

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SYNAFFIX B.V.,
Petitioner

v.

HANGZHOU DAC BIOTECH CO., LTD.,
Patent Owner

IPR2022-01531
Patent No 10,131,682

**DECLARATION OF DR. LAWRENCE NATHAN TUMEY
IN SUPPORT OF PATENT OWNER'S PRELIMINARY RESPONSE**

I, Lawrence Nathan Tumey, Ph.D., declare as follows:

I. INTRODUCTION

1. I have been retained by Quinn Emanuel Urquhart & Sullivan LLP on behalf of Patent Owner Hangzhou DAC Biotech Co., Ltd. (“DAC”) as an independent technical expert in the above-captioned proceeding concerning an *inter partes* review (“IPR”) petition (“Petition”) filed by SynAffix B.V. (“SynAffix” or “Petitioner”) against U.S. Patent No. 10,131,682 (the “’682 Patent”). I understand that SynAffix filed the IPR petition of claims 1–17, 20–21, 24–26, and 29–34 (“the challenged claims”) of the ’682 Patent, which also includes the Declaration of Dr. Ravi Chari.

2. I have been asked to provide certain opinions and information in support of arguments in the Patent Owner Preliminary Response (“POPR”), which I understand will be filed concomitantly with my Declaration. Specifically, I have been asked to analyze and explain the technical background of the ’682 Patent. I have also been asked to offer my opinions regarding the meaning of certain terms recited in the claims of the ’682 Patent, as these terms would be understood by a person of ordinary skill in the pertinent art (a “POSITA”) at the time of the invention, which I define below. I have also been asked to review the Declaration of Dr. Ravi Chari (“Chari Dec.”) (EX1003). Finally, I have been asked to analyze the following publications by Morales-Sanfrutos (EX1005), Straus (EX1006), Harris (EX1007),

Singh (EX1008), Snow (EX1010), and Bhakta (EX1011) and explain the disclosures therein.

3. Omission of a particular claim, limitation, or topic from my discussion should not be interpreted as agreement with arguments put forth in the Petition or by SynAffix's expert, Dr. Chari, unless I have explicitly stated this to be the case.

4. This Declaration is based on information currently available to me. I reserve the right to continue my investigation and analysis, which may include a review of documents and information not listed above, including any documents and information that may be submitted by Petitioner. I also reserve the right to expand or otherwise modify my opinions and conclusions as my investigation and study continues, and to supplement my opinions and conclusions in response to any additional information that becomes available to me. I also reserve the right to respond to any argument that Petitioner may advance in this proceeding.

5. I am being compensated for my time preparing this Declaration for this proceeding at a rate of \$350/hour. My compensation is in no way contingent on the substance of my opinions and testimony or the outcome of this proceeding or any other proceeding. I have no other interest in this proceeding.

II. QUALIFICATIONS

6. My qualifications and professional experience are described in my curriculum vitae, a copy of which is provided with this Declaration as EX.2002. The following is a summary of my qualifications and professional experience.

7. In 1997, I received a bachelor of science (B.S.) degree in chemistry from King University. Subsequently, I obtained my Ph.D. in chemistry from Duke University in 2001 where my research focused on the medicinal chemistry of LpxC inhibitors as antibacterial agents.

8. Following graduate school, I spent nearly 15 years in the pharmaceutical and biotechnology industry. From 2002 to 2005, I worked as a Research Scientist at Athersys where I designed and synthesized compounds that targeted and suppressed the activity of CRTH2 receptors expressed on certain immune cell populations for the treatment of asthma. I was the lead inventor on U.S. Patent No. 7,405,215 which claimed these compounds. I also designed and synthesized compounds that selectively increased the activity of 5HT_{2C} cell surface receptors for the treatment of obesity and related disorders. Additionally, I developed protein kinase inhibitor compounds for the treatment of certain autoimmune and inflammatory diseases, which is claimed in U.S. Patent No. 7,781,591, on which I am a named inventor.

9. From 2005 to 2017, I worked at Pfizer and led multiple drug-discovery programs, including the development of PKC-theta inhibitors for asthma, IRAK4 inhibitors for rheumatoid arthritis and antibody-drug-conjugates (ADCs) for the treatment of cancer. In particular, I supervised a team of conjugation and bioanalytical scientists to design and synthesize antibody-drug conjugates for use in oncology applications. The design and synthesis of specific cysteine-engineered antibody drug conjugates is claimed in U.S. Patent No. 11,364,303, on which I am a named inventor. Moreover, I directly prepared bioconjugates for *in vitro* and *in vivo* evaluation, optimized conjugation conditions in order to minimize aggregation and maximize drug-loading, and developed a variety of bioanalytical methods to assess the purity, identity, and stability of preclinical antibody-drug-conjugates in the Pfizer portfolio. My expertise further involved developing and optimizing HIC, SEC, reverse phase, and LCMS methods for protein analysis. I also designed and implemented protein purification strategies to remove aggregate, free drug, and under-loaded species as well as enhanced purification methods for scaleup campaigns to support exploratory toxicology studies. Finally, I oversaw the development of innovative conjugation solutions in order to optimize ADC drug loading, stability, and efficacy.

10. In 2017, I joined the faculty at Binghamton University. At Binghamton, I am currently an Assistant Graduate Director and Associate Professor

in the School of Pharmacy and Pharmaceutical Sciences where I lead a team of research scientists specializing in the application of antibody-drug conjugates (ADCs) and related modalities for the treatment of cancer and auto-immune disorder. My laboratory also investigates bioconjugate stability, ADC linker design and new modalities for targeted drug-delivery.

11. I possess over 30 years of expertise and experience that span the areas of organic chemistry, medicinal chemistry, targeted drug delivery, bioconjugate bioanalysis, ADC design, antibody metabolism, and site-specific conjugation chemistry. I further possess considerable expertise in analyzing chemical structures, including evaluating properties such as polarity, hydrophilicity, solubility, and chemical reactivity. I have extensive knowledge of functional groups employed in ADCs and can analyze conjugation sites and interaction of specific moieties, which facilitate designing linkers to improve overall ADC performance.

12. I have published across the aforementioned fields, with approximately 40 peer-reviewed publications in high-impact academic journals and have received over \$3 million in funding from various national, government, and non-profit agencies to support my research. I have served as the lead editor for a book entitled “Antibody-Drug-Conjugates: Methods and Protocols” by Springer Publishing (2020). I have also presented my work at various high-profile national and international conferences and symposia related to ADCs.

13. I am currently on the scientific advisory board of various companies, including Araris Biotech and Manhattan Biosolution, and have served as a technical consultant for numerous pharmaceutical companies, law firms, and financial firms.

III. MATERIALS CONSIDERED

14. The opinions contained in this Declaration are based on the documents I reviewed, as well as my education, years of professional experience, and knowledge. In forming my opinions expressed in this Declaration, I have reviewed and considered the '682 Patent as a whole, including the specification and accompanying figures. I have also considered the language of the patent's claims, as those terms would have been understood by a person having ordinary skill in the relevant field at least at the time of the '682 Patent's earliest possible priority date, November 24, 2012. I have also reviewed the prosecution (the "file history") of the '682 Patent.

15. In forming my opinions, I have also reviewed technical literature relevant to the field of the '682 Patent. These materials are attached as Exhibits to my Declaration. Additionally, I may discuss my own work, teachings, and knowledge of the state of the art in the relevant time period. I may rely on handbooks, textbooks, technical literature, and the like to demonstrate the state of the art in the relevant period and the evolution of relevant technologies.

16. Additionally, in preparing this Declaration, I have relied on my personal knowledge, education, training, and professional experience in order to form my opinions concerning the '682 Patent, including my experience in researching, studying, developing, or using ADC and linker technology. I have also relied upon my expertise and experience as stated herein in the fields of organic chemistry, medicinal chemistry, targeted drug delivery, bioconjugate bioanalysis, ADC design, antibody metabolism, and site-specific conjugation chemistry. I have also relied on my underlying knowledge of the principles of chemistry, biochemistry, and physiology, and my extensive personal research and experimental work. My opinions and conclusions are supported by established and accepted principles and practices in the fields of organic chemistry, medicinal chemistry, targeted drug delivery, bioconjugate bioanalysis, ADC design, antibody metabolism, and site-specific conjugation chemistry.

IV. LEGAL STANDARDS

17. In this section I describe my understanding of certain legal principles that I have relied upon in forming my opinions set forth in this Declaration.

18. I have been informed of these legal standards by counsel for DAC. I am not an attorney and I have not researched patent law. I am relying only on DAC's attorneys relating to these legal standards.

A. Person of Ordinary Skill in the Art

19. I am informed that patent validity is determined from the perspective of a person of ordinary skill in the pertinent art at the time of the invention (“POSITA”). I understand that a POSITA is a hypothetical person who is presumed to be aware of all pertinent art, conventional wisdom in the art, and is a person of ordinary creativity—not an automaton.

20. In deciding the level of ordinary skill in the art, I am informed that the following factors may be considered: the levels of education and experience of persons working in the field; the types of problems encountered in the field; and the sophistication of the technology.

B. Claim Construction

21. I am informed that a patent may include two types of claims, independent claims and dependent claims. An independent claim stands alone and includes only the limitations it recites. A dependent claim can depend from an independent claim or another dependent claim. I am informed that a dependent claim includes all the limitations that it recites, in addition to the limitations recited in the claim from which it depends.

22. I understand that patent claim terms can be interpreted, or “construed.” I understand that, in construing a claim, the words of a patent claim are given their plain meaning, as a POSITA would understand them at the time of the invention, in view of the patent and file history (which I understand is considered “intrinsic”

evidence), unless their meaning is defined or disclaimed. I am informed that dictionaries, treatises, and other “extrinsic” sources of evidence may assist in determining the plain meaning of a term, but they cannot override a meaning that is otherwise unambiguous based on the intrinsic evidence.

23. I have been informed by DAC’s counsel that claim construction is a matter of law for the arbiter of law to decide. I am informed that, in an *inter partes* review, the Patent Trial and Appeal Board interprets claims in the same way as a district court would. Likewise, I understand that a person of ordinary skill in the art interprets claims in the same way in both types of proceedings.

24. I reserve my right to amend or alter my analysis and opinions in view of any claim constructions adopted by the arbiter of law.

V. PERSON OF ORDINARY SKILL IN THE ART

25. For purposes of this Declaration, I have been asked to apply the following definition of a person of ordinary skill in the art (“POSITA”), proposed by SynAffix and Dr. Chari, with respect to the ’682 Patent as of November 24, 2012. SynAffix contends that a POSITA would have had highly specialized knowledge in the field of linkers and conjugates for biologically-active molecules, which would entail (1) a PhD degree in organic chemistry, biochemistry, medicinal chemistry and/or pharmacology, along with 1-2 years of relevant applied research and/or industry experience in the field of linkers and conjugates for biologically-active

molecules or (2) alternatively, a POSITA would have had a Masters or Bachelors degree in one of these fields with, respectively, at least 3-5 or 5-7 years work experience. Petition at 18-19.

26. By applying the above description of a POSITA, I am not implying agreement with the proposed POSITA at all times moving forward. I reserve the right to supplement my opinion should SynAffix amend its proposed definition. I understand that DAC reserves the right to further address SynAffix's definition of a POSITA if trial is instituted.

27. All of my opinions in this Declaration are from the perspective of a POSITA, as defined above. At the relevant time (November 24, 2012), I possessed at least the qualifications of the POSITA as defined above.

VI. TECHNOLOGY OVERVIEW

28. I have been asked to review the state of the relevant art as of November 24, 2012, and to provide a background of the relevant technology of the invention.

