

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ONCUSP THERAPEUTICS, INC,
Petitioner,

v.

DAIICHI SANKYO COMPANY, LTD,
Patent Owner.

Case PGR2023-00037

U.S. Patent 11,446,386

Title: Anti-CDH6 Antibody and
Method of Producing an Anti-CDH6 Antibody-Drug Conjugate

PETITION FOR POST-GRANT REVIEW

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1008	Mark L. Chiu, et al., <i>Antibody Structure and Function: The Basis for Engineering Therapeutics</i> , 8 ANTIBODIES 55 (2019)
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I. INTRODUCTION

Petitioner OnCusp Therapeutics, Inc. (“OnCusp” or “Petitioner”) requests post-grant review (“PGR”) in accordance with 35 U.S.C. §§ 321-326 and 37 C.F.R. § 42.200 *et seq.* of claims 1-18 of U.S. Patent 11,446,386 (the ’386 patent) (Ex. 1001), which issued on September 20, 2022, and is owned by Daiichi Sankyo Company, Limited (“Patent Owner,” “PO,” or “Daiichi”).

Claims 1-18 of the ’386 patent (the “Challenged Claims”) are directed to human or humanized monoclonal antibodies, or a functional fragment thereof, that binds to the EC3 domain of CDH6 and possesses an ability to internalize that permits cellular uptake.

Among these Challenged Claims is a group of very broad claims which classically represent unsupported genus claims to antibodies that Courts, including as recently as last month, the Supreme Court, have **consistently invalidated** for lack of written description and/or lack of enablement. This is based on the fact that these genus antibody claims are directed to not what the inventions are, but rather what they do functionally, which fails to adequately describe the scope of the invention and enable others to reasonably practice the claimed invention. The inventors of the ’386 patent only made four (4) antibodies satisfying the claims, which all share about 98% or more sequence identity, and are in fact clones of each other. (Ex. 1003, ¶¶99.) They were created only by first screening vast amounts

(millions) of antibodies that could potentially bind to the EC3 domain of CDH6, and then by running assay after assay to randomly determine whether any actually could bind to EC3 and then internalize into cells. But the inventors did not determine anything about these antibodies that allowed them to function as claimed in terms of their structure or sequence.¹ The only way the inventors knew that these four antibodies would actually bind and internalize, compared to those that would not, was by actually making and screening for them. Despite this, Patent Owner obtained broad genus claims that cover all human or humanized antibodies from any species of origin, from any germline, in any format, of any isotype or subtype, that bind to any part of EC3, and have the ability to internalize.² However,

¹ While the Challenged Claims contain SEQ ID NO; 4 as an element, this is not a sequence within the claimed antibodies, but rather the 115 amino acid length EC3 region of the target CDH6 antigen. The inventors never identified in their functionally defined claims any specific amino acids within this EC3 region that any of the claimed antibodies bind to (*i.e.*, epitopes).

² In fact, the '386 patent itself makes the critical admission that one cannot predict the claimed antibody's functional ability to internalize based on the structure of the antibody. (Ex. 1001, 2:49-52 ("It is difficult to predict an antigen-binding site suitable for internalization from the molecular structure of a target or to predict an

this make-and-screen approach of claiming a broad genus of antibodies claimed solely by function has repeatedly been struck down over and over again as invalid for lack of written description and/or lack of enablement.

To satisfy the written description requirement, an inventor seeking patent protection for broad functional antibody genus claims, like the Challenged Claims, must either identify structural features that are common to all antibodies within the genus or must provide a representative number of species of antibodies within the genus. Here, because Patent Owner has failed to describe either requirement, these claims lack written description. *See AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014).

Moreover, where, as here, the claims are directed to a genus of antibodies claimed broadly by function, and there are only a handful of working examples disclosed in the patent without any guidance in the specification as to how to practice the full scope of the invention except through random trial-and-error screening and experimentation, the claims are not enabled. *See Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021), *aff'd* 598 U.S. ___, 143 S.Ct. 1243 (2023) (“Amgen I”).

antibody having high internalization ability based on binding strength, physical properties, and the like of the antibody.”)).

Even though some of the dependent claims of the Challenged Claims are limited to certain structural features, these claims still lack written description and enablement, because like all the Challenged Claims, these claims still cover not only the claimed human or humanized antibody, but any “functional fragment” of the antibody, which the ’386 patent broadly defines as any “partial fragment of the antibody having binding activity against an antigen.” (Ex. 1001 at 17:40-43.) Clearly, by disclosing just four exemplified antibodies that are mere clones of each other, the inventors did not show that they possessed all claimed functional fragments that have binding activity to EC3 **and** possess an ability to internalize, and did not teach one of ordinary skill in the art to practice all such claimed functional fragments. Thus, all the Challenged Claims, including these narrower dependent claims, are invalid under 35 U.S.C. § 112 based on this fatal defect of claiming “functional fragment[s].”

In addition, the very broad claims are anticipated or rendered obvious by PCT/IB2015/056032, filed on August 7, 2015, and which published on February 18, 2016, as WO 2016/024195 A1 (“Novartis”) (Ex. 1005). Novartis’s prior art patent application actually disclosed - more than one year prior to the effective filing date of the Challenged Claims - the claimed humanized monoclonal antibodies that bind to the EC3 domain of CDH6 and possess an ability to internalize. While Patent Owner overcame a similar rejection under 35 U.S.C. §

102(a)(1) over the Novartis prior art during prosecution of the Challenged Claims, this was based on Patent Owner's clear misrepresentation that this reference did not disclose binding to EC3 and internalization.³ As shown herein, the Novartis reference does disclose this.

Finally, at least claims 1-5 and 14-18 are invalid under 35 U.S.C. § 101 for claiming patent-ineligible subject matter. For example, claim 1 covers a "human" monoclonal antibody that specifically binds to EC3 and internalizes, and as such, covers naturally occurring anti-CDH6 antibodies that exist naturally in human cancer patients, or antibodies that are not markedly different from these naturally occurring antibodies. Since these claims do not add significantly more to the covered natural product that could transform them into patent-eligible subject matter, these claims are invalid under 35 U.S.C. § 101.

As this Petition shows, along with the Declaration of Dr. Stylianos Bournazos in support of this Petition ("Bournazos Decl.") (Ex. 1003), the Challenged Claims are invalid for lack of written description, lack of enablement,

³ Notably, when confronted with a prior art rejection based on this Novartis reference in a related application, Patent Owner was forced to amend the broad claims to overcome the rejection. *See infra* at § IV.B.

for being anticipated and/or obvious over the prior art, and for claiming patent-ineligible subject matter.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

Petitioner OnCusp Therapeutics, Inc., as well as OnCusp Therapeutics and Multitude Therapeutics Inc. are real parties-in-interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this Petition.

C. Counsel and Service Information (37 C.F.R. §§ 42.8(b)(3) and (4))

Petitioner identifies its lead and backup counsel as shown below:

Lead Counsel	Backup Counsel
Gerard P. Norton, Ph.D. USPTO Registration 36,621 FOX ROTHSCHILD LLP Princeton Pike Corporate Center 997 Lenox Drive Lawrenceville NJ 08648-2311 (609) 844-3020 gnorton@foxrothschild.com	Ryan N. Miller USPTO Registration 68,262 FOX ROTHSCHILD LLP 2000 Market St. 20th Floor Philadelphia PA 19103-3222 (215) 299-2901 rmiller@foxrothschild.com Howard S. Suh (<i>pro hac vice</i> to be filed) FOX ROTHSCHILD LLP 101 Park Avenue, 17 th Floor New York, NY 10178 (212) 878-7914 hsuh@foxrothschild.com Jianming Jimmy Hao

	USPTO Registration 54,694 Fox Rothschild LLP 997 Lenox Drive Lawrenceville, NJ 08648 Telephone: (609) 895-7065 Facsimile: (609) 896-1469 JHao@foxrothschild.com Joe G. Chen (Reg. No. 70,066) Fox Rothschild LLP 997 Lenox Drive Lawrenceville, NJ 08648 Telephone: (609) 844-3024 Facsimile: (609) 896-1469 joechen@foxrothschild.com
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Please address all correspondence to the lead and backup counsel at the above addresses. Petitioner consents to electronic service to the e-mail addresses above for lead and backup counsel (gnorton@foxrothschild.com, rmiller@foxrothschild.com, hsuh@foxrothschild.com, jhao@foxrothschild.com, joechen@foxrothschild.com) with a copy to_ipdocket@foxrothschild.com (referencing Attorney Docket No. 345522.00002).

III. ADDITIONAL REQUIREMENTS

A. Payment of Fees

Pursuant to 37 C.F.R. §§ 42.203(a) and 42.15(a), the required fees are submitted herewith. If additional fees are due during this proceeding, the Office is authorized to charge Deposit Account 50-1943.

B. Time for Filing Petition

The '386 patent issued on September 20, 2022, and this Petition was timely filed on June 16, 2023, which is no later than nine months after the date of the grant of the '386 patent. *See* 37 C.F.R. § 42.202.

C. Grounds for Standing

Petitioner certifies, pursuant to 37 C.F.R. § 42.204(a), that the '386 patent is available for PGR, and that Petitioner is not barred or estopped from requesting PGR of the Challenged Claims on the grounds identified in this Petition.

Moreover, Petitioner further certifies that at least one claim of the '386 patent has an earliest possible “effective filing date” of May 15, 2017, which is later than March 16, 2013, and is therefore subject to the first-to-file provisions of the America Invents Act (“AIA”).

D. Identification of Challenge Under 37 C.F.R. § 42.204(b) and Relief Requested

The Challenged Claims are unpatentable under 35 U.S.C. § 112 due to lack of written description and lack of enablement. Claims 1, 5, and 13-18 are also invalid for being anticipated over Novartis under 35 U.S.C. § 102(a)(1) and/or obvious over Novartis and other prior art identified below under 35 U.S.C. § 103. Moreover, at least claim 1-5 and 14-18 are invalid as patent-ineligible under 35 U.S.C. § 101.

The following is a list of prior art that anticipate and/or render obvious claims 1, 5, and 13-18.

Exhibit	Description	Publication Date
1005	Int'l Patent Application Publication No. WO 2016/024195 A1 ("Novartis")	February 18, 2016
1006	US 20160317656A1 to Urano et al. ("Urano")	November 3, 2016
1007	US20160046720A1 to Sato et al. ("Sato")	February 18, 2016

Petitioner requests cancellation of claims 1-18 on the following grounds:

Ground	Claims	Description
1	1-18	Lack of Written Description under 35 U.S.C. § 112.
2	1-18	Lack of Enablement under 35 U.S.C. § 112.
3	1, 5, and 13-16, and 18	Anticipated under 35 U.S.C. § 102(a)(1) by Novartis.
4	1, 5, and 13-18	Obvious under 35 U.S.C. § 103 by Novartis or by Novartis in combination with Urano and/or Sato as to claims 14-17.
5	1-5 and 14-18	Patent-ineligible under 35 U.S.C. § 101

IV. BACKGROUND AND SUMMARY OF THE '386 PATENT

Antibodies are among the most diverse biological agents known to science. (Ex. 1003, ¶39.) The representative Y-shaped structure of an antibody of the IgG

class is shown below in Figure 1. (*Id.*, ¶33. A typical Y-shaped antibody has two sets of heavy chain-light chain pairs, and variability in the antibody structure is well-documented. (*Id.*, ¶34.) Human antibodies are categorized into five immunoglobulin groups: IgA, IgD, IgE, IgG, and IgM. (*Id.*, ¶35.) Each of these groups may be further subcategorized into different subclasses, *e.g.*, IgG1, IgG2, IgG3, and IgG4. (*Id.*) Light chains have similarly been subclassified into two classes: lambda (λ) or kappa (κ). (*Id.*) The variable regions are primarily responsible for interactions between the antibody and an antigen. (*Id.*, ¶¶37-39.) Even minimal alterations can have significant functional effects – antibodies with highly similar amino acid sequences may fail to bind the same or similar antigens, and antibodies with incredibly diverse amino acid sequences may nevertheless bind the same or similar antigens. (*Id.*, ¶39.) While specific antibodies targeting certain epitopes can be designed and generated, ultimately, physical experimentation is required to confirm whether an antibody has desired characteristics, such as actually binding to an antigen, affinity of that binding, and functional effects (*e.g.*, internalization) of the antibody-antigen interactions. There is no means to measure an antibody's actual functionality based on sequence analysis alone. (*Id.*, ¶54.)

