led patent examiners to hold inventors to increasingly higher standards and require more detailed antibody information[8]. The courts have now supported these more stringent standards (cases and examples cited here are summarized in Table 1). Following the landmark 2023 *Amgen v. Sanofi* ruling, a case that began in 2014, broad functional antibody patent claims based on antigen or epitope binding are no longer valid in the USA[2,9,10]. In brief, Amgen sued Sanofi alleging infringement of its patents for antibodies against the protein PCSK9, where the antibodies inhibited interactions with the low-density lipoprotein (LDL) receptor to lower LDL cholesterol[11,12]. Amgen's patent claims were based on a set of 26 antibodies and claimed any antibody that bound the corresponding epitope of PCSK9. Sanofi countered that Amgen's claims were not enabled. In 2023 the US Supreme Court unanimously ruled that the broad genus claims of Amgen's patents were invalid because the antibodies and methods described did not enable a person skilled in the art to make the complete set of claimed antibodies without undue experimentation. Instead, the court ruled that Amgen had merely provided methods that could be used to generate mAbs that bind and block the PCSK9–LDL receptor interaction. The court stated that instead of providing a proper roadmap, the information disclosed in the Amgen patents were "little more than two research assignments" and commented that "the more one claims, the more one must enable"[2].

Subsequently, the Federal Circuit applied these same factors in several other biotech cases to emphasize that enablement requires reduction to practice (that is, a demonstration that an invention is operable), not just instructions or predictions. For example, in the 2023 decision in *Baxalta v. Genentech*, the court invalidated claims directed to a genus of mAbs that bind blood coagulation factors IX or IXa to increase procoagulant activity[13]. The patent in question disclosed 11 mAbs with this function, along with a method of producing and screening for similar mAbs[14]. The courts determined that the facts of this case were "materially indistinguishable from those in *Amgen*" and that "the roadmap simply directs skilled artisans to engage in the same iterative, trial-and-error process the inventors followed to discover the eleven antibodies they elected to disclose"[13].

In Europe, requirements around enablement are different than in the USA. Target- and epitope-based patent claims are still deemed patent eligible by the European Patent Office (EPO) provided that the respective target or epitope is novel. This is because (i) the Boards of Appeal of the EPO considers that disclosure of a well-characterized target or epitope enables the skilled person to make antibodies based on routine methods and (ii) the European Patent Convention does not have a written description requirement. This means that cases in Europe are typically decided on the issue of obviousness. Canada, Australia, Japan and India essentially adopt the EPO position, and China and most Latin American countries apply a similar approach to the USPTO's.



	1 F	2 P	3 R	4 S	5 V	6 W	7 I
A	12	4	6	70	5	4	54
C	4	3	95	48	16	12	5
D	19	19	16	12	19	7	30
E	9	3	8	5	59	9	6
F	100	7	4	8	7	15	8
G	7	9	60	9	9	19	15
H	16	14	79	17	16	15	18
I	69	18	18	19	70	9	100
K	18	5	17	7	4	16	7
L	89	19	7	16	78	17	97
M	15	16	9	19	98	2	80
N	18	14	12	89	19	9	9
P	9	100	17	19	16	17	34
Q	8	4	6	5	8	19	16
R	17	19	100	7	6	13	6
S	3	15	18	100	18	4	17
T	16	17	14	89	15	8	60
V	9	7	7	19	100	6	89
W	4	15	9	5	3	100	17
Y	86	19	12	78	9	4	4

Fig. 2 | CDR scanning strategy to meet enablement and written description requirements. Robust patent protection can be achieved by scanning antibody CDR regions to delineate the paratope as the defining common structural feature of the antibody genus, where the genus encompasses all permissible substitutions within the CDRs.

Written description requirement for antibodies

Separately from requiring enablement, US patent law also requires that patentees "describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention"[1]. This 'written description' requirement prevents an inventor from filing a patent without actually possessing the invention, an inherent principal of the quid pro quo nature of the patent system that provides inventors with the right to exclude others from practicing their inventions in exchange for disclosing the knowledge that underlies the invention.

