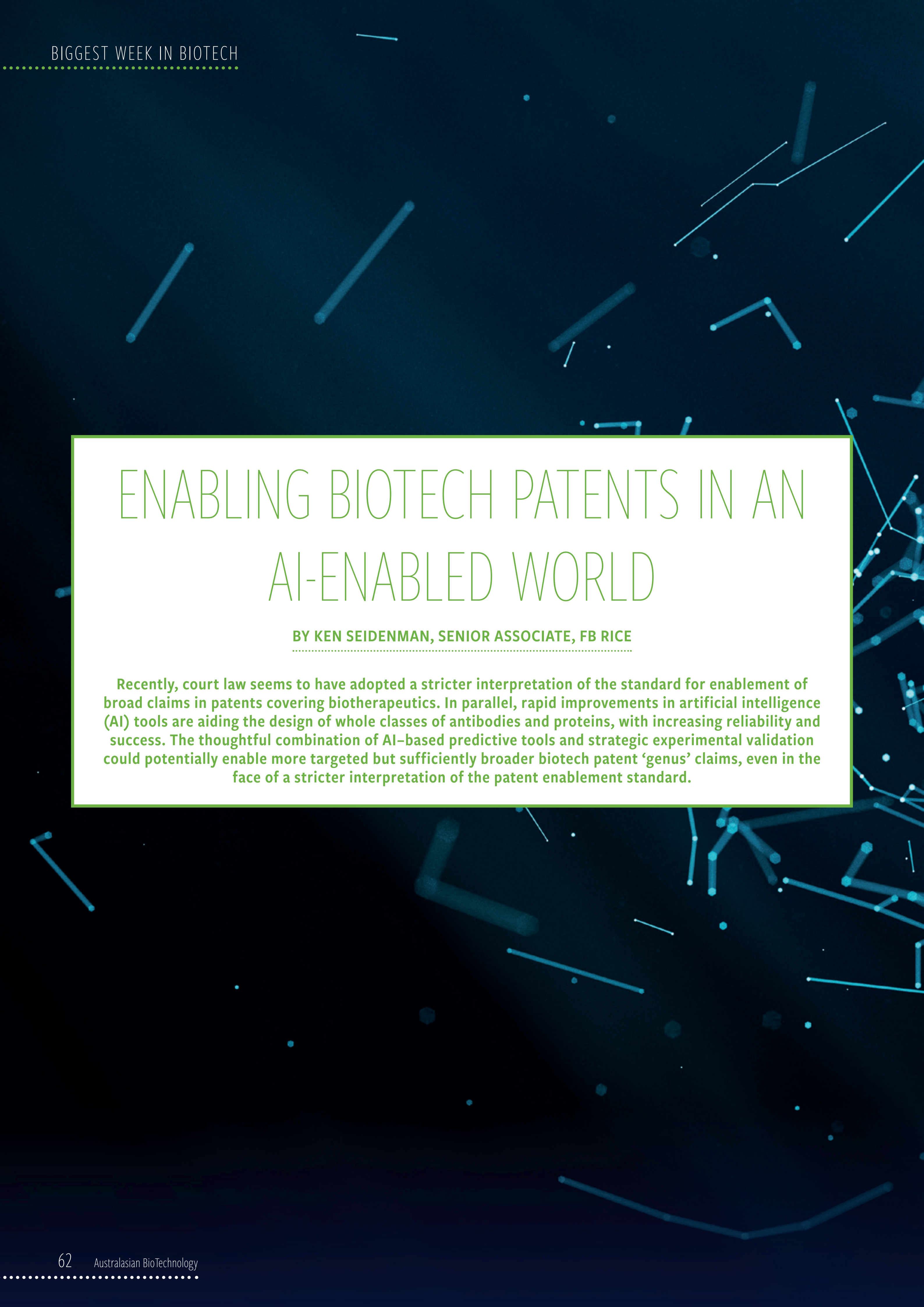

ENABLING BIOTECH PATENTS IN AN AI-ENABLED WORLD

BY KEN SEIDENMAN, SENIOR ASSOCIATE, FB RICE

Recently, court law seems to have adopted a stricter interpretation of the standard for enablement of broad claims in patents covering biotherapeutics. In parallel, rapid improvements in artificial intelligence (AI) tools are aiding the design of whole classes of antibodies and proteins, with increasing reliability and success. The thoughtful combination of AI-based predictive tools and strategic experimental validation could potentially enable more targeted but sufficiently broader biotech patent 'genus' claims, even in the face of a stricter interpretation of the patent enablement standard.