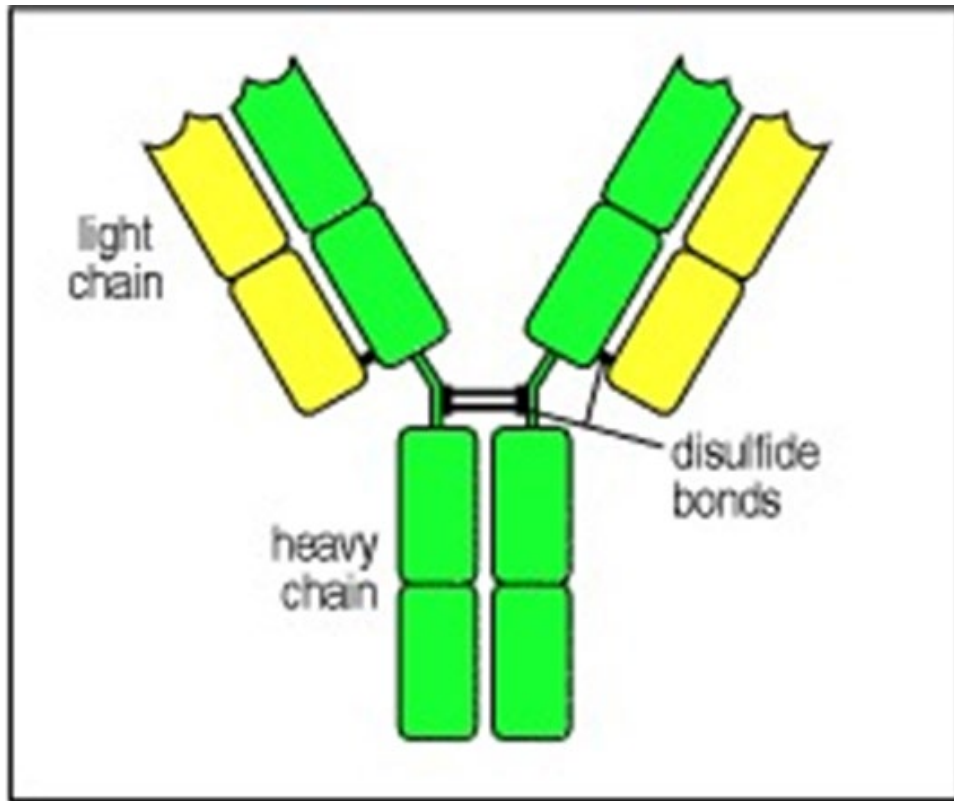


Fig. 1. Representative IgG antibody structure (reproduced from Ex. 1010 at 118 (Fig. 3.2).)

Against this backdrop, the '386 patent, titled “Anti-CDH6 antibody and method of producing an anti-CDH6 antibody-drug conjugate,” issued from US Application No. 16/613,203, which was filed on May 14, 2018, and claims priority to Japanese Patent Application No. JP2017-096749 filed May 15, 2017. (Ex. 1001).

The '386 Patent has 18 claims. Claim 1 is the only independent claim, which is reproduced below:

Claim 1: A human or humanized monoclonal antibody that specifically binds to the amino acid sequence shown of SEQ ID NO: 4 [*i.e.*, *EC3 domain*] and possesses an ability to internalize that permits cellular uptake, or a functional fragment of the antibody that binds to the amino acid sequence of SEQ ID NO: 4 [*i.e.*, *EC3 domain*] and possesses an ability to internalize that permits cellular uptake.

Thus, claim 1 covers human or humanized monoclonal antibodies and functional fragments of the human or humanized monoclonal antibodies that specifically bind to the amino acid sequence shown of SEQ ID NO: 4 and possess an ability to internalize that permits cellular uptake. (Ex. 1003, ¶206).

SEQ ID NO: 4 is a 115 amino acid (“aa”) sequence of human CDH6 extracellular domain 3 (EC3) (aa 269-383). (Ex. 1001, 19:62-65 and Table 1-1.) Although this 115-amino-acid sequence (SEQ ID NO: 4) includes a large number of epitopes to which millions of human or humanized monoclonal antibodies and their functional fragments can bind, claim 1 merely recites the entire EC3 domain as an antigen, without specifying a specific epitope within the EC3 domain to which the human or humanized monoclonal antibodies and their functional fragments can bind. (Ex. 1003, ¶79 at 80.)

As discussed in more detail below, the claimed human or humanized monoclonal antibodies and functional fragments represent a vast genus of human or humanized monoclonal antibodies and functional fragments defined purely by their functional characteristics, *i.e.*, their ability to specifically bind to SEQ ID NO: 4, and their ability to internalize permitting cellular uptake. (Ex. 1003, ¶76.)

The '386 patent includes nine examples, sixteen figures, and *only four working examples* of the claimed antibodies - H01L02, H02L02, H02L03, and H04L02, which are all derived from a single chG019 clone and share the same set of complementarity determining regions (CDRs). (Ex. 1003, ¶¶81, 146.) Accordingly, these four exemplary humanized antibodies bind to the same epitope within the EC3 domain. (Ex. 1003, ¶146.)

Examples 1-2 and Figures 1-4 of the patent show that these humanized antibody clones were constructed by first screening for rat anti-human CDH6 (hCDH6) monoclonal antibodies (named rG019, rG055, rG056, and rG061, respectively) and then evaluating whether these rat antibodies have binding and internalization activity. (Ex. 1003, ¶81.) This screening process involved testing millions of different potential antibodies through antibody-producing hybridomas. Only after random screening for binding activity were these rat antibodies purified, and then subjected to more assays to determine whether they bind to the EC3

domain of hCDH6, as measured by flow cytometry. (Ex. 1001, 76:3-9, 66-67; Ex. 1003, ¶¶82-84.)

The nucleotide sequences of complementary DNA (“cDNA”) encoding the variable regions of the rat antibodies were amplified from the total RNA, and then sequenced. (Example 3) (Ex. 1001, 78:9-67; Ex. 1003, ¶85.) The rat antibodies were subjected to further assays to determine their internalization activity. (Ex. 1001, 77:44-46; Ex. 1003, ¶86.) (anti-rat IgG reagent Rat-ZAP conjugated with a toxin (saporin) inhibiting protein synthesis). It was demonstrated that the four rat antibodies bind CDH6 and are internalized. (Ex. 1001, 78:6-7; Ex. 1003, ¶86.)

Example 4 and Figure 5 describe the production of a single human chimeric anti-CDH6 antibody: chG019, derived from the rat rG019 antibody having a humanized IgG1 heavy chain constant region. (*Id.*, 26:34-40, 79:50-54; Ex. 1003, ¶87.)

Example 5 shows the creation of the four working examples of the Challenged Claims. Based on CDR grafting, clones H01L02, H02L02, H02L03, and H04L02 of the humanized hG019 antibody were developed from the human chimeric chG019 antibody. (Ex. 1001, 81:38-50; Ex. 1003, ¶88.) The four humanized anti-CDH6 antibodies were generated by combining different heavy chains (H01, H02, or H04) and light chains (L02 or L03). (Ex. 1001, 82:6-15; Ex. 1003, ¶88.) As a result, three of these four humanized antibodies share the same

light chain, and two of these four humanized antibodies share the same heavy chain. (Ex. 1003, ¶88.)

In Example 6 and Figures 6-10, the humanized hG019 antibody was evaluated *in vitro* against NOV0712, which is a humanized anti-CDH6 antibody described in the prior art in WO2016024195A1 (Ex. 1005) (“Novartis”) and its US national stage application US20160046711A1, issued as US Patent No. 9,982,045. It was demonstrated that the four humanized hG019 antibodies specifically bind to hCDH6 EC3, although at least H01L02 and H04L02 have cross-reactivity against other EC domains (*i.e.*, EC1, EC2, EC4, or EC5). (Ex. 1001, 86:30-37, Fig. 7-4; Ex. 1003, ¶89.) While the ’386 Patent does not perform epitope mapping, the data in Fig. 9 shows that H01L02, H02L02, H02L03, and H04L02 have competitive inhibitory activity against each other, suggesting that they bind to the same epitope. (Ex. 1003 at, ¶ 90.) In addition, based on the data in Fig. 10, the ’386 Patent concluded that the four humanized hG019 antibodies exhibit higher internalization activity than NOV0712. (*Id.*, at ¶ 91.)

No human anti-hCDH6 antibody or functional fragment is described in the ’386 Patent. (Ex. 1003, ¶93). Nor does the ’386 Patent describe any materials (*e.g.*, transgenic animals) or methods to produce human anti-hCDH6 antibodies or their functional fragments. (*Id.*)

The '386 patent lists six humanized antibodies (*i.e.*, H01L02, H02L02, H04L02, H01L03, H02L03, H04L03), only four of which were actually generated and characterized. (Ex. 1003, ¶¶95, 97.) They were all derived by merely mixing and matching combinations of a humanized heavy chain variable region (*i.e.*, H01, H02, or H04) with a humanized light chain variable region (*i.e.*, L02 or L03). (Ex. 1001, 27-32; Ex. 1003, ¶95.) These humanized heavy chain variable regions (*i.e.*, H01, H02, H04) and humanized light chain variable regions (*i.e.*, L02, L03) were all derived from a single human chimeric antibody, chG019. (Ex. 1001, 81:51-67, 82:1-5; Ex. 1003, ¶95.)

The '386 Patent also lists twenty-two hypothetical partially “humanized” anti-hCDH6 antibodies, described by again mixing and matching a humanized heavy chain variable region (*i.e.*, H01, H02, or H04) with a light chain variable region of the four rat or chimeric anti-hCDH6 antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061), or by combining a humanized light chain variable region (*i.e.*, L02 or L03) with a heavy chain variable region of the four rat or chimeric anti-hCDH6 antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061). (*Id.*, 27-32; Ex. 1003, ¶96.) Critically, unlike the four working example antibodies of the Challenged Claims, the '386 patent never discloses any data from any experiments showing whether these additional “mix and match” antibodies actually

perform the claimed functions of binding to the EC3 region of CDH6 and internalizing. (*Id.*)

As to the four exemplary antibodies of the Challenged Claims, since they were all derived from a single starting antibody, chG019, they all share the identical CDR regions (*i.e.*, CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3) and bind to the same epitope. (Ex. 1003 at, ¶¶97, 146.)

Moreover, the heavy chains of H01, H02, and H04 of the four exemplified antibodies share about 99% sequence identity, and their light chains of L02 and L03 share about 98% sequence identity. (Ex. 1003, ¶¶99.) Similarly, very high sequence identity also exists in the heavy chain variable region (with 95% sequence identity) and the light chain variable region (with 93% sequence identity) of these four exemplary humanized antibodies. (*Id.*) Taken together, the four working example antibodies of the Challenged Claims share a sequence identity of more than 98% in their overall structures (*i.e.*, heavy chains and light chains)

Based on the disclosure of the '386 patent, the inventors never described structural features that are shared among the vast scope of the claimed human or humanized antibodies which bind to EC3. Instead, the inventors merely screened millions of potential rat antibodies, found some that did have binding and internalization activity, and then grafted the CDR portions of one of these rat

antibodies (*i.e.*, rG019) to create the 4 humanized antibodies of the working examples.

Notably, as to the claimed antibody's ability to internalize, the '386 patent admits that there is no structural characteristic of the antibody which can predict internalization, and, therefore, this functional aspect of the of the claimed antibody can only be accomplished through random screening. (Ex. 1003, ¶102.) The '386 patent states that:

[t]he internalization ability of the antibody depends on the properties of both the target antigen and the antibody...[i]t is difficult to predict an antigen-binding site suitable for internalization from the molecular structure of a target or to predict an antibody having high internalization ability from binding strength, physical properties, and the like of the antibody.

(Ex. 1001, 2:47-53; Ex. 1003, ¶102.)

V. PROSECUTION OF THE '386 PATENT AND RELATED APPLICATIONS

A. U.S. Application No. 16/613,203 (“’203 Application”)

The application that issued as the '386 patent, Serial No. 16/613,203, was filed on November 13, 2019. (Ex. 1002 at 9.) Through a series of preliminary amendments, corrections were made to the specification, certain claims were amended to remove multiple dependencies, and claims were cancelled to avoid

excess claim fees. (*Id.* at 438-443 (filed November 13, 2019), 1613-1639 (filed March 5, 2020), 1642-1655 (filed September 2, 2020).)

The Office issued a Restriction Requirement on November 12, 2021 (*Id.* at 13067-13074) (“Requirement”) segregating the claims into three groups:

- Group I drawn to antibodies that bind to SEQ ID NO: 4;
- Group II drawn to polynucleotides, vectors, and host cells encoding antibodies that bind to SEQ ID NO: 4; and
- Group III drawn to methods of making antibody drug conjugates.

In the Requirement, the Office noted that Novartis “teaches an anti-CDH6 antibody drug conjugate [that] binds specifically to the extracellular domain of human CDH6 ... which comprises the amino acid sequence of SEQ ID: 4 of the present application.” (*Id.* at 13071.) The Office also noted that Novartis “teaches an anti-CDH6 antibody, NOV0719, which binds to an epitope that falls within the amino acid sequence of SEQ ID NO: 4 and corresponds to amino acid residues 7-34 of SEQ ID NO: 4 of the present application.” (*Id.* at 13071-13072.) In response to the Requirement, Patent Owner elected Group I, corresponding to originally filed claims 1-13 and 24-28. (*Id.* at 13337.)

The Office issued a Non-Final Office Action on February 14, 2022 containing the following rejections:

- Claims 1, 2, and 24 as anticipated by Dunne (Ex. 1002 at 13345.);

- Claims 1, 2, and 24 as anticipated by Shimazui (*Id.* at 13346.);
- Claims 1, 2, 13, and 24 as anticipated by Cho (*Id.*);
- Claims 1, 2, 5, 13, and 24 as anticipated by Bialucha (*Id.*), the issued U.S. counterpart to Novartis, referencing the application publication, U.S. 2016/0046711 (*Id.*).
- Claims 1-13 and 24-28 for non-statutory double patenting over U.S. 11,077,202 (*Id.* at 13347.); and
- Claims 1-13 and 24-28 for provisional non-statutory double patenting over Serial No. 17/293,577 (*Id.*).

Regarding the rejection over Novartis, the Office stated that the reference “teaches human CDH6, which is expected to be identical to the instant human CDH6.” (Ex. 1002 at 13346.) Novartis further teaches “antibodies as part of an ADC ... which would be expected to internalize.” (*Id.*) The Office also explicitly noted that no rejection of claim 8 for lack of enablement was made “since it is believed that the recited regions of the light and heavy chains comprise all 6, full-length, CDRs.” (*Id.* at 13344.)

In response to the Non-Final Office Action filed on April 27, 2022, Patent Owner amended independent claim 1 limiting the claim as follows (underlined text indicates material added and stricken text indicates material deleted):

1. (Currently Amended) A human or humanized monoclonal ~~An~~ antibody that specifically binds ~~binding~~ to the amino acid sequence shown of ~~in~~ SEQ ID NO: 4 and possesses an ability to internalize ~~having internalization ability~~ that permits cellular uptake, or a functional fragment of the antibody that binds to the amino acid sequence of SEQ ID NO: 4 and possesses an ability to internalize that permits cellular uptake.

No other claims were amended. In its remarks, Patent Owner argued, incorrectly, that Novartis “fails to expressly indicate that any of the antibodies disclosed therein bind specifically to EC3 of the extracellular region of human CDH6 (*i.e.*, SEQ ID NO: 4) and possess an ability to internalize....” (*Id.* at 13665.) Patent Owner supported its argument by falsely asserting that “there is no indication in the record that binding to any or all of the various extracellular domains will always necessarily result in internalization of an antibody.” *Id.* Patent Owner concluded based on this assertion that “there is no legal or scientific basis for assuming that any of the antibodies disclosed in Novartis necessarily possess both (i) specific binding to SEQ ID NO: 4 and (ii) an ability to internalize, as recited in the claims.” (*Id.* at 13665-13666.) The Office was led into error by Patent Owner’s mischaracterization of the Novartis reference. As detailed below as Grounds 3 and 4 of this Petition (anticipation and obviousness over Novartis), the

Novartis reference clearly disclosed a humanized anti-CDH6 antibody that binds to SEQ ID NO: 4 and possesses an ability to internalize. (Ex. 1003, ¶¶232-37.) In response to the Patent Owner's April 27, 2022 response, the Office allowed claims 1-13 and 24-28. (Ex. 1002 at 13672-13678.) The Office provided no reasons for allowance. (*Id.*) The Issue Fee was paid on August 1, 2022, and the '386 patent issued on September 20, 2022. (*Id.* at 14280.)

Thus, the Patent Owner never had to overcome the specific 35 U.S.C. § 112 lack of written description and lack of enablement arguments of Grounds 1 and 2, or the 35 U.S.C. § 101 lack of patent-eligible subject matter arguments of Ground 5 of this Petition, since the Office never entered Office Action rejections of the pending claims for those reasons.

While the Patent Owner did overcome a 35 U.S.C. § 102(a)(1) rejection based on the Novartis prior art reference, for the reasons discussed above, this was based on Patent Owner's clear misrepresentation of the disclosure of this reference which let the Office into material error.

Moreover, as demonstrated below, the Office did enter rejections to similar claims in a related application to the '203 application based on lack of written description and obviousness over the Novartis reference that were similar to the instant Grounds 1, 2, and 3 of the Petition, resulting in amendment of those claims.

B. U.S. Application No. 17/010,162 (“’162 Application”)

The ’162 application was filed, along with a Track One request, on September 2, 2020, as a continuation of the ’203 application. (Ex. 1038 at 258, 265.) The Office granted Patent Owner’s Track One request on October 6, 2020. (*Id.* at 10154.) On November 17, 2020, the Office issued a Restriction Requirement segregating the claims to two groups:

- Group I drawn to an antibody-drug conjugate comprising an antibody specifically binding to SEQ ID NO: 4 and having internalization ability that permits cellular uptake, or a functional fragment of the antibody;
- Group II drawn to a method for treating a tumor comprising administering to an individual any component selected from the antibody-drug conjugate of claim 1, a salt thereof, and a hydrate of the conjugate or the salt

(*Id.* at 10183-10192.) Patent Owner elected Group I and claims 7, 11, and 21-24 were withdrawn from prosecution, leaving claims 1-6, 8-10, and 12-20. (*Id.* at 10193-10195, 10200.)

The Office, through a different examiner, issued a Non-Final Office Action on December 24, 2020, rejecting all claims on various grounds:

- Claims 1-6, 8, and 12-20 for non-statutory double patenting over non-statutory obviousness-type double patenting as being unpatentable over claims 1-47 of U.S. Patent No. 9,872,924, claims 1-14 of U.S. Patent No. 9,850,312, claims 1-18 of U.S. Patent No. 9,808,537, claims 1-35 of U.S. Patent No. 10,195,288, or claims 1-8 of U.S. Patent No. 10,155,821 in view of Novartis (Ex. 1038 at 10203-10204.);
- Claims 1-6, 8-10, and 12-20 as failing to comply with the written description requirement of §112(a) (Ex. 1038 at 10204-10207.);
- Claims 1-6, 8, and 12-20 as obvious over Nakada or U.S. Patent Application Publication No. 2015/0352224 in view of Novartis (Ex. 1038 at 10208-10210.);

(*Id.* at 10199-10211.) With regard to the written description rejection, the Office noted that “Claim 1 is drawn to an antibody-drug conjugate comprising an antibody specifically binding to the amino acid sequence shown in SEQ ID NO: 4 and having internalization ability that permits cellular uptake, or a functional fragment of the antibody, conjugated to a drug.” (*Id.* at 10205.) This is nearly identical to the scope of Challenged Claim 1. After noting that the claims “do not require that the antibody or the drug possess any particular conserved structure other disclosed distinguishing feature,” the Office found that the “claims

encompass a huge genus of antibody-drug conjugates without a structural limitation for the antibody and/or the drug.” (*Id.*) The Office concluded that “the instant disclosure does not adequately support the huge genus of the anti-CDH6 antibodies that specifically bind to the amino acid sequence of SEQ ID NO: 4” and that “one skilled in the art would not recognize from the disclosure that Applicant was in possession of the genus of antibody drug conjugates.” (*Id.* at 10207.)

In the obviousness-type double patenting and obviousness rejections, the Office found that Novartis “teaches an anti-CDH6 antibody drug conjugate [that] binds specifically to the extracellular domain of human CDH6, which comprise the amino acid sequence of SEQ ID NO: 4 of the present application.” (*Id.* at 10203, 10208.) In particular, the Office found that Novartis “teaches an anti-CDH6 antibody, NOV0719, which binds to an epitope [that] falls within the amino acid sequence of SEQ ID NO: 4 and corresponds to amino acid residues 7-34 of SEQ ID NO: 4 of the present application.” (*Id.*)

In a response dated March 1, 2021, Patent Owner amended claim 1 of the ’162 application to include “specific combinations of CDR sequences that are expressly disclosed and described in the present specification.” (*Id.* at 10905-10919.) Patent Owner did not argue against the substance of the written description rejection but rather limited the claims to embodiments that were expressly

disclosed and described. (*Id.* at 10917-10918.) Patent Owner relied on the same claim amendments to resolve the obviousness rejections as well. (*Id.* at 10918.)

In response to Patent Owner's amendments, the Office allowed the claims on March 25, 2021, which ultimately issued as U.S. Patent 11,077,202B2 on August 3, 2021. (*Id.* at 10927-10922.)

VI. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art at the time of the alleged invention on or before the earliest possible priority date of May 15, 2017, would typically have had a Ph.D. in immunology, molecular biology, cellular biology, or a similar field, or an MD with similar experience. (Ex. 1003, ¶137.) A person of ordinary skill in the art would typically have had at least about five years of experience with antibodies and antibody engineering, or access to other individuals with that knowledge and experience. (*Id.*) Likewise, a person of ordinary skill in the art would have had knowledge and experience in inflammatory or autoimmune disorders, or access to a person with that knowledge and experience. (*Id.*)

VII. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(B)(3)

The Challenged Claims subject to Post-Grant Review are evaluated under the same claim construction standard used by Article III federal courts and the ITC, both of which follow *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). Under the *Phillips* standard, the terms of the Challenged Claims should be given

their “ordinary and customary meaning” – that is, “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention.” (*Id.* at 1312-13.) Petitioner submits that all claim terms of the ’386 patent should be interpreted accordingly.

In particular, the following terms of the Challenged Claims should be construed accordingly as shown in the chart below based on their plain meaning in view of the specification and file history.

Claim term	Claim construction	Support
“specifically binds to the amino acid sequence shown of SEQ ID NO: 4”	“strongly binds to the EC3 domain of CDH6 compared with the other extracellular domains of CDH6”	(Ex. 1001, 20:24-30)
“humanized” antibody	An antibody developed by incorporating only complementarity determining regions (CDRs) into a human-derived antibody, by incorporating the amino acid residues from some frameworks, as well as CDR sequences, into a human antibody according to a CDR grafting method, or by modifying the amino acid sequences of some CDRs while maintaining antigen-binding ability.	(Ex. 1001, 27:30-39.)
“functional fragment”	“a partial fragment of the antibody having binding activity against an antigen, and includes Fab, F(ab') ₂ , scFv, a diabody, a linear antibody and a multispecific antibody formed from antibody fragments, and the like. Fab', which is a monovalent fragment of	(Ex. 1001, 17:40-56.)

	antibody variable regions obtained by treating F(ab') ₂ under reducing conditions, is also included in the antigen-binding fragment of an antibody. However, the antigen-binding fragment of an antibody is not limited to these molecules, as long as the antigen-binding fragment has antigen-binding ability. These antigen-binding fragments include not only those obtained by treating a full-length molecule of an antibody protein with an appropriate enzyme, but proteins produced in appropriate host cells using a genetically engineered antibody gene.”	
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VIII. SUMMARY OF THE PRIOR ART

A. Int'l Application PCT/IB2015056032 (“Novartis”)

Int'l Application PCT/IB2015056032 (“Novartis”), titled “Anti-CDH6 Antibody Drug Conjugates,” was filed on August 7, 2015, by Novartis AG, published on February 18, 2016 as WO 2016/024195 A1 (Ex. 1005), and issued as US Patent No. 9,982,045. Novartis was effectively filed for purposes of 35 U.S.C. § 102(d)(2) on August 12, 2014, through a claim of priority to U.S. Provisional Application No. 62/036,382 filed on that date. Because Novartis published more than 1 year before May 15, 2017, the earliest possible effective filing date of the Challenged Claims, it is prior art under 35 U.S.C. § 102(a)(1).

B. U.S. Patent Application No. 15/027,489 (“Urano”)

U.S. Patent Application No. 15/027,489, entitled “Combination of anti-fgfr2 antibody and other agent,” was filed October 7, 2014, by Daiichi Sankyo Co Ltd and published as US20160317656A1 (Ex. 1006) on November 3, 2016, and issued on April 3, 2018 as U.S. Patent 9,931,401, which is assigned to Daiichi Sankyo Co Ltd. Urano is prior art to the ’386 Patent under 35 U.S.C. §102(a)(1). Urano was not before the Office during prosecution of the Challenged Claims.

