

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ONCUSP THERAPEUTICS INC,
Petitioner,

v.

DAIICHI SANKYO CO LTD,
Patent Owner.

Case No. PGR2023-00037

Patent No. 11,446,386

**EXPERT DECLARATION OF
STYLIANOS BOURNAZOS, Ph.D.**

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I, Stylianos Bournazos, declare as follows:

1. I am over the age of 21 years and am fully competent to make this Declaration. I make the following statements based on personal knowledge and, if called to testify to them, could and would do so.

I. QUALIFICATIONS

2. I received my BS in Genetics and Immunology in 2005 from the University of Aberdeen, Aberdeen, United Kingdom. I received my MS in Life Science in 2006 from the University of Edinburgh, Edinburgh, United Kingdom. I received my Ph.D. in Immunology in 2010 from the University of Edinburgh. I did my postdoctoral work at the Rockefeller University in the division of virology and antibody therapeutics.

3. I am currently employed by the Rockefeller University, where I am a Research Associate Professor. I was also a member of American Association of Immunologists, New York Academy of Science, American Heart Association, and WHO Expert Group for the development of preclinical models of COVID-19 disease.

4. I have over 15 years of research experience in the study of antibody and FcR function in health and disease. My studies have demonstrated a critical role for IgG Fc-FcγR interactions in the protective activity of antibodies against bacterial and viral pathogens, leading to the clinical development of Fc-optimized

antibodies with improved effector function. Additionally, my research on the mechanisms by which antibodies contribute to dengue disease pathogenesis identified specific glycan changes at the IgG Fc domain as robust predictive biomarkers for symptomatic dengue disease. In addition, I have determined the *in vivo* immunological mechanisms by which Fc-FcγR interactions drive dengue pathogenesis.

5. I have served as a scientific reviewer for peer-reviewed scientific journals, such as PLoS One, Journal of Experimental Medicine, Lung, Cell Reports, Cell Host & Microbe, International Archives of Allergy and Immunology, European Journal of Immunology, The Journal of Immunology, Nature Microbiology, Nature Communications, Frontiers in Immunology, Immunity, Cell Reports Medicine, iScience, EBioMedicine, and Scientific Reports.

6. I have also served as a grant reviewer for the National Cancer Institute, the National Institute on Aging, the Medical Research Council (MRC) (United Kingdom), Deutsche Forschung Gemeinschaft (DFG) (Germany), and the Israeli Ministry of Innovation, Science and Technology (Israel).

7. Since 2012, I have been an invited speaker of various scientific meetings, including NIAID Workshop on Clinical Development of Broadly Neutralizing Antibodies (bnAbs) for HIV-1, 2022; EMBO Workshop on Antibodies and complement: Effector functions, therapies and technologies,

Girona, Spain; PEGS Europe: Protein & Antibody Engineering Summit, 2017, Lisbon, Portugal; 2nd Next-Generation Antibodies and Protein Analysis 2017, Gent, Belgium; NIAID Workshop on Mechanisms of Fc-Dependent, Antibody-Mediated Killing, Rockville, MD; Keystone Biobetters and Next-Generation Biologics: Innovative Strategies for Optimally Effective Therapies 2017, Snowbird, UT; and AIDS vaccine 2012 conference, Boston, MA.

8. A copy of my current CV is enclosed. (Ex. 1004.)

II. RELEVANT FIELD AND LEVEL OF ORDINARY SKILL IN THE ART

9. I have reviewed US Patent No. 11,446,386 (“the ’386 Patent”) (Ex. 1001) and relevant portions of its prosecution history with the United States Patent and Trademark Office. Specifically, I have reviewed the ’386 Patent and its prosecution history in relation to the asserted prior art and arguments at issue in the present post-grant review (PGR).

10. Based on my experience described above and contained in my CV, I have an established understanding of the relevant field in the relevant timeframe, and the knowledge that would have been known by a person of ordinary skill in the art (POSA), as defined above and during the relevant time frame (on or before May 15, 2017 – the claimed priority date of the ’386 Patent).

III. MATERIALS REVIEWED

11. I have reviewed the Petition and supporting evidence. I have also reviewed all challenged claims of the '386 Patent (Claims 1-18), as well as the '386 specification and parts of its file history. I have examined the prior art references asserted against the '386 Patent in the Petition. I will use the exhibit numbers listed on the "LIST OF EXHIBITS" the Petition, which I have included for ease of reference below:

TABLE OF EXHIBITS

Exhibit No.	Description
1001	US Patent No. 11,446,386 to Atsuko Saito, et al., issued September 20, 2022 ("the '386 Patent")
1002	Prosecution History of the '386 Patent
1003	Declaration of Stylianos Bournazos, Ph.D.
1004	<i>Curriculum Vitae</i> of Stylianos Bournazos, Ph.D.
1005	International PCT Application WO2016/024195A1 to Carl Bialucha, <i>et al.</i> , published February 18, 2016
1006	U.S. Application Publication No. 2016/0317656A1 to Atsushi Urano <i>et al.</i> , published November 3, 2016

1007	U.S. Application Publication No. 2016/0046720A1 to Hiromu Sato, <i>et al.</i> , published February 18, 2016
1008	Mark L. Chiu, <i>et al.</i> , <i>Antibody Structure and Function: The Basis for Engineering Therapeutics</i> , 8 ANTIBODIES 55 (2019)
1009	Inbal Sela-Culang, <i>et al.</i> , <i>The Structural Basis of Antibody-Antigen Recognition</i> , 4 FRONTIERS IN IMMUNOLOGY, Oct. 8, 2013, at 1
1010	Charles A. Janeway <i>et al.</i> , IMMUNOBIOLOGY: THE IMMUNE SYSTEM IN HEALTH AND DISEASE (Garland Publishing, 5th ed. 2001)
1011	Cristina Caldas, <i>et al.</i> , <i>Humanization of the Anti-CD18 Antibody 6.7: An Unexpected Effect of a Framework Residue in Binding to Antigen</i> , 39 MOLECULAR IMMUNOLOGY 941 (2003)
1012	Vered Kunik, <i>et al.</i> , <i>Structural Consensus Among Antibodies Defines the Antigen Binding Site</i> , 8 PLoS COMPUTATIONAL BIOLOGY, Feb. 2012, at 1
1013	Sanjib Bhattacharyya, <i>et al.</i> , <i>Nanoconjugation Modulates the Trafficking and Mechanism of Antibody Induced Receptor Endocytosis</i> , 107 PROC. NAT. ACAD. SCI. USA 14541 (2010)

1014	Cecile Chalouni & Sophia Doll, <i>Fate of Antibody-Drug Conjugates in Cancer Cells</i> , 37 J. EXP. & CLINICAL CANCER RESEARCH, no. 20, 2018, at 1
1015	Christina Peters & Stuart Brown, <i>Antibody-Drug Candidates as Novel Anti-Cancer Chemotherapuetics</i> , 35 BIOSCIENCE REP. 4 (2015)
1016	Madeleine K. Ramos, <i>et al.</i> , <i>Valency of HER2 Targeting Antibodies Influences Tumor Cell Internalization and Penetration</i> , 20 MOLECULAR CANCER THERAPEUTICS 1956 (2021)
1017	Stephen A. Beers, <i>et al.</i> , <i>Antigenic Modulation Limits the Efficacy of Anti-CD20 Antibodies: Implications for Antibody Selection</i> , 115 BLOOD 5191 (2010)
1018	Hilal A. Parray, <i>et al.</i> , <i>Hybridoma Technology a Versatile Method for Isolation of Monoclonal Antibodies, its Applicability Across Species, Limitations, Advancement, and Future Perspectives</i> , 85 INT’L IMMUNOPHARMACOLOGY, May 27, 2020, at 1
1019	Phei Er Saw & Er-Wei Song, <i>Phage Display Screening of Therapeutic Peptide for Cancer Targeting and Therapy</i> , 10 PROTEIN & CELL 787 (2019)

1020	Thilo Riedl, <i>et al.</i> , <i>High-Throughput Screening for Internalizing Antibodies by Homogeneous Fluorescence Imaging of a pH-Activated Probe</i> , 21 J. BIOMOLECULAR. SCREENING 12 (2016)
1021	Yutaka Shimoyama, <i>et al.</i> , <i>Isolation and Sequence Analysis of Human Cadherin-6 Complementary DNA for the Full coding Sequence and Its Expression in Human Carcinoma Cells</i> , 55 CANCER RESEARCH 2206 (1995)
1022	Fabian Sievers, <i>et al.</i> , <i>Fast, Scalable Generation of High-Quality Protein Multiple Sequence Alignments Using Clustal Omega</i> , 7 MOLECULAR SYSTEMS BIOLOGY, Oct. 11, 2011, at 1
1023	Veronique Giudicelli, <i>et al.</i> , <i>IMGT/V-QUEST: IMGT Standardized Analysis of the Immunoglobulin (IG) and T Cell Receptor (TR) Nucleotide Sequences</i> , 6 COLD SPRING HARBOR PROTOCOLS, June 1, 2011, at 1
1024	Carlen M. Niessen, <i>et al.</i> , <i>Tissue Organization by Cadherin Adhesion Molecules: Dynamic Molecular and Cellular Mechanisms of Morphogenetic Regulation</i> , 91 PHYSIOLOGY REV. 691 (2011)
1025	Roger Paul, <i>et al.</i> , <i>Cadherin-6: A New Prognostic Marker for Renal Cell Carcinoma</i> , 171 J. UROLOGY 97 (2004)

1026	Toru Shimazui, <i>et al.</i> , <i>Expression of Cadherin-6 as a Novel Diagnostic Tool to Predict Prognosis of Patients with E-Cadherin-Absent Renal Cell Carcinoma</i> , 4 CLINICAL CANCER RESEARCH 2419 (1998)
1027	Valentina Sancisi, <i>et al.</i> , <i>Cadherin 6 is a New RUNX2 Target in TGF-β Signalling Pathway</i> , 8 PLOS ONE, Sept. 12, 2013, at 1
1028	Martin Kobel, <i>et al.</i> , <i>Ovarian Carcinoma Subtypes are Different Diseases: Implications for Biomarker Studies</i> , 5 PLOS MEDICINE, Dec. 2, 2008, at 1
1029	Ming Meng, <i>et al.</i> , <i>CDH6 as a Prognostic Indicator and Marker for Chemotherapy in Gliomas</i> , 13 FRONTIERS IN GENETICS, July. 22, 2022, at 1
1030	Brent A. Kochert, <i>et al.</i> , <i>Hydrogen-Deuterium Exchange Mass Spectrometry to Study Protein Complexes</i> , in METHODS IN MOLECULAR BIOLOGY 1764 (Joseph A. Marsh ed., 2018)
1031	Jeffrey G. Mandell, <i>et al.</i> , <i>Identification of Protein-Protein Interfaces by Decreased Amide Proton Solvent Accessibility</i> , 95 PROC. NAT. ACAD. SCI. USA 14705 (1998)

1032	Carl U. Bialucha, <i>et al.</i> , <i>Discovery and Optimization of HKT288, a Cadherin-6-Targeting ADC for the Treatment of Ovarian and Renal Cancers</i> , 7 CANCER DISCOVERY 1030 (2017)
1033	Ruth Muchekehu, <i>et al.</i> , <i>The Effect of Molecular Weight, PK, and Valency on Tumor Biodistribution and Efficacy of Antibody-Based Drugs</i> , 6 TRANSLATIONAL ONCOLOGY 562 (2013)
1034	Ben T. Ruddle, <i>et al.</i> , <i>Characterization of Disulfide Bond Rebridged Fab-Drug Conjugates Prepared Using a Dual Maleimide Pyrrolobenzodiazepine Cytotoxic Payload</i> , 14 CHEMMEDCHEM 1185 (2019)
1035	Lutz Riechmann, <i>et al.</i> , <i>Reshaping Human Antibodies for Therapy</i> , 332 NATURE 323 (1988)
1036	Josee Golay, <i>et al.</i> , <i>Role of Fc Core Fucosylation in the Effector Function of IgG1 Antibodies</i> , 13 FRONTIERS IN IMMUNOLOGY, June 30, 2022, at 1
1037	Christian Klein, <i>et al.</i> , <i>Epitope Interactions of Monoclonal Antibodies Targeting CD20 and Their Relationship to Functional Properties</i> , 5 MABS 22 (2013)
1038	Prosecution History of U.S. Application No. 17/010,162

IV. SUMMARY OF MY OPINIONS

12. I have been asked to consider whether the disclosure in the '386 Patent demonstrates possession of the full scope of the invention recited in claims 1-18. The '386 patent claims antibodies and their functional fragments that are defined solely by their functions (i) an ability to specifically bind to the amino acid sequence shown of SEQ ID NO: 4 and (ii) an ability to internalize that permits cellular uptake. The claims cover a diverse genus of antibodies and their functional fragments having different amino acid sequences, associated higher order structures, isotypes, subclasses, and corresponding functions. The claims also cover antibodies and their functional fragments generated by various methods, as well as antibodies and their functional fragments containing various modifications.

13. In my opinion, none of claims 1-18 are adequately described or supported. The '386 Patent not only fails to provide sufficient representative examples across the claimed genus of antibodies that exhibit the desired binding and internalization functions, but also fails to identify any common structural features required or in correlation with the desired binding and internalization functions. Furthermore, based on the limited information provided in the patent, a skilled artisan could not visualize what other antibody sequences might provide the

claimed ability to specifically bind to the amino acid sequence shown of SEQ ID NO: 4 and internalize. As admitted by the '386 Patent, predicting the sequences of antibodies that provide the internalization function simply was not possible at the time this patent was effectively filed, which is the claimed priority date of the '386 Patent.

14. I have also considered whether the disclosure in the '386 patent would enable a person of ordinary skill in the art to make and use the antibodies and their functional fragments of claims 1-18. For similar reasons, a skilled artisan at or around the claimed priority date would not have had sufficient guidance to make and use the many different antibodies and their functional fragments covered by the claims, nor would they have such guidance today. The specification offers testing data for only four highly similar humanized antibodies. The very limited guidance provided by the '386 Patent amounts to invitation to carry out a research plan, which cannot be accomplished without undue experimentation.

15. I have been asked to consider whether the claims of the '386 Patent are anticipated or otherwise obvious in view of the references published before the claimed priority date. I find that the prior art reference WO2016024195A1 ("Novartis") (Ex. 1005) discloses all the limitations of at least claims 1, 5, 13-16, and 18 of the '386 Patent. I also find that Novartis or a combination of Novartis and another prior art references U.S. Patent Application No. 15/027,489 ("Urano")

(Ex. 1006) and/or U.S. Patent Application No. 14/927,007 (“Sato”) (Ex. 1007) disclose or suggest all the limitations of at least claims 1, 5, and 13-18 of the ’386 Patent.

16. I have also been asked to consider whether any of the claims of the ’386 Patent are directed to patent ineligible subject matter. In particular, I have considered whether the claims are directed to a product of nature or a product that is not markedly different from what occurs in nature, and if so, whether the claims include additional features that could add significantly more to the product of nature. I find that claims 1-5 and 14-18 of the ’386 Patent cover either a naturally occurring anti-Cadherin 6 (CDH6) antibody or an anti-CDH6 antibody that is not markedly different from a naturally occurring anti-CDH6 antibody. In addition, none of claims 1-5 and 14-18 includes additional features that add significantly more to the product of nature to transform it into patent eligible subject matter. Therefore, it is my opinion that all the claims of the ’386 Patent are patent ineligible.

V. THE UNDERSTANDING APPLIED TO MY ANALYSIS

17. In preparing this Declaration, certain patent law concepts have been explained to me, including the legal standard for interpreting claims, as well as

those for assessing written description, enablement, anticipation, obviousness, and patent eligibility.

18. I understand that in a PGR proceeding, claims should be construed as having their ordinary and customary meaning as understood by a POSA at the time of the invention. I understand that claims should be read in the context of the claim language of which they are a part. I further understand that the specification and file history can also inform the scope of the claims. If, after a review of this evidence, the construction is not apparent, I understand that extrinsic evidence, such as dictionary definitions, treatises, and trade journals, may be consulted to discern the meaning of a term. For terms where no construction is necessary, I have simply read the terms according to their ordinary and customary meaning. My understandings herein are made in light of how a person of ordinary skill in the art in or around 2017 would view the ordinary and customary meaning of the claim terms. I reserve the right to supplement my Declaration should any claim terms be given different constructions.

19. I understand that a claim in a granted patent must be sufficiently supported by the disclosure in the patent's specification, read in the context of what one of ordinary skill in the art would have known at the time of the claimed invention. I understand that the basic inquiry for written description is whether the

specification provides sufficient information for a skilled artisan to recognize that the named inventors possessed the full scope of the claimed invention.

20. The claims of the '386 Patent recite a human or a humanized monoclonal antibody that binds to a 115-amino acid region on CDH6 defined by SEQ ID NO: 4, covering diverse antibodies defined by their function rather than any particular structure. (Ex. 1001, 181:58-65.) To satisfy the written description requirement for such claims, I understand that the specification must disclose either a representative number of species falling within the scope of the claimed genus or structural features common to the members of the genus such that one skilled in the art can “visualize or recognize” the members of the claimed genus.

21. I understand that, in addition to written description, a patent specification must also enable a person of ordinary skill in the art to make and use the full scope of the claimed invention without undue experimentation as of its effective filing date. I understand that multiple factors should be considered when making this determination. These factors include: (a) the breadth of the claims; (b) the nature of the claimed invention; (c) the state of the prior art; (d) the level of predictability or unpredictability of the art; (e) the knowledge of one of ordinary skill; (f) the amount of direction provided by the named inventor(s); (g) the presence or absence of working examples; and (h) the quantity of experimentation needed to make or use the claimed invention based on the content of the disclosure.

22. I understand that a claim is anticipated if a single prior art reference discloses each and every limitation of the claimed invention. I understand that a limitation can be expressly disclosed by the reference or be inherent. I further understand that for a feature to be inherently disclosed, a POSA would understand the inherent feature would necessarily and inevitably be present when the teaching of the reference is practiced. That is, I understand that if a feature is not necessarily and inevitably present, it is not inherently disclosed.

23. I understand that a patent claim may be unpatentable for obviousness if the difference between the claimed subject matter and the prior art is such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. I understand that a finding of obviousness requires a determination of: (1) the scope and content of the prior art; (2) the difference(s) between the claimed invention and the prior art; and (3) the level of skill of the ordinary artisan in the pertinent art. I understand this analysis looks at whether the differences are such that the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. I further understand that any obviousness analysis must consider objective evidence of non-obviousness, where such evidence is present.

24. I understand that objective evidence of non-obviousness includes (1) copying, (2) long felt but unsolved need, (3) failure of others, (4) commercial

success of the invention, (5) unexpected results created by the claimed invention, (6) unexpected properties of the claimed invention, (7) licenses showing industry respect for the invention, (8) skepticism of skilled artisans before the invention, (9) recognition of invention's advancement, and (10) contemporaneous invention by others or absence thereof. In general, there must be a connection between any of the factors and the claimed invention. For instance, the "commercial success" of a product practicing the claimed invention is relevant to the obviousness analysis only if the commercial success is attributable to advantages from the use of the invention that were not available to the purchasing public before the invention was made.

25. My understanding is that the obviousness inquiry is not limited to just the prior art references being applied, but includes the knowledge and understanding of one of ordinary skill in the art.

26. However, I understand that merely demonstrating that each element, independently, was known in the prior art is, by itself, insufficient to establish a claim was obvious. My understanding is that the test for obviousness is not whether the features of one reference can be incorporated into the structure of another reference, but rather what the combined teachings would have suggested to those of ordinary skill in the art. I further understand that a party seeking to invalidate a patent must show a person of ordinary skill in the art would have been

motivated to combine the teachings of the prior art references to achieve the claimed invention.

27. It is my understanding that each prior art reference must be considered as a whole, including the portions that would lead away from the claimed invention. I have been informed that some prior art combinations are improper, or not combinable. For instance, the reference cannot be non-analogous art. In order for a reference to be used to show obviousness, the reference must be analogous art to the claimed invention. I understand that to be analogous, the art must be from the same field of endeavor or be reasonably pertinent to the problem – and therefore logically would command the artisan’s attention in considering her/his problem. I also understand that when (1) the combination of prior art references teaches away from the claimed invention or from each other, (2) the combination makes one invention unsatisfactory for its intended purpose, or (3) when the combination would change the principle of operation of prior art reference, such a combination is improper and does not show obviousness.

28. I understand that a combination of old, familiar, or known elements according to known methods is likely to be obvious when it does no more than yield predictable results. Predictable variations of a work from one field are likely to be obvious, even if the variation is in another field. For example, where a technique has been used to improve a device, use of the same technique to improve

similar devices is a predictable variation and likely obvious. Likewise, if the use of prior art for improvements is simply done according to the prior art's established functions, a person of ordinary skill in the art has simply implemented a predictable variation. If there existed at the time of invention a known problem for which there was an obvious solution, a patent claim encompassing that solution is not patentable.

29. I understand that a claimed invention is patent eligible if it claims a new and useful process, machine, manufacture, or composition of matter, unless the claims are directed to judicial exceptions, such as laws of nature, natural phenomena, and abstract ideas. I understand that a two-step inquiry has been adopted to determine whether a claim is patent eligible. In step one, a determination is made as to whether the claimed invention is directed to one of the four statutory categories. If the claimed invention is directed to a statutory category (*e.g.*, composition of matter), step two requires a determination as to whether the claimed invention is directed to a judicial exception, such as a product of nature. If the claim encompasses a product that does not have markedly different characteristics from any found in nature, the claim is still directed to a "product of nature" exception. If the claim is directed to an exception, it is patent ineligible if the claim does not include additional features that could add significantly more to the exception itself. A feature is not deemed significantly more if it merely adds

well-understood, routine, conventional activity already engaged in by the scientific community to the product of nature.

30. Although the following analysis cites to particular pages, lines, paragraphs, or figures of many of the references discussed, these citations are intended to assist in understanding the various bases of my conclusions, and prior art teachings used to reach them. These citations are not intended to be an exhaustive recitation of every page, line number, or paragraph in which these teachings may be found. Similar teachings or disclosures may be found at other pages, lines, or paragraphs, as well as in other references, and it is to be understood that my opinions and statements are made in view of all of the references and teachings I have reviewed.

VI. BACKGROUND AND STATE OF THE ART

A. Introduction to Antibodies and Overview of the State of Art

31. Antibodies are a foundational component of the immune system's defense against both foreign agents (*e.g.*, viruses, bacteria, fungi, and protozoa) and aberrant self-made components of the body (*e.g.*, cancers and auto-immune diseases). Each antibody can recognize a specific target molecule called an antigen. Through binding to its specific antigen, an antibody can trigger additional

biological processes to occur, depending on the biological context in which the binding occurs. (Ex. 1008 at 38.)

32. In recent decades, through the painstaking development of unique antibodies targeting specific antigens, scientists have been able to develop prophylactic, diagnostic, and therapeutic antibody-based tools that have collectively transformed modern medicine. Importantly, many different antibody structures may functionally bind to the same target antigen. (Ex. 1010 at 151.)

1. Antibody Structures

33. The generic structure of a representative antibody of the IgG class is shown below in Figure 1. (Ex. 1010 at 118.) Antibodies are typically composed of four amino acid chains: two longer, identical “heavy chains” and two shorter, identical “light chains.” (Ex. 1010 at 117-118.) The terms heavy and light refer to the chains’ respective molecular weights – heavy chains have additional amino acids at their C-terminal ends, resulting in a “heavier” molecular weight. (*Id.*) The four chains typically pair up to form two arms in a characteristic “Y” shape, as in Figure 1. (*Id.*)

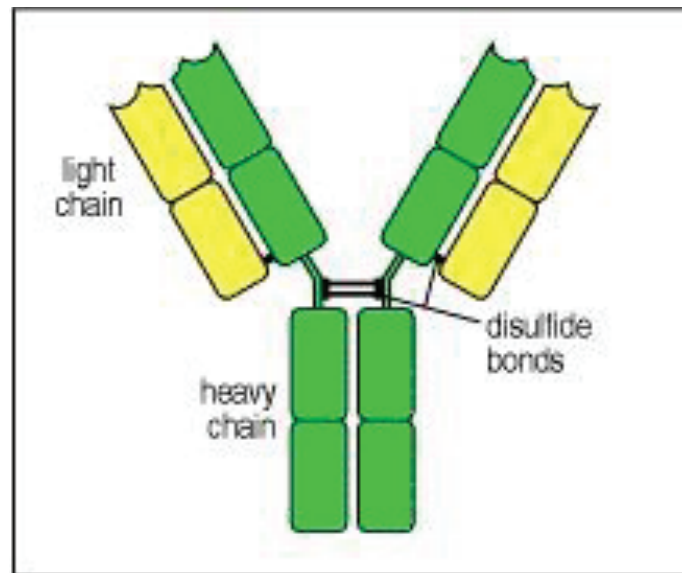


Figure 1. Representative IgG antibody structure (reproduced from Ex. 1010 at 118 (Fig. 3.2).)

34. Typically, one heavy chain pairs with one light chain to form an arm of the Y-shaped antibody structure. (*Id.* at 117-18.) The heavy chain and light chain are connected through one or more disulfide bonds that bridge the chains together. (*Id.*) A typical Y-shaped antibody will have two sets of heavy chain-light chain pairs, one constituting each arm, although variability in this general Y-shaped antibody structure is well-documented. (*Id.*)

35. Every heavy chain and every light chain each contain at least one variable region and at least one constant region. (*Id.* at 118.) Human antibodies have historically been categorized based on the amino acid sequences in the constant region of the heavy chain into one of five immunoglobulin groups: IgA, IgD, IgE, IgG, and IgM. (*Id.*) 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.*)

36. In a standard IgG antibody, each light chain is typically composed of one constant domain (*i.e.*, C_L), while each heavy chain has three constant domains (*i.e.*, C_{H1} , C_{H2} , and C_{H3}). (*Id.*) The two latter domains of the antibody's two heavy chains form a fragment-crystallizable "Fc" region. (*Id.*) The constant region of each antibody is typically responsible for interacting with the host immune system to initiate immunological responses.

37. In contrast to the constant regions, the amino acid sequences of the variable light chain (V_L) and variable heavy chain (V_H) domains are incredibly diverse. (*Id.*) The V_L and V_H domains combine to form a three-dimensional structure that interacts with potential antigens. (*Id.* at 118-19.)

38. Researchers have developed multiple antibody engineering techniques allowing for the artificial modification of standard antibody structures. (Ex. 1008 at 10-11.) These modifications include different fragments of a full antibody structure that retain their ability to bind to antigens. For example, researchers have created a single-chain fragment containing one V_H domain linked to a V_L domain by an artificial short amino acid sequence (the "single chain Fv" or "scFv"). (Ex. 1010 at 874; Ex. 1008 at 42.) The Fab fragment includes a complete light chain and the variable domain and one constant domain of one heavy chain, creating a single arm

of the typical Y-shaped antibody structure. (Ex. 1010 at 119.) The F(ab')₂ fragment comprises both antigen-binding arms joined with a disulfide bond. (*Id.* at 119-20.) A shorter fragment that includes the variable domains of a heavy chain and a light chain is known as the “Fv” fragment. (*Id.* at 120.) These shorter fragments each comprise less than a full antibody yet retain their ability to functionally bind to a target antigen, allowing for greater diversity in the artificial manipulation of molecules with antigen-binding functionality. (*Id.*; Ex. 1008 at 42-43.)

2. Antibodies Comprise Diverse Amino Acid Sequences that Influence Functionality and Antigen Binding Affinity

39. Antibodies are the primary means by which the immune system targets foreign antigens. Given the infinite array of bacteria, viruses, fungi, protozoa, and other foreign antigens the immune system may theoretically confront, antibodies are among the most diverse biological agents known to science. (Ex. 1010 at 151.) The variable domains, which are primarily responsible for interactions between the antibody and an antigen, are the primary drivers of this adaptability. (*Id.* at 30.) 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. (Ex. 1010 at 151; Ex. 1009 at 5-6.) Sequence differences may also result in functional effects beyond simply whether an antibody binds a particular antigen at all or with a particular

strength, such as agonistic or antagonistic effects on downstream extracellular and intracellular biological processes. (Ex. 1010 at 229, 612.)

40. Antigen binding is primarily located in the “antigen binding pocket” created via interactions between the three light chain complementarity-determining regions (CDRs) and three heavy chain CDRs. (Ex. 1010 at 123, 125.) Even a single amino acid substitution in a variable domain, particularly in a CDR, may significantly affect the structure of the antigen binding pocket and its ability to interact with its antigen. (Ex. 1010 at 127; Ex. 1009 at 7.) In contrast, highly divergent sequences may nevertheless result in functionally similar antigen binding pockets and show unexpected antigen binding. Ex. 1009 at 4-7.) Whether a given mutation in an antibody amino acid sequence will have any functional effects is often unpredictable and requires experimentation to assess.

3. The Substantial Diversity of Antibody Sequences is Essential for the Immune Response to Novel Antigens

41. The ability of the immune system to produce antibodies with vastly diverse sequences that nevertheless bind a similar antigen is a consequence of the immune system’s almost infinite adaptability.

42. As part of the adaptive immune response to exogenous antigens in humans, as well as other vertebrate animals, B lymphocytes (“B cells”) are responsible for the production of antibodies through a two-stage response. (Ex. 1010 at 150-51.) In the first or primary stage, each segment of an antibody,

including multiple variable region gene segments of both heavy and light chains, can be combined in a combinatorial manner to generate an immense amount of antibodies to a specific antigen with diverse sequences, three-dimensional structures, and binding characteristics. (*Id.* at 31-32, 159.) From this immense pool of candidate antibodies targeting an antigen, the immune system selects those with the most effective sequences for binding and clearing the antigen for continued antibody production. (*Id.* at 258.)

43. There are estimated to be at least 10^{11} B-cells in the human body, representing the primary antibody repertoire available to mount an immune response at any given moment. (Ex. 1010 at 159.) B cells express receptors on their cell surface (“B-cell receptors”), which can bind to antigens. (*Id.* at 115.) Mature B cells are primarily found in the spleen, which is constantly exposed to potential antigens. (*Id.* at 22.) If an antigen binds to a B-cell receptor, the B cell will transform into an antibody-producing factory cell known as a plasma cell; antibodies produced from a plasma cell will have the same variable region sequences as that cell’s B-cell receptor. (*Id.* at 115.) In order to provide the most effective means of rapidly clearing a foreign antigen, many different B-cell receptors may recognize a single antigen. (*Id.* at 162.) This is the fundamental purpose of the nearly incalculable diversity in the antibody variable regions – to provide as many weapons as possible in the immune system’s arsenal to bind and

remove any given foreign antigen quickly and efficiently. The activation of many different B-cell receptors by a single antigen is known as a polyclonal immune response and results in diverse antibodies binding to different fragments of the antigen. (*Id.* at 423.)

44. The secondary antibody response develops while B cells are actively producing antibodies to an antigen. A process called somatic hypermutation introduces slight variations into antibody sequences. (*Id.* at 162.) Subsequent antibodies with increased affinity or specificity for the stimulating antigen as a result of these somatic mutations are favored in the immune response, a process called affinity maturation. (*Id.*) In particular, the amino acid sequences of the CDRs within the variable regions are mutated to generate additional antibody diversity. (*Id.* at 162-63.) B cells showing these variant antibodies on their surfaces interact with the stimulating antigen; those with mutations that increase binding are more likely to differentiate into fully developed plasma cells, causing increased production of antibodies with favorable mutations. (*Id.* at 163.)

45. In these ways, incredible sequence and structural diversity in antibodies can be harnessed to functionally clear antigens efficiently from the body as part of the overall immune response.

4. Antibody Interactions with Target Antigens Focus on Specific Antigen Segments

46. Additional diversity can be found in the ability of various antibodies to bind to different segments of an antigen. Antigens are typically large proteins with multiple subregions. Antibodies typically bind to a particular subregion of an antigen, known as an “epitope.” (Ex. 1009 at 1-2.) These epitopes can be linear segments or non-linear segments that are brought into physical proximity through protein folding in three-dimensional space within the antigen binding pocket of the antibody. (*Id.*) As part of an overall immune response, multiple antibodies can target distinct epitopes to clear a given antigen. (*Id.*) Three-dimensional modeling of a target antigen can be used to attempt to predict specific epitopes that may be targeted by various antibodies; however, even with advances in computer modeling, it remains difficult to predict antibody binding to particular epitopes without experimentation. (*Id.*)

47. Therefore, antibodies can exhibit vast sequence and structural diversity while binding with varying degrees of affinity to a particular antigen.

5. Antibody-Antigen Binding: Structure Drives Function

48. Within each variable region are three hypervariable regions that primarily allow binding of the antibody to a complementary antigen. These hypervariable regions are known as complementarity-determining regions (“CDRs”), which can be further specified as CDR1, CDR2, and CDR3,

respectively. (Ex. 1009 at 3.) It is these six variable regions (three light chain CDRs and three heavy chain CDRs) that largely determine whether an antibody will bind to a particular antigen, as well as how tightly the antibody will interact with the complementary segment of that antigen. Importantly, a small alteration in the sequence of the variable regions may dramatically influence antigen binding by that antibody. (*Id.*)

49. The CDRs on each of the light and heavy variable domain regions are located between four scaffolding or framework regions (“FRs”) (*e.g.*, FR1 - CDR1 – FR2 – CDR2 – FR3 – CDR3 – FR4). (Ex. 1010 at 123.) The interspersing of the CDRs between the FRs permits the CDRs to adopt the precise orientation needed in three-dimensional space to interact with their complementary antigen. (*Id.*) Any changes to the FRs may therefore affect the binding of the antibody to its cognate antigen, even if the CDRs are not altered. (Ex. 1009 at 7-8.) Therefore, while CDRs are the primary influencers of antigen interactions, FRs also play an important role in determining functional antibody interactions with target antigens. (*Id.*) For example, Caldas *et al.* reported that a framework residue can have an unexpected effect in binding to an antigen. (Ex. 1011 at 941-942.) In agreement with Caldas *et al.*, Kunik *et al.* also found that 20% of the antibody residues that actually bind the antigen fall outside the CDRs. (Ex. 1012 at 1.)

6. Antibodies or Fragments Capable of Internalization

50. Antibodies typically encounter foreign antigens circulating in the blood stream, where the antigen is “outside” of the cells that constitute the organ systems through which the blood is passing. One of the downstream consequences of antibody binding to an antigen can be the uptake of that antigen into particular cells through, for example, endocytosis – a process called “internalization.” (Ex. 1013 at 14541-14546.) Once internalized into appropriate cells and subcellular organelles, the foreign antigen can be targeted for destruction by normal cellular degradation processes. (*Id.*)

51. The ability to internalize is an important characteristic for antibody-drug conjugates (ADCs) to deliver and release a cell-destroying payload into cancer cells. During an internalization process, the antibody binds to the target cell surface antigen, and the antibody-antigen complex is internalized. (Ex. 1014 at 2-3 and Fig. 1.) The internalization process finishes with the formation of a clathrin-coated early endosome containing the ADC-antigen complex. (Ex. 1015 at 4 and Fig. 3.)

52. However, it remains challenging to predict whether an antibody, when bound to the extracellular region of a cell surface molecule, is capable of triggering internalization. The rate and efficiency of internalization also depends on various factors, including the type of target antigen, the affinity of antibody for the antigen,

the capacity of the antibody to crosslink two membrane receptors through bivalent binding, as well as the affinity of the Fc domain for Fc γ R receptors. (Ex. 1015, Fig. 3; Ex. 1017, Figs. 2 and 4.) Some targets internalize regardless of antibody binding, whereas others reside permanently on the cell surface. (*Id.*)

53. Even for antibodies that bind the same or overlapping epitope (*i.e.*, the same region on the antigen), antibody binding could have different effects on the receptor structure (there are examples of monoclonal antibodies (“mAbs”) triggering allosteric changes upon binding), clustering to the cell membrane, internalization, and intracellular degradation. (Ex. 1017 at 5197.) One of the most well-studied examples is CD20, for which two main types of antibodies (type I and type II) have been described. (*Id.* at 5191, 5197.) Each type triggers differential effects (receptor internalization, cell death induction, homotypic aggregation, etc.). However, the classification of type I and type II mAbs only relates to their biological effects and has nothing to do with the epitopes that these mAbs target. Among type I mAbs, there are cases of mAbs that target distinct, non-overlapping epitopes, and yet they mediate the same biological effects. For example, the most well-studied anti-CD20 antibodies are rituxumab (type I) and GA101/obinutuzumab (type II). These two antibodies share the same epitope on CD20, their CDRs interact with almost the same residues, but they demonstrate different biological activities, which is the outcome of how these antibodies bind to

CD20 (affinity, angle, and orientation of their Fab domains, ability to crosslink CD20, etc.). (Ex. 1017 at 5191-5200; Ex. 1037, Fig. 1 and Table 1.)

7. Antibody Identification and Production for Testing

54. Antibodies can be generated in the laboratory by a number of techniques. (Ex. 1008 at 10-24.) While specific antibodies targeting certain epitopes can be designed and generated, ultimately physical experimentation is required to confirm whether an antibody actually binds to an antigen, the affinity of that binding, and the functional effects of the antibody-antigen interactions; there is no means to measure an antibody's actual functionality based on sequence analysis alone.

55. To have the best chance of identifying an antibody with desired characteristics, a researcher typically generates a group of candidate antibodies and then screens this larger pool to identify desirable antibodies for further production. There are several methods available for the generation of such a pool of candidate antibodies, including classical techniques, hybridoma generation, phage display, recombination, and chimeric and humanizing techniques.

i. Monoclonal Antibody Screening

56. Classical antibody generation techniques involve injecting a model animal with a target antigen. (Ex. 1018 at 2.) The animal's B cells will produce a wide array of antibodies targeting the antigen in response. (*Id.*) Individual B cells

can be collected, separated, and then immortalized by fusing the individual B cells with cancer cells to create hybridomas, cell lines producing a steady source of the individual antibody. (*Id.*) Studies investigating various properties of the individual antibodies produced from these hybridomas can then be conducted. (*Id.*)

57. Antibodies isolated from a single B cell have identical genetic sequences and are therefore termed “monoclonal.” (*Id.*) In contrast, a pool of antibodies isolated from multiple B cells will have nonidentical amino acid sequences and is termed “polyclonal.” (*Id.*) Investigations using both polyclonal and monoclonal antibodies can be performed; monoclonal antibody investigations are often preferred due to the reduced variability attributable to different antibodies. (*Id.*)

58. One means of screening large libraries of candidate antibodies is known as “phage display.” In this approach, genes encoding various antibody variable domain sequences are inserted into a virus that infects bacteria known as bacteriophage. (Ex. 1019 at 788.) These modified viruses are then used to infect bacteria, which in turn express the genes encoding the variable domain sequences and display the resulting antibody fragments on the outer surface of infected bacteria. (*Id.*) This approach is a cost-effective means of screening a number of different variable domain sequence fragments for desired properties, such as

antigen binding. (*Id.*) A typical phage display library may screen as many as 10^8 different sequences. (Ex. 1008 at 23.)

59. In addition to inserting variable domain sequences isolated from an animal or human exposed to a particular antigen, the phage display approach can also be used to screen artificially generated variable domain regions with particular mutations of interest introduced by researchers. (*Id.*; Ex. 1010 at 749-50.) In this way, variable domain region sequences that are known to result in antigen binding can be systematically mutated to determine whether new mutations affect antigen binding to that antibody.

60. Any of these approaches will ultimately require extensive experimental screening. Depending on the particular characteristics the researcher is investigating, candidate antibodies can be efficiently identified for further characterization. One particular characteristic of interest is the strength of antigen binding to the antibody, known as affinity. (Ex. 1010 at 736.) Affinity is often reported as an equilibrium binding constant (“ K_D ”) representing the formation of the antigen-antibody complex and can be measured by a number of techniques known to one of ordinary skill in the art, including surface plasmon resonance, radioimmunoassay, ELISA, and fluorescence measurements, among others, depending on the target antigen and the conditions under study. (*Id.* at 736-774.)

61. Although the techniques above can be used to effectively generate and screen monoclonal antibodies for desired characteristics, substantial experimentation is required to ultimately assess antibodies with the required antigen-binding properties. Although amino acid sequences and structures of potential antibodies can be artificially created, there is no means to accurately predict whether such antibodies will be functional without doing the appropriate experiments.

ii. Generation of Recombinant, Chimeric, and Humanized Antibodies

62. Early in the course of antibody research, scientists discovered a problem with generating antibodies in animals for further investigation in humans – humans mounted an immune response to the non-human features of the animal-created antibody, rather than the desired antigen-targeting regions. (Ex. 1008 at 11-19.) Antibodies generated in non-human animals must therefore be “humanized” to prevent this interference. (*Id.*)

63. For example, if antibodies are generated in a mouse, researchers can substitute some (recombinant), most (chimeric), or nearly all (humanized) of the murine antibody regions for human ones, retaining only the murine CDRs (full-length or smaller segments) to generate the antigen-binding pocket in an antibody with a human constant region and framework regions. (*Id.*) Such humanized antibodies show significantly reduced interference with subsequent human

experiments, including reduced inflammation and toxic side effects, while preserving the desired antigen-binding capacity of the antibody. (*Id.*)

64. This approach involves: 1) identifying a desired non-human donor antibody (such as a rat antibody), 2) specifically identifying the non-human CDRs of the donor antibody, 3) choosing a desired human acceptor antibody, and 4) grafting the non-human CDRs into the acceptor antibody framework sequences. (*Id.*)

65. As with general antibody sequence mutation, it is known in the art that CDR grafting can result in a reduction in binding affinity. (*Id.*) Researchers therefore developed an iterative “back mutation” process of modifying positions within the human framework residues surrounding the grafted CDRs to mimic those of the donor framework regions and screening the resultant antibodies for those showing restored binding affinity. (*Id.*) Through these approaches, humanized antibodies with high binding affinity can be generated.

iii. Identification of Antibodies Capable of Internalization

66. As with monoclonal antibody affinity screening, several techniques have been developed to screen for antibodies that induce internalization of specific antigens, including flow cytometry (with or without surface quenching or radiolabeled antibodies), pH-dependent fluorescence imaging, direct imaging

(confocal imaging or with high-throughput plate readers), and direct and indirect cytotoxic assays). (Ex. 1020 at 13.)

67. Flow cytometry involves exposing a population of cells to a fluorescently labeled probe and then using a flow cytometer to measure the amount of fluorescent probe located within the target cell population. (Ex. 1010 at 759-62.) Flow cytometry relies on cells that can be suspended in liquid for analysis; it may also require significant washing steps at different pH levels to remove excess fluorescent probes from the surface of the target cells, which may damage the target cells themselves. (*Id.*; Ex. 1020 at 20.)

68. pH-dependent fluorescence imaging involves the use of specialized fluorescent probes that only emit a measurable signal under certain pH conditions, such as the acidic environment found within specific organelles responsible for intracellular degradation. (Ex. 1020 at 13.) If a fluorescence signal is detectable, the probe has been successfully internalized.

69. Direct imaging involves simply visualizing individual cells through specialized microscopes to assess whether internalization of a particular probe or antigen has occurred.

70. Direct and indirect cytotoxicity assays involve exposure of target cells to antibody linked to toxins that lead to cell death if internalized. (*Id.*) Percentages of cells surviving after various periods of exposure can be calculated to assess

whether the antibody is successfully internalized, with greater cell death indicating greater internalization of the antibody-toxin conjugate.

71. Importantly, analysis of a given antibody's ability to induce internalization upon antigen binding depends on experimentation. As described above, the form of this experimentation can take many forms depending on the type of antibody and antigen of interest. However, predicting an antibody's ability to induce internalization based on sequence analysis alone is difficult and unreliable, and is not particularly useful in the absence of detailed experimentation.

VII. THE '386 PATENT

72. 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.)

A. Claims of the '386 Patent

73. The '386 Patent has 18 claims. Claim 1 is the only independent claim. I have reproduced the claims below for reference (Ex. 1001, 181:58-186:53):

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.

Claim 2: The antibody or the functional fragment of the antibody according to claim 1, which has competitive inhibitory activity, for binding to the amino acid sequence shown in SEQ ID NO: 4, against at least any one antibody selected from the group consisting of the following antibodies (1) to (5):

(1) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 53 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 56,

(2) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,

(3) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,

(4) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and

(5) an antibody having a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

Claim 3: The antibody or the functional fragment of the antibody according to claim 1, which comprises CDRL1, CDRL2 and CDRL3 in any one combination selected from the group consisting of the following combinations (1) to (4):

(1) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence

shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14,

(2) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24,

(3) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and

(4) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and

CDRH1, CDRH2 and CDRH3 in any one combination selected from the group consisting of the following combinations (5) to (9):

(5) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,

(6) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,

(7) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

(8) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(9) CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19.

Claim 4: The antibody or the functional fragment of the antibody according to claim 1, which comprises CDRL1, CDRL2 and CDRL3, and CDRH1, CDRH2 and CDRH3 in any combination selected from the group consisting of the following combinations (1) to (5):

(1) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 18, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19,

(2) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 22, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 23, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 24, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 27, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 28, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 29,

(3) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 32, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 33, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 34, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 37, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 38, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 39,

(4) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 42, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 43, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 44, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 47, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 48, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 49, and

(5) CDRL1 consisting of the amino acid sequence shown in SEQ ID NO: 12, CDRL2 consisting of the amino acid sequence shown in SEQ ID NO: 13, and CDRL3 consisting of the amino acid sequence shown in SEQ ID NO: 14, and CDRH1 consisting of the amino acid sequence shown in SEQ ID NO: 17, CDRH2 consisting of the amino acid sequence shown in SEQ ID NO: 60, and CDRH3 consisting of the amino acid sequence shown in SEQ ID NO: 19.

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

Claim 6: The antibody or the functional fragment of the antibody according to claim 1, which has any one light chain variable region selected from the group consisting of the following variable regions (1) to (4):

(1) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63,

(2) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 67,

(3) an amino acid sequence having a sequence identity of at least 95% or more to the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (1) and (2), and

(4) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (1) to (3), and

any one heavy chain variable region selected from the group consisting of the following variable regions (5) to (9):

(5) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 71,

(6) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75,

(7) a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 79,

(8) an amino acid sequence having a sequence homology of at least 95% or more to the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (5) to (7), and

(9) an amino acid sequence comprising a deletion, substitution or addition of one or several amino acids in the sequence of a framework region other than at each CDR sequence in the amino acid sequences of (5) to (8).

Claim 7: The antibody or the functional fragment of the antibody according to claim 1, which comprises a light chain variable region and a heavy chain variable region in any of the following combinations (1) to (4):

(1) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 71,

(2) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75,

(3) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 67 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 75, and

(4) a light chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 63 and a heavy chain variable region consisting of the amino acid sequence shown in SEQ ID NO: 79.

Claim 8: The antibody or the functional fragment of the antibody according to claim 1, which has any of the following combinations (1) to (4):

(1) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69,

(2) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73,

(3) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73, and

(4) a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

Claim 9: The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 69.

Claim 10: The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

Claim 11: The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 65 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 73.

Claim 12: The antibody or the functional fragment of the antibody according to claim 8, which has a light chain consisting of the amino acid sequence at positions 21 to 233 in SEQ ID NO: 61 and a heavy chain consisting of the amino acid sequence at positions 20 to 471 in SEQ ID NO: 77.

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.

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.

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.

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.

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

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.

74. I understand that Petitioner is challenging claims 1-18 of the '386 Patent.

75. In short, I understand that the '386 Patent claims 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.

76. I understand the claimed human or humanized monoclonal antibodies and functional fragments represent a vast genus of human or humanized monoclonal antibodies and functional fragments defined by their functions –

specifically bind to the amino acid sequence shown of SEQ ID NO: 4 and possess an ability to internalize that permits cellular uptake.

77. The '386 Patent defines “humanized” antibodies as ones being 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.)

78. The '386 Patent defines “the phrase ‘specifically recognize an amino acid sequence comprising the amino acid sequence shown in SEQ ID NO: 4’ or ‘specifically recognize an EC3 domain’ as applied to an antibody is used to mean that the antibody strongly recognizes or strongly binds to the EC3 domain of CDH6 compared with the other extracellular (EC) domains of CDH6.” (*Id.*, 20:24-30.) Based on this definition, I understand that the claimed human or humanized monoclonal antibodies and functional fragments can have cross-reactivity against other EC domains of CDH6 so long as they strongly recognize or strongly bind to the EC3 domain of CDH6. Indeed, the data in Figure 7-4 of the '386 Patent shows that at least the humanized anti-CDH6 antibodies H01L02 and H04L02 have residual binding to EC3-deleted hCDH6-transferred cells, indicating that H01L02

and H04L02 have cross-reactivity against other EC domains (*i.e.*, EC1, EC2, EC4, or EC5). (*Id.*, Fig. 7-4.)

79. I understand SEQ ID NO: 4 recited in claim 1 contains 115 amino acids and is the amino acid (“aa”) sequence of human CDH6 extracellular domain 3 (EC3) (aa 269-383). (*Id.*, 19:62-65 and Table 1-1.) I also understand that the 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. However, claim 1 merely recites the entire EC3 domain as an antigen, without specifying any specific epitope within the EC3 domain to which the human or humanized monoclonal antibodies and their functional fragments bind, whereas the data in the competition assays shown in Figure 9 of the ’386 Patent indicates only four exemplary humanized hG019 anti-CDH6 antibodies (clones H01L02, H02L02, H02L03, and H04L02) likely bind to the same epitope. (*Id.*, Fig. 9.)

80. The ’386 Patent defines the term “high internalization ability” to mean that the survival rate (which is indicated by a ratio relative to a cell survival rate without antibody addition defined as 100%) of CDH6-expressing cells to which the aforementioned antibody and a saporin-labeled anti-rat IgG antibody have been administered is preferably 70% or less, and more preferably 60% or less. (*Id.*, 20:66-67, 21:1-5.)

B. The '386 Patent's Disclosure

81. The '386 Patent includes nine examples and sixteen figures. (*Id.*) Examples 1-2 and Figures 1-4 show identification of four rat anti-human CDH6 (hCDH6) monoclonal antibodies (named rG019, rG055, rG056, and rG061, respectively) and *in vitro* evaluation of binding of the rat antibodies to hCDH6 and their internalization activity. (*Id.*, Figs.1-4)

82. Rat antibodies were generated by immunizing rats with hCDH6 expression vector pcDNA3.1-hCDH6. (*Id.*, 72:52-64.) Antibody-producing hybridoma screening was performed using a Cell-ELISA method. (*Id.*, 73:15-67.) Hybridomas that produced a culture supernatant exhibiting higher absorbance in the 293a cells transfected with the pcDNA3.1 expression vector than that in the 293a cells transfected with the control pcDNA3.1 were selected as hybridomas producing antibodies binding to hCDH6. (*Id.*, 73:61-67.)

83. Clones rG019, rG055, rG056, and rG061 suggested to bind strongly to human CDH6 and monkey CDH6 were selected from the rat anti-CDH6 antibody-producing hybridomas. (*Id.*, 74:52-62.) The rat anti-hCDH6 monoclonal antibodies rG019, rG055, rG056, and rG061 were purified from the hybridoma culture supernatants using Protein G affinity chromatography. (*Id.*, 75:10-26.)

84. The binding activity of the rat antibodies to hCDH6 was evaluated by flow cytometry. (*Id.*, 75:28-67.) In particular, flow cytometry was used to determine

the binding site on hCDH6 by analyzing binding of the rat antibodies to the full-length extracellular domain, an EC1-deletion mutant, an EC2-deletion mutant, an EC3-deletion mutant, an EC4-deletion mutant, or an EC5-deletion mutant of hCD6. (*Id.*, 76:3-9.) It was found that the four rat antibodies bind to the EC3 domain of hCDH6. (Ex. *Id.*, 76:66-67.)

85. Example 3 describes determination of the nucleotide sequence of cDNA encoding variable regions of rat anti-CDH6 antibody rG019, rG055, rG056, or rG061. (*Id.*, 78:9-67.) cDNA encoding the heavy chain variable region or the light chain variable region of rG019, rG055, rG056, or rG061 was amplified from the total RNA, and sequences of the cDNA were determined by sequencing. (*Id.*)

86. Internalization activity of the rat antibodies was detected by an anti-rat IgG reagent Rat-ZAP (Advanced Targeting Systems) conjugated with a toxin (saporin) inhibiting protein synthesis. (*Id.*, 77:44-46.) It was demonstrated that the four rat antibodies bind CDH6 and cause internalization. (*Id.*, 78:6-7.)

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

88. Example 5 describes production of four humanized hG019 anti-CDH6 antibodies (clones H01L02, H02L02, H02L03, and H04L02) from a single clone chG019 by CDR grafting. (*Id.*, 81:38-50.) The four humanized anti-CDH6

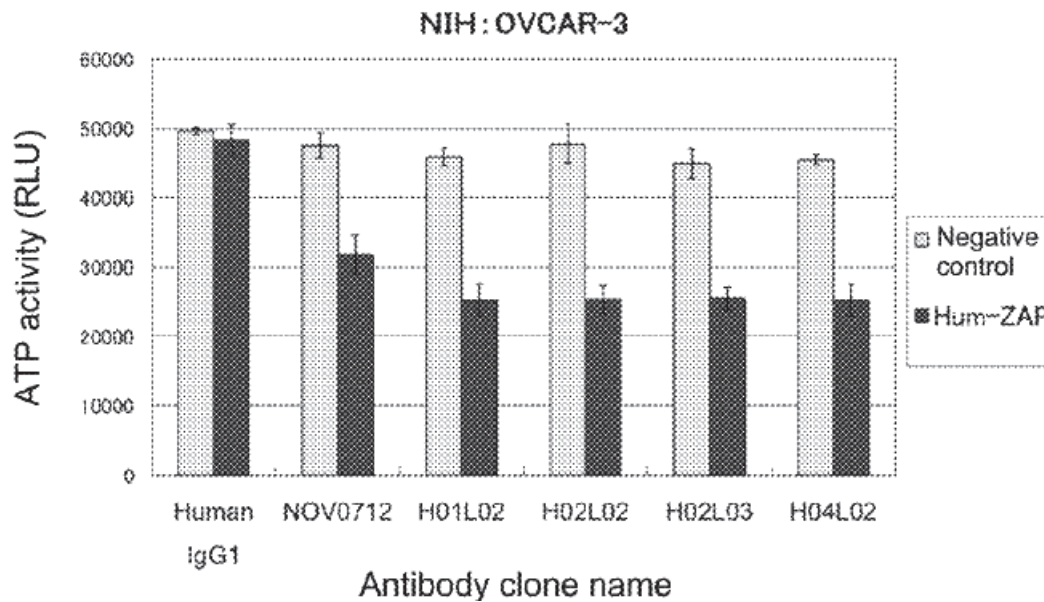
antibodies were generated by pairing heavy chains (H01, H02, or H04) and light chains (L02 or L03). (*Id.*, 82:6-15.) As a result, three of these four humanized antibodies share the same light chain, and two of these four humanized antibodies share the same heavy chain.

89. Example 6 and Figures 6-10 demonstrated that the four humanized hG019 antibodies (clones H01L02, H02L02, H02L03, and H04L02) specifically bind to hCDH6 EC3. (*Id.*, 86:30-37, Figs. 6-10.) As shown in Figure 7-4, at least the humanized anti-CDH6 antibodies H01L02 and H04L02 have residual binding to EC3-deleted hCDH6-transferred cells, indicating that H01L02 and H04L02 have cross-reactivity against other EC domains (*i.e.*, EC1, EC2, EC4, or EC5). (*Id.*, Fig. 7-4.)

90. The '386 Patent does not carry out epitope mapping. However, 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. (*Id.*, Fig. 9.)

91. In addition, based on the data shown in FIG. 10-1, the '386 Patent concluded that the four humanized hG019 antibodies exhibit higher internalization activity than NOV0712, although there is no statistical comparison or discussion on reproducibility of the assay. (*Id.*, Fig. 10-1.) FIG. 10-1 is reproduced as follows:

(Figure 10-1 of the '386 Patent)



92. Examples 7-9 and Figures 11-16 describe production and characterization of humanized hG019-drug conjugates. (*Id.*, 89-102, Figs. 11-16.)

C. Antibodies Described by the '386 Patent

93. No human anti-hCDH6 antibody or functional fragment is described in the '386 Patent. (*Id.*) 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.*)

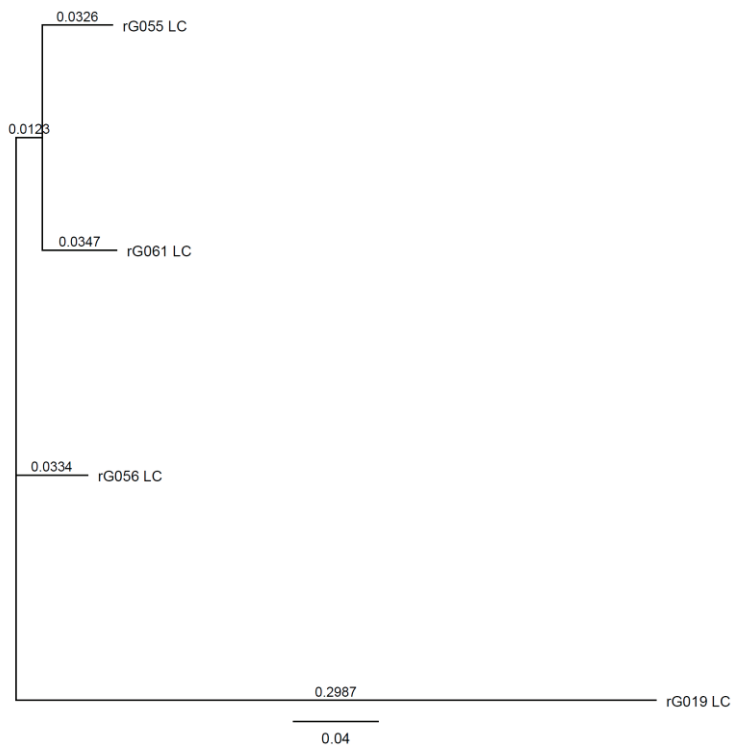
94. The '386 Patent identifies four rat antibody clones (rG019, rG055, rG056, and rG061) by immunizing rats with hCDH6. (*Id.*, 72:52-64, 74:52-62.) My sequence analysis as shown below by IMGT¹ indicates that these four rat clones are in fact from only two germ lines, with rG055, rG056, and rG061 are clonal

¹ IMGT (https://www.imgt.org/IMGT_vquest/input); Brochet, X., *et al.* Cold Spring Harb Protoc. 2011 Jun 1;2011(6).

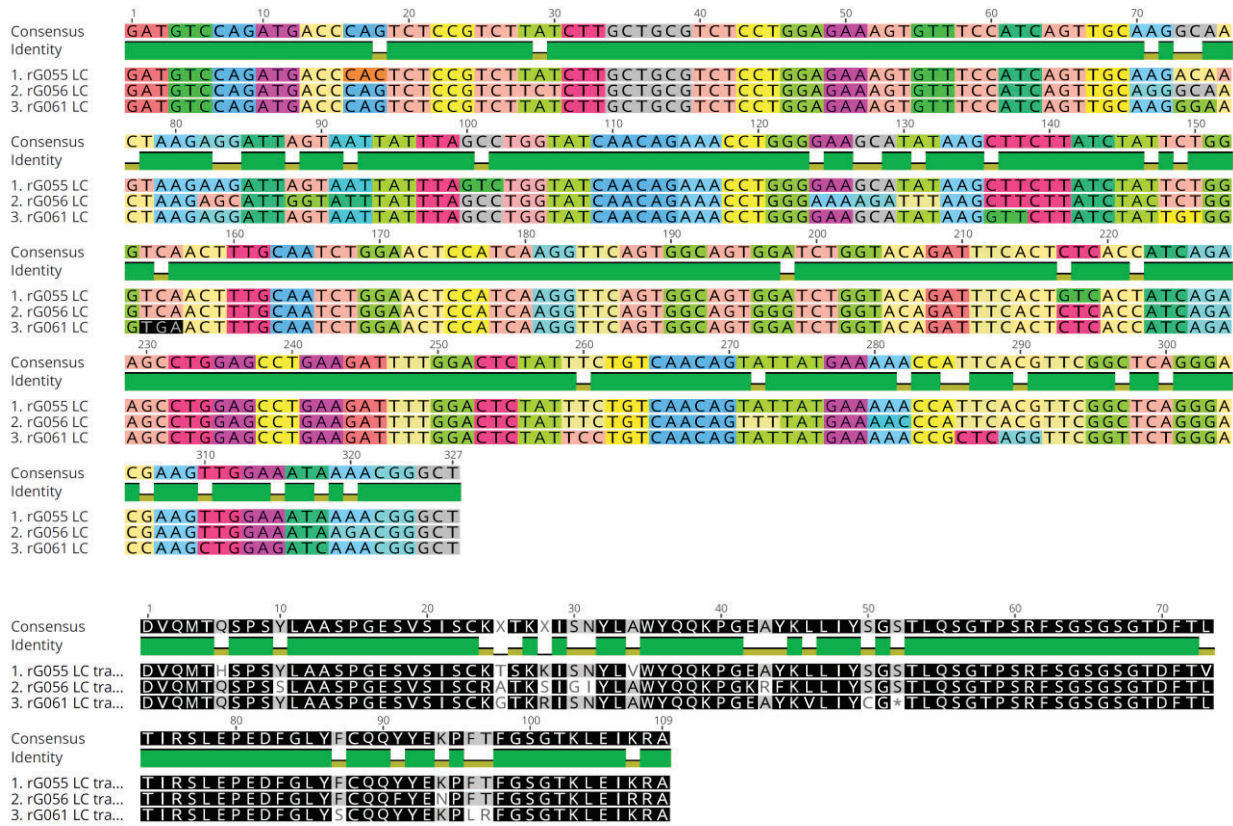
variants of the same germline. The fact that rG055, rG056, and rG061 originated from the same germline is consistent with their high sequence identity at both the nucleotide and protein levels.