MANY BIOTECHNOLOGY AND pharmaceutical patents include so-called 'genus' claims directed to a broad class of molecules defined around a limited number of working examples. Typically, the number of molecules/embodiments covered by such genus claims far exceeds the number that were made and tested (i.e., shown to be 'enabled' in patent terms) or would be likely to be made and/or tested in practice.

On the other hand, a claim limited to literally only the antibodies or proteins actually tested and shown to work would, in many cases, provide an ineffective commercial barrier to the patentee's competitors, who could quickly 'design around', with just a few changes, the few claimed embodiments. Competitors could thereby realise the benefit of the patentee's disclosed invention while avoiding infringement of the patentee's claims. The tension between these considerations is a continuing theme in patent law, which is well illustrated by the recently decided *Amgen Inc. v Sanofi* case at the Supreme Court of the United States (SCOTUS).

Amgen Inc. v Sanofi – a stricter enablement standard for genus claims?

Amgen's genus claims (in US patents 8,829,165 and 8,859,741) related to a class of antibodies based on their functions: 1) binding to specific amino acid residues on a target ligand protein (PCSK9); and 2) blocking PCSK9 from binding to low-density lipoprotein receptors. In the patent at issue, Amgen identified the amino acid sequences of 26 antibodies that perform these two functions, and depicted the 3D structures of two of these 26 antibodies. In its efforts to enable claims far broader than the 26 exemplified antibodies, Amgen offered scientists two methods: 1) a so-called 'road map', which directs scientists to generate antibodies and then test whether the antibodies achieve the functional features recited in the claims (i.e., how to go about screening for additional members of the genus); and 2) the use of 'conservative substitutions' to replace select amino acids in the antibody with other amino acids having similar properties, and then test the resulting antibody to see if it also achieves the claimed functional features.

In no uncertain terms, SCOTUS stated that these approaches typically presented in many biotechnology patent applications 'amount to little more than two research assignments', leaving a scientist to engage in 'painstaking experimentation' to see what works. In the court's view, 'that is not enablement. More nearly, it is a hunting licence'.

Notwithstanding the difficulty involved in showing that each and every member of a claimed class is enabled, the court held that 'if a patent claims an entire class of processes, machines, manufactures, or compositions of matter, the patent's specification must enable a person in the art to make and use the entire class. In other words, the specification must enable the full scope of the invention as defined by its claims. The more one claims, the more one must enable'.


Ken Seidenman

Drawing a better road map in silico

The rapid progress of computational methods in the ability to predict the structure and function of antibodies and other proteins ever more accurately from just their sequences promises a paradigm shift. It is increasingly possible to 'mine' vast sequence spaces efficiently to yield more focused and claimable genuses of in silico–vetted sequences predicted to correspond to functional antibodies or proteins. In effect, the strategic application of artificial intelligence AI-driven platforms could provide a far more reliable road map to the location of many or most of all functional embodiments within a far broader genus of possible antibody or protein sequences.

Such AI-enabled focused genuses would likely still be broad enough to present an effective barrier to design-around by competitors seeking to leverage the invention while avoiding patent claims. Importantly, as discussed below, patent claims to such genuses should be reasonably considered to be enabled across their full scope and not, as cautioned by SCOTUS, a mere 'hunting licence'.

AI – a potential game-changer for enabling genus claims for biotherapeutics

Increasingly sophisticated developments in the application of AI deep learning neural networks (DLNNs) to infer protein sequence-structure/function relationships are rapidly driving the evolution of a new paradigm to support the enablement of sequence/structure-based genus claims. The availability of rapidly expanding protein sequence and structure databases to train DLNNs is certainly accelerating progress in this area.

Among the notable milestones in the development of these AI platforms is the arrival of DeepMind's AlphaFold and AlphaFold2[1] AI deep learning–based protein structure prediction software. Building off the success of AlphaFold2, a similar approach has been applied specifically to antibody structure prediction (e.g., ABody Builder2).[2] Machine learning approaches have been used recently to efficiently model the 3D-antibody-antigen binding interactions of 6.9 million heavy chain complementarity determining region sequences to 159 antigens (one billion antibody-antigen binding

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[1] Jumper et al., (2021), 'Highly accurate protein structure prediction with AlphaFold,' *Nature*, 596:583-589

[2] Abanades et al., (2023), 'ImmuneBuilder: Deep-Learning models for predicting the structures of immune proteins,' *Communications Biology*, 6:574