C. U.S. Patent Application No. 14/927,007 (“Sato”)

U.S. Patent Application No. 14/927,007, entitled “Novel anti-human tslp receptor antibody,” was filed October 29, 2015 by Astellas Pharma Inc and published as US20160046720A1 (Ex. 1007) on February 18, 2016, and issued on May 3, 2016 as U.S. Patent 9,328,171, which is assigned to Upstream Bio Inc. Sato is prior art to the ’386 Patent under 35 U.S.C. §102(a)(1). Sato was not before the Office during prosecution of the Challenged Claims.

IX. IT IS MORE LIKELY THAN NOT THAT AT LEAST ONE OF THE CHALLENGED CLAIMS OF THE ’386 PATENT IS UNPATENTABLE

A. Ground 1: Lack of Written Description of Claims 1-18 of the ’386 patent

The written description requirement of 35 U.S.C. § 112(a) provides, in pertinent part, that a patent specification:

shall contain a written description of the invention, and
of the manner and process of making and using it, in such
full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A patent's written description "must 'clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.'" *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*) (internal quotations omitted). "[T]he applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,'" and demonstrate this possession by disclosure in the specification of the patent. *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1122 (Fed. Cir. 2008) (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)); *Ariad*, 598 F.3d at 1351. Such "possession as shown in the disclosure" requires "an objective inquiry into the four corners of the specification," *Ariad*, 598 F.3d at 1351, and it must "describ[e] the invention, with all its claimed limitations," *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997) (emphasis removed).

When a genus is claimed, the written description requirement demands "more than a generic statement of an invention's boundaries." *Ariad*, 598 F.3d at 1349. Merely describing a claimed genus by its function has been held to be

insufficient because it provides “only a definition of a useful result rather than a definition of what achieves that result.” *Id.* at 1350 (citing *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). Functional descriptions which amount to no more than a “wish” or “plan” for obtaining the invention do not provide adequate written description for a genus. *Ariad*, 598 F.3d at 1350. “[M]erely drawing a fence around the outer limits of a purported genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.” *Ariad*, 598 F.3d at 1350.

“The essence of the written description requirement is that a patent applicant, as part of the bargain with the public, must describe his or her invention so that the public will know what it is and that he or she has truly made the claimed invention.” *AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1298 (Fed. Cir. 2014). The written description requirement thus ensures “that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor’s contribution to the field” by “curtailing claims” that the applicant has not invented and cannot describe. *Id.* at 1299 (internal citations omitted).

The Federal Circuit has emphasized that antibody claims do not merit special exemption from these general principles of patentability. *Amgen Inc. v.*

Sanofi, 872 F.3d 1367, 1378-79 (Fed. Cir. 2017), *cert. denied*, 139 S. Ct. 787 (2019) (“Amgen II”). In particular, *Amgen II* held that a patentee cannot establish written description support merely by characterizing the antigen to which an antibody binds. *See id.*

When claiming antibodies that cover a broad genus, an adequate written description can only be satisfied if the person of ordinary skill in the art (“POSA”) can “visualize or recognize” the members of the genus when examining the specification based on whether it (a) discloses “a representative number of species falling within the scope of the genus,” or (b) discloses “structural features common to members of the genus.” *Abbvie*, 759 F.3d at 1299 (quoting *Ariad*, 598 F.3d at 1350). Here, the Challenged Claims are invalid for lack of written description because they fail ***both*** prongs of this test.

1. The Very Broad Claims (Claims 1-6 and 13-18) Cover A Vast Number of Antibodies That Are Not Supported By Any Common Structural Features

As Dr. Bournazos explains, the very broad claims cover billions of potential antibodies of great structural variability. (Ex. 1004, ¶139.) For example, even though the claims cover any one of the 5 different isotypes of antibodies – IgA, IgD, IgE, IgG and IgM, each of which has their own subtypes, the ’386 patent only discloses four examples of a single subclass of IgG called IgG1. (*Id.*, ¶153.)

Moreover, these claims cover either a “human” or a “humanized” monoclonal antibody, which are well known antibody formats which can also potentially cover multitudes of different structure. For example, rat generated antibodies can be “humanized” where nearly all of their rat antibody regions are substituted for human ones, while retaining only the rat CDR regions that bind to the antibody. In fact, this is the process used by the inventors to generate the four working example antibodies of the Challenged Claims. But as explained by Dr. Bournazos, while the inventors chose one set of “humanized” regions to replace the non-CDR rat regions, the combination of different human heavy and light chains that could be used as the desired human acceptor antibody would number in the millions. (*Id.*, ¶145.)

As to the claimed fully “human” antibodies, these can be generated by either inoculating a human with an antigen to form an antibody response or by creating transgenic organisms, such as transgenic mice where nearly the entire immunoglobulin loci have been introduced recombinantly such that the transgenic organism mimics a human response. But as Dr. Bournazos explains, these methods of creating a fully human antibody can result in countless different variations in structure. (*Id.*, ¶144.) Critically, *the inventors failed to disclose a single “human” antibody*, despite claiming this antibody format. (*Id.*)

The main reason, however, that these claims cover so many potential antibodies is because they are not defined by any structure, but rather by their functional capacity to bind to EC3 and internalize. As Dr. Bournazos explains, there is nothing in these claims that limits the various ways a POSA could undertake in identifying and assembling the claimed antibodies. When looking for potential antibodies that bind to EC3 based on the limited disclosure of the '386 patent, the POSA would have to resort to hybridoma or phage display technology to screen for literally billions of different antibodies. Even then, the POSA would still have to undertake even more screening to determine whether the candidate antibodies possess the ability to internalize. (*Id.*, ¶196.)

Moreover, the '386 patent never identifies any structural information of the potential epitopes within EC3 which could bind to the antibody. As Dr. Bournazos explains, SEQ ID NO:4 is the entire 115 amino acid length EC3 domain of human CDH6, which includes a large number of epitopes to which millions of human or humanized antibodies or their functional fragments can bind. (*Id.*, ¶79.)} Dr. Bournazos notes that while several epitopes were known in the art as of the filing date of the Challenged Claims, the breadth of claiming binding sites across this span of 115 amino acids opens the claims up to covering innumerable other unknown binding sites or combination of binding sites, resulting in millions of potential antibodies that can bind to these epitopes. (*Id.*, ¶¶79, 140.) Moreover,

each such epitope on EC3 can give rise to a whole subgenus of human or humanized monoclonal antibodies and their functional fragments, thus exacerbating the number of potential binding sites. (*Id.*)

Just comparing the extent of the structural differences between the prior art NOV0710 antibody in the Novartis reference and the four working example antibodies of the Challenged Claims demonstrates the sheer breadth of these claims. As explained in more detail below as part of Ground 3 (*infra* at VIII.C), the NOV0710 antibody anticipates many of the very broad claims, including claim 1, because NOV0710 is a humanized antibody that binds to EC3 and internalizes. Despite this, the amino acid sequences of the CDR regions of these exemplary humanized antibodies of the '386 patent are wildly different from those of NOV0710 (45%, 57%, 50%, 20%, 11%, and 33% sequence identity for CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively). (*Id.*, ¶155.) Similarly, the amino acid sequences of the heavy chain and light chain variable regions of these exemplary humanized antibodies are also remarkably different from those of NOV0710 (58% sequence identity for heavy chain variable regions (HCVRs) and 84% sequence identity for light chain variable regions (LCVRs)), as compared to high sequence identity values among the amino acid sequences of the heavy chain and light chain variable regions of the exemplary humanized

antibodies (95% sequence identity for HCVRs and 93% sequence identity for LCVRs). (*Id.*, ¶155.)

As Dr. Bournazos concludes, this amount of variability between the inventors' working examples and another antibody that falls within the scope of the claims only confirms that the scope of these very broad claims covers a vast number of antibodies which are not represented in the specification. (*Id.*, ¶156.) *See Abbvie*, 759 F.3d at 1301 (in affirming the jury's decision to invalidate an antibody patent for lack of written description, the Court recognized that "[t]he asserted claims attempt to claim every fully human IL-12 antibody that would achieve a desired result, *i.e.*, high binding affinity and neutralizing activity, and cover an antibody as different as Stelara [accused product], whereas the patents do not describe representative examples to support the full scope of the claims.").

Critically, when it comes to the claimed antibodies' ability to internalize, the '386 patent itself provides the key admission that there are no common structural features that can predict whether these antibodies function as claimed. The '386 patent states that:

The internalization ability of the antibody depends on the properties of both the target antigen and the antibody. It is difficult to predict an antigen-binding site suitable for internalization from the molecular structure of a target or

to predict an antibody having high internalization ability from binding strength, physical properties, and the like of the antibody. Hence, an important challenge in developing ADC having high efficacy is obtaining an antibody having high internalization ability against the target antigen (Non Patent Literature 11).

(Ex. 1001, 2:47-57.)

Thus, the specification of the Challenged Claims makes no attempt to identify any structural features that contribute to an antibody's possession of an ability to internalize that permits cellular intake. This is not surprising, since the Federal Circuit has previously noted that claims to antibodies by function are "inherently vulnerable to invalidity challenge for lack of written description" given the "highly unpredictable" state of the art and the difficulty establishing a correlation between structure and function. *Abbvie*, 759 F.3d at 1301.

Dr. Bournazos confirms that no such correlation exists between the structure of the antibody and its ability to internalize. (Ex. 1003, ¶190.) Even today, with advanced computer modeling, a POSA could not design sequences of antibodies that internalize just by relying on their sequences, and instead the POSA would have to rely on randomly screening millions of potential antibody sequences to evaluate their ability to internalize. (*Id.*) However, a POSA's ability to screen for

compounds providing a desired function, *fails* to show that the inventors were in *possession* of the claimed genus.

In *University of Rochester v. Searle*, 358 F.3d 916 (Fed. Cir. 2004), the Federal Circuit found that claims to inhibitory compounds lacked written description support because the specification disclosed methods of screening for those compounds rather than identifying representative examples or common structural features. 358 F.3d at 927. Applied here, characterization within the '386 patent of antibody internalization based on four working example antibodies and reliance on the POSA's ability to screen for suitable antibodies do not suffice to establish a structure-function correlation or otherwise demonstrate possession of antibodies claimed by function. *See, id.*; *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997) (adequate written description not satisfied by “*a mere wish* or plan for obtaining the claimed chemical invention.” (emphasis added)).

While claim 2 recites an additional functional feature – a competitive inhibitory activity relative to the five reference antibodies (*i.e.*, chG019, H01L02, H02L02, H02L03, and H04L02), this claim is still defined by a further functional element – competitive inhibitory activity – rather than any structure of the claimed antibody. As such, this claim still suffers from a lack of written description because

the specification does not identify any common structural features that would allow for this competitive inhibitory activity with the recited antibodies.

Claim 5 specifies “the antibody or the functional fragment of the antibody is humanized,” and claim 13 specifies “the functional fragment is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv.” Claim 14 specifies “the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amination of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus.” Claim 15 specifies “one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof,” and claim 16 specifies “one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.” Claim 17 specifies “a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated,” and claim 18 specifies “sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity.” However, none of these features specified in claims 5 and 13-18 are identified by the '386 Patent as the common structural features for binding to EC3 and internalization recited by the Challenged Claims. As such, these dependent

claims are also invalid for lack of written description because the specification still fails to disclose structural features common to members of the broad genus of these claims.

Claim 3 specifies six CDR sequences obtained through a mix-and-match approach by combining light chain CDRs (CDRL1, CDRL2, and CDRL3) of the four rat antibodies (*i.e.*, rG019, rG055, rG056, and rG061) with heavy chain CDRs (CDRH1, CDRH2, and CDRH3) of the four rat or chimeric antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061). However, the data from the binding assay using the EC3-deletion mutant cannot rule out the possibility that rG019, rG055, rG056, or rG061 binds to a joint region between EC3 and EC2 or between EC3 and EC4—rather than binding to EC3—which could lead to the same results as depicted in Figure 2 of the '386 Patent. Furthermore, as Dr. Bournazos explained, there is no definitive evidence that the anti-CDH6 antibodies having these CDR sequences would internalize into cells, because claim 3 does not specify any additional common structural features required for internalization. (Ex. 1004, ¶¶168-170.)

Claim 4 specifies six CDR sequences of four antibody clones, *i.e.*, rG019/chG019, rG055, rG056, and rG061. However, as with claim 3, claim 4 also fails to provide sufficient common structural features required for both binding and

internalization functions of the human or humanized antibodies and their functional fragments.

Claim 6 specifies the heavy chain and light chain variable region sequences, again through a mix-and-match approach by combining the light chain variable region of L02 or L03 with the heavy chain variable region of H01, H02, or H04. Claim 6 also covers variants of these combinations with “an amino acid sequence having at least 95% or more to the sequence of a framework region.” Claim 7 specifies the heavy chain and light chain variable region sequences of H01L02, H02L02, H02L03, and H04L02. As with claims 3 and 4, claims 6-7 also fail to specify any common structural features required for both binding and internalization functions of the human or humanized antibodies and their functional fragments.

Claim 8 specifies the heavy chain and light chain amino acid sequences of H01L02, H02L02, H02L03, or H04L02. Claims 9-12 specify the heavy chain and light chain amino acid sequences of H01L02, H02L02, H02L03, and H04L02, respectively. Claims 8-12 also cover functional fragments of the claimed antibodies as well as antibody variants having various modifications. However, there is no evidence indicating that the functional fragments or antibody variants would retain common structures required for both binding and internalization functions. As Dr. Bournazos explains, functional fragments or antibody variants

often exhibit different activities compared to intact, full-length antibodies. (Ex. 1003, ¶162.)

2. The Limited Number Of Working Examples In The Patent Are All Nearly Identical And Are Therefore An Extremely Narrow Subset That Is Not Representative Of The Diverse Genus Of The Challenged Claims

As discussed above, there are only four working examples of the Challenged Claims - H01L02, H02L02, H02L03, and H04L02 - which are all clones of each other, and therefore share over 95% identity in sequence. After all, these antibodies were all generated from the same chimeric antibody clone (chG019), three out of the four antibodies share the same light chain (*i.e.*, L02), and two of these four humanized antibodies share the same heavy chain (*i.e.*, H02).

Based on Dr. Bournazos' calculations, the light chain of L02 (SEQ ID NO: 61) and the light chain of L03 (SEQ ID NO: 65) share about 98% sequence identity. (Ex. 1003, ¶99.) This limited variability only occurs in the framework region since L02 and L03 share the exact same light chain constant region.

The light chain variable region of L02 (SEQ ID NO: 63) and the light chain variable region of L03 (SEQ ID NO: 67) share about 93% sequence identity, and the amino acid sequences of the L02 light chain CDRs (*i.e.*, CDRL1, CDRL2, and CDRL3) of L02 *are identical* to those of L03. (*Id.*)

The amino acid sequences of the heavy chain of H01 (SEQ ID NO: 69), the heavy chain of H02 (SEQ ID NO: 73), and the heavy chain of H04 (SEQ ID NO:

76) are all about 99% identical, and the only variability again occurred in the framework region because H01, H02, and H04 share the same heaving chain constant region.

The heavy chain variable region of H01 (SEQ ID NO: 69), the heavy chain variable region of H02 (SEQ ID NO: 73), and the heavy chain variable region of H04 (SEQ ID NO: 76) are all about 95% identical.

Moreover, the amino acid sequences of heavy chain CDRs (*i.e.*, CDRH1, CDRH2, and CDRH3) of H01 are identical to those of H02 and H04.

Thus, all four exemplary humanized anti-hCDH6 antibodies (i) share extensive sequence identity in their heavy and light chain variable domains, (ii) share identical heavy chain and light chain CDRs and identical heavy chain and light chain constant regions, and (iii) bind to the same epitope. (*Id.*, ¶154.) The very limited variability among the working example antibodies is only found in the framework regions.

As Dr. Bournazos concludes, this lack of diversity among the four exemplary humanized anti-hCDH6 antibodies is not surprising given the restricted manner in which the humanized anti-hCDH6 antibodies were derived from a single starting chimeric human antibody chG019 with only a limited number of variations in the framework regions. (*Id.*, ¶154.)

The patent also lists a number of prophetic antibodies such as (a) H01L03 and H04L03 and (b) the twenty hypothetical partially “humanized” anti-hCDH6 antibodies. However, *these paper examples were never tested to actually show their ability to bind to EC3 or internalize*, but were instead made up (not in a lab, but most likely from just pen and paper) by merely mixing and matching combinations of a humanized heavy chain variable region (*i.e.*, H01, H02, or H04) with a humanized light chain variable region (*i.e.*, L02 or L03) or by combining humanized heavy chain variable regions (*i.e.*, H01, H02, or H04) with a light chain variable region of the four rat or chimeric anti-hCDH6 antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061), or by combining a humanized light chain variable region (*i.e.*, L02 or L03) with a heavy chain variable region of the four rat or chimeric anti-hCDH6 antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061). (Ex. 1001, col. 27-32.)

However, as Dr. Bournazos points out, the four rat clones are in fact from only two germ lines, with rG055, rG056, and rG061 being clonal variants of the same germline. (Ex. 1003, ¶94.) The fact that rG055, rG056, and rG061 are originated from the same germline is consistent with their high sequence identity at both nucleotide and protein levels. (*Id.*) Because these mix-and-match paper examples of antibodies were merely assembled from already highly structurally similar parts, these combinations also provide very limited structural diversity, as

explained by Dr. Bournazos. (*Id.*, ¶159.) Moreover, all of these paper examples are still in the same IgG1 subtype and originated from the same hybridoma screening process resulting in the rat anti-hCDH6 antibodies.

In this way, the '386 patent is analogous to the antibody patent that was invalidated in *Abbvie*, where the Federal Circuit held that a narrow disclosure of highly similar antibodies and a mere “wish list” to claim a far broader genus of unknown and undisclosed antibodies defined solely by function did not satisfy the written description requirement. *See* C at 1300-1302. In *Abbvie*, the Federal Circuit held that a claimed genus of anti-IL12 antibodies defined solely by their binding function was invalid for lack of written description even though the specification disclosed 300 examples. *See id.* The Federal Circuit recognized that the disclosed antibodies all derived from a single parent antibody and therefore constituted only a **narrow subset** of the claimed genus. *See id.* In evaluating written description, the Federal Circuit first examined the breadth of the claims by making the following analogy.

One factor in considering the question is how large a genus is involved and what species of the genus are described in the patent. If the genus is not large or, even if it is, the specification discloses species representing the genus throughout its scope, the requirement may be met.

On the other hand, analogizing the genus to a plot of land, if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus. He only described a portion of it. That is the case here...

...With the *written description* of a genus, however, merely drawing a fence around a perceived genus is not a description of the genus. One needs to show that one has truly invented the genus, *i.e.*, that one has conceived and described sufficient representative species encompassing the breadth of the genus. Otherwise, one has only a research plan, leaving it to others to explore the unknown contours of the claimed genus. *See Ariad*, 598 F.3d at 1353 (The written description requirement guards against claims that “merely recite a description of the problem to be solved while claiming all solutions to it and ... cover any compound later actually invented and determined to fall within the claim's functional boundaries.”).

Id. at 1299-1300 (emphasis in original).

The Federal Circuit then noted that antibodies described in the *Abbvie* patent were all derived from a single parent (Joe-9), and that although the disclosed antibodies had different amino acid sequences at the CDRs, they shared more than 90% sequence identity in the variable regions. *See id.* at 1291.

Applied here, the facts of this case are even more compelling to find a lack of written description, since the four exemplary antibodies share 100% identity in their CDRs and the 20 or so prophetic “mix and match” antibodies of the ’386 patent have even higher sequence homology in the CDR regions and variable regions than the disclosed antibodies in *Abbvie*.

Clearly, the limited disclosure of the ’386 patent would not allow the POSA to visualize the genus of antibodies covered by the Challenged Claims. As Dr. Bournazos explains, if one started with the four exemplary antibodies of the ’386 patent and made random amino acid substitutions to arrive at another antibody covered by the Challenged Claims, such as the NOV0710 antibody, the number of possible antibodies made this way would number in the billions based on the fact that the NOV0710 antibody differs so much by amino acid sequence from the four exemplary antibodies of the ’386 patent. (Ex. 1003, ¶155.) There is simply no way to predict the amino acid sequences of the antibodies claimed purely by function in the Challenged Claims, and thus these claims are invalid for lack of written description under *Abbvie* and *Ariad*.

3. The Narrower Dependent Claims (Claims 7-12) Also Lack Written Description Because They Still Claim A “Functional Fragment” Of The Claimed Genus

While there is a set of narrower dependent claims within the Challenged Claims that provide some structural limitations to the claimed antibodies, these too lack written description because, among other reasons, these narrower claims (as do all the Challenged Claims) cover not just human or humanized monoclonal antibodies that bind to EC3 and internalize, but also to any “functional fragment” that is supposed to accomplish these claimed functions.

“Functional fragment” is defined very broadly in the '386 patent to mean:

[A] partial fragment of the antibody having binding activity against an antigen, and includes Fab, F(ab')₂, scFv, a diabody, a linear antibody and a multispecific antibody formed from antibody fragments, and the like. Fab', which is a monovalent fragment of antibody variable regions obtained by treating F(ab')₂ under reducing conditions, is also included in the antigen-binding fragment of an antibody. However, the antigen-binding fragment of an antibody is not limited to these molecules, as long as the antigen-binding fragment has antigen-binding ability. These antigen-binding fragments

include not only those obtained by treating a full-length molecule of an antibody protein with an appropriate enzyme, but proteins produced in appropriate host cells using a genetically engineered antibody gene.

Ex. 1001, at 17:40-56.

As Dr. Bournazos explains, this definition of “functional fragment” conceivably covers *an astronomical amount* of variability among the amino acid structure of these claimed antibody fragments because this element includes any partial fragment of an antibody that binds to EC3 and internalizes. (Ex. 1003, ¶163.) Apart from this broad generic disclosure, the POSA would clearly have no guidance from the specification of the Challenged Claims to be able to visualize whether the inventors possessed the functional fragments broadly covered by these claims.

After all, as discussed above, the '386 patent does not disclose any structural features common to complete human or humanized antibodies, let alone “functional fragments” that would allow for binding to EC3 and internalization. Moreover, the four exemplary antibodies and the mix-match paper examples of the '386 patent are not representative of the vast amounts of “functional fragments” covered by these claims.

Critically, *there are no examples* of “functional fragments” that satisfy an adequate written description of these claims, and even if there were, the immeasurable breadth of these claims based on this element would not satisfy written description under *Abbvie*, which requires either a representative number of antibodies falling within the scope of the genus or disclosure of structural features common to members of the claimed antibody genus. *See* 759 F.3d at 1299.

B. Ground 2: Lack of Enablement of Claims 1-18 of the '386 Patent

“Section 112 requires that the patent specification enable ‘those skilled in the art to make and use the full scope of the claimed invention without ‘undue experimentation.’” *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1070-71 (Fed. Cir. 2005) (citations omitted).

“Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Factors to be considered include (i) the breadth of the claims, (ii) the presence or absence of working examples, (iii) the amount of direction or guidance presented, (iv) the predictability or unpredictability of the art, (v) the nature of the invention, (vi) the state of the prior art, (vii) the relative skill of those in the art, and (viii), the quantity of experimentation. (“*Wands* factors”) *See Id.* “[A]ll of the factors need not be reviewed when determining whether a disclosure is enabling,” and the

relevant factors are dependent on the particular circumstances of each case. *See Enzo BioChem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999).

1. The Make-and-Screen Approach Of the Invention Renders The Challenged Claims Invalid For Lack of Enablement

In cases like this, where there are a large number of potential embodiments based on broad functional claims, relatively few working examples disclosed in the patent that are all structurally similar, and little guidance in the patent as to how to practice the full scope of the claims except through random trial and error, Courts have consistently invalidated the claims for lack of enablement. *See Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087 (Fed. Cir. 2021), *aff'd* 598 U.S. ___, 143 S.Ct. 1243 (2023) (“Amgen I”); *Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1155–56 (Fed. Cir. 2019) (broad functional claims directed to efficacy against hepatitis C virus found not enabled based on random screening a large number of drug candidates); *Enzo Life Scis., Inc. v. Roche Molecular Sys., Inc.*, 928 F.3d 1340, 1346–47 (Fed. Cir. 2019) (claims directed to non-radioactively labeled polynucleotides found not enabled where claims were broadly defined by the polynucleotide’s ability to bind and be detected but the specification failed to disclose representative embodiments); *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1385–86 (Fed. Cir. 2013) (broad functional claims directed to rapamycin analogs found not enabled because it would have required undue

experimentation to synthesize and screen each drug candidate to determine whether it functioned as claimed to prevent restenosis).

In *Amgen I*, the Supreme Court and the Federal Circuit affirmed the invalidation of Amgen's patents for lack of enablement ***based on facts that are remarkably similar here***. See generally *Amgen I*. Just as with this case, the claims in *Amgen I* were directed to a genus of antibodies claimed broadly in terms of functional ability to bind to an antigen. The claims were directed to monoclonal antibodies to treat elevated low-density lipoprotein ("LDL") cholesterol. *Amgen I*, 987 F.3d at 1082–83. LDL cholesterol is normally removed from the blood stream using LDL receptors. *Id.* at 1082. However, a naturally occurring protein called PCSK9 can bind and destroy these LDL receptors, thus preventing them from removing the LDL cholesterol. *Id.* at 1082–83. Amgen's patents broadly claimed antibodies that prevent the destruction of LDL receptors by binding to a specific region of the PCSK9 protein such that PCSK9 can no longer bind to the LDL receptors. *Id.* at 1083. Despite claiming all antibodies that bind to a specific region of PCSK9, the specification disclosed only 26 working example antibodies that satisfied these functional limitations. *Id.*

In recognizing the "high hurdles in fulfilling the enablement requirement for claims with broad functional language," the Federal Circuit found that the specification did not enable the full scope of the asserted claims which were

defined by antibodies that bind a specific target. *Amgen I*, 987 F.3d at 1087. The Court emphasized the fact that the “claims [we]re far broader in functional diversity than the disclosed examples,” and that “the only ways for a person of ordinary skill to discover undisclosed claimed embodiments would be through either ‘trial and error, by making changes to the disclosed antibodies and then screening those antibodies for the desired binding and blocking properties,’ or else ‘by discovering the antibodies *de novo*’ according to a randomization-and-screening ‘roadmap.’” *Id.* at 1088 (quoting *Amgen Inc. v. Sanofi*, 2019 WL 4058927, at *11 (D. Del. 2019)); *see also Idenix*, 941 F.3d at 1161 (“A specification that requires a [POSA] to ‘engage in an iterative, trial-and-error process to practice the claimed invention’ does not provide an enabling disclosure.” (internal citations omitted)).

The holding in *Amgen I* should apply with even greater force here, since the Challenged Claims are directed to not one but at least two functional requirements: (1) binding to EC3; and (2) possessing an ability to internalize that permits cellular uptake. As discussed above, the inventors had to screen millions of antibodies using hybridomas to find antibodies that bind to EC3, and even then, these antibodies had to be repeatedly screened and assayed to confirm their binding ability and their ability to internalize. As Dr. Bournazos explains, the only way the POSA could create human or humanized monoclonal antibodies that function as

claimed would be to randomly screen and test millions of different antibodies, especially given the inherent unpredictability in this field and the lack of guidance in the specification. (Ex. 1003, ¶¶190, 191, 196, 197.) After all, the Challenged Claims are extremely broad – they cover a vast genus of antibodies and functional fragments of the antibodies of any sequence, germline, isotypes, and subclasses, and the guidance in the '386 Patent is extremely limited. At best, the '386 Patent includes four highly similar exemplary humanized anti-CDH6 antibodies derived from a single starting antibody clone and other hypothetical antibodies constructed from sequences of four starting rat antibodies originated from only two germlines and generic instructions to identify any and all other antibodies or functional fragments with the claimed function of binding to EC3 and internalization. No other specific information is provided.

Importantly, as mentioned above, the '386 Patent did not even attempt to predict the common structural features required for internalization. As the '386 Patent admits, “it is difficult to predict an antigen-binding site suitable for internalization from the molecular structure of a target or to predict an antibody having high internalization ability from binding strength, physical properties, and the like of the antibody.” (Ex. 1001, 2:47-56.)

Similarly, the '386 Patent does not attempt to demonstrate identification or generation of any human anti-hCDH6 antibodies capable of specifically binding to

hCDH6 EC3 and internalizing into cells. (Ex. 1003, ¶186.) Nor is there any demonstration for any functional fragments of anti-hCDH6 antibodies capable of specifically binding to hCDH6 EC3 and internalizing into cells. (*Id.*, ¶186.)

Moreover, while the 115-amino acid sequence of SEQ ID NO: 4 encompasses a large number of epitopes, the '386 Patent does not demonstrate identification or generation of anti-hCDH6 antibodies capable of binding to an epitope different from that of the four exemplary humanized anti-CDH6 antibodies. (*Id.*, ¶188.)

Absent sufficient guidance, identifying such antibodies and functional fragments falling within the very broad scope of the claimed invention requires random trial and error, by constructing and screening a vast number of candidate antibodies and functional fragments that have diverse and unpredictable sequences, and characterizing them for desired binding and internalization functions.

Therefore, the Challenged Claims are at most a *mere wish* of an invitation to carry out a research plan that cannot be accomplished without undue experimentation and are thus invalid for lack of enablement. *See Idenix*, 941 F.3d at 1162 (finding claims not enabled where “to get from a large number of candidate compounds to a relatively speaking small number of effective compounds...leaves a [POSA] searching for a needle in a haystack to determine which of the ‘large number of...[candidate compounds] falls into [the scope of the claims].”); *Wyeth*, 720 F.3d at 1384 (patent found not enabled because even if “one of ordinary skill could

routinely use the assays disclosed in the specification to determine” which rapamycin compounds met the claim terms, “there [we]re still at least tens of thousands of candidates to screen.”).

2. The Application of the *Wands* Factors Compels A Finding Of Undue Experimentation

As demonstrated below, application of the *Wands* factors shows that undue experimentation would be needed to practice the full scope of the claimed inventions, and therefore the Challenged Claims are invalid for lack of enablement.

a. The Nature of the Invention and Breadth of the Claims

The Challenged Claims read on any human or humanized antibodies or their functional fragments, regardless of any sequences, germlines, isotypes, and subclasses, that specifically bind to the amino acid sequence shown of SEQ ID NO: 4 and possess an ability to internalize that permits cellular uptake. This would include antibodies with extremely diverse sequences that are nothing like the related sequences of the four exemplary and other hypothetical antibodies identified in the '386 patent.

Indeed, as discussed above for written description, the claims encompass antibodies having sequences as different as NOV0710, which vary wildly in their CDR regions and heavy and light chain variable regions from any of the exemplary humanized antibodies of the '386 patent. The claims also encompass various isotypes and subclasses of antibodies or functional fragments, as well as various

modifications on antibodies or functional fragments, yet only subclass IgG1 was demonstrated in the '386 patent. This would also be the case for all of the narrower dependent claims (claims 7-12) since all of these claims have the impermissibly broad element covering a “functional fragment” of the antibody.

As a result, this *Wands* factor weighs heavily in finding that undue experimentation would be required to practice the full scope of the claims.

b. The State of the Art, Predictability in the Field, and the Level of Ordinary Skill

While basic techniques for generating and screening antibodies existed in 2017, these are still inherently unpredictable today. (Ex. 1003, at ¶195.) Without trial and error, the skilled artisan could not predict which antibody sequences would bind hCDH6 EC3 and provide the claimed internalization function. Rather, it would require undue experimentation to evaluate billions of different potential antibody sequences to identify those that specifically bind to the amino acid sequence shown in SEQ ID NO: 4 and possess an ability to internalize that permits cellular uptake and thereby practice the full scope of the claimed invention of the '386 patent.

Indeed, even after screening billions of antibodies in an immunized animal's repertoire that are able to bind hCDH6 EC3, there is no guarantee that they will possess an ability to internalize that permits cellular uptake. because the '386 patent itself confirms this when it made the critical admissions that “the

internalization ability of the antibody depends on the properties of both the target antigen and the antibody” and that “it is difficult to predict an antigen-binding site suitable for internalization from the molecular structure of a target or to predict an antibody having high internalization ability from binding strength, physical properties, and the like of the antibody,” as recognized by the ’386 patent. (Ex. 1001, 2:47-56.).

Moreover, since the claims are functionally defined, a skilled artisan would need to carry out an unguided screening process through a large number of candidate sequences to construct, produce, and test antibodies across this genus of indeterminate scope for the claimed binding and internalization functions. This represents undue experimentation in light of the unpredictable state of the art for making and using antibodies and functional fragments of different sequences, structures, germ lines, isotypes, and subtypes encompassed by the broadly worded claims. As with the first factor, this unpredictability would also be the case for all of the narrower dependent claims (claims 7-12) since their broad coverage of any “functional fragment” of the antibody would vastly increase the unpredictability of screening for these fragments.

Thus, this *Wands* factor also weighs heavily in finding undue experimentation in practicing the full scope of the claims.

c. The Knowledge Of One Of Ordinary Skill

While the knowledge of one of ordinary skill was relatively high as of 2017, this knowledge of the prior art does not outweigh the other *Wands* factors, which clearly show that undue experimentation is required to practice the full scope of the Challenged Claims. Moreover, while the specification need not disclose what is well known in the art, this is “merely a rule of supplementation, not a substitute for a basic enabling disclosure.” *Genentech v. Novo Nordisk*, 108 F.3d 1361, 1366 (Fed. Cir. 1997). The ’386 patent specification, not the POSA with knowledge of the prior art, “must supply the novel aspects of [the] invention in order to constitute adequate enablement.” *Id.* While the “omission of *minor details* does not cause a specification to fail to meet the enablement requirement,” where there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required.” *Id.* (emphasis added). Applied here, Patent Owner should not be able to rely on the POSA’s knowledge of the prior art to improperly correct its defects of disclosure, and therefore, this factor also compels invalidation of the Challenged Claims based on non-enablement.

d. The Amount of Direction or Guidance Provided And The Lack of Representative Examples

The ’386 Patent provides no guidance on how to arrive at any antibody that specifically binds to the amino acid sequence shown in SEQ ID NO: 4 and possesses an ability to internalize that permits cellular uptake, other than through

the trial-and-error process of generating antibodies by animal immunization and testing every potential sequence in diverse antibody libraries and its combinations with other sequences. As explained previously with regard to written description, antibodies and functional fragments with the desired binding and internalization functions can have vastly different sequences and binding regions, as illustrated by the comparison between the four exemplary antibodies of the Challenged Claims and the prior art antibody NOV0710 in the Novartis reference (Ex. 1005). Yet, other than the four exemplary humanized antibodies derived from a single starting antibody and binding to the same epitope, the '386 Patent offers no guidance on how to arrive at other antibodies or functional fragments with the claimed functions (*i.e.*, capable of binding to various epitopes within EC3 and internalizing into cells) across this diverse and unpredictable genus of antibody sequences without requiring extensive screening. The mere disclosure of the four exemplary humanized antibodies derived from a single starting antibody and some hypothetical antibodies constructed from unrepresentative four rat antibodies would not allow the skilled artisan to routinely make and use the wildly different antibody sequences encompassed by the claims without undue experimentation. As with the other factors discussed, this lack of guidance also applies to the narrower dependent claims (claims 7-12) that cover functional fragments. Apart from a generic discussion that broadly defines a functional fragment as any “partial”

fragment that can bind EC3, the '386 patent has no examples of any functional fragments that satisfy the elements of these claims.

As a result, these *Wands* factors also weigh substantially in favor of finding undue experimentation.

e. The Quantity of Experimentation Required To Practice The Full Scope of the Claims

As discussed above, other than the four exemplary humanized antibodies described in the '386 patent, no other examples or guiding principles are provided. For example, the '386 patent does not provide any examples of human anti-hCDH6 antibodies or their functional fragments. Nor does it describe necessary materials (*e.g.*, transgenic mice) and methods for producing and screening human antibodies or their functional fragments. Virtually every step in the process of producing, identifying, and characterizing of antibodies across the vast scope of Challenged Claims is left up to the skilled artisan, without any enabling guidance from the '386 patent.

The skilled artisan would therefore need to screen numerous antibody sequences to make and use antibodies across the broad genus of the claims. Given the diverse, and indeed unknowable, scope of the claimed functional genus, unguided screening of potentially billions of candidate antibodies with the claimed binding and internalization functionality constitutes undue experimentation. This is particularly true considering the significant amount of work carried out by the

inventors of the '386 patent in producing, identifying, purifying, and characterizing just the four rat anti-CDH6 antibodies used as starting material for the claimed antibodies, as well as the additional work required to obtain cDNAs of antibodies, determine their sequences, construct and generate humanized versions of the antibodies, and characterize binding and internalization functions of the humanized antibodies and their functional fragments. (Ex. 1003, ¶203.)

Even after screening an entire naive immune cell repertoire of up to billions of different antibody sequences, the skilled artisan still likely would not have arrived at sequences with sufficient diversity to represent the broad scope of the claimed invention, given the highly divergent immune repertoires in different host animals. This undue amount of experimentation also applies to the narrower dependent claims (claims 7-12) that cover functional fragments, since, as discussed above, the sheer breadth of having to screen not just full antibodies, but any number of partial fragments that could bind and EC3 and internalize would be staggering. (*Id.*, ¶203.)

Thus, this *Wands* factor also weighs heavily in finding undue experimentation when practicing the full scope of the Challenged Claims.

C. Ground 3: Anticipation of Claims 1, 5, 13-16, and 18 By Novartis

“A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention.” *Schering Corp. v. Geneva*

Pharms., Inc., 339 F.3d 1373, 1377 (Fed. Cir. 2003). “[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” (*Id.*) As demonstrated below, claims 1, 5, 13-16, and 18 are anticipated by the Novartis prior art (Ex. 1005).

1. **Claim 1: “A human or humanized monoclonal antibody that specifically binds to the amino acid sequence shown of SEQ ID NO: 4 and possesses an ability to internalize that permits cellular uptake, or a functional fragment of the antibody that binds to the amino acid sequence of SEQ ID NO: 4 and possesses an ability to internalize that permits cellular uptake.”**

Novartis discloses human or humanized monoclonal antibodies, including at least twenty NOV anti-hCDH6 antibodies, including NOV0670, NOV0672, NOV0674, NOV0682, NOV0685, NOV0689, NOV0690, NOV0691, NOV0692, NOV0693, NOV0695, NOV0699, NOV0705, NOV0709, NOV0710, NOV0712, NOV0713, NOV0718, NOV00719, and NOV0720, and shows that all of them bind strongly to human, cynomolgus, rat or mouse CDH6, as determined by a cellular binding assay and Biacore measurement. (Ex. 1005, ¶[00241], Tables 5, 7 and 8, Figures 1 and 2.)

Among these Novartis anti-hCDH6 antibodies, Novartis demonstrates that at least NOV0710 is able to bind strongly to hCDH6 EC3, particularly to region (aa 303-315) IEYSITDGEGLDM (SEQ ID NO: 343), region (aa 316-330)

FDVITDQETQEGIIT (SEQ ID NO: 344), region (aa. 337-358)

FEKKKVYTLKVEASNPYVEPRF (SEQ ID NO: 346), region (aa 564-586)

YLLPWISDNDYPVQSSTGTVTV (SEQ ID NO: 351), and region (aa 295-315)

ADVGENAEIEYSITDGEGLDM (SEQ ID NO: 352), as determined by the HDx study. (*Id.*, ¶¶[00397], [00399]-[00401], [00403].)

Novartis also demonstrates NOV0719 binds strongly to hCDH6 EC3, though with a binding affinity lower than that of NOV0710 to hCDH6 EC3.

With respect to internalization, Novartis discloses that all the NOV anti-hCDH6 antibodies as listed in Table 5, including NOV0710 and NOV0719, possess an ability to internalize that permits cellular uptake. The above NOV anti-hCDH6 antibodies were selected from a series of assays confirming their binding affinity, cellular internalization, as well as *in vitro* and *in vivo* cytotoxic activity in surrogate ADC assays. (Ex. 1005, ¶[00379].) Thus, all the NOV anti-hCDH6 antibodies have an ability to internalize.

Therefore, claim 1 of the '386 patent is anticipated by Novartis.

2. Claim 5: “The antibody or the functional fragment of the antibody according to claim 1, which is humanized.”

As stated above for claim 1, Novartis discloses human or humanized monoclonal antibodies, including at least twenty NOV anti-hCDH6 antibodies, including NOV0670, NOV0672, NOV0674, NOV0682, NOV0685, NOV0689, NOV0690, NOV0691, NOV0692, NOV0693, NOV0695, NOV0699, NOV0705,

NOV0709, NOV0710, NOV0712, NOV0713, NOV0718, NOV00719, and NOV0720, and shows that all of them bind strongly to human, cynomolgus, rat or mouse CDH6, as determined by a cellular binding assay and Biacore measurement. (Ex. 1005, ¶[00241], Tables 7 and 8, Figures 1 and 2.)

Therefore, claim 5 of the '386 patent is also anticipated by Novartis.

3. Claim 13: “The functional fragment of the antibody according to claim 1, wherein the functional fragment is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv.”

Novartis discloses “antigen binding fragments” that include “single-chain Fvs (scFv), disulfide-linked Fvs (sdFv), Fab fragments, F(ab') fragments, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)₂ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CHI domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment.” (Ex. 1005, ¶¶[0075], [00181].) In addition, Novartis demonstrates the generation and expression of soluble Fab fragments. (*Id.*, ¶[00351], [00181].)

Therefore, claim 13 of the '386 patent is also anticipated by Novartis.

4. Claim 14: “The antibody or the functional fragment of the antibody according to claim 1, wherein the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal

processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus.”

Novartis discloses that “an antibody can be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody.” (Ex. 1005, ¶[00244].) Novartis also discloses “Asn(297)-linked carbohydrates” which is a type of “N-linked glycosylation” recited in claim 14. (*Id.*, ¶[00252].)

Therefore, claim 14 of the '386 patent is also anticipated by Novartis.

5. Claim 15: “The antibody according to claim 14, wherein one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof.”

Novartis discloses that “for polypeptide sequences, ‘conservatively modified variants’ include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid.” (Ex. 1005, ¶[0093].) As explained by Dr. Bournazos, such deletions would include deletion of one or two amino acids from the carboxyl terminus of a heavy chain thereof. (Ex. 1003, ¶222.)

Thus, claim 15 the '386 patent is also anticipated by Novartis.

6. Claim 16: “The antibody according to claim 15, wherein one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.”

As discussed above, Novartis discloses that “for polypeptide sequences, ‘conservatively modified variants’ include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid.” (Ex. 1005, ¶[0093].) As also explained by Dr. Bournazos, such deletions would include deletions of one or two amino acids each of the carboxyl termini of both of the heavy chains thereof. (Ex. 1003, ¶225.)

Therefore, claim 16 of the ’386 patent is also anticipated by Novartis.

7. Claim 18: “The antibody or the functional fragment of the antibody according to claim 1, wherein sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity.”

As discussed above, Novartis discloses that “an antibody can be chemically modified (*e.g.*, one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody.” (Ex. 1005, ¶[00244].) Novartis also discloses “Asn(297)-linked carbohydrates” which is a type of “N-linked glycosylation” recited in claim 14. (*Id.*, ¶[00252].)

Novartis further discloses that “an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts

of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies,” where ADCC stands for the “antibody-dependent cellular cytotoxic activity” element of this claim. (*Id.*, ¶[00251].)

Thus, claim 18 of the '386 Patent is also anticipated by Novartis.

D. Ground 4: Obviousness of Claims 1, 5, and 13-18 Over Novartis or Novartis in Combination with Urano and or Sato As To Claims 14-17

A claimed invention is unpatentable if the differences between it and the prior art are such that the claimed invention as a whole would have been obvious at the time it was made to a person having ordinary skill in the pertinent art. *In re Kahn*, 441 F.3d 977, 985 (Fed. Cir. 2006); 35 U.S.C. § 103.

The prior art is not limited to what the inventors actually were aware or what another person might have been aware; rather, “one of ordinary skill is presumed to have knowledge of all pertinent prior art – be it obscure or unknown to actual individuals.” *Senju Pharm. Co. Ltd., v. Apotex Inc.*, 717 F.Supp 2d 404, 422 (D. Del. 2010). “One of the ways in which a patent’s subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent’s claims.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007); *see also Stored Value Solutions, Inc. v. Card Activation Technologies, Inc.*, 796 F.Supp. 2d 520 (D. Del.

2011). If a patent claims a structure that is known and was created by substituting one element for another, that combination must do more than yield predictable result to be patentable. *See KSR Int'l Co.*, 550 U.S. at 416.

When the combined teachings of prior art references disclose each claim limitation, it can be said that insubstantial differences exist between the prior art references. *See Tokai Corp. v. Easton Enterprises*, 632 F.3d 1358 (Fed. Cir. 2011). The motivation to combine need not be found explicitly in references, but equally can be found in the knowledge generally available to a person having ordinary skill in the art, such as knowledge of a problem to be solved. *See Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006).

As explained above, Novartis discloses all of the limitations of claims 1, 2, 5, 13-16, and 18 of the '386 patent more than one year prior to the earliest effective filing date of the '386 patent. Because it is well-settled that anticipation is the epitome of obviousness, these Challenged Claims are also obvious over Novartis. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1373 (Fed. Cir. 2019) (“[I]t is well settled that a disclosure that anticipates under § 102 also renders the claim invalid under § 103, for anticipation is the epitome of obviousness.”) (internal quotations omitted).

Moreover, as demonstrated below, Novartis in combination with Urano (Ex. 1006) and/or Sato (Ex. 1007) disclose or suggest all of the limitations claims 14-17.

1. **Claim 14: “The antibody or the functional fragment of the antibody according to claim 1, wherein the heavy chain or the light chain has undergone one or two or more modifications selected from the group consisting of N-linked glycosylation, O-linked glycosylation, N-terminal processing, C-terminal processing, deamidation, isomerization of aspartic acid, oxidation of methionine, addition of a methionine residue to the N-terminus, amidation of a proline residue, conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid, and a deletion of one or two amino acids from the carboxyl terminus.”**

In addition to the disclosure of Novartis, Urano discloses a modified form of the antibody or functional fragment thereof having post-translational modification (*e.g.*, N-linked or O-linked glycosylation, N-terminal or C-terminal processing, deamidation, isomerization of aspartic acid, or oxidation of methionine), or a methionine residue added to the N-terminus by expression using prokaryotic host cells. (Ex. 1003, ¶246.) Urano also discloses the advantages of some of the modification, such as glycosylation in enhancing the antibody-dependent cellular cytotoxic activity. (*Id.*, ¶247.)

Sato discloses a modified antibody or fragment “in which glutamine or glutamic acid of the N terminal of the heavy chain is modified to pyroglutamic acid due to pyroglutamylation.” (*Id.*, ¶248.)

In view of the disclosures of Novartis, Urano, and Sato, it would have been obvious for the POSA to be motivated, who would also motivated, to generate a human or humanized monoclonal antibody or functional fragment thereof with the heavy chain or the light chain that has undergone one or two or more modifications as claimed. (*Id.*, ¶¶249-251.)

Therefore, claim 14 of the '386 patent is also taught or suggested by Novartis in combination with Urano and/or Sato. (*Id.*, ¶252.)

2. Claim 15: “The antibody according to claim 14, wherein one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof.”

In addition to the disclosure of Novartis, Urano and Sato disclose a molecule that is derived from the antibody protein by the deletion of 1 to several or more amino acid(s) at its amino terminus and/or carboxy terminus.

Therefore, claim 15 of the '386 patent is also taught or suggested by Novartis in combination with Urano and/or Sato. (Ex. 1003, ¶257.)

3. Claim 16: The antibody according to claim 15, wherein one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.

In addition to the disclosure of Novartis, Urano discloses a molecule that is derived from the antibody protein by the deletion of 1 to several or more amino acid(s) at its amino terminus and/or carboxy terminus.

Therefore, claim 16 of the '386 patent is also taught or suggested by Novartis in combination with Urano and/or Sato. (Ex. 1003, ¶262.)

4. Claim 17: “The antibody according to claim 14, wherein a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated.”

As discussed above with respect to claim 14, Novartis discloses all of the elements of this claim because it states that “for polypeptide sequences, ‘conservatively modified variants’ include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid.” (Ex. 1005, ¶[0093].) Dr. Bournazos explains that such deletions would include deletions of one or two amino acids each of the carboxyl termini of each or both of the heavy chains thereof, which is covered by Claim 14. (Ex. 1003, ¶¶224-226.)

Urano discloses “a molecule that is derived from the antibody protein by the deletion of 1 to several or more amino acid(s) at its amino terminus and/or carboxy terminus and maintains at least a portion of the functions of the antibody is also encompassed in the meaning of the functional fragment of the antibody.” (*Id.* Ex. 1005, ¶[0302].) Urano further provides an example where “the heavy chain of an antibody produced by cultured mammalian cells is known to lack a lysine residue at the carboxy terminus.” *Id.*

Urano further discloses the “the heavy chain of such an antibody is known to lack two amino acid residues (glycine and lysine) at the carboxy terminus and instead have an amidated proline residue at the carboxy terminus.” (*Id.*)

In view of the disclosures of Novartis and Urano, it would have been obvious for a person of ordinary skill to generate a human or humanized monoclonal antibody or functional fragment thereof with a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated.

Therefore, claim 17 of the '386 patent is also taught or suggested by Novartis in combination with Urano.

E. Ground 5: At Least Claims 1-5 and 14-18 Are Patent-Ineligible Under 35 U.S.C. § 101

1. Legal Standard For 35 U.S.C. § 101 Patent Ineligibility

A claimed invention is not patent-eligible if its claims are directed to “[l]aws of nature, natural phenomena, and abstract ideas.” 35 U.S.C. § 101; *Alice Corp. v. CLS Bank Int’l*, 573 U.S. 208, 216 (2014). The Supreme Court formulated a two-step framework to determine whether a claim falls within one of these excluded categories of patent eligibility. *Id.* at 217-18 (citing *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 75-77 (2012)).

In step one, one has to first determine whether the claim at issue is *directed to* a patent-ineligible concept by “looking to the specification to understand the ‘problem facing the inventor’” as well as “what the patent describes

as the invention.” *Id.* at 218; *ChargePoint, Inc. v. SemaConnect, Inc.*, 920 F.3d 759, 765-68 (Fed. Cir. 2019).

Under this framework, patent claims directed to isolated DNA, single-stranded pieces of DNA (a “primer”), a cloned sheep, and a mixture of bacteria have all been found to be patent-ineligible products of nature. *See Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 569 U.S. 576, 580 (2013); *Univ. of Utah Rsch. Found. v. Ambry Genetics*, 774 F.3d 755, 758-59 (Fed. Cir. 2014); *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333, 1337 (Fed. Cir. 2014); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). However, when a patent claim has “markedly different characteristics from any found in nature,” such as genetically modified bacteria or a complementary DNA (cDNA) molecule that required removing certain regions of naturally occurring DNA (introns) which resulted in claims directed to an exons-only molecule, these were deemed *not* naturally occurring and thus found to be patent-eligible. *Diamond v. Chakrabarty*, 44 U.S. 303, 310 (1980); *Myriad*, 569 U.S. at 595.

If the claim at issue is “directed to” a patent-ineligible subject matter,⁴ then step two of the Supreme Court’s framework requires determining whether the claim contains “‘an inventive concept’ sufficient to ‘transform’ the claimed [ineligible subject matter] into a patent-eligible application.” *Alice*, 573 U.S. at 221 (citations omitted). Thus, a claim that only adds “well-understood, routine, conventional activity already engaged in by the scientific community” to the ineligible concept will not be patent-eligible. *Mayo*, 566 U.S. at 79-80; *see also BSG Tech LLC v. Buyseasons, Inc.*, 899 F.3d 1281, 1290-91 (Fed. Cir. 2018) (“If a claim’s only ‘inventive concept’ is the application of an abstract idea using conventional and well-understood techniques, the claim has not been transformed into a patent-eligible application of an abstract idea.”); *Genetic Techs. Ltd. v. Merial L.L.C.*, 818 F.3d 1369, 1376 (Fed. Cir. 2016) (“The inventive concept ... cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself”).

⁴ If the claim is not directed to patent-ineligible subject matter, then the patent is deemed patent-eligible under Section 101 and there is no need move on to step two of the Supreme Court framework. *See, e.g., Alice*, 573 U.S. at 221.

2. At Least Claims 1-5 and 14-18 Are Patent-Ineligible Under The Two-Step Framework of *Mayo* and *Alice*

Because claim 1 of the '386 patent is directed to a product of nature, it satisfies the first step under *Mayo* and *Alice*. After all, claim 1 covers not only a humanized monoclonal antibody, but a fully *human* monoclonal antibody which binds to EC3 and internalizes. As explained by Dr. Bournazos, the sheer breadth of claim 1 would cover antibodies that bind to EC3 and internalize that are isolated from a human subject without any further modification. (Ex. 1003, ¶274.) The human CDH6 protein is a tumor-associated antigen and therefore, in cancer patients, the human body will produce naturally occurring antibodies that bind to CDH6 (including its EC3 region) in cancer cells expressing this protein. (*Id.*, ¶274.) Based on the immense breadth claim 1 and the fact that it covers any possible anti-CDH6 antibody that binds to EC3, Dr. Bournazos concluded that one cannot exclude the high likelihood that at least one of these naturally occurring antibodies will also internalize and therefore satisfy all of the elements of claim 1. (*Id.*)

Regarding step 2 under *Mayo* and *Alice*, claim 1 clearly does not contain “an inventive concept” sufficient to transform it into patentable subject matter. *Alice*, 573 U.S. at 221 (quotation marks omitted). Here, claim 1 does not have any other structural characteristics which would take it outside of a naturally occurring antibody isolated from a human. The only other elements of this claim are that the

antibody binds to EC3 and internalizes, and as Dr. Bournazos concludes, an antibody with these same functional characteristics likely exists naturally in human cancer patients. (*Id.*, ¶274.) Because claim 1 does not include any additional features that are markedly different from the naturally occurring product, it is not eligible under 35 U.S.C. § 101.

Claim 2 covers human or humanized antibodies or their functional fragments having a competitive inhibitory activity against one of the reference anti-CDH6 antibodies, *i.e.*, chG019, H01L02, H02L02, H02L03, and H04L02. As Dr. Bournazos explains, one cannot exclude the high likelihood that at least one of these naturally occurring antibodies will internalize and have a competitive inhibitory activity against one of the reference anti-CDH6 antibodies, therefore satisfying all of the elements of claim 2. (*Id.*, ¶275.) Thus, claim 2 also encompasses antibodies that are structurally identical to a naturally occurring human anti-hCDH6 antibody having a competitive inhibitory activity against one of the reference anti-CDH6 antibodies, *i.e.*, chG019, H01L02, H02L02, H02L03, and H04L02. (*Id.*)

Claim 3 specifies six CDR sequences by combining light chain CDRs (CDRL1, CDRL2, and CDRL3) of the four rat antibodies (*i.e.*, rG019, rG055, rG056, and rG061) with heavy chain CDRs (CDRH1, CDRH2, and CDRH3) of the four rat or chimeric antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061).

Claim 4 specifies six CDR sequences of four antibody clones, *i.e.*, rG019/chG019, rG055, rG056, and rG061. As Dr. Bournazos explains, since the four rat antibodies were raised against human CDH6, one cannot exclude the high likelihood that their CDRs are identical to those of a naturally occurring anti-hCDH6 antibody, which satisfies all of the elements of claim 3 or 4. (*Id.*, ¶276.) Thus, claims 3 and 4 encompass antibodies that are structurally identical to a naturally occurring human anti-hCDH6 antibody or a fragment thereof having the desired binding and internalization functions. (*Id.*)

Claim 5 specifies that the antibodies or their functional fragments are humanized. As Dr. Bournazos concludes, humanized antibodies are not markedly different from naturally occurring human antibodies. (*Id.*, ¶277.) Humanized antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibody variants produced naturally in humans. (*Id.*) In addition, as demonstrated in the '386 patent, the four exemplary humanized antibodies were generated by grafting CDRs from rat anti-hCDH6 antibodies raised against human CDH6 and placed in a human IgG. Thus, for at least the same reasons discussed above for claims 3 and 4, claim 5 encompasses antibodies that are structurally identical to a naturally occurring human anti-hCDH6 antibody or a fragment thereof having the desired binding and

internalization functions or antibodies that are not markedly different from naturally occurring human antibodies. (*Id.*)

Claim 14 specifies one or more conventional modifications, including N-linked glycosylation or O-linked glycosylation, on the heavy chain or light chain of the claimed antibodies or their functional fragments. Claim 18 specifies that sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity. As Dr. Bournazos explains, a naturally occurring antibody can also undergo N-linked glycosylation or O-linked glycosylation, and such glycosylation can enhance antibody-dependent cellular cytotoxic activity of the antibody. (Ex. 1003, ¶278.) Thus, claims 14 and 18 encompass antibodies that are structurally identical to a naturally occurring human anti-hCDH6 antibody or a fragment thereof having the desired binding and internalization functions. (*Id.*)

Importantly, as addressed in Grounds 3 and 4, at least the one or more features specified in claims 2, 5, and 13-18 are well-understood, routine, and conventional in the art, thus failing to add significantly more to transform the patent in eligible product of nature into patent-eligible subject matter. (*Id.*, ¶279.)

X. INSTITUTION OF TRIAL SHOULD NOT BE DISCRETIONARILY DENIED UNDER *BECTON* AND *ADVANCED BIONICS*

Institution should not be denied pursuant to 35 U.S.C. § 325(d) under the framework set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential as to §III.C.5, first

paragraph) and *Advanced Bionics LLC v. MED-EL Elektromedizinische Gerate GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020) (precedential). In determining whether discretionary denial is warranted, the Board evaluates: (1) whether the same or substantially similar art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, whether the Petition has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, at 8-9. In evaluating the *Advanced Bionics* two-part framework, the Board is guided by the *Becton* factors. *Id.* at 9-10, n. 10 (citing *Becton* at 17-18). *Becton* factors (a), (b), and (d) relate to whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Id.* at 10. *Becton* factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.*

As to the first prong of *Advanced Bionics*, the written description and enablement arguments presented in this petition were not before the patent office at any time during prosecution of the Challenged Patent. Although the Office noted that it was not issuing a lack of enablement rejection of claim 8, the question of enablement regarding the compositions of the antibody is distinct from the written description and enablement problems of an unbounded genus claim such as

Challenged Claim 1. Therefore, the arguments made here in the §112-based grounds are new and are not the same or substantially the same as those previously presented to the office. Further, because the first prong is not met, the second prong of the *Advanced Bionics* framework need not be reached by the Board, since the Office's failure to consider these arguments was in error. *Oticon Medical AB v. Cochlear Limited*, IPR2019-00975, Paper 15, at 19-20 (PTAB Oct. 16, 2019) (precedential as to §§II.B and II.C) (presence of an unconsidered reference or argument is alone sufficient to show error under the second prong of *Advanced Bionics*).

The Ground under § 101 was also not previously presented before the Office and, because it was not raised during prosecution, the Office committed error by not considering it. *See Oticon Medical*, at 19-20.

With regard to the anticipation and obviousness rejections, while the Novartis reference was before the Office in a rejection, the Office made a clear error in allowing the claims over Novartis. As noted above, Patent Owner argued falsely that "there is no indication in the record that binding to any or all of the various extracellular domains will always necessarily result in internalization of an antibody." §IV.A, *supra* (incorporated herein); (Ex. 1002 at 13665-13666.) The apparent acceptance of this argument by the Office was material error for the reasons stated above in Grounds 3 and 4 regarding anticipation and obviousness of

claims 1, 5, 13-18 based on the Novartis reference. *See* §IV.A, *supra* (incorporated herein); *see also Advanced Bionics*, IPR2019-01469 at 8 n.9 (material error may be demonstrated by showing that an examiner “misapprehend[ed] or overlook[ed] specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.”).

Thus, the Board should not discretionarily deny this Petition under 35 U.S.C. § 325(d).

XI. CONCLUSION

For the reasons set forth above, Petitioner submits that the Challenged Claims are invalid for lack of written description and enablement under 35 U.S.C. § 112; that claims 1, 5, and 13-18 are anticipated or obvious under 35 U.S.C. §§ 102 and 103; and that at least claims 1-5 and 14-18 are patent-ineligible under 35 U.S.C. § 101. Accordingly, Petitioner requests institution of post-grant review of these claims for each ground presented herein and a determination that the Challenged Claims are unpatentable.

Dated: June 16, 2023

Respectfully submitted,

s/Gerard P. Norton

Gerard P. Norton, Ph.D.

Reg. No. 36,621

FOX ROTHCHILD LLP

Princeton Pike Corporate Center

997 Lenox Drive

U.S. Patent No. 11,446,386

Lawrenceville NJ 08648-2311

Tele: (609) 844-3020

gnorton@foxrothschild.com

*Counsel for Petitioner OnCusp
Therapeutics, Inc.*

**CERTIFICATE OF SERVICE ON PATENT OWNER
UNDER 37 C.F.R. § 42.205(a)**

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.205(b), the undersigned certifies that on the 16th day of June, 2023 a complete and entire copy of this Petition for Post Grant Review and all supporting exhibits was provided via Federal Express to:

FOLEY & LARDNER LLP
3000 K Street N.W.
Suite 600
Washington D.C. 20007-5109
United States

Dated: June 16, 2023

s/Gerard P. Norton
Gerard P. Norton, Ph.D.
Reg. No. 36,621
FOX ROTHSCHILD LLP
Princeton Pike Corporate Center
997 Lenox Drive
Lawrenceville NJ 08648-2311
Tele: (609) 844-3020
gnorton@foxrothschild.com

*Counsel for Petitioner OnCusp
Therapeutics, Inc.*

CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. §§ 42.24(a)(1)(ii) and 42.24(d), I hereby certify that the number of words in this Petition is 17,444, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, and appendix listing of exhibits.

Dated: June 16, 2023

Respectfully submitted,

s/Gerard P. Norton

Gerard P. Norton, Ph.D.

Reg. No. 36,621

FOX ROTHSCHILD LLP

Princeton Pike Corporate Center

997 Lenox Drive

Lawrenceville NJ 08648-2311

Tele: (609) 844-3020

gnorton@foxrothschild.com

*Counsel for Petitioner OnCusp
Therapeutics, Inc.*