3 of 4 mAbs are clonal variants (light chain)

Result summary: rG019_LC	Productive IGK rearranged sequence (no stop codon and in-frame junction)		
V-GENE and allele	Ratnor IGKV22S2*01 F	score = 1251	identity = 94.27% (263/279 nt)
J-GENE and allele	Ratnor IGKJ1*01 F	score = 158	identity = 91.89% (34/37 nt)
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[26.17.36.10]	[6.3.8]	CQQYYSGWAF
JUNCTION length (in nt) and decryption	30 nt = (21)-3{0}-1(9)	(3'V)3'(N)5'(5'J)	
Result summary: rG055LC	Productive IGK rearranged sequence (no stop codon and in-frame junction)		
V-GENE and allele	Ratnor IGKV16S1*01 F	score = 1179	identity = 91.40% (255/279 nt)
J-GENE and allele	Ratnor IGKJ4*01 F	score = 185	identity = 100.00% (37/37 nt)
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[26.17.36.10]	[6.3.9]	CQYYEKPFTF
JUNCTION length (in nt) and decryption	33 nt = (24)-2{0}-1(9)	(3'V)3'(N)5'(5'J)	
Result summary: rG056_LC	Productive IGK rearranged sequence (no stop codon and in-frame junction)		
V-GENE and allele	Ratnor IGKV16S1*01 F	score = 1170	identity = 91.04% (254/279 nt)
J-GENE and allele	Ratnor IGKJ4*01 F	score = 176	identity = 97.30% (36/37 nt)
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[26.17.36.10]	[6.3.9]	CQQFYENPFTF
JUNCTION length (in nt) and decryption	33 nt = (24)-2{0}-1(9)	(3'V)3'(N)5'(5'J)	
Result summary: rG061_LC	Unproductive IGK rearranged sequence (stop codons)		
V-GENE and allele	Ratnor IGKV16S1*01 F	score = 1197	identity = 92.11% (257/279 nt)
J-GENE and allele	Ratnor IGKJ5*01 F	score = 181	identity = 97.37% (37/38 nt)
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[26.17.36.10]	[6.3.9]	CQQYYEKPLRF
JUNCTION length (in nt) and decryption	33 nt = (23)-3{0}0(10)	(3'V)3'(N)5'(5'J)	

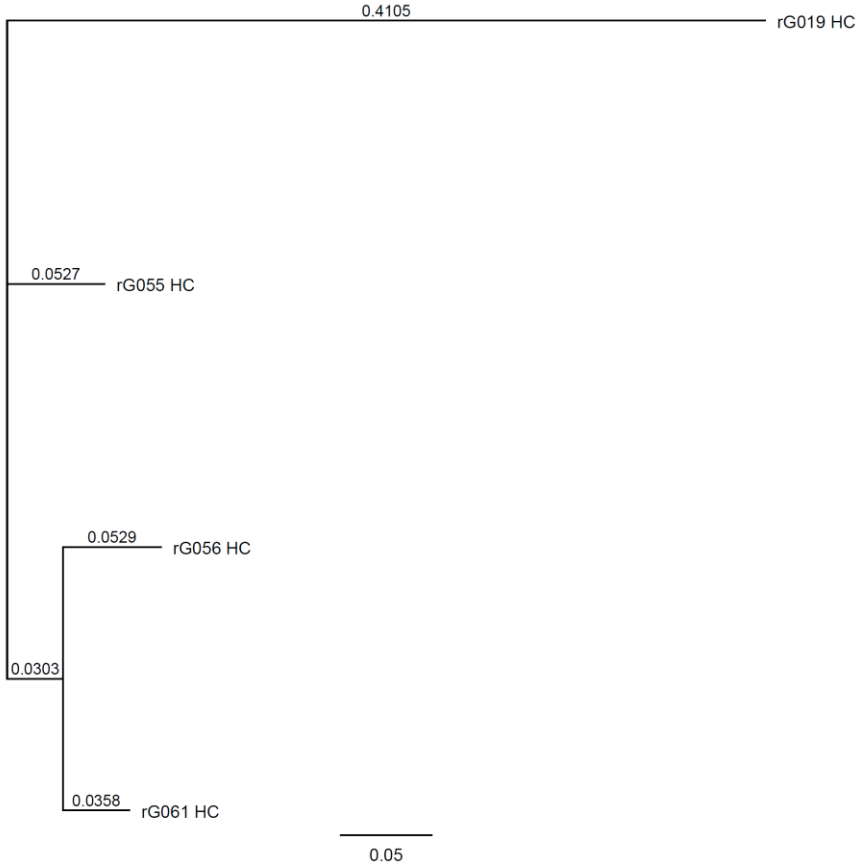


Light chain sequence comparison of mAb clonal variants

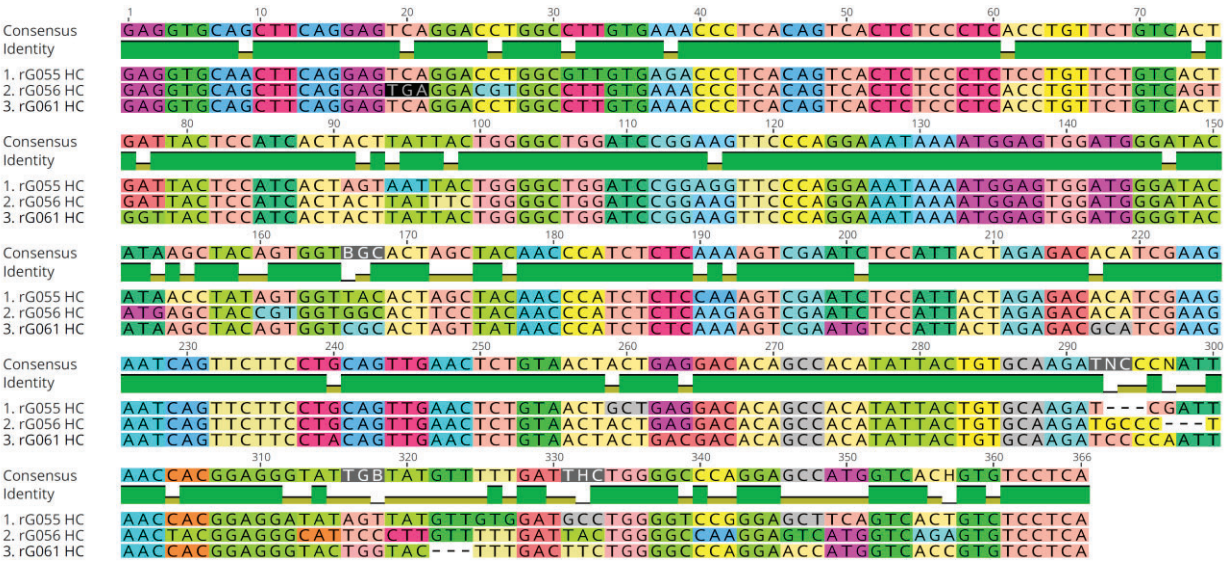


3 of 4 mAbs are clonal variants (heavy chain)

Result summary: rG019_HC		Unproductive IGH rearranged sequence (stop codons)	
V-GENE and allele	Ratnor IGHV1-28*01 F	score = 1251	identity = 92.71% (267/288 nt)
J-GENE and allele	Ratnor IGHJ2*01 F	score = 218	identity = 93.88% (46/49 nt)
D-GENE and allele by IMGT/JunctionAnalysis	Ratnor IGHD1-11*01 F	D-REGION is in reading frame 3	
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[25.17.38.11]	[8.8.15]	CARGVYGGFAGGYFDFW
JUNCTION length (in nt) and decryption	51 nt = (9)0(6)-5(10)-8(10)-3(16)	(3'V)3'(N1)5'(D)3'(N2)5'(5'J)	
Result summary: rG055_HC		Productive IGH rearranged sequence (no stop codon and in-frame junction)	
V-GENE and allele	Ratnor IGHV3-1*01 F	score = 1299	identity = 95.09% (271/285 nt)
J-GENE and allele	Ratnor IGHJ4*01 F	score = 211	identity = 88.68% (47/53 nt)
D-GENE and allele by IMGT/JunctionAnalysis	Ratnor IGHD1-11*01 F	D-REGION is in reading frame 3	
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[25.17.38.11]	[8.7.15]	CARSINHGGSYVVDW
JUNCTION length (in nt) and decryption	51 nt = (10)-1(2)+1(20)-3(0)-5(18)	(3'V)3'(N1)5'(D)3'(N2)5'(5'J)	
Result summary: rG056_HC		Unproductive IGH rearranged sequence (stop codons)	
V-GENE and allele	Ratnor IGHV3-1*01 F	score = 1290	identity = 94.74% (270/285 nt)
J-GENE and allele	Ratnor IGHJ2*01 F	score = 164	identity = 81.63% (40/49 nt)
D-GENE and allele by IMGT/JunctionAnalysis	Ratnor IGHD1-11*01 F	D-REGION is in reading frame 3	
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[25.17.38.11]	[8.7.15]	CARCPNYGGHSLVFDYW
JUNCTION length (in nt) and decryption	51 nt = (10)-1(4)-1(16)-6(9)-7(12)	(3'V)3'(N1)5'(D)3'(N2)5'(5'J)	
Result summary: rG061_HC		Productive IGH rearranged sequence (no stop codon and in-frame junction)	
V-GENE and allele	Ratnor IGHV3-1*01 F	score = 1317	identity = 95.79% (273/285 nt)
J-GENE and allele	Ratnor IGHJ1*01 F	score = 239	identity = 92.73% (51/55 nt)
D-GENE and allele by IMGT/JunctionAnalysis	Ratnor IGHD1-11*01 F	D-REGION is in reading frame 3	
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[25.17.38.11]	[8.7.15]	CARSPINHGGSYVYFDFW
JUNCTION length (in nt) and decryption	51 nt = (10)-1(4)+2(14)-9(0)-4(21)	(3'V)3'(N1)5'(D)3'(N2)5'(5'J)	



Heavy chain sequence comparison of mAb clonal variants





95. The '386 Patent describes six humanized anti-hCDH6 antibodies (*i.e.*, H01L02, H02L02, H04L02, H01L03, H02L03, and H04L03) derived from 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). (*Id.*, col. 27-32.) Humanized heavy chain variable regions (*i.e.*, H01, H02, H04) and humanized light chain variable regions (*i.e.*, L02, L03) are derived from a single human chimeric antibody chG019. (*Id.*, 81:51-67, 82:1-5.)

96. The '386 Patent also describes twenty-two hypothetical partially “humanized” anti-hCDH6 antibodies by combining 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.*, col. 27-32.) However, no functional data were provided for these hypothetical humanized anti-hCDH6 antibodies.

97. I understand only four exemplary humanized anti-hCDH6 antibodies (*i.e.*, clones H01L02, H02L02, H02L03, and H04L02) were produced, as described in Example 5. These four humanized hG019 anti-CDH6 antibodies were constructed from the same starting antibody chG019 by CDR grafting. (*Id.*, 81:38-50.) 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.

98. I understand the '386 Patent concluded these four humanized anti-hCDH6 antibodies (*i.e.*, clones H01L02, H02L02, H02L03, and H04L02) bind to hCDH6 EC3 and have internalization activity. (*Id.*, 86:35-37, 88:63-66, Fig. 10.)

99. I compared the amino acid sequences of the heavy chains of H01, H02, and H04 by a multiple sequence alignment using Clustal Omega² and found they share about 99% sequence identity. I also compared the amino acid sequences of the light chains of L02 and L03 by multiple sequence alignment using Clustal Omega and found that they share about 98% sequence identity. 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.

² Clustal Omega is a multiple alignment tool available at <https://www.ebi.ac.uk/Tools/msa/clustalo/> (Sievers F, *et al.* Molecular Systems Biology 7 Article number: 539)

100. Since these four exemplary humanized anti-hCDH6 antibodies were derived from a single starting antibody, chG019, they share identical CDR regions (*i.e.*, CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3).

101. As will be further analyzed below for prior art reference WO2016024195A1 (“Novartis”), the amino acid sequences of the CDR regions of these exemplary humanized antibodies are wildly different from those of a prior art anti-hCDH6 antibody NOV0710 (45%, 57%, 50%, 20%, 11%, and 33% for CDRL1, CDRL2, CDRL2, CDRH1, CDRH2, and CDRH3, respectively). 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 HCVRs and 84% sequence identity for 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).

102. Regarding internalization activity, I understand that the ’386 Patent does not provide structural characteristics of the anti-hCDH6 antibodies that are necessary or important for internalization activity. 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.” (*Id.*, 2:47-53.)

VIII. OVERVIEW OF PRIOR ART

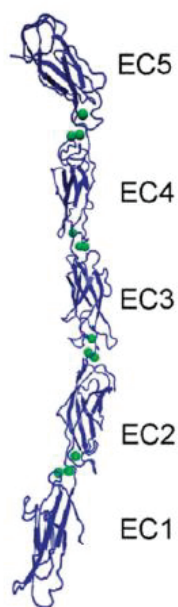
A. WO2016024195A1 (“Novartis”)

103. I understand prior art reference WO2016024195A1 (and its US national stage application US20160046711A1, entitled “Anti-CDH6 antibody drug conjugates,” issued as US Patent No. 9,982,045) to Bialucha *et al.* (Ex. 1005) (“Novartis”) was cited under 35 U.S.C. §102(a)(1) during prosecution of the ’386 Patent. Novartis was assigned to Novartis AG. Novartis discloses antibodies and antibody fragments (*e.g.*, antigen binding fragments) that bind to CDH6 and internalize upon such binding. (Ex. 1005, ¶[00147].)

104. CDH6 is a type II cadherin with five extracellular cadherin repeats (EC1-EC5), a transmembrane domain, and a cytoplasmic domain. (Ex. 1021 at 2206.) CDH6 is composed of 790 amino acids, and its sequence is available under, for example, accession Nos. NM_004932 and NP_004923 (NCBI). (Ex. 1001, 1:44-51.)

105. I provide a crystal structure below of the extracellular region (including EC1-EC5 domains) of CDH6 to show the three-dimensional

configuration of EC1-EC5 domains of CDH6. (Ex. 1024 at 63, Fig. 8.) However, it should be noted that the structure shown below is only an ensemble of many possible three-dimensional configurations of EC1-EC5 domains. For example, EC1-EC5 domains can undergo conformational changes and adopt different three-dimensional configurations in response to interactions of a binding partner (*e.g.*, an anti-CDH6 antibody).



106. It was found that CDH6 expression correlated with certain types of cancers. (Ex. 1025 at 4.) For example, renal cell carcinoma patients who expressed CDH6 and lacked E-cadherin expression had a poor prognosis. (Ex. 1026 at 2419.) It was also discovered that CDH6 was a TGF-B target and plays a role in thyroid cancer. (Ex. 1027 at 1.) Lastly, CDH6 was shown to be a biomarker for ovarian cancer. (Ex. 1028 at 1.) It was also found that CDH6 correlates strongly with

commonly recognized markers of immune cells, such as B cells, CD8+ T cells, and DCs. (Ex. 1029 at 8.)

107. Novartis discloses anti-CDH6 antibodies, such as NOV0670, NOV0672, NOV0674, NOV0682, NOV0685, NOV0689, NOV0690, NOV0691, NOV0692, NOV0693, NOV0695, NOV0699, NOV0705, NOV0709, NOV0710, NOV0712, NOV0713, NOV0718, NOV00719, and NOV0720 (collectively “the NOV anti-hCDH6 antibodies”), that are capable of binding strongly to human, cynomolgus, rat or mouse CDH6, as determined by a cellular binding assay and Biacore measurement (Ex.1005 at 113-57, 163-65, Tables 5, and 7-8, Figs. 1 and 2.)

108. My review of the relevant portion of the prosecution history of the ’386 Patent suggests that in rejections against claims 1, 2, 5, 13, and 24 of Application No. 16/613,203 (corresponding to claims 1, 2, 5, 13, and 14 of the ’386 Patent) as anticipated by Novartis, the Examiner did not discuss the binding and/or internalization properties of any specific NOV anti-hCDH6 antibodies described in Novartis. (Ex. 1002 at 13341-13348.) The Examiner cited paragraphs [0009], [0016], [0022], [0149], [0359], and [0380] of Novartis. (*Id.* at 13346.) But none of these cited paragraphs mentions any specific NOV anti-hCDH6 antibodies. (Ex. 1005 at 3-11, 40-41, 109, 113, ¶¶ [0009], [0016], [0022], [0149], [0359], [0380].)

109. In mapping binding sites on hCDH6 for the anti-CDH6 antibodies, hydrogen-deuterium exchange (HDx) in combination with mass spectrometry (MS) (“HDx-MS”) was performed for the NOV anti-CDH6 antibodies on the full-length extracellular domain (ECD) of full-length human CDH6 (hCDH6) (aa 54-615), which includes cadherin domains EC1-EC5 (Table 9). (Ex. 1005, ¶[00391].) In addition, HDx was also performed on a truncated ECD consisting of EC1-EC3 using antibodies such as NOV0710 (Table 10). (*Id.*)

110. HDx-MS can provide valuable information about binding, allostery, and other conformational effects of interaction in protein complexes. (Ex. 1030 at 1.) In HDx, exchangeable amide hydrogens (such as solvent accessible amide hydrogens) of proteins are replaced by deuterium. (*Id.*, ¶[00391].) A decrease in deuterium uptake reflects decreased solvent accessibility of the region caused, for example, by local stabilization due to ligand binding or protein-protein complex formation. (Ex. 1031 at 14706, 14710.)

111. Within EC3 (aa 269-383), the region (aa 303-315) IEYSITDGEGLDM (SEQ ID NO: 343) exhibits a decrease in deuterium uptake by all antibodies, but the decrease is more pronounced by NOV0710 relative to the other antibodies. (Ex. 1005, ¶[00397].) The region (aa 316-330) FDVITDQETQEGIIT (SEQ ID NO: 344) exhibits a decrease in deuterium uptake for all antibodies but the decrease is the least by NOV0719. (*Id.*)

112. Within EC5 (aa 487-608), only the region (aa 564-586 YLLPWISDNDYPVQSSTGTVTV (SEQ ID NO: 351) exhibits a borderline decrease in deuterium uptake when hCDH6 complexes with NOV0710. (*Id.*, ¶[00399].)

113. When HDx was performed for hCDH6 construct consisting of only EC3-EC5, hCDH6 (aa 267-615), in EC3, a decrease in deuterium uptake is observed in the region (aa 295-315) ADVGENAEIEYSITDGEGLDM (SEQ ID NO: 352) for NOV0710. (*Id.*, ¶[00400] and [00401].) In the EC5 of hCDH6 (267-615), the regions (aa 492-505) YETFVCEKAKADQL (SEQ ID NO:353), (aa 551-563) TRKNGYNRHEMST (SEQ ID NO:354), and (aa 572-586) DNDYPVQSSTGTVTV (SEQ ID NO:355) exhibited the most significant decrease in deuterium uptake upon binding NOV0710 or NOV0712. (*Id.*, ¶[00403].)

114. In my opinion, the above results from the HDx-MS study suggest anti-CDH6 antibodies such as NOV0710 can bind strongly to both EC3 and EC5 of CDH6.

115. The above results from the HDx-MS study also suggest that NOV0719 binds strongly to the EC3 domain of hCDH6, albeit likely at a lower binding affinity compared to NOV0710.

116. Novartis also reports co-crystal structures of the CDH6 EC5/NOV0710 Fab complex to further identify the epitopes on EC5 for

NOV0710. (*Id.*, ¶¶[00412]-[00416].) Novartis did not make attempts to obtain a co-crystal structure of NOV0710 in complex with EC3 or with both EC3 and EC5. It should be noted that the structures containing EC1-EC5 shown in Figure 6 were not experimentally determined from X-ray crystallography. (*Id.*, ¶[00412].) Rather, they were generated based on the superposition of EC5 of CDH6 with the full-length extracellular domain (ECD) of CDH2. (*Id.*) Accordingly, the three-dimensional configuration of EC1-EC5 does not represent the actual three-dimensional configuration of the binding pose between EC1-EC5 and NOV0710.

117. I was asked to consider what information is or is not revealed by the co-crystal structures of the CDH6 EC5/NOV0710 Fab complex. I note that the co-crystal structures contain only one antigen-binding arm (*i.e.*, Fab of NOV0710) and contain only EC5 – thus missing the other antigen-binding arm and EC3. Accordingly, the co-crystal structures do not reveal the interactions between EC3 and NOV0710. Therefore, the co-crystal structures do not contradict the results determined by the HDx study that NOV0710 can bind strongly to EC3.

118. Regarding internalization activities, Novartis also describes a protocol for “assessment of antibody cellular internalization propensity” by microscopy using a VTI ArrayScan® HC reader (ThermoFischer, Waltham, MA) and using the Spot Detector V4 algorithm (ThermoScientific Cellomics®, Thermo Scientific, Rockford, IL). (*Id.*, ¶[00372].)

119. I understand all the NOV anti-hCDH6 antibodies described by Novartis were identified from 47 candidate IgG clones that “were subjected to a series of characterization assays including human/cyno/rat/mouse cross-reactivity by FACS, affinity ranking by Octet, cellular internalization assays as well as surrogate ADC assays using an anti-human IgG Fab-SMCC-DM1 secondary reagent. Based on these assays, human IgGs were selected for scaled up production, subsequent direct conjugation to ADC linker/payloads and testing as ADCs in in vitro and in vivo experiments.” (*Id.*, ¶[00379].) Table 5 lists the anti-CDH6 IgGs, including NOV0710 and NOV0719, selected for further in-depth characterization. (*Id.*, ¶[00380], Table 5.) In my view, at least the NOV anti-hCDH6 antibodies listed in Table 5 bind strongly to hCDH6 and have the ability of cellular internalization. (*Id.*)

120. For the results of surrogate ADC assays, Novartis also reports that SMCC-DM1 conjugates of the anti-CDH6 antibodies (such as NOV0710 and NOV0719) significantly inhibited proliferation of several CDH6-positive cell lines (such as OVCAR3, JHOS4, and KNS42 cell lines) and exhibited high ant-tumor efficacy in a xenograft mouse model of ovarian cancer. (*Id.*, Examples 12-24.)

121. In my view, *in vitro* or *in vivo* anti-tumor activities of antibody-drug conjugates generated from the anti-CDH6 antibodies are also indicative of internalization of the anti-CDH6 antibodies. It was found by Bialucha *et al.* in

another research article that “antibody internalization propensity correlated positively with potency in the surrogate ADC assay ($r^2 = 0.630$; $P < 0.0001$), strongly implying that target-dependent, intracellular delivery of ADC payload drives ADC activity.” (Ex. 1032 at 3.)

122. I was also asked to consider sequence identity between NOV0710 and the four exemplary humanized anti-hCDH6 antibodies (*i.e.*, H01L02, H02L02, H02L03, and H04L02). I compared the amino acid sequences of CDRs, heavy chain and light chain variable regions, and heavy chain and light chain of NOV0710 and those of the four exemplary humanized antibodies (*i.e.*, H01L02, H02L02, H02L03, and H04L02) described in the '386 Patent by a multiple sequence alignment using Clustal Omega. The sequence comparison is summarized in Table 1 below.

Table 1. Sequence Identity Comparisons

	Sequence identity among four humanized antibodies (H01L02, H02L02, H02L03, and H04L02) described in the '386 Patent	Sequence identity: prior art antibody NOV0710 vs. four humanized antibodies (H01L02, H02L02, H02L03, and H04L02) described in the '386 Patent
LCVR	93%	84%
HCVR	95%	58%
CDRL1	100%	45%
CDRL2	100%	57%

CDRL3	100%	50%
CDRH1	100%	20%
CDRH2	100%	11%
CDRH3	100%	33%

123. It is clear that the sequences of the CDR regions of NOV0710 are wildly different (45%, 57%, 50%, 20%, 11%, and 33% sequence identities for CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3, respectively) from those of the exemplary humanized antibodies of the '386 Patent. Similarly, the sequences of the heavy chain and light chain variable regions are also remarkably different from those of the exemplary humanized antibodies of the '386 Patent, with 58% sequence identity for HCVRs and 84% sequence identity for LCVRs, as compared to high sequence identity values among the heavy chain and light chain variable regions of the exemplary humanized antibodies (with 95% sequence identity for HCVRs and 93% sequence identity for LCVRs).

124. 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 also demonstrates generation and expression of soluble Fab fragments. (*Id.*, ¶[00351], [00181].)

125. Novartis discloses “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].)

126. Novartis discloses “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].)

127. Novartis further discloses “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.” (*Id.*, ¶[00252].)

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

128. 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. I was informed that Urano is prior art to the ’386 Patent under 35 U.S.C. §§102(a)(1) and 102(a)(2). I understand that Urano was not before the USPTO during prosecution of the ’386 Patent.

129. Urano discloses an anti-FGFR2 antibody as well as various modifications to the antibody. (Ex. 1006, ¶[0302].)

130. Urano discloses “a modified form of the antibody or functional fragment thereof. The modified form of the antibody of the present invention, or the functional fragment thereof, means an antibody of the present invention, or a functional fragment thereof, provided with chemical or biological modification. The chemically modified form includes, for example, a form having an amino acid skeleton conjugated with a chemical moiety, and a form having a chemically modified N-linked or O-linked carbohydrate chain. The biologically modified form includes, for example, a form that has undergone 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), and a

form containing a methionine residue added to the N-terminus by expression using prokaryotic host cells.” (Ex. 1006, ¶[0352].)

131. Urano discloses “the antibody dependent cellular cytotoxic activity of the antibody of the present invention, or the functional fragment thereof, may be enhanced by regulating the modification (glycosylation, defucosylation, etc.) of the sugar chain bound with the antibody or functional fragment.” (Ex. 1006, ¶[0355].),

132. 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. For example, the heavy chain of an antibody produced by cultured mammalian cells is known to lack a lysine residue at the carboxy terminus.” (Ex. 1006, ¶[0302].)

133. Urano further discloses “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.*)

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

134. 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. I was informed that Sato is prior art to the '386 Patent under 35 U.S.C. §§102(a)(1) and 102(a)(2). I understand that Sato was not before the USPTO during prosecution of the '386 Patent.

135. Sato discloses an anti-human TSLP receptor antibody as well as various modifications to the antibody. (Ex. 1007, ¶¶[0048], [0050].) In particular, Sato discloses “an antibody modified after translation during expression in cells such as an antibody comprising a heavy chain lacking lysine of a C terminal, an antibody in which glutamine or glutamic acid of the N terminal of the heavy chain is modified to pyroglutamic acid due to pyroglutamylation, and the like in addition to an antibody comprising a full length of heavy chain. Further, the antigen-binding fragment of the present invention includes an antigen-binding fragment modified after translation during expression in cells such as an antigen-binding fragment in which glutamine or glutamic acid of the N terminal of the heavy chain is modified to pyroglutamic acid due to pyroglutamylation.” (*Id.*, ¶[0050].)

IX. LEVEL OF ORDINARY SKILL IN THE ART

136. I have been informed that I must analyze the claims of the '386 Patent from the perspective of what a person of ordinary skill in the relevant field at the time of the claimed invention would have known or understood.

137. In my opinion, a person of ordinary skill in the art (“skilled artisan”) at the time of the alleged invention on or before the claimed priority date 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. In my opinion, 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. 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.

X. THE ’386 PATENT DOES NOT SUPPORT OR ENABLE ANY OF CLAIMS 1-18

138. As I explain below, I do not believe any of claims 1-18 find written description support in the specification of the ’386 Patent, nor does that specification enable the skilled artisan to make and use the full scope of the claimed invention without undue experimentation.

A. The ’386 Patent Lack of Written Description for Any of Claims 1-18

139. The ’386 Patent claims a vast genus (billions) of human or humanized monoclonal antibodies and a vast genus (billions) of functional fragments of human or humanized monoclonal antibodies of great structural variability by the

following functions: (i) ability to specifically binds EC3 domain of hCDH6 as defined by SEQ ID NO: 4, and (ii) ability to internalize that permits cellular uptake, without specifying any associated sequences or structural features.

140. SEQ ID NO: 4 covers the 115-amino acid sequence of the entire EC3 domain of hCDH6, which includes a large number of epitopes within EC3 to which millions of human or humanized antibodies or their functional fragments can bind. These epitopes include at least those binding regions known in the art (*e.g.*, 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). (Ex. 1005, ¶¶[00397], [00399]-[00401], [00403].) Each binding region on EC3 can be recognized by distinct human or humanized monoclonal antibodies and their functional fragments. In addition, each such epitope on EC3 can give rise to a whole subgenus of human or humanized monoclonal antibodies and their functional fragments, thus expanding the number of potential binding sites. Therefore, the claims of the '386 Patent cover an even broader genus scope than those defining antibodies by an epitope.

141. I have been informed that a claim to this type of functional genus satisfies the written description requirement if the specification provides a representative number of species falling within the scope of the claimed invention or structural features common to the members of the claimed invention such that a skilled artisan could visualize or recognize its members. In my opinion, the '386 Patent does not satisfy any of these requirements.

142. I also understand that Daiichi Sankyo Co Ltd ("Patent Owner") may argue that the four exemplary humanized anti-CDH6 antibodies derived from a single starting antibody clone and other hypothetical antibodies formed from sequences of four starting rat antibodies that originated from only two germ lines, as described in the '386 Patent, would represent constructs falling within the claim scope. I have been asked to explain why the claims would still lack written description support. This is the case because claims 1-18 encompass a genus of diverse and unpredictable antibody sequences that can bind the EC3 domain of hCDH6 defined by SEQ ID NO: 4 and can internalize to permit cellular uptake, while the only four rat antibodies that were tested to bind EC3 and to be internalized represent a narrow and unrepresentative subset of those claims. This is also because none of claims 1-18 specifies common structural features required for both desired antigen binding and internalization functions.

1. The exemplary humanized anti-CDH6 antibodies at best are Narrow and Unrepresentative Subset

143. First of all, antibodies or their functional fragments falling within the scope of claim 1 of the '386 Patent would cover an enormous number (billions) of antibody candidates with diverse antibody sequences that could be obtained, among other things, by animal immunization and phage display techniques. In view of the vast number of antibody or functional fragment candidates, it would accordingly require a significant number of representative antibodies or functional fragments that meet the functional limitations. The representative antibodies or functional fragments should have sufficient diversity to represent the members of the claimed invention.

144. Although the claims cover a vast genus of human monoclonal antibodies and their functional fragments, the '386 Patent does not provide any example of fully human anti-CDH6 antibodies or their functional fragments. Fully “human” antibodies can be generated by either inoculating a human with an antigen in order to form an antibody response or by creating transgenic organisms, such as transgenic mice where nearly the entire immunoglobulin loci has been introduced recombinantly such that the transgenic organism mimics a human response. These methods of creating a fully human antibody can result in countless different variations in structure. Critically, the '386 Patent fails to disclose a single “human” antibody, despite claiming this antibody format.

145. Regarding humanized antibodies and their functional fragments, I was also asked to consider the diversity of the four exemplary humanized anti-hCDH6 antibodies (*i.e.*, clones H01L02, H02L02, H02L03, and H04L02) described in Example 5 of the '386 Patent. These four humanized hG019 anti-CDH6 antibodies were generated from a single chimeric human antibody clone chG019 by CDR grafting, thus having identical CDRs. (Ex. 1001, 81:38-50.) Three of these four humanized antibodies share the same light chain (*i.e.*, L02), and two of these four humanized antibodies share the same heavy chain (*i.e.*, H02). While the inventors of the '386 Patent chose one set of “humanized” regions to replace the non-CDR rat regions, the potential combinations of different human heavy and light chains that could be used as the desired human acceptor antibody would number in the millions.

146. Although the 115-amino acid sequence of SEQ ID NO: 4 encompasses a large number of epitopes to which anti-hCDH6 antibodies can bind, the '386 Patent demonstrates only four exemplary humanized anti-hCDH6 antibodies (*i.e.*, clones H01L02, H02L02, H02L03, and H04L02) that have the same CDRs and bind to the same epitope.

147. I compared the amino acid sequences of the light chain of L02 (SEQ ID NO: 61) and the light chain of L03 (SEQ ID NO: 65) by multiple sequence alignment (see below) using Clustal Omega and found that the two amino acid

sequences share high sequence identity (about 98% sequence identity). I also found that L02 and L03 share the same light chain constant region and the limited variability only occurs in the framework region.

L02_LC	MVLQTQVFISLLLWISGAYGDIQMTQSPSSLSASVGDRVTITCKASQNIYKNLAWYQQKP	60
L03_LC	MVLQTQVFISLLLWISGAYGDIQMTQSPSSLSASVGDRVTITCKASQNIYKNLAWYQQKL	60

L02_LC	GKAPKLLIYDANTLQTGVPSRFSGSGSGSDFTLTISSLQPEDFATYFCQQYYSGWAFGQG	120
L03_LC	GEGPKLLIYDANTLQTGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWAFGQG	120
	*:*****:*****:*****	
L02_LC	TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE	180
L03_LC	TKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE	180

L02_LC	SVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	233
L03_LC	SVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC	233

148. I compared the amino acid sequences of the light chain variable region of L02 (SEQ ID NO: 63) and the light chain variable region of L03 (SEQ ID NO: 67) by multiple sequence alignment (see below) using Clustal Omega and found that the two amino acid sequences share high sequence identity (about 93% sequence identity).

L02_LCVR	DIQMTQSPSSLSASVGDRVTITCKASQNIYKNLAQYQQKPGKAPKLLIYDANTLQTGVPS	60
L03_LCVR	DIQMTQSPSSLSASVGDRVTITCKASQNIYKNLAWYQQKLGEKPKLLIYDANTLQTGVPS	60
	***** *:******	
L02_LCVR	RFSGSGSGSDFTLTISSLQPEDFATYFCQQYYSGWAFGQGTKVEIKRT	108
L03_LCVR	RFSGSGSGTDFTLTISSLQPEDFATYYCQQYYSGWAFGQGTVEIKRT	107
	*****:*****:***** *	

149. I also found that the amino acid sequences of light chain CDRs (*i.e.*, CDRL1, CDRL2, and CDRL3) of L02 are identical to those of L03, consistent with the fact that these CDRs were grafted from the same clone chG019.

150. I compared 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: 77) by multiple sequence alignment (see below) using Clustal Omega and found that the two amino acid sequences share high sequence identity (about 99% sequence identity). I also found that H01, H02, and H04 share the same heavy chain constant region (including CH1, CH2, and CH3 regions) and the limited variability only occurs in the framework region.

H01_HC	MKWLWFFLLLVAAPRWVLSVQLVQSGAEVKKPGASVKVSCKASGYTFTRNFMHWVRQAP	60
H02_HC	MKHLWFFLLLVAAPRWVLSVQLVQSGAEVKKPGASVKVSCKASGYTFTRNFMHWVRQAP	60
H04_HC	MKHLWFFLLLVAAPRWVLSVQLVQSGAEVKKPGASVKVSCKASGYTFTRNFMHWVRQAP	60
	*****:	
H01_HC	GQGLEWMGWIYPGDGETEYAQKFQGRVTITADTSTSTAYMELSSLRSEDVAVYYCARGVY	120
H02_HC	GQGLEWMGWIYPGDGETEYNQKFQGRVTITADRSTSTAYMELSSLRSEDVAVYFCARGVY	120
H04_HC	GQGLEWMGWIYPGDGETEYAQKFQGRVTITADRSTSTAYMELSSLRSEDVAVYYCARGVY	120
	*****:	
H01_HC	GGFAGGYFDWQGGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV	180
H02_HC	GGFAGGYFDWQGGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV	180
H04_HC	GGFAGGYFDWQGGLTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV	180

H01_HC	SWNSGALTSGVHTFPAVLQSSGLYSLSSWTPSSSLGTQTYICNVNHKPSNTKVDKRVPEP	240
H02_HC	SWNSGALTSGVHTFPAVLQSSGLYSLSSWTPSSSLGTQTYICNVNHKPSNTKVDKRVPEP	240
H04_HC	SWNSGALTSGVHTFPAVLQSSGLYSLSSWTPSSSLGTQTYICNVNHKPSNTKVDKRVPEP	240

H01_HC	KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCWVDVSHEDPEVKFNWY	300
H02_HC	KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCWVDVSHEDPEVKFNWY	300
H04_HC	KSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCWVDVSHEDPEVKFNWY	300

H01_HC	VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK	360
H02_HC	VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK	360
H04_HC	VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK	360

H01_HC	AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV	420
H02_HC	AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV	420
H04_HC	AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPV	420

H01_HC	DSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHLEALHNHYTQKSLSLSPGK	469
H02_HC	DSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHLEALHNHYTQKSLSLSPGK	469
H04_HC	DSDGSFFLYSKLTVDKSRWQQGNVFSQSVMHLEALHNHYTQKSLSLSPGK	469

151. I compared the amino acid sequences of 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: 77) by multiple sequence alignment (see below) using Clustal Omega and found that the three amino acid sequences share high sequence identity (about 95% sequence identity).

unsurprising 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 substitutions in the framework regions.

155. The extensive sequence identity of these exemplary humanized antibodies does not represent diverse and unpredictable sequences of antibodies or their functional fragments within the scope of the claimed invention. Indeed, when compared with the sequences of the prior art antibody NOV0710, I found the amino acid sequences of the CDR regions (*i.e.*, CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and CDRH3) of these exemplary humanized antibodies 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). Similarly, the sequences of the heavy chain and light chain variable regions (HCVRs and LCVRs) of these exemplary humanized antibodies are also remarkably different from those of NOV0710 (58% sequence identity for HCVRs and 84% sequence identity for LCVRs), as compared to high sequence identity values among the heavy chain and light chain variable regions of the exemplary humanized antibodies (95% sequence identity for HCVRs and 93% sequence identity for LCVRs). Considering extensive sequence identity among the exemplary humanized antibodies of the '386 Patent and their low sequence identity with the prior art antibody, it is clear that these exemplary humanized antibodies

merely represent a narrow, unrepresentative subset of the vast genus of antibodies and functional fragments covered by the claims.

156. Also, this amount of variability between the exemplary antibodies and another prior art 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.

157. In addition, 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 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 by so much by amino acid sequence from the four exemplary antibodies of the '386 Patent.

158. I understand the '386 Patent also describes twenty-two hypothetical partially "humanized" anti-hCDH6 antibodies by combining 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). (Ex. 1001, col. 27-32.)

159. However, these hypothetical partially humanized anti-hCDH6 antibodies) resulted from a “mix-and-match” approach based on the sequences derived from the only four starting rat or chimeric antibodies (*i.e.*, rG019/chG019, rG055, rG056, and rG061) do not remedy the defects of the ‘386 Patent in providing sufficient written description support for the genus claims. For example, such hypothetical partially humanized anti-hCDH6 antibodies are constructed by combining a light chain variable region (*i.e.*, L02 or L03) derived from chG019 with a heavy chain variable region of rat or chimeric antibody rG019/chG019, rG055, rG056, or rG061, or by combining a heavy chain variable region (*i.e.*, H01, H02, or H04) derived from chG019 with a light chain variable region of rat or chimeric antibody rG019/chG019, rG055, rG056, or rG061. The sequence diversity offered by these hypothetical humanized anti-hCDH6 antibodies is also very limited because all the sequences of the rat or chimeric antibodies (*i.e.*, rG019/chG019, rG055, rG056, or rG061) originated from only two germ lines and all the sequences of the humanized anti-hCDH6 antibodies originated from a single clone. Additionally, the ‘386 Patent does not provide any binding or functional data indicating that these hypothetical partially humanized anti-hCDH6 antibodies have an ability to specifically bind to CDH6 EC3 defined by SEQ ID NO: 4 and an ability to internalize that permits cellular uptake.

160. I was additionally asked to address the written description support for claims 8-12 that specify heavy chain and light chain sequences. I understand claims 8-12 also cover human or humanized antibodies and their functional fragments having various modifications, so long as the amino acid sequences of the antibodies or their functional fragments remain unchanged. The '386 Patent describes a number of modifications that can be made to the antibodies or their functional fragments, including "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." (Ex. 1001, 8:40-49.)

161. Accordingly, the human or humanized antibodies and their functional fragments containing one or more of these modifications represent a large genus of antibodies and functional fragments. As discussed above, these modifications can alter the properties of antibodies and cause them to lose the desired binding and internalization functions. However, the '386 Patent does not exemplify any antibodies or their functional fragments containing any of the above modifications to confirm that anti-CDH6 having one or more of these modifications would still retain the desired binding and internalization functions. In my view, claims 8-12

also lack written description support even though they specify heavy chain and light chain sequences.

162. I understand all claims 1-18 cover a vast genus of functional fragments of human or humanized monoclonal antibodies defined by their functions: (i) ability to specifically bind EC3 domain of hCDH6 as defined by SEQ ID NO: 4 and (ii) ability to internalize that permits cellular uptake. The functional fragments conceivably cover 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. Thus, they suffer the same defects in written description support as the functionally defined human or humanized monoclonal antibodies as discussed above. It is known that fragments of antibodies are expected to have very different functional properties and internalization activity. For example, cytotoxic activities often rely on the bivalent nature of IgGs, and Fab fragments or scFvs generally do not have comparable activity to an intact, full-length IgG (Ex. 1033 at 570, Fig. 6; Ex. 1034 at 1190, Fig. 8.) Yet, the '386 Patent does not provide any binding or functional data indicating that such functional fragments have an ability to specifically bind to CDH6 EC3 defined by SEQ ID NO: 4 and an ability to internalize that permits cellular uptake.

163. This reiterates how the disclosed humanized anti-hCDH6 antibodies represent at best a small corner of a much more diverse functional genus of human or humanized antibodies and their functional fragments that specifically bind the EC3 domain of hCDH6 as defined by SEQ ID NO: 4 and possesses an ability to internalize that permits cellular uptake.

164. Due to the breadth of the genus of the antibodies, it simply would not have been possible for a skilled artisan at Patent Owner's claimed priority date in 2017, or even today, to extrapolate from those unrepresentative humanized anti-hCDH6 antibodies to conclude that the named inventors were in possession of the genus of all other antibodies and the genus of functional fragments that specifically binds hCDH6 EC3 as defined by SEQ ID NO: 4 and possesses an ability to internalize that permits cellular uptake.

2. The Claims of the '386 Patent Do Not Specify Structural Features Common to the Members of the Claimed Invention That are Required for Binding hCDH6 EC3 and Internalization

165. I understand an alternative way for claims with a functionally defined genus to satisfy the written description requirements is to specify structural features common to the members of a functionally defined genus. However, as discussed above, independent claim 1 does not specify any common structural features of the human or humanized monoclonal antibodies or their functional fragments that confer the human or humanized monoclonal antibodies or their

functional fragments the ability to specifically bind the EC3 domain of hCDH6 as defined by SEQ ID NO: 4 and the ability to internalize that permits cellular uptake.

166. Dependent 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). Dependent claims 5 and 13-18 specify some non-distinguishing, secondary features. However, none of dependent claims 2, 5, and 13-18 specifies any particular common structural features required for both binding and internalization functions of the human or humanized monoclonal antibodies or their functional fragments.

167. 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 the binding and internalization functions.

168. Claim 3 covers a genus of antibodies or their functional fragments by reference to their six CDR sequences 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, as will be further explained below, 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. Even for binding to EC3, the data from the binding assay using 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, which could lead to the same results as depicted in Figure 2 of the '386 Patent.

169. Moreover, as a result of this mix-and-match approach, the claim covers antibodies or their functional fragments with light chain CDRs and heavy chain CDRs from different rat or chimeric antibodies. The '386 Patent does not provide any data indicating that the antibodies or their functional fragments merely characterized by the combinations of six CDRs generated from this mix-and-match approach will sufficiently confer the antibodies or their functional fragments an ability to specifically bind the EC3 domain of hCDH6 as defined by SEQ ID NO: 4 and an ability to internalize that permits cellular uptake. In this regard, the structural features (six CDRs from different rat antibodies) are not common structural features of the claimed antibodies or their functional fragments required for the binding and internalization functions.

170. In addition, claim 3 does not specify all residues required for recognition of a target antigen. In my view, the residues in framework regions can also play a significant role in antibody-antigen interactions. In a report by Caldas *et al.*, it was found that a framework residue can have an unexpected effect in binding to an antigen. (Caldas *et al.*, Molecular Immunology, Volume 39, Issue 15, 2003, pages 941-952) (Ex. 1011 at 941.) In agreement with Caldas *et al.*, Kunik *et al.* also reported that “20% of the antibody residues that actually bind the antigen fall outside the CDRs.” (Ex. 1012 at 1-2.)

171. Furthermore, claim 3 also fails to provide any common structural features required for the internalization function. I understand the '386 Patent acknowledges 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." (Ex. 1001, 2:47-56.) The '386 Patent thus considers it is "an important change ... is obtaining an antibody having high internalization ability against the target antigen." (*Id.*) Thus, it is unsurprising that claim 3 cannot specify common structural features required for the internalization function.

172. In my opinion, although claim 3 recites CDR sequences, it does not provide common structural features required for both binding and internalization functions for the claimed human or humanized antibodies and their functional fragments.

173. Claim 4 covers a genus of antibodies or their functional fragments by reference to six CDR sequences of four antibody clones, *i.e.*, rG019/chG019, rG055, rG056, and rG061. Accordingly, claim 4 has defects similar to those of claim 3 as discussed above. Claim 4 does not provide sufficient common structural features required for antigen binding by omitting residues in the

framework region. Nor does it provide any common structural features required for the internalization function of the human or humanized antibodies and their functional fragments.

174. Claim 6 covers a genus of antibodies or their functional fragments by reference to 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 expands the scope of the genus to cover variants of these combinations with “an amino acid sequence having at least 95% or more to the sequence of a framework region.”

175. As a result of this mix-and-match approach, the claim covers antibodies or their functional fragments including combinations of H01 and L03 (“H01L03”), H04 and L03 (“H04L03”), in addition to characterized clones H01L02, H02L02, H02L03, and H04L02. However, the ’386 Patent does not provide any data indicating H01L03 and H04L03 possess an ability to specifically bind the EC3 domain of hCDH6 as defined by SEQ ID NO: 4 and an ability to internalize that permits cellular uptake.

176. Since claim 6 allows variations in the framework region, there is no guarantee such variations would not eliminate framework residues that have an impact on antigen binding. Further, I note that the ’386 Patent does not provide

any data indicating such framework variants still possess an ability to specifically bind the EC3 domain of hCDH6 as defined by SEQ ID NO: 4 and an ability to internalize that permits cellular uptake.

177. As with claims 3 and 4, claim 6 also fails to specify any common structural features required for the internalization function of the human or humanized antibodies and their functional fragments.

178. Claim 7 covers a genus of antibodies or their functional fragments by reference to the heavy chain and light chain variable region sequences of H01L02, H02L02, H02L03, and H04L02. However, it suffers the same defects as claims 3-6 by failing to specify any common structural features required for both binding and internalization functions of the human or humanized antibodies and their functional fragments.

179. Claim 8 covers a genus of functional fragments of antibodies and the antibodies have the heavy chain and light chain amino acid sequences of H01L02, H02L02, H02L03, or H04L02. Claim 9 covers a genus of functional fragments of antibodies and the antibodies have the heavy chain and light chain amino acid sequences of H01L02. Claim 10 covers a genus of functional fragments of antibodies and the antibodies have the heavy chain and light chain amino acid sequences of H02L02. Claim 11 covers a genus of functional fragments of antibodies and the antibodies have the heavy chain and light chain amino acid

sequences of H02L03. Claim 12 covers a genus of functional fragments of antibodies and the antibodies have the heavy chain and light chain amino acid sequences of H04L02.

180. I understand that the '386 Patent defines the term “functional fragment of an antibody” or “antigen-binding fragment of an antibody” as “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.” (Ex. 1001, 17:40-49.)

181. As defined, functional fragments of the claimed antibodies will retain binding activity against antigen, but do not need to retain any internalization activity (if any) of the antibodies. Therefore, in my view, claims 8-12 do not specify any common structural features encompassed by functional fragments that will ensure internalization of the functional fragments to occur. Indeed, the '386 Patent does not provide any data confirming internalization of any functional fragment of H01L02, H02L02, H02L03, or H04L02.

182. As discussed above, claims 8-12 also cover a large genus of antibodies and functional fragments that have various modifications. However,

they do not specify any common structural features containing any of the modifications that are required for the internalization function. Nor does the '386 Patent provide any data showing that the exemplary humanized antibodies or their functional fragments containing one or more modifications still possess an ability to internalize.

183. The claimed human or humanized antibodies and their functional fragments can have various modifications, so long as the amino acid sequences of the antibodies or their functional fragments remain unchanged. The '386 Patent describes a number of modifications that can be made to the antibodies or their functional fragments, including “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.” (Ex. 1001, 8:40-49.) The human or humanized antibodies and their functional fragments with these modifications represent a large genus of antibodies and functional fragments.

B. The '386 Patent Lack of Enablement for Any of Claims 1-18

184. I have been informed that a claimed invention satisfies the enablement requirement if the disclosure provided by the inventors, viewed in light of the general knowledge in the art at the time of the invention, would allow a skilled

artisan to make and use the full scope of the claimed invention without undue experimentation. I have also been informed that, when determining whether experimentation is undue, I should consider: (a) the breadth of the claims, (b) the nature of the claimed invention, (c) the state of the prior art, (d) the level of predictability or unpredictability of the art, (e) the knowledge of one of ordinary skill, (f) the amount of direction provided by the named inventor(s), (g) the presence or absence of working examples, and (h) the quantity of experimentation needed to make and use the claimed invention. I have considered these factors in reaching my conclusions.

185. In my view, the '386 Patent does not enable one of skill in the art to make and use the full scope of the claimed invention without undue experimentation. Even with today's advanced technologies, the claims are not enabled across their scope.

186. Claims 1-18 are extremely broad – they cover a vast genus of antibodies and a vast genus of functional fragments of the antibodies of any sequence, germline, isotypes, and subclasses. Regardless of whether the claims are limited to those antibodies that only bind hCDH6 EC3 and possess an ability to internalize that permits cellular uptake, the guidance in the '386 Patent is extremely limited. In fact, the '386 Patent does not even attempt to demonstrate identification or generation of any human anti-hCDH6 antibodies capable of

specifically binding to hCDH6 EC3 and internalizing into cells. Nor is there any demonstration for any functional fragment of anti-hCDH6 antibodies capable of specifically binding to hCDH6 EC3 and internalizing into cells.

187. 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 and generic instructions to identify any and all other antibodies or functional fragments with required functionality in binding to EC3 and internalization. No other specific information is provided

188. Even though the 115-amino acid sequence of SEQ ID NO: 4 encompasses a large number of epitopes, the '386 Patent only demonstrates the four exemplary humanized anti-CDH6 antibodies that have identical CDRs and bind to the same epitope. 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.

189. Importantly, as mentioned above, the '386 Patent did not even attempt to provide guidance as 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.)

190. Indeed, no correlation exists between the structure of the antibody and its ability to internalize. Even today, with advanced computer modeling, a skilled artisan could not design sequences of antibodies that internalize just by relying on their sequences, and instead the skilled artisan would have to rely on randomly screening millions of potential antibody sequences to evaluate their ability to internalize.

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

192. Therefore, the claims at most are an invitation to carry out a research plan that cannot be accomplished without undue experimentation.

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

193. Claims 1-18 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. They 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.

194. 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. 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.

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

195. While basic techniques for generating and screening antibodies existed by 2017, some aspects of the process were, and still largely are, unpredictable. Without trial and error, the skilled artisan could not predict which antibody sequences would bind hCDH6 EC3 and provide desired internalization function. Rather, undue burden exists to evaluate billions of different potential antibody sequences to identify those that specifically bind to the amino acid sequence shown of 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.

196. In addition, there is nothing in these claims that limits the various ways the skilled artisan 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 skilled artisan would have to resort to hybridoma or phage display technology to screen for literally billions of different antibodies. Even then, the skilled artisan would still have to undertake even more screening to determine whether the candidate antibodies possess the ability to internalize.

197. 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. This is in part because "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," as recognized by the '386 Patent. (Ex. 1001, 2:47-56.)

198. 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 desired binding and internalization functions. This represents a particularly undue burden in light of the limited and unpredictable state of the art for making and using antibodies and functional fragments of different sequences, structures, germlines, isotypes, and subtypes encompassed by the broadly worded claims.

3. The Amount of Direction or Guidance Provided

199. The '386 Patent provides no guidance on how to arrive at any 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, other than through trial and error generating antibodies by animal immunization and testing every potential sequence in diverse antibody libraries and its combinations with other sequences.

200. 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 comparison with the prior art antibody NOV0710. 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 desired 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.

201. 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 burden.

4. The Amount of Experimentation Required

202. Other than the four exemplary humanized antibodies described in Example 5 of the '386 Patent, no other examples or guiding principles are provided. For example, the '386 Patent does not provide any example 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 antibodies across the vast scope of claims 1-18 is left up to the skilled artisan.

203. 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 desired binding and internalization functionality represents an undue burden. 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 four rat anti-CDH6 antibodies, not to mention additional work required to obtain cDNAs of antibodies and 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. This undue amount of work is further required for functional fragments, since as discussed above, the '386 Patent cover a vast genus of functional fragments, the skilled artisan has to screen not just full antibodies, but any number of partial fragments that could bind and EC3 and internalize.

204. 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.

XI. CLAIMS 1, 5, 13-16, and 18 ARE ANTICIPATED BY PRIOR ART

205. I have been informed that I should evaluate the relevant literature published up to the claimed priority date of the application that became the '386 Patent. Before that date, other researchers had disclosed isolated 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. As explained below, it is my opinion that Novartis discloses all of the limitations of claims 1, 2, 5, 13-16, and 18 of the '386 Patent at the relevant time.

A. Claim 1

206. Independent claim 1 recites 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. SEQ ID NO: 4 recited contains 115 amino acids and is the amino acid sequence of hCDH6 EC3 (aa 269-383). (Ex. 1001, 19:62-65 and Table 1-1.)

207. 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 show 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, Figs. 1 and 2).

208. Among these NOV 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. (Ex. 1005, ¶¶[00397], [00399]-[00401], [00403].)

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

210. With regard to internalization, Novartis discloses all the NOV anti-hCDH6 antibodies as listed in Table 5, including NOV0710 and NOV0719, that possess an ability to internalize that permits cellular uptake. The 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.

211. Therefore, it is my opinion that independent claim 1 of the '386 Patent is anticipated by Novartis at least in view of the disclosed NOV anti-hCDH6 antibodies, such as NOV0710 and NOV0719.

B. Claim 5

212. Claim 5 depends from claim 1 and specifies “the antibody or the functional fragment of the antibody ... is humanized.” (Ex. 1001, 184:52-53.)

213. 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 show 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 and 7-8, Figs. 1 and 2.)

214. Therefore, it is my opinion that claim 5 of the '386 Patent is also anticipated by Novartis at least in view of the disclosed NOV anti-hCDH6 antibodies, such as NOV0710 and NOV0719.

C. Claim 13

215. Claim 13 depends from claim 1 and specifies “wherein the functional fragment is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv.” (Ex. 1001, 186:27-28.)

216. 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 also demonstrates generation and expression of soluble Fab fragments. (*Id.*, ¶[00351], [00181].)

217. Therefore, it is my opinion that claim 13 of the '386 Patent is also anticipated by Novartis.

D. Claim 14

218. Claim 14 depends from claim 1 and 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, 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.” (Ex. 1001, 186:30-40.)

219. Novartis discloses “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].)

220. Therefore, it is my opinion that claim 14 of the ’386 Patent is also anticipated by Novartis.

E. Claim 15

221. Claim 15 depends from claim 14 and further specifies “one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof.” (Ex. 1001, 186:41-43.)

222. Novartis discloses “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].) Such deletions would include

deletion of one or two amino acids from the carboxyl terminus of a heavy chain thereof.

223. Therefore, it is my opinion that claim 15 the '386 Patent is also anticipated by Novartis.

F. Claim 16

224. Claim 16 depends from claim 15 and further specifies “one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.” (Ex. 1001, 186:44-46.)

225. Novartis discloses “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].) Such deletions would include deletion of one or two amino acids each of the carboxyl termini of both of the heavy chains thereof.

226. Therefore, it is my opinion that claim 16 of the '386 Patent is also anticipated by Novartis.

G. Claim 18

227. Claim 18 depends from claim 1 and further specifies “sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity.” (Ex. 1001, 186:50-53.).

228. Novartis discloses “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].)

229. Novartis further discloses “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.” (*Id.*, ¶[00251].)

230. Therefore, it is my opinion that claim 18 of the '386 Patent is also anticipated by Novartis.

XII. CLAIMS 1, 5, AND 13-18 ARE OBVIOUS OVER THE PRIOR ART

231. As explained below, it is my opinion that Novartis discloses or suggests all of the limitations of claims 1, 5, 13-16, and 18 of the '386 Patent at the relevant time. In addition, Novartis in combination with Urano discloses or suggests all of the limitations of claim 17.

A. Claim 1

232. Independent claim 1 recites 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. SEQ ID NO: 4 recited contains 115 amino acids and is the amino acid sequence of hCDH6 EC3 (aa 269-383). (Ex. 1001, 19:62-65 and Table 1-1.)

233. 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 show 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, Figs. 1 and 2.)

234. Among these NOV 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. (Ex. 1005, ¶¶[00397], [00399]-[00401], [00403].)

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

236. With regard to internalization, Novartis discloses all the NOV anti-hCDH6 antibodies as listed in Table 5, including NOV0710 and NOV0719, that 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.

237. Therefore, it is my opinion that independent claim 1 of the '386 Patent is taught or suggested by Novartis at least in view of the disclosed NOV anti-hCDH6 antibodies, such as NOV0710 and NOV0719.

B. Claim 5

238. Claim 5 depends from claim 1 and specifies “the antibody or the functional fragment of the antibody ... is humanized.” (Ex. 1001, 184:52-53.)

239. 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 show 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 and 7-8, Figs. 1 and 2).

240. Therefore, it is my opinion that claim 5 of the '386 Patent is also taught or suggested by Novartis at least in view of the disclosed NOV anti-hCDH6 antibodies, such as NOV0710 and NOV0719.

C. Claim 13

241. Claim 13 depends from claim 1 and specifies “wherein the functional fragment is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv.” (Ex. 1001, 186:27-28.)

242. 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 also demonstrates generation and expression of soluble Fab fragments. (*Id.*, ¶[00351], [00181].)

243. Therefore, it is my opinion that claim 5 of the '386 Patent is also taught or suggested by Novartis.

D. Claim 14

244. Claim 14 depends from claim 1 and 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, 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.” (Ex. 1001, 186:30-40.)

245. Novartis discloses “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].)

246. Urano discloses “a modified form of the antibody or functional fragment thereof. The modified form of the antibody of the present invention, or the functional fragment thereof, means an antibody of the present invention, or a functional fragment thereof, provided with chemical or biological modification. The chemically modified form includes, for example, a form having an amino acid skeleton conjugated with a chemical moiety, and a form having a chemically modified N-linked or O-linked carbohydrate chain. The biologically modified form includes, for example, a form that has undergone 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), and a form containing a methionine residue added to the N-terminus by expression using prokaryotic host cells.” (Ex. 1006, ¶[0352].)

247. Urano discloses the advantages of some of the modifications. For example, the antibody-dependent cellular cytotoxic activity of the antibody or the functional fragment thereof may be enhanced by regulating the modification (glycosylation, defucosylation, etc.) of the sugar chain bound with the antibody or functional fragment. (Ex. 1006, ¶[0355].)

248. Sato discloses “an antibody modified after translation during expression in cells such as an antibody comprising a heavy chain lacking lysine of a C terminal, an antibody in which glutamine or glutamic acid of the N terminal of

the heavy chain is modified to pyroglutamic acid due to pyroglutamylation, and the like in addition to an antibody comprising a full length of heavy chain. Further, the antigen-binding fragment of the present invention includes an antigen-binding fragment modified after translation during expression in cells such as an antigen-binding fragment in which glutamine or glutamic acid of the N terminal of the heavy chain is modified to pyroglutamic acid due to pyroglutamylation.” (Ex. 1007, ¶[50].)

249. 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 the heavy chain or the light chain that 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, and a deletion of one or two amino acids from the carboxyl terminus.

250. In addition, in view of the advantages of some of the modifications described by Urano, a person of ordinary skill would also be 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 specified in the claim.

251. In view of the disclosures of Novartis and Sato, it would have been obvious for a person of ordinary skill 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, such as conversion of N-terminal glutamine or N-terminal glutamic acid to pyroglutamic acid.

252. Therefore, it is my opinion that claim 14 of the '386 Patent is also taught or suggested by Novartis, or by a combination of Novartis and Urano, or additionally and/or alternatively by a combination of Novartis and Sato.

E. Claim 15

253. Claim 15 depends from claim 14 and further specifies “one or two amino acids are deleted from the carboxyl terminus of a heavy chain thereof.” (Ex. 1001, 186:41-43.)

254. Novartis discloses “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].) Such deletions would include

deletion of one or two amino acids from the carboxyl terminus of a heavy chain thereof.

255. 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. For example, the heavy chain of an antibody produced by cultured mammalian cells is known to lack a lysine residue at the carboxy terminus.” (Ex. 1006, ¶[0302].)

256. In view of Novartis, and further in view of Urano, and/or Sato, it would have been obvious for a person of ordinary skill to generate a human or humanized monoclonal antibody or functional fragment thereof with deletion of one or two amino acids from the carboxyl terminus of a heavy chain thereof.

257. Therefore, it is my opinion that claim 15 of the '386 Patent is also taught or suggested by Novartis or by a combination of Novartis and Urano, or additionally and/or alternatively by a combination of Novartis, Urano, and Sato.

F. Claim 16

258. Claim 16 depends from claim 15 and further specifies “one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.” (Ex. 1001, 186:44-46.)

259. Novartis discloses “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].) Such deletions would include deletion of one or two amino acids each of the carboxyl termini of both of the heavy chains thereof.

260. 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. For example, the heavy chain of an antibody produced by cultured mammalian cells is known to lack a lysine residue at the carboxy terminus.” (Ex. 1006, ¶[0302].)

261. In view of Novartis, and further in view of Urano, and/or Sato, it would have been obvious for a person of ordinary skill to generate a human or humanized monoclonal antibody or functional fragment thereof with one amino acid is deleted from each of the carboxyl termini of both of the heavy chains thereof.

262. Therefore, it is my opinion that claim 16 of the '386 Patent is also taught or suggested by Novartis or by a combination of Novartis and Urano, or additionally and/or alternatively by a combination of Novartis, Urano, and Sato.

G. Claim 17

263. Claim 17 depends from claim 14 and further specifies “a proline residue at the carboxyl terminus of a heavy chain thereof is further amidated.” (Ex. 1001, 186:47-49.)

264. Novartis discloses “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].) Such deletions would include deletion of one or two amino acids each of the carboxyl termini of each or both of the heavy chains thereof.

265. 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. For example, the heavy chain of an antibody produced by cultured mammalian cells is known to lack a lysine residue at the carboxy terminus.” (Ex. 1006, ¶[0302].)

266. Urano further discloses “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.*)

267. In view of Novartis, and further in view of Urano, and/or Sato, 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.

268. Therefore, it is my opinion that claim 17 of the '386 Patent is also taught or suggested by Novartis and Urano, or additionally and/or alternatively by a combination of Novartis, Urano, and Sato.

H. Claim 18

269. Claim 18 depends from claim 1 and further specifies “sugar chain modification is regulated in order to enhance antibody-dependent cellular cytotoxic activity.” (Ex. 1001, 186:50-53.)

270. Novartis discloses “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].)

271. Novartis further discloses “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.” (*Id.*, ¶[00251].)

272. Therefore, it is my opinion that claim 18 of the '386 Patent is also taught or suggested by Novartis.

XIII. CLAIMS 1-5 AND 14-18 ARE PATENT INELIGIBLE

273. I was informed that the anti-CDH6 antibodies or their functional fragments claimed in the '386 Patent fall in the category of compositions of matter, and thus, the claims of the '386 Patent are directed to a statutory subject matter. I was asked to consider whether the claims of the '386 Patent cover a naturally occurring human anti-CDH6 antibody or an anti-CDH6 antibody that is not markedly different from a naturally occurring human anti-CDH6 antibody. In my view, at least claims 1-5 and 14-18 of the '386 Patent cover a naturally occurring human anti-CDH6 antibody or an antigen-binding fragment thereof or an anti-CDH6 antibody that does not have markedly different structural or functional characteristics from a naturally occurring human anti-CDH6 antibody.

274. Independent claim 1 of the '386 Patent claims a genus of human or humanized monoclonal antibodies and a genus of functional fragments of human or humanized monoclonal antibodies by their functions: (i) ability to specifically bind EC3 domain of hCDH6 as defined by SEQ ID NO: 4, and (ii) ability to

internalize that permits cellular uptake, without specifying any associated sequences or structural features. The breadth of claim 1 covers antibodies that bind to EC3 and internalize that are isolated from a human subject without any further modification. The human CDH6 protein is a tumor-associated antigen and therefore, in certain cancer patients, the human body will produce naturally occurring antibodies that bind to CDH6 (including its EC3 region) in cancer cells expressing this protein. (Ex. 1029 at 2.) 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. Thus, claim 1 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, *i.e.*, an ability to specifically bind hCDH6 EC3 defined by SEQ ID NO: 4 and an ability to internalize that permits cellular uptake.

275. 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. 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. 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.

276. Claim 3 covers a genus of antibodies or their functional fragments by reference to their 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 covers a genus of antibodies or their functional fragments by reference to six CDR sequences of four antibody clones, *i.e.*, rG019/chG019, rG055, rG056, and rG061. 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. 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.

277. Claim 5 specifies that the antibodies or their functional fragments are humanized. In my opinion, humanized antibodies are not markedly different from naturally occurring human antibodies. This is at least because 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. (Ex. 1035 at 323.) 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 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 that are not markedly different from naturally occurring human antibodies.

278. 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. It is known that 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. 1036 at 1-2.) In my opinion, for the same reasons discussed above for claim 1 or 2, 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.

279. I also considered if the claims include additional features that could add significantly more to the product of nature exception to transform the patent ineligible product of nature into a patent eligible invention. In my opinion, none of claims 1-5 and 14-18 adds additional features that are beyond well-understood, routine, conventional activity already engaged in by the scientific community to the product of nature. For example, as discussed in the sections above regarding anticipation and obviousness, at least the one or more features specified in claims 1, 5, and 13-18 are well-understood, routine, and conventional in the art.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on __June 16th, 2023_____.

**Stylianos
Bournazos** Digitally signed by
Stylianos Bournazos
Date: 2023.06.16
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Stylianos Bournazos, Ph.D.