Continued on page 66

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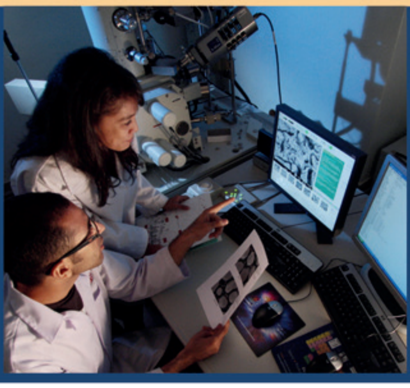

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Continued from page 64

pairs), as demonstrated for the Absolut! simulation framework.[3] Importantly, these tools are being combined with methods to optimise searching in otherwise hopelessly large sequence spaces (e.g., using techniques such as Bayesian optimisation to efficiently hone in on sequences of antibodies that will match or exceed the binding affinity of a starting antibody).[4]

Another promising approach to sequence diversification and optimisation of antibodies is to generate an initial set of antibodies (containing single mutations) to generate a training set of binding and non-binding sequences to develop a DLNN able to predict specific antigen-binding antibody sequences with high accuracy.[5]

Large-scale sequencing of human antibody repertoires and the availability of the sequences in databases, such as the Observed Antibody Space, is also facilitating the humanisation and developability of candidate therapeutic antibody sequences using deep learning platforms such as BioPhi.[6] Not surprisingly, machine learning approaches are also being implemented for other types of proteins (e.g., enzymes) to identify sequence variants that increase catalytic activity, stability, solubility, and/or substrate specificity.[7]

More recently, generative AI approaches have been used to design antibodies and proteins de novo – a so-called 'zero shot' design rather than as variations from a pre-existing antibody or protein.[8, 9] Indeed, this approach underlies the business model of emerging biotechnology companies, such as Absci, which are developing antibodies and other biologics starting from purely in silico–generated protein designs. In fact, generative AI methods have recently been applied to the problem of small-molecule drug design, as exemplified by the whimsically named Drug-GPT.[10]

Potential implications for biotechnology patent protection

While it is still too early to appreciate the full implications of AI-supported platforms to obtain genus claim coverage for antibodies and proteins, there is little doubt that such tools can be used to great effect to leverage a small set of starting sequences/structures to define large, AI-selected genuses of functional variants. Over the next few years, we are likely to see a great increase in the use of AI-based approaches to enhance and broaden the patent protection of antibodies and other biologics, and potentially small drug molecules.

Biotechnology innovators and patent practitioners alike would do well to explore the wealth of increasingly sophisticated AI platforms available, and devise sensible strategies to apply them, where relevant, to potentially support the enablement of sufficiently broad claims. Before making use of any AI-based platforms, particularly ones available on web servers, it will be critical for patentees to ensure that data confidentiality and ownership are maintained.

Hear Ken Seidenman and other experts discuss the impact of AI on biotech patents during the AusBiotech 2023 panel session, 'What does AI and machine learning mean for our innovators' IP?', on Thursday 2 November in Brisbane, Queensland.

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[3] Robert et al., (2021), 'Unconstrained generation of synthetic antibody-antigen structures to guide machine learning methodology for real-world antibody specificity prediction,' bioRxiv, p. 2021

[4] Akbar et al., (2023), 'Toward real-world automated antibody design with combinatorial Bayesian optimization,' *Cell Reports Methods* 3, 100374

[5] Mason et al., (2021), 'Optimization of therapeutic antibodies by predicting antigen specificity from antibody sequence via deep learning,' *Nature Biomedical Engineering*, 5:600-612

[6] Prihoda et al., (2022), 'BioPhi: A platform for antibody design, humanization and humanness evaluation based on natural antibody repertoires and deep learning,' MAbs, 14(1): 2020203

[7] Shin et al., (2023), 'Protein design and variant prediction using autoregressive generative models,' *Nature Communications*, doi.org/10.1038/s41467-021-22732

[8] Shanehsazzadeh et al., (2023), 'Unlocking de novo antibody design with generative artificial intelligence,' bioRxiv, doi.org/10.1101/2023.01.08.523187

[9] Watson et al., (2023), 'De novo design of protein structure and function with RFdiffusion,' *Nature*, doi.org/10.1038/s41586-023-06415-8

[10] Li et al., (2023), 'DrugGTP: A GPT-based strategy for designing potential ligands targeting specific proteins,' bioRxiv, doi.org/10.1101/2023.06.29.543848