A. Targeted Drug Delivery for Cancer Therapy

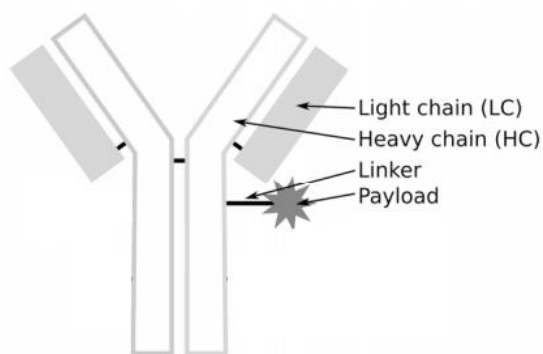
29. Delivery of an effective dose of a therapeutic agent to specific tissue and cell types is of paramount importance for efficacy in disease treatment, particularly in the context of cancer. Cancer is characterized by the continual unregulated proliferation of cells that invade normal tissues and organs and

eventually spread throughout the body. The majority of therapies rely on small molecule drugs to eradicate the cancer cells, called chemotherapy. EX.2003 at 409-410. Despite its widespread usage, chemotherapy is limited by undesired side effects, primarily due to non-specific action on cells beyond the tumor and its environment, resulting in systemic toxicity and a narrow therapeutic window. *Id.*

30. To avoid damaging normal tissues, scientists have endeavored to target cancer selectively. EX.2004 at 1191. To this end, certain cancer cells can be identified by unique markers on their surfaces that distinguish them from surrounding tissues. EX.2005 at 2528. These markers are called “cell surface antigens.” EX.2006 at 397-398. Scientists can design antibodies that bind to these cell surface antigens. *Id.*

31. These cancer-specific antibodies can be used as targeted delivery agents for chemotherapies, including for highly toxic drugs. EX.2005 at 2528. In particular, these antibodies can be used to form a therapeutic construct called an antibody-drug conjugate (“ADC”). *Id.* As shown in Fig. 1 below, ADCs typically consist of three components: (1) an antibody responsible for the selective recognition and binding to a cell surface antigen, (2) a drug responsible for inducing cancer cell death (sometimes called a “payload”), and (3) the linker that physically connects the antibody and payload. EX.2007 at 5.

Fig. 1: Antibody-Drug Conjugate Showing Major Components



32. Because ADCs selectively recognize cancer cells, ADCs allow highly potent delivery of a toxic drug payload directly to a target with minimal off-target toxicity. *Id.* Binding of the ADC to a cell-surface antigen initiates internalization of the ADC into the cell, whereupon degradation of the ADC results in release of the payload in a biologically active form, typically leading to the death of the cancer cell. EX.2005 at 2528. The amount of the payload within a cell is determined in part by the number of surface antigens per cell as well as the number of drug payload molecules per ADC (called drug-antibody ratio, DAR). EX.2008 at 154, 163.

33. Designing an ADC is a complex process both in synthesis and downstream performance. EX.2007 at 5. ADC design typically involves the assessment of multiple criteria, including the particular antibody to be used, where and how to attach the linker to the antibody, the linker structure to use to connect the antibody to the payload, impact of the linker structure on ADC stability and drug release, how many drug molecules to attach per antibody, how to connect the linker

and the payload, and selection of the optimal drug payload to achieve therapeutic efficacy. EX.2008 at 154. The major structural components (antibody, payload, and linker) are discussed in turn below.

1. Antibody

34. Proteins, such as antibodies, are an attractive targeting modality to facilitate cancer treatment. When compared to traditional small molecule drugs, ADC therapies offer a number of advantages including selectivity and favorable therapeutic windows. EX.2004 at 1191-92. However, due to their reliance on three dimensional tertiary and quaternary structure for activity, proteins are often sensitive to a range of external stressors including temperature, pH change, light, and agitation which can lead to irreversible degradation or aggregation. EX.2009 at 689. Furthermore, after administration, a number of *in vivo* clearance mechanisms exist such as the immune reactions, protease cleavage, and renal filtration that can limit their desired effect. *Id.* at 694. As a means to mitigate these challenges, polymeric linker structures can be used to stabilize proteins against both external stressors and *in vivo* clearance mechanisms. *Id.* at 701.

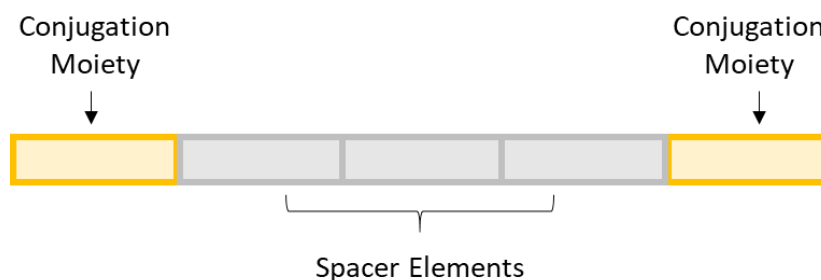
2. Drug

35. The drug payload component of ADC generally exhibits cytotoxic or cytostatic effects, possesses a well-defined target and action mechanism, and contains a chemical attachment site for conjugation to the linker. Cytotoxic drugs

are highly potent agents used to kill cancer cells usually by disrupting microtubule assembly to inhibit cell division or inducing DNA damage that triggers cell death. EX.2006 at 402-404. The repertoire of drugs typically employed in ADCs for chemotherapy fall into different classes based on their mechanism of action, some of which include microtubule inhibitors (*e.g.*, auristatins, maytansinoids, tubulysins), and DNA damaging drugs (*e.g.*, pyrrolobenzodiazepines, indolinobenzodiazepine, camptothecin). *Id.* Auristatins and maytansinoids are frequently used for ADC development. *Id.* at 397.

3. Linker Structure

36. The linker component of an ADC connects the antibody to the cytotoxic payload via covalent conjugation. EX.2008 at 162. To achieve this goal, linkers have two discrete components, which are referred to as “conjugation moieties” and “spacer elements.” I summarize these structures in an exemplary graphic below.



37. The term “conjugation moiety” is an art-accepted term to describe an ADC structural element. For example:

“New conjugation methods are most needed to conjugate a wide variety of targeting small molecules and peptidomimetic compounds. Here, we exploited a keto-oxime method for conjugation of protease susceptible linkers to an antibody. This modified method involves two steps: (i) introduction of methyl ketone linkers (referred to as linker moiety) to the primary amines present in the antibody and (ii) conjugation of ketone linkers to aminoxy functional group present in the conjugated moiety (referred to as functional moiety). We have optimized this conjugation method and shown that ~10 functional moieties can be conjugated to antibody. Conjugation was verified by MALDITOF MS and Western blot analysis. The acidic pH conditions used in this method did not change the immune reactivity of the Ab. In addition, in Vitro protease susceptibility assay was performed to validate this method for prodrug release assay as well as to remove excess radioimmune conjugates from circulation. This orthogonal method is compatible with peptides containing a thiol, amino, or carboxyl groups in the ***conjugation moiety***.”

EX.2010 at 1313 (emphasis added).

38. The term “spacer element” (or simply “spacer”) is also art-accepted terms to describe structural features of linkages. For example:

Our goal was to modify the β -glucuronide linker to contain a dimethylethylene diamine (DMED) self-immolative ***spacer*** (12) for stable linkage and facile release of 3 [*psymberin, a drug*]. Drug release would involve enzymatic deglucuronidation, 1,6-elimination, decarboxylation, and cyclization of the DMED carbamate to liberate free phenol (Scheme 1).

EX.2011 at 277 (emphasis added).

39. As a POSITA would understand, “conjugation moieties” have different structural and functional roles in the linker than “spacers.” Below, I provide an overview of the typical roles of these two structures.

(a) Conjugation Moieties

40. Conjugation moieties are reactive sites on the two terminal ends of the linker that attach to a reactive site on the antibody and a reactive site on the payload, respectively. Accordingly, a conjugation moiety requires structures that enable the formation of a covalent bond. EX.2012 at 523. This is sometimes described as “functional reactivity.” Only functional groups that possess this reactivity on the ends of the linker by facilitating the flow of electrons to or from the antibody and drug can participate in the formation of a new covalent bond with specific functional groups present on the antibody and drug, respectively. *Id.* Generally, this requires the conjugation moiety to be electrophilic (electron accepting) in nature and the functional group on the antibody or drug to be nucleophilic (electron donor) to drive the conjugation reaction and form a covalent bond. *Id.* at 489. The absence of conjugation moiety means that a covalent bond will not form and the linker will not attach to the antibody or drug, respectively.

41. Certain types of conjugation moieties were long known in the art such as N-hydroxysuccinimide esters, maleimides, and haloacetates. EX.2013 at 305,

307-08; EX.2014 at 363. N-hydroxysuccinimide esters are commonly used as conjugation moieties to react with amine functional groups on lysine residues of an antibody. EX.2013 at 305. For conjugation to cysteine residues on an antibody, a thiol-reactive maleimide or a bromoacetamide is typically employed as a conjugation moiety. EX.2013 at 308; EX.2015 at 7064. As I discuss further below, another conjugation moiety is vinyl sulfone. EX.2013 at 305.

42. The antibody component of an ADC may be attached to the linker in a variety of ways. Importantly, the conjugation moiety that binds an antibody must have a structure that will enable it to react with the intended portion of the antibody. EX.2014 at 362-63. In the case of native (non-engineered) antibodies, endogenous amino acids such as lysine and cysteines serve as attractive attachment sites. *Id.* Most ADCs exploit the presence of lysine and cysteine residues as the junction sites of the antibody. *Id.* The nucleophilic amine group of lysine and thiol of cysteine are typically used for the chemical conjugation of the antibody-linker, which, in turn, is modified with an electrophilic conjugation moiety. EX.2015 at 7069.

43. To increase the site specificity of ADC conjugation, antibodies can be engineered to introduce non-native amino acid sequences. For example, cysteine engineered antibodies utilize engineered (non-natural) reactive cysteines as attachment sites for the linker. EX.2016 at 925. These engineered cysteine mutations are designed to facilitate functionalization of the antibody with cytotoxic

payloads while maintaining antibody stability and binding affinity, and minimizing the ADC aggregation. *Id.* at 925-26.

(b) Spacer Elements

44. Spacer design depends on the developer's goal for the ADC. Spacer elements stabilize the ADC by offsetting steric issues created by bulky payloads. EX.2012 at 523. For example, polyethylene glycol (PEG) is often integrated into ADCs as a spacer element on the linker because of its inert, biocompatible nature. *Id.*

45. Spacer elements can contribute to the chemical and physical stability of the overall ADC within the bloodstream and allow for rapid release of the payload at the target site after cellular internalization. EX.2007 at 5. For example, spacers can also be designed to allow the linker to be susceptible to cleavage, which is desirable for releasing the drug inside the cancer cell. *Id.*

46. Generally, linkers fall into two categories based on the composition of the spacer elements: cleavable linkers and non-cleavable linkers. *Id.* at 6, 9. Cleavable linkers are stable in blood circulation for a long time and efficiently release their payload in the tumor microenvironment. *Id.* at 6. ADCs containing chemically labile linkers, including acid-cleavable spacer elements and reducible spacer elements, take advantage of the differential properties between plasma and the cytoplasmic compartments to release the payload. *Id.* at 6-8. However,

chemically labile linkers often have limited plasma stability, thereby leading to premature drug release. *Id.* As an alternative strategy, enzyme-cleavable spacer elements may be incorporated into the linker that take advantage of the high concentration of unique hydrolytic enzymes in cellular compartments to degrade peptides and carbohydrates. *Id.* at 8-9. Another class of cleavable linkers include those with peptide-based spacers. Valine–citrulline (Val–Cit), phenylalanine–lysine (Phe–Lys), and valine–alanine (Val–Ala) dipeptide are common spacer elements that utilize an intracellular protease, such as Cathepsin B, which recognizes and cleaves a dipeptide bond, thus leading to the release of the cytotoxic drugs. *Id.*

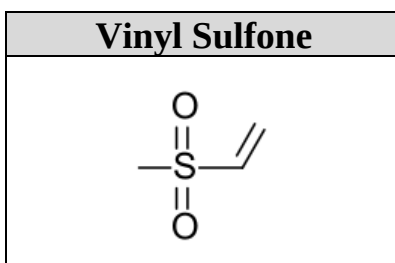
47. In contrast, non-cleavable linkers, such as thioether or maleimidocaproyl, consist of stable bonds among the spacer elements that prevent proteolytic cleavage and ensure greater plasma stability than their cleavable counterparts. EX.2017 at 424, 426. ADCs containing this type of linker depend on the complete intracellular enzymatic degradation of the antibody to release payloads after internalization, resulting in the simultaneous detachment of the linker. *Id.* at 424.

48. Designing a spacer, including the length, geometry, and composition, is a complex process due to multifactorial considerations associated with providing the critical and “sophisticated function” of that is “required” of ADCs (i.e. providing high therapeutic efficacy). EX.2004 at 1197. Certain contemplations for spacer

function and structure include, for example, reducing the potential for immunogenicity, avoiding interference with both the antibody function and drug function, providing stability during storage and in blood during treatment, preventing rapid clearance from the body, and enabling separation of the drug from the antibody after internalization in the target cell. *Id.*; EX.2009 at 700; EX.2014 at 362l. These competing criteria are difficult to address simultaneously as improving one function of the spacer through its structure may result in poor performance in other aspects. EX.2007 at 13.

(c) Vinyl Sulfone as a Conjugation Moiety

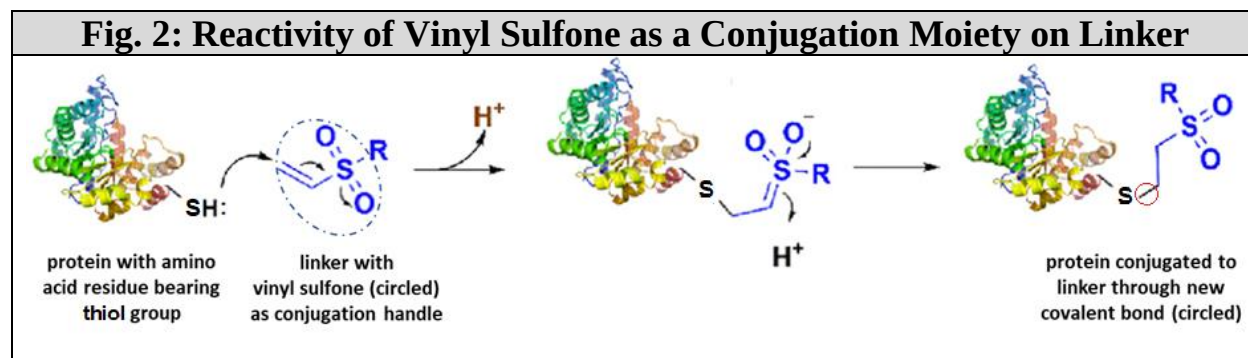
49. The functional group vinyl sulfone ($-\text{CH}_2=\text{CH}_2-\text{SO}_2-$) as shown in the graphic below has long been used in the art as a conjugation moiety. EX.2018 at 111, 113.



50. The entirety of the vinyl sulfone functional group acts as a conjugation moiety because the whole structure is necessary for the group to react with endogenous amino acids on a protein or protein fragment. EX.2012 at 488-89. I explain mechanisms underlying this reactivity in greater detail below.

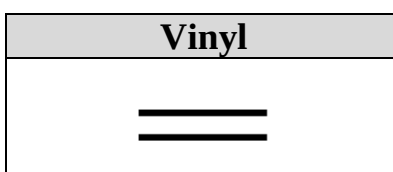
51. Vinyl sulfone is a functional group composed of a vinyl substituent and a sulfonyl (also called sulfone) substituent directly bonded to each other, which has unique properties that cannot be ascribed to its vinyl or sulfonyl components alone. EX.2013 at 303-307. Here, an electron withdrawing substituent, sulfonyl, is directly bonded to vinyl without any intervening atoms, facilitating the flow of electrons and enabling the vinyl sulfone moiety as a whole to serve as a conjugation moiety. *Id.* I have illustrated the underlying mechanism (sometimes referred to as Michael addition) in Figure 2 below. EX.2012 at 488-89. Here, as an electron withdrawing group, the sulfonyl pulls electrons away from the vinyl group towards its oxygen atoms, leaving the vinyl slightly destabilized and attracted to a nucleophilic substituent (electron donor) that can contribute electrons to fill this void, such as an endogenous amino acid residue bearing an amine or thiol group. *Id.* at 488-89, 523. Thus, when a protein undergoes a reaction with a linker bearing vinyl sulfone as a conjugation moiety, the electrons from nucleophilic group on the protein will be attracted to the destabilized vinyl and facilitate the conversion of the vinyl (C=C) into an ethyl (C-C), thereby creating a new covalent bond between the terminal carbon on the linker and the nucleophilic group on the protein. *Id.* It is important to reiterate that vinyl sulfone as a whole is a conjugation moiety because it is specifically reactive with endogenous amino acids on a protein or protein fragment. As explained in the next section, if the vinyl is not directly bonded to a strong

electron withdrawing group, such as sulfonyl, the vinyl is not reactive as a conjugation moiety. *Id.*



(d) Vinyl Alone Is Non-Reactive as a Conjugation Moiety to Attach A Linker to a Protein

52. A vinyl group ($\text{CH}_2=\text{CH}_2$) is a carbon sharing a double bond with another carbon ($\text{C}=\text{C}$) as shown in the graphic below.



53. Vinyl is energetically very stable due to the arrangement of the electrons within the double bond and is considered non-reactive with any amino acid residue on a protein. EX.2012 at 488-89; EX.2019 at 933. Even in the presence of a protein with a thiol group (see figure above), the double bonded carbons in the non-destabilized vinyl group will preferentially remain in this energetically stable configuration and, therefore, a new bond will not form between the linker and the protein. For this reason, vinyl alone cannot be a conjugation moiety. EX.2012 at 491. In other words, vinyl alone lacks the reactive functionality to be a conjugation

moiety because it is non-reactive with an amine substituent, a thiol substituent, or a hydroxyl substituent found in amino acids of a protein or protein fragment. *Id.* at 488-89, 491.

VII. OVERVIEW OF THE ASSERTED PRIOR ART REFERENCES

A. Morales-Sanfrutos (EX1005)

54. Morales-Sanfrutos (EX1005) is a peer-reviewed article published in 2010 in the *Journal of Organic Chemistry* and titled “Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins.” In my opinion, Morales-Sanfrutos is not in the field of therapeutic protein-drug conjugates. For example, the reference does not disclose antibody-drug conjugates. Morales-Sanfrutos also lacks disclosure of cytotoxic drugs, and particularly, does not describe a functional group capable of attachment to a cytotoxic drug (or drugs more broadly). Instead, Morales-Sanfrutos concerns a reporter system, which is specifically used to observe the activity of biomolecules and does not disclose any therapeutic system.

55. Morales-Sanfrutos discloses that attaching multiple labels onto a biomolecule to monitor its *in vitro* activity is generally a sequential process limited by chemical reaction, stoichiometry, and degradation concerns. *Id.* at 4040. A fluorophore and biotin are two different types of labels and are “among the tags most commonly used in *omic* sciences.” *Id.* Biotin, in particular, is “widely used to mediate between a recognition system (*e.g.*, antibody antigen or lectin carbohydrate)

and a reporter group (*e.g.* enzymatic activity of fluorescence).” *Id.* Morales-Sanfrutos discloses the synthesis of a bifunctional tagging compound having biotin (affinity tag) and a fluorophore (fluorescent tag). EX1005 at 4039.

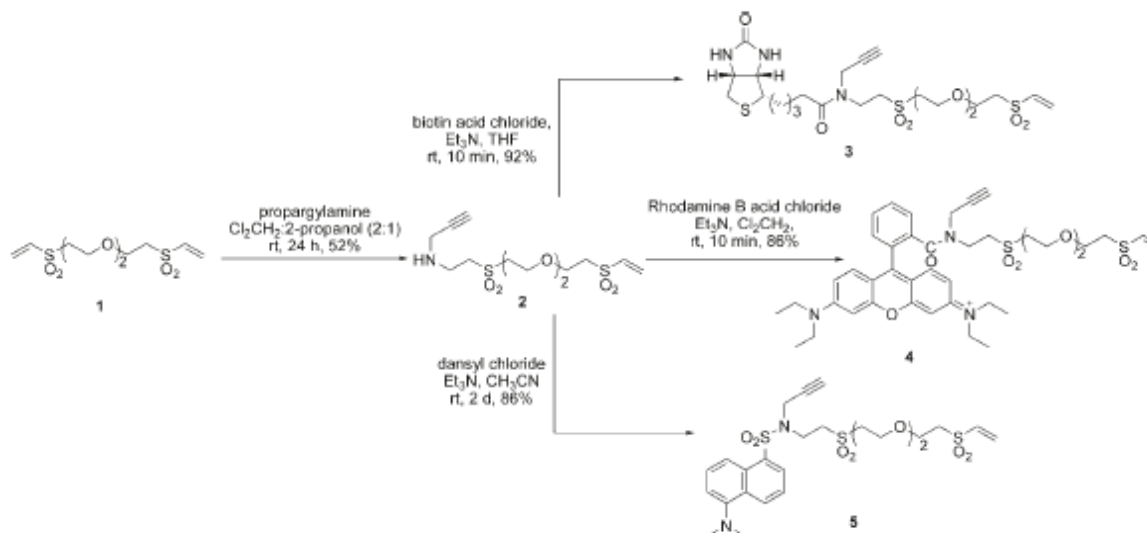
56. Morales-Sanfrutos further discloses conjugation of the disclosed bifunctional tagging compounds to horse radish peroxidase (HRP). According to Morales-Sanfrutos, “because [of] its biotechnological relevance (HRP has been coupled to other molecules to use the peroxidase activity as a reporter).” *Id.* at 4041. Indeed, “[f]or the particular case of HRP, the conjugation yields a dual reporter group (fluorescence and peroxidase activity) that can be coupled to any recognition system via biotin avidin affinity.” *Id.* at 4044.

57. Morales-Sanfrutos uses a vinyl sulfone ($-\text{CH}_2=\text{CH}_2-\text{SO}_2-$) chemistry in the context of synthesizing bifunctional tagging compounds as shown in Fig. 3 below. The reference discloses a bis vinyl sulfone structure bearing two vinyl sulfone groups (compound 1) undergoes reaction with propargylamine to form a new structure (compound 2) having three functional groups: a terminal alkynyl ($\text{C}\equiv\text{C}$), an amine, and a terminal vinyl sulfone. *Id.* The amine group is then reacted with a first functional tag (forming compounds 3, 4, 5) and the alkynyl group is subsequently reacted with a second functional tag (forming compounds 9, 10, 11). *Id.* Morales-Sanfrutos discloses that the vinyl sulfone group (not vinyl alone) possesses a broad reactivity as it is reactive with amine, thiol, and imidazole groups

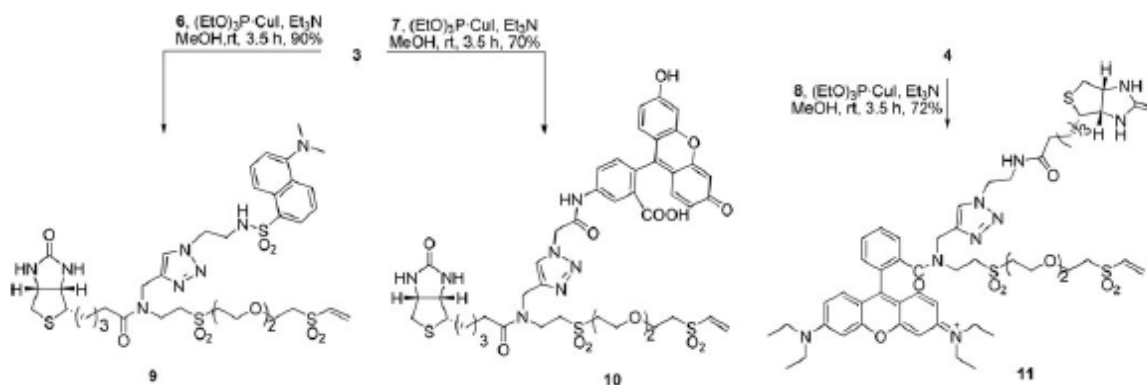
naturally present in proteins. *Id.* at 4044. Morales-Sanfrutos discloses the vinyl sulfone on compound 11, which is already tagged with a rhodamine label and a biotin label, undergoes reaction with HRP via vinyl sulfone to form a new reporter structure that is fluorescent (due to rhodamine), recognizable by avidin, and possesses peroxidase activity. *Id.* For example, Morales-Sanfrutos specifically discloses, “Labeling of HRP with Vinyl Sulfone Based BTSAP Reagents 9 11 and 17. HRP ... was incubated with vinyl sulfone derivatized bifunctional tags ...The resulting labeled proteins (... HRP-11, ...).” *Id.* at 4046. Morales-Sanfrutos also discloses PEG (CH₂CH₂O) groups are spacer elements in these compounds while phosphate-based or sulfur-based moieties are not disclosed as spacers. *See supra* Section VI.A.3.

Fig. 3: Synthesis of Morales-Sanfrutos' Bifunctional Tagging Compounds

SCHEME 1. Synthesis of Alkyne Vinyl Sulfone Derivatized Tags (AVST) 3-5



SCHEME 2. Synthesis of Vinyl Sulfone Bifunctional Tag Single-Attachment-Point Reagents (BTSAP)



58. Further, Morales-Sanfrutos does not disclose binding of any of its compounds to a cell or a functional group capable of attachment to a cell-binding agent. Additionally, Morales-Sanfrutos does not expressly or inherently¹ disclose a “cell-binding agent” as I understand that term in the context of the ’682 Patent (see Section IX.D). In my experience, HRP is not a known cell-binding agent or used as a cell-binding agent. HRP is an enzyme that catalyzes the oxidation of certain organic substrates by hydrogen peroxide and is widely utilized in cell-free biochemistry assays (*e.g.*, western blotting, ELISA) to detect the presence of a specific protein in a solubilized cell lysate. EX.2020 at 6.2.1. Thus, cell-binding is not an intrinsic property of HRP.

B. Straus (EX1006)

59. Straus (EX1006) is a journal article published in July 1986 in *Histochemistry* titled, “Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells.” Straus has only been cited 14 times since its publication more than 40 years ago. EX.2021 at 1-3. Notably, two of these 14 references are “self-citations” by the author of the original article. *Id.* Moreover, only two of the 14 references were published in the past 20 years. *Id.* Accordingly, Straus’ disclosures about HRP having purported cell-binding activity

¹ I understand from counsel that inherency means an implicit teaching that is necessarily true based on the express disclosure and cannot be established by probabilities or possibilities.

are not mainstream, well-known, or relied upon. HRP is routinely used in cell-free assays, usually as a reporter to detect the presence of a protein. EX.2020 at 6.2.1. In my opinion, Straus is not in the field of therapeutic protein-drug conjugates. For example, Straus does not disclose targeted therapeutic cell-binding agents, such as a cancer-specific antibody.

60. From my review of Dr. Chari's declaration, I see that he says "Straus discloses that horseradish peroxidase (HRP) enzyme **may** bind to the surface of a variety of cells" (emphasis added). EX1003 at 36. Thus, he does not opine that HRP necessarily binds to cell surfaces. Dr. Chari's statement is consistent with my review of Straus. Specifically, Straus does not show that HRP necessarily has cell-binding capabilities, or that such properties are inherent to HRP. In particular, Straus does not show that HRP necessarily or inherently binds to any particular kind of cell in the body (*in vivo*)—*e.g.*, cells that could be therapeutically targeted with a bioconjugate, such as an ADC.

61. Straus states that "binding sites for HRP with unusual properties were detected at the surface of cultured and isolated cells." EX1006 at 277. However, Straus does not identify any specific structure that acts as a cell surface binding partner to HRP. The reference discloses that "the possibility may be considered" that HRP binds to a glycosyltransferase (a surface protein found in most cell types) but also states that such binding is inhibited by compounds containing carbohydrates

(*e.g.*, UDP, CDP, GTP, NAD, and ribose 5-phosphate), which are all present *in vivo*. *Id.* at 284. Straus also notes that calcium is a separate component that plays a role in binding of HRP to the cell surface of its tested cell lines, indicating that HRP lacks cell-binding functionality when calcium is absent. *Id.* at 282-284. Straus also describes various caveats of its study, including artifacts, which further emphasize the uncertainty of any purported conclusions and indicate that, in fact, HRP's ability to bind cells is atypical or poorly characterized.

62. Notably, Straus only examined laboratory-adapted transformed and immortalized cell lines from mouse, rat, hamster, and human lineages, which have been manipulated to proliferate indefinitely to enabling long-term culturing and, thus, largely do not resemble their *in vivo* counterparts, particularly on the cell surface. *Id.* at 277-278. Straus does not convey that cell-binding is a necessary or inherent feature of HRP.

C. Harris (EX1007)

63. Harris (EX1007) is an International Patent Publication with a filing date of November 14, 1994 titled "Water Soluble Active Sulfones of Poly(Ethylene Glycol)." In my opinion, Harris is not in the field of therapeutic protein-drug conjugates. Harris only broadly describes pharmaceuticals stating that "almost any substance could be modified" (EX1007:1:2-6), but does not specifically disclose

conjugating a drug to a protein or antibody to selectively target and treat a specific cell population (*e.g.*, targeting and inducing cancer cell death).

64. Harris discloses a poly(ethylene glycol) (PEG) derivative compound with a vinyl sulfone or haloethyl sulfone moiety that selectively attaches to thiol moieties on molecules and surfaces as well as methods for synthesizing the PEG derivative compound and for preparing conjugates. Harris discloses, “The invention provides ... poly(ethylene glycol) (“PEG”) polymers ... having one or more active sulfone moieties ... [which] are highly selective for coupling with thiol moieties ... on molecules and on surfaces.” EX1007, 6:8-14. Harris does not disclose vinyl alone as having this reactivity. Specifically, Harris discloses water soluble and hydrolytically stable derivatives of PEG polymers have one or more active vinyl sulfone or haloethyl sulfone moieties. *Id.* at 6:8-15. The sulfone moieties are highly selective for coupling with thiol moieties compared to amino moieties. *Id.* Harris discloses preparing a conjugate with a PEG derivative compound having an active sulfone moiety, such as a vinyl sulfone. *Id.* at 9:12-14. Harris further discloses that PEG vinyl sulfone is stable, thiol-selective, and can form hydrolytically stable linkages. *Id.* at 14:26-28.

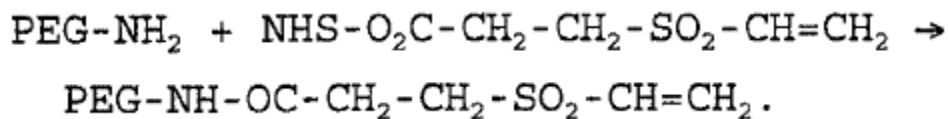
65. Harris discloses PEG groups as spacer element and that PEG is used in biological applications due to its “highly desirable” properties. *Id.* at 11:25-27. Specifically, PEG is “clear, colorless, odorless, soluble in water, stable to heat, inert

to many chemical agents, does not hydrolyze or deteriorate, and is nontoxic.” *Id.* at 11:28-31. Additionally, PEG is not considered immunogenic as it “does not tend to produce an immune response in the body.” *Id.* at 11:35-36. Harris discloses that when attached to a moiety having “some desirable function in the body,” PEG tends to mask the moiety and reduce the potential immune response. *Id.* at 11:37-12:3.

66. Harris discloses synthesis of a sulfone-activated PEG derivative, which “has the basic structure: $R-(OCH_2CH_2)_n-Y$.” *Id.* at 19:10-12. Here, “Y represents $SO_2-CH=CH_2$ or $SO_2-CH_2-CH_2-X$ where X is a halogen” and R may be the same or different than Y. *Id.* at 19:24-27. Specifically, “R can be H-, H_3C- , $CH_2=CH-SO_2-$, $Cl-CH_2-CH_2-SO_2-$, or a polymer activating group other than $CH_2=CH-SO_2-$, $Cl-CH_2-CH_2-SO_2-$.” *Id.* at 19:27-29. Finally, “n” can be a value from about 5 to 3,000. Harris discloses that PEG vinyl sulfone is stable, and that it can form thiol-selective and hydrolytically stable linkages. *Id.* at 14:26-27.

67. Harris discloses synthesis of another PEG derivative, called an amino activated PEG. An amino activated PEG ($PEG-NH_2$) is reacted with a small molecule that has a succinimidyl active ester moiety $NHS-O_2C-$ at one terminus and a vinyl sulfone moiety at the other terminus. *Id.* at 15-24. As shown in Fig. 4 below, the amino activated PEG forms a stable linkage with the succinimidyl ester at one end and the vinyl sulfone remains intact at the other end.

Fig. 4: Harris' Amino Activated PEG



68. Harris discloses bifunctional and heterofunctional structures of PEG derivative compounds. In the bifunctional variation of a linear PEG derivative compound, both ends are identical (*e.g.*, bis vinyl sulfone having the structure $\text{CH}_2=\text{CH-SO}_2\text{-(OCH}_2\text{CH}_2\text{)}_n\text{-SO}_2\text{-CH=CH}_2$). *Id.* at 16:37-17:8. The bifunctional PEG derivative may be used “to attach a biologically active molecule to a surface or to attach more than one such biologically active molecule to the PEG molecule.” *Id.* at 17:3-5. Harris discloses that “[t]he stability of the sulfone moiety against hydrolysis makes it particularly useful for bifunctional or heterobifunctional applications.” *Id.* at 17:6-8. In the heterofunctional variation, Harris discloses a PEG derivative compound having a sulfone moiety on one terminus and a different moiety at the other end to attach to a different molecule. *Id.* at 17:24-28. Specifically, the heterofunctional PEG derivative may contain a sulfone-specific moiety on one terminus while the other end may be one of the following exemplary functional groups: aldehydes, trifluoroethylsulfonate, which is also sometimes called tresylate, n-hydroxylsuccinimide ester, cyanuric chloride, cyanuric fluoride, acyl azide, succinate, the p-diazo benzyl group, or the 3-(p-diazophenyloxy)-2-hydroxy propyloxy group. *Id.* at 18:11-15.

D. Singh (EX1008)

69. Singh (EX1008) is a U.S. Patent Publication that was published on May 27, 2010 titled, “Potent Conjugates and Hydrophilic Linkers.” Singh is directed to various structures of linkers for binding drugs (*e.g.*, maytansinoids) to cell binding agents. EX1008 at Abstract. Singh discloses linkers with a polyethylene glycol (PEG) spacer to enhance the potency and efficacy of the cell-binding agent drug-conjugates. *Id.* Singh also discloses a “method for preparing maytansinoids bearing a thioether moiety and a reactive group which allows the maytansinoid to be linked to a cell-binding agent in essentially a single step.” *Id.* at Abstract.

70. Singh discloses the use of hydrophilic polyethylene glycol or polyethylene oxide linkers $(\text{CH}_2\text{CH}_2\text{O})_n$ with PEG spacer elements for use in cell-binding-drug conjugates. As shown in Fig. 5 below, exemplary linker structures and cell-binding-drug conjugates are represented by Formulas 1, 1', 2, and 2'. Here, Z represents a reactive functionality that can form an amide or a thioether bond with a cell-binding agent; CB represents a cell-binding agent; D represents a drug; X represents an aliphatic, an aromatic or a heterocyclic group attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond; and Y represents an aliphatic, an aromatic or a heterocyclic group attached to the drug via a covalent bond selected from the group consisting of a thioether bond, an amide bond, a carbamate bond, an ether bond, an amine bond, a carbon-carbon

bond and a hydrazone bond. *Id.* at [0080], [0084]. Singh discloses vinyl sulfone as a conjugation moiety for thiol-reactivity, disclosing that Z includes “a vinyl sulfone to give a thioether bond.” *Id.* at [0134].

Fig. 5: Singh’s Linker Structures with PEG Spacer	
$Z-X_1-(CH_2-CH_2-O)_n-Y_p-D$	Formula 1
$D-Y_p-(CH_2-CH_2-O)_n-X_1-Z$	Formula 1’
$CB-[X_1-(CH_2-CH_2-O)_n-Y_p-D]_m$	Formula 2
$[D-Y_p-(CH_2-CH_2-O)_n-X_1]_m-CB$	Formula 2’

71. In other embodiments, exemplary linker structures and cell-binding-drug conjugates are represented by Formulas 3, 3’, 4, and 4’ as shown in Fig. 6 below. Here, Z represents a reactive functionality that can form an amide or a thioether bond with a cell-binding agent; CB represents a cell-binding agent; D represents a drug; X represents an aliphatic, an aromatic or a heterocyclic group attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond; and Y represents an aliphatic, an aromatic or a heterocyclic group attached to the drug via a disulfide bond. *Id.* at [0090], [0093].

Fig. 6: Singh’s Linker Structures with PEG Spacer	
$Z-X_1-(CH_2-CH_2O)_n-Y-D$	Formula 3
$D-Y-(CH_2-CH_2O)_n-X_1-Z$	Formula 3’
$CB-(X_1-(CH_2-CH_2O)_n-Y-D)_m$	Formula 4
$[D-Y-(CH_2-CH_2O)_n-X_1]_m-CB$	Formula 4’

72. Singh discloses that “examples of suitable linkers include linkers having an N-succinimidyl ester or N-sulfosuccinