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Cancer Drugs: Strategies For Patenting Antibody-Drug Conjugate Inventions

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Antibody-drug conjugate (ADC) is a promising class of cancer treatments with accelerating U.S. Food and Drug Administration (FDA) approval and rapidly growing market size as discussed in previous articles in this series. This article discusses patent strategies for ADC inventions.

Introduction

ADCs provide abundant opportunities for new cancer treatments, innovation, and collaboration across different industries because they combine three distinct technologies: (1) an antibody, (2) a toxic payload, and (3) a linker that joins them. While ADCs are based on the seemingly simple idea of using the targeting ability of antibodies to deliver more toxically potent drugs to specific cancer cells, ADCs are complicated molecules that pose significant technical, regulatory, and intellectual property challenges.

Indeed, development of an effective and safe ADC therapy requires significant research and innovation to ensure that the right components are combined in the right way to avoid side effects, inefficiency, tumor resistance, and pharmacokinetic profiles that make the drug delivery unpractical. In some cases, overcoming these challenges requires development of new generations of ADC modalities by using novel payloads, modified antibody backbones, and new drug linker-release mechanisms, as reviewed in *Tsuchikama, K. et al.,* Nature Rev. Clin. Oncol., 21, 203–223; 2024.

Even though the development of an effective ADC requires intense research to find the right combination, Patent Offices or Courts may find ADCs to be an “obvious” combination in cases where the components of the ADC were previously used for the same purpose as the ADC. Obviousness may present a major obstacle for patent protection of ADC innovations if the patent claims are not sufficiently supported by evidence and patent prosecution strategies.

Strategies For Addressing Obviousness Challenges To ADC

The Legal Standard for Obviousness

The current framework for analyzing obviousness was established by the Supreme Court decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). According to KSR, when a

claimed invention is rejected for obviousness because the invention appears to be a combination of known elements, the Examiner must, "*identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.*" *See KSR*, 550 U.S. at 401. The Federal Circuit further explained in post-KSR decisions that the mere plausibility of prior art combinations is insufficient to establish a prima facie case of obviousness. *See PersonalWeb Tech v. Apple*, 848 F.3d 987, 994 (Fed. Cir. 2017) stating that:

[The] reasoning seems to say no more than that a skilled artisan, once presented with the two references, would have understood that they could be combined. And that is not enough: it does not imply a motivation to pick out those two references and combine them to arrive at the claimed invention.

A prima facie case of obviousness may be rebutted by submitting objective evidence that the claimed invention provided unexpected results. The post-KSR decision in *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) determined that "particularly probative" evidence of unexpected results "establish[es] that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention."

Thus, an ADC should not be held obvious merely because the different components of the ADC were previously known. Rather, the ADC can be held obvious if sufficient guidance or motivation to combine the specific components the same way as in the claimed ADC has been established. Even if there is motivation to combine known components into a specifically claimed ADC, the ADC may still be patentable if the ADC provides unexpected results. Therefore, patenting ADCs with known components will often hinge on finding reasons a skilled artisan would *not* combine the specific ADC components or showing that the particular ADC yielded *unexpected results* compared to the components, as further discussed and illustrated below.

Demonstrating a lack of motivation to make the claimed combination

1) ADC therapy claims may be nonobvious because they recite features that the antibody portion of the ADC failed to perform by itself.

Patent claims covering a particular ADC therapy may be found nonobvious due to a lack of motivation to combine known elements into the claimed ADC if the antibody and/or conjugate failed to treat a particular patient population individually. For example, U.S. Patent 7,575,748 survived an *Inter Partes Review* (IPR) challenge based on obviousness because the claimed ADC could be used to treat a particular indication that the antibody portion of the ADC could not treat by itself as highlighted in the quoted claim language below. *See Phigenix, Inc. v. Genentech, Inc. and Immunogen, Inc.*, IPR2014-00842. The allowed claims in U.S. 7,575,748 recited:

> A method for the treatment of a tumor in a mammal, comprising the steps of
>
> (i) identifying said tumor as being characterized by overexpression of an ErbB2 receptor and as being **a tumor that does not respond, or responds poorly, to treatment with an anti-ErbB antibody**, and
>
> (ii) intravenously administering to the mammal a therapeutically effective amount of a conjugate of a humanized antibody huMab 4D5-8 covalently linked via a thioether linking group with a maytansinoid DM1….

U.S. Patent 7,575,748 illustrated that method claims covering an ADC formed by known components can be found allowable based on properties of the ADC.

2) Establishing that a component of the ADC was discouraged

U.S. Patent 8,337,856 is directed to ADC composition claims, and upon challenge the claims were held valid even though they recited known antibodies and conjugates. *See Phigenix, Inc. v. Immunogen, Inc.*, Case IPR-2014-00676, Final Written Decisions dated October 27, 2015 (Paper 39). Independent claim 1 of the ‘856 patent recites:

1. An immunoconjugate comprising an anti-ErbB2 antibody conjugated to a maytansinoid, wherein the antibody is huMAb4D5-8.

huMAB4D5-8 was commercialized in the prior art product, Herceptin®, and used for treating breast cancer in combination with other cytotoxic agents. In addition, maytansinoid had already been used as a conjugate to different antibodies. The patent challenger, therefore, argued that it would be obvious to use Herceptin® with maytansinoid.

However, the Patent Owner successfully presented evidence suggesting to a skilled artisan that “Herceptin-maytansinoid immunoconjugates would have been expected to exhibit unacceptable levels of antigen-dependent toxicity in normal human liver tissue in patients.” See pages 16–22 of IPR-2014-00676 (Paper 39). The Board found this argument persuasive because the patent challenger had not explained that an ordinary artisan would have been motivated to make the claimed ADC, given the reported liver toxicities of maytansinoid immunoconjugates.