As per court rulings and USPTO guidelines, the written description for genus claims must provide sufficient description of either a representative number of species or common structural features that establish a strong correlation between structure and function to show that the inventor is in possession of the full scope of the claimed genus[1].

Before *Amgen v. Sanofi*, the USPTO considered fulfillment of the "newly characterized antigen test" as acceptable written description for antibodies, with the rationale that disclosure of a novel antigen would allow one skilled in the art to use conventional techniques to generate and screen for antibodies that bound the antigen[15]. In the Amgen case, "the court stressed that this ... test could not stand because it contradicted the quid pro quo of the patent system whereby one must describe an invention in order to obtain a patent." In February 2018, a USPTO memorandum was issued to discontinue the use of the newly characterized antigen test[16].

The courts have subsequently upheld the new requirements for written description, with an emphasis on demonstrating a common structural feature of a genus. For example, in *AbbVie v. Janssen*[17], AbbVie's patent specifications provided a mix of structural and functional claims that attempted to protect antibodies binding interleukin-12 with a specific binding strength[18,19]. A large number of antibodies (approximately 300) were included in the specification. However, the antibodies described were deemed not to have a common structural feature that was representative of the defined genus of antibodies, so the Federal Circuit invalidated the claims for failing the written description requirement[20].

A common patent strategy currently used to deter competitors from 'inventing around' a claimed species of antibody is to draft a claim covering all antibodies with a certain level of amino acid sequence identity to the parental antibody, typically >90 or >95% identity. Although such claims are usually still allowed in the USA, they are increasingly susceptible to written description challenge because, in most cases, written description of these claimed variants is not actually provided — that is, such variants are not made or tested in most patents[4]. Even if written description is provided, it is worth noting that such per cent identity claims are often easy to circumvent using modern technologies. For example, the average heavy-chain third CDR (HCDR3) for therapeutic mAbs is about 11 amino acids, so changing even a single amino acid would avoid a patent claim that specified >95% identity to HCDR3 (10/11 = 90.1%). Claiming per cent identity to the entire variable chain is even easier to circumvent, as antibody frameworks and variable portions of the CDRs (not including the paratope residues) are often easy to substitute using current antibody knowledge and experimentation. In Europe, the EPO considers that even minor modifications of the CDRs can affect binding to the target, so the EPO typically rejects CDR claims that provide a homology range. However, the EPO is presently less restrictive to claims of sequence identity within the variable chains[21].

Certain claim formats, such as 'means plus function' claims (for example, "a composition comprising a means for binding to antigen X") have been proposed as a potential workaround to expand patent coverage. Such claim sets are designed to cover the specific antibodies possessed while expanding patent enforcement to cover antibodies with 'equivalent' functions but different structural characteristics[4]. For example, the patents in the 2024 USPTO Appeals Review Panel (ARP)'s invalidation of Xencor's anti-C5 complement antibodies[22] use such a means-plus-function genus claim format. A March 2024 memo by the USPTO also addresses the use of means-plus-function claims[23]. Using a similar strategy, patents in the 2023 *Teva v. Lilly* case[24] tried to broadly claim antibodies written in the format of "a method of treating X by administering an antibody against Y" but were invalidated by the court. Although these strategies have not yet been definitively settled by the courts, the decisions so far suggest that such claim formats will also be subjected to stringent written description tests and thus are prone to being invalidated.

Comprehensive CDR scanning to enable genus claims

As part of its decision in *Amgen v. Sanofi*, the Supreme Court reiterated that a patent should provide specific instructions rather than simply propose random trial-and-error experiments, and should preferably describe some "general quality running through the genus that gives rise to the claimed function"[2]. The January 2024 USPTO *Guidelines for Assessing Enablement* explains why Amgen's functional antibody genus claims were invalidated as a result of lack of enablement[3]. However, the guidelines also clarify the Supreme Court's position that specifications do not need to "describe with particularity how to make and use every single embodiment within a claimed class." Instead, experimentation should be "reasonable" and consistent with the patent evaluation framework (known as the *Wands* factors)[25]. Although these guidelines clarify the requirements for enablement and written description, they do not prescribe any technical approaches to fulfill these requirements for antibody genus claims.

We propose that USPTO guidance and case law increasingly point toward a strategy for robust patent protection that can be achieved by mutational scanning of antibody CDR regions to (1) delineate the critical paratope residues as the defining common structural feature of an antibody genus and (2) identify all permissible substitutions within the CDR regions (Fig. 2). Paratope amino acids are the defining element of an antibody's specificity that are directly responsible for antigen binding. This means that paratope residues form the common structural feature of an antibody genus that either cannot be changed at all without diminishing binding or can be changed to only certain other very specific amino acids (for example, with similar side chains). CDR residues not encompassed by the paratope are usually more variable in nature and can be changed to a much broader array of amino acids without affecting binding. An inventor who makes and tests every individual CDR substitution could undisputably claim every individual CDR substitution with both enablement and written description fulfilled, thereby clearly defining the antibody genus being patented.

To define all permissible substitutions within the CDRs, each CDR residue must be individually mutated to all 19 other amino acids and tested to identify those that permit antibody binding to the target. This strategy defines residues that comprise the paratope, any additional non-paratope CDR residues that are critical for binding, and all permissive substitutions at each CDR residue. The 6 CDRs of an immunoglobulin G (IgG)-based antibody typically encompass up to 60 amino acids. With 19 possible natural amino acid substitutions, making and testing 19 variants at each individual residue ($60 \times 19 = 1{,}140$ individual substitutions) is reasonable using modern high-throughput laboratory techniques. By actually making and testing these variants (that is, reducing them to practice), the patentee clearly fulfills both enablement and written description requirements. Applicants can claim the structural genus that comprises the permissive variants, as well as combinations thereof. The resulting data enable one skilled in the art to "visualize or recognize" members of the genus (as per the language used in *AbbVie v. Janssen*) without the undue "trial and error" process disdained by the courts and the USPTO. By contrast, testing all possible combinations of variations, 19^{60} permutations, would not be considered "reasonable" and in any case it would probably be deemed unnecessary to demonstrate "every single embodiment within a claimed class."

An example claim using CDR scanning data could be written as:

"An antibody comprising a heavy chain variable region (HVR) and light chain variable region (LVR), wherein the HVR comprises an … HCDR3 comprising an amino acid sequence of $X_1PX_2X_3X_4WX_5$, wherein X_1 is an amino acid selected from F, I, L, Y, … ".

Rather than testing all 19 amino acid variants at each position, an alternative and more traditional approach is to assess only a subset of similar amino acids (for example, conserved substitutions representative of the class of amino acid). Although this is still feasible, it is often difficult to predict what class of substitutions are permissible. As there are only 19 possible natural amino acid substitutions (rather than an infinite number of R group substitutions around chemical scaffolds), it is reasonable and advantageous to test all possible amino acid substitutions (that is, all individual species that comprise the genus) to achieve the broadest patent coverage.

As an added benefit, binding data from comprehensive CDR scanning also identify substitutions that improve antibody binding, which provides valuable data for antibody engineering. This also provides the basis for additional IP, with patent composition claims that are novel and non-obvious independent of the original sequence claims. Aside from binding, other properties of antibodies can similarly be protected using this same strategy, for example, residues that define an antibody's function, pharmacokinetics, stability, pH sensitivity or other properties.

Table 2 | Laboratory methods to evaluate binding of antibody libraries of mutated CDRs

CDR scanning method	Practical considerations	Supports genus claims?
High-throughput arrayed expression of individual proteins	• Individual expression and testing of about 1,000 mAbs • Also provides binding improvement data for antibody engineering applications and new independent patents	Yes
Yeast display	• Screens pooled mAb variants • Does not quantify the binding activity of individual substitutions	Yes
Phage display	• Screens pooled mAb variants • Does not quantify the binding activity of individual substitutions	Yes

Mutagenesis methods to identify permissive CDR substitutions

The experimental methods to mutate, express and physically test every individual variant of an antibody's CDRs are now reasonable using a number of technical approaches, including high-throughput (for example, arrayed) protein production of individual clones[26], phage display[27,28] and yeast display[29] (Table 2).

A range of other experimental methods exist to identify the paratope of an antibody (Table 3). Several of these methods, such as co-crystallography and cryo-electron microscopy, are extensively used by the scientific community to understand antibody interactions. Further techniques include nuclear magnetic resonance spectroscopy, hydrogen deuterium exchange, mass spectrometry, hydroxyl radical footprinting, shotgun mutagenesis alanine scanning[30] and fast photochemical oxidation of proteins[31]. Although these methods can offer detailed visualization of the binding interface between the antibody and protein of interest, they do not provide written description of amino acid substitutions that are permissive for target binding. Thus, although these methods are effective in defining the paratope, they would still require follow-up studies with CDR scanning mutagenesis studies to support

Table 3 | Technologies to identify antibody paratopes and CDR substitutions for patent support

Paratope mapping method	Identifies	Practical considerations	Supports genus claims?
Comprehensive mutagenesis scanning of CDRs	• All energetically important paratope residues • Any other CDR residues critical for binding • All permissible substitutions at every CDR residue	• Requires construction and testing of a large antibody library • Critical residues identified may be involved in antigen contact or serve other essential functions	Yes
Alanine scanning of CDRs	• All energetically important paratope residues • Any other CDR residues critical for binding	• Does not identify permissible substitutions at each residue	No
X-ray crystallography, cryo-EM, NMR	• All contact paratope residues	• Does not identify permissible substitutions at each residue • Does not identify energetically important CDR residues required for binding	No
HDX/MS, HRPF/MS, FPOP/MS	• Contact paratope regions	• Does not identify permissible substitutions at each residue • Does not identify energetically important CDR residues required for binding	No
Computational predictions	• Theoretical predictions of paratope residues and permissible substitutions	• Predictions must be experimentally 'reduced to practice' • Predictions are unlikely to satisfy written description	No

Cryo-EM, cryo-electron microscopy; NMR, nuclear magnetic resonance; HDX, hydrogen deuterium exchange; MS, mass spectrometry; HRPF, hydroxyl radical protein footprinting; FPOP, fast photochemical oxidation of proteins.

robust claim sets around a structural genus of antibodies. Structural modeling using artificial intelligence algorithms can also be used to predict antibody paratopes and possible substitutions, but it is unlikely that the USPTO and courts would deem such computational predictions satisfactory for written description requirements, as they are not currently regarded as experimental "reduction to practice."

Conclusions

Patent strategies for claiming broad antibody genera require a fundamental change in strategy following recent guidance and case law. Although new requirements for enablement and written description have been defined, a consensus for fulfilling these requirements has not yet emerged. This void leaves existing antibody patents vulnerable as a result of their previous reliance on functional claims and their limited composition claims, with even a single substitution in a CDR evading infringement of many existing antibody patents.

Comprehensive CDR scanning offers a solution to craft antibody genus composition claims based on the structural commonality of the paratope and permissible substitutions across the CDRs. This strategy, based on antibody sequence and structure, aligns with new legal guidelines, case law and current technical feasibility, and it mirrors the long-accepted compositional claim format for small-molecule structure–activity relationships. Aside from antibodies, other emerging protein-based therapeutics, such as cytokines, hormones, enzymes and viral vectors, are of increasing importance. These molecules, too, could benefit from a similar active-site scanning approach to support structure-based genus claims for broader patent protection.

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Competing interests

Integral Molecular is a biotech company that offers protein engineering services on a fee-for-service basis. X.D., S.S.R.B, E.D. and B.J.D. are current employees and shareholders of Integral Molecular.