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CRISPR patents: guidance from US courts

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Several recent cases from the US Court of Appeals for the Federal Circuit offer guidance on navigating the §101 legal framework with respect to CRISPR patent claims, as Pat Carson and Mira Atanassova Mulvaney of Kirkland & Ellis report.

The CRISPR gene manipulation system—an adaptive immune system used by microbes to defend against viruses, which has been repurposed into an efficient and reliable gene-editing technique in mammalian cells—has taken the genome engineering world by storm and has attracted much attention for its immense promise in the development of innovative diagnostic tools and therapies.

Since the filing of the first patent claiming CRISPR as a gene-editing tool in 2012, the US Patent and Trademark Office (USPTO) has granted more than 1,000 patents pertaining to CRISPR in some form, and over 600 applications with claims pertaining to CRISPR remain pending.

Building on the original CRISPR patents, which modestly claimed methods of sequencing certain CRISPR regions, and similarly narrow applications encompassing strain typing, phage resistance and uses in bacteria, the current CRISPR patent landscape appears enormously varied, both in terms of the patentees and applicants involved and the types of claims sought.

Pending claims include, for example, methods for editing DNA, methods of treating a neurodegenerative disease, methods for producing RNA compositions, compositions for treating a lysogenic virus, CRISPR assays, and kits for the treatment or prophylaxis of HIV infections.

Court challenges

Because CRISPR claims are fundamentally based on a naturally occurring phenomenon—a DNA sequence that helps bacteria recognise and fend off viruses—they may be susceptible to patent eligibility challenges under 35 USC §101. The Supreme Court's seminal decision in *Mayo Collaborative Services v Prometheus Labs* set the stage for the application of patent eligibility challenges to the biotechnology field.

In *Mayo*, the court struck down claims pertaining to the use of thiopurine drugs in the treatment of autoimmune diseases and articulated a framework for §101 analysis. The Supreme Court subsequently elucidated the *Mayo* test in *Alice Corp v CLS Bank* (2014), arriving at what has become known as the two-step *Alice/Mayo* test: (1) determine whether the claims are directed to a patentineligible concept (ie, a law of nature, a natural phenomenon, or an abstract idea); and, if so, (2) consider whether additional elements "transform the nature of the claim" into a patent-eligible application, such that there is an "inventive concept" that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Since *Alice*, courts have applied the *Alice/Mayo* test in a number of cases spanning diverse technologies. In the biotechnology field, *Ariosa Diagnostics v Sequenom* (2015) appeared to signal the US Court of Appeals for the Federal Circuit's hostility to method claims premised on the recognition of a natural phenomenon.

In *Ariosa*, the Federal Circuit struck down claims directed to a method of using cell-free foetal DNA (cffDNA) in non-invasive prenatal testing. Although agreeing that "the patent does not claim cffDNA" but rather "certain methods of using cffDNA" and noting that the claimed method "reflects a significant human contribution in [combining] man-made tools of biotechnology in a new way that revolutionised prenatal care," the panel ultimately found that the method at issue "amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to detect cffDNA" that does not provide an "inventive concept" sufficient to render the claims patent-eligible. The Supreme Court declined to revisit the issue.

In *Rapid Litigation Management v CellzDirect* (2016), however, the Federal Circuit appeared to change course. At issue in *CellzDirect* were claims directed to an improved process of preserving hepatocytes, stemming from the discovery that some hepatocytes could survive repeated freezethaw cycles. In finding that the claims were directed to patent-eligible subject matter, the court held that, although ostensibly based on a natural law, the claims were not directed to the natural law, but were

rather “directed to a new and useful laboratory technique for preserving hepatocytes,” which “requires an artisan to carry out a number of concrete steps.”

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This was different from *Mayo* and *Alice*, the court noted, where the claims “amounted to nothing more than observing or identifying the ineligible concept itself.” Rather, the *CellzDirect* claims were “like thousands of others that recite processes to achieve a desired outcome, eg, methods of producing things or methods of treating disease.”

The Federal Circuit again applied the *Alice/Mayo* test in the pharmaceutical context in *Vanda Pharmaceuticals v West-Ward Pharmaceuticals* (2018), addressing claims directed to a method of treating schizophrenia with a known drug—iloperidone—wherein the iloperidone dosage was based on the patient’s genotype, such that patients with lower activity of the CYP2D6 enzyme that metabolises iloperidone receive a lower dose of the drug than patients with normal CYP2D6 activity in order to avoid certain cardiac complications.

In finding the claims patent-eligible, the Federal Circuit again emphasised that the first step of the *Alice/Mayo* test looks to whether claims are “directed to” a patent ineligible-concept; claims that merely “depend upon”, “touch upon” and “address” laws of nature are not necessarily rendered patent-ineligible by step one. Although premised on the recognition of the relationship between iloperidone, CYP2D6 metabolism, and certain heart conditions, the claims were not directed to the relationship itself, but rather to an application of that relationship to treat a particular disease by engaging in a series of specific steps.

Guidance

In June 2018, the USPTO issued guidance to assist examiners in applying the Federal Circuit’s reasoning in *Vanda*. In highlighting what it understood to be the key lessons of the case, the USPTO suggested that method of treatment claims, “which apply natural relationships as opposed to being ‘directed to’ them” are generally patent-eligible, regardless of whether the treatment steps themselves are routine or conventional.

As the CRISPR field continues to progress and as new uses are developed for this technology, §101 challenges are likely to become a central focus of the CRISPR patent landscape. The current legal framework carries several implications for CRISPR claims.

First, in order to survive §101 scrutiny, CRISPR composition claims will likely require more than isolated CRISPR sequences that are otherwise naturally occurring. On the other hand, under the Federal Circuit’s reasoning in *Vanda*, claims directed to methods of treating diseases using CRISPR are more likely to be patent-eligible as applications of natural principles.

The claims that are likely to attract most attention from courts and practitioners alike will likely fall somewhere between these extremes. It is more difficult to predict how these claims will fare, but courts’ non-CRISPR jurisprudence offers some lessons.

A factor that courts do not discuss expressly in this context, but that nonetheless appears to play a role in the analysis of method claims, is the tangibility of what is claimed. Courts have tended to be less receptive to claims that seem to be directed to a mental inference than to claims that appear to involve concrete, tangible steps, even if the individual steps are well-known and conventional.

Courts likewise appear more willing to find patent-eligible claims that represent a significant improvement in the underlying technology, although the innovative nature of the claimed invention has not always been sufficient to save claims that courts have perceived as directed to the mere "identification" or "observation" of a natural principle.

Following the teaching of *CellzDirect*, claims directed to manipulating genetic sequences or to laboratory techniques to make use of genetic sequences are more likely to be found to be patenteligible, particularly if they include elements that clearly distinguish them from pre-existing technologies and their uses.

In the past decade, §101 has evolved from an obscure patentability requirement rarely raised by litigants and addressed by courts to a potential bar to biotechnology claims which courts deem too dependent on (or directed to) laws of nature and natural phenomena. Although recent years have seen many biotechnology claims fail the §101 enquiry, recent Federal Circuit jurisprudence offers guidance to practitioners on how to navigate the §101 legal framework with respect to CRISPR claims, keeping patents a viable and strong protection for CRISPR innovation.

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