Given these cases, strategies for overcoming obviousness rejections could be found by determining if:

- There are known problems of toxicity associated with the toxic payload component of the ADC or other reasons not to use the toxic payload as claimed, and
- The antibody portion of the ADC has previously been reported to be ineffective by itself against the claimed indication.

As will be discussed further below, the claims of U.S. Patent 8,337,856 were also found valid because of unexpected results, which is another central strategy for obtaining patent coverage of ADCs.

Unexpected Results achieved by the ADC

1) Example of ADC claims found valid based on unexpected results

The claims of U.S. Patent 8,337,856 were found valid based on unexpected results even though the components of the claimed ADC were known. *See Immunogen, Inc.*, IPR-2014-00676 (Paper 39). In particular, the Board held that the Herceptin-maytansinoid immunoconjugate claims were non-obvious because the Patent Owner provided substantial evidence of unexpectedly superior results compared to the “closest prior art” composition. *See* pages 23-25, Immunogen, Inc., IPR-2014-00676 (Paper 39). The “closest prior art” was the antibody by itself, and the results demonstrated that the ADC overcame some limitations of the “naked” antibody.

2) Example of evidence of unexpected results not sufficient to establish nonobviousness

Demonstrating unexpected results can be challenging, as shown in *Hospira v. Genentech,* IPR2017-00731 (Paper 120, at page 23 (PTAB October 3, 2018)), where the claims of U.S. Patent No. 7,846,441 were found unpatentable. The claims of U.S. Patent No. 7,846,441 are represented by claim 1:

> 1. A method for the treatment of a human patient with a malignant progressing tumor or cancer characterized by overexpression of ErbB2 receptor, comprising administering a combination of an intact antibody which binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid, in the absence of an anthracycline derivative, to the human patient in an amount effective to extend the time to disease progression in said human patient, without increase in overall severe adverse events.

The ADC covered by this patent contains an antibody that binds to epitope 4D5 within the ErbB2 extracellular domain sequence and a taxoid. A previous publication asserted against this patent disclosed *the same antibody conjugated with a taxoid tested in a mouse model*. The Patent Owner argued that the claimed method yielded unexpected results in humans as compared to the previous mouse studies. However, the Board held that a mouse study is a "reliable predictor of success in humans," and the results from the mouse study in prior art predict that the ADC would also be effective in humans. *See Hospira v. Genentech,* IPR2017-00731 (Paper 120, at page 26 (P.T.A.B. Oct. 3, 2018).

In addition, the Board in *Hospira v. Genentech* found the Patent Owner's statements to the FDA to be evidence of obviousness of the claims. The Patent Owner had requested FDA approval of a combination of an antibody binding ErbB2 (trastuzumab) and a taxoid (paclitaxel) because a skilled artisan would *expect* that this combination was effective based on the same prior art as asserted against U.S. Patent 7,846,441. Hence, the Board considered the Patent Owner's statements at the FDA as evidence that the results obtained with the claimed ADC were expected. *See Hospira v. Genentech,* IPR2017-00731 (Paper 120, at pages 27-28 (P.T.A.B. Oct. 3, 2018).

The argument for nonobviousness based on unexpected results in *Hospira v. Genentech* failed because the closest prior art was a combination of the same components as the claimed ADC. Accordingly, in cases where the closest prior art to a claimed ADC only discloses one of the components of the ADC, the availability of beneficial results obtained with the ADC will help obtaining allowance of the claims or surviving a challenge based on obviousness.

Main Takeaways

Based on the above review, we provide the following considerations for determining strategies for obtaining patent coverage of ADCs in cases where the components of the ADC are known:

> 1) Is use of one of the ADC components discouraged for the claimed method (e.g., would it be too harmful)?
>
> 2) Could the selected payload interfere with the properties of the antibody or vice versa (e.g., cause aggregation, lower solubility, or changes to important post-translational modifications of the antibody)?

3) Have the components of the ADC been used for treating the same indications or is there a lack of guidance for using one or more of the ADC components as claimed (i.e., lack of motivation)?

4) Is objective evidence of unexpected results from the ADC available (such as improved efficacy or tolerability as compared to individual components)?

Finally, it should be noted that the linker chemistry is also an important part of the ADC and patentability of the ADC. The ADC linker was not central to the above discussed cases because it was not recited by the independent claims. However, the Board did analyze dependent claims reciting specific non-cleavable linkers IPR-2014-00676, which would further distinguish U.S. Patent 8,337,856 from prior art. Accordingly, linker chemistry may confer patentability to an ADC.

Indeed, the linker chemistry offers fertile grounds for innovation and development of new generations of ADCs. *See Tsuchikama, K. et al.,* Nature Rev. Clin. Oncol., 21, 203–223; 2024. The linker chemistry can, for example, be used to regulate the amount of toxic payload (i.e., the drug-antibody ratio), and when and where the payload is released to improve the efficacy and tolerability of the ADC. Even though the linker chemistry by itself may not be new, there may be a lack of motivation to use a particular linker strategy in an ADC because the linker interferes with the antibody structure, changes post-translational modification of the antibody, causes aggregation, or provides too high or too low payload-antibody ratio. Thus, a careful consideration of the linker and its effects on the function of the ADC could also be critical for obtaining patent protection of the ADC.

Ultimately, successful strategies of patenting ADCs will depend on the results obtained with the ADC, and what results would be expected based on common knowledge of the antibodies, toxic payloads, and linker chemistry that make up the ADC.

Read Article 1

Read Article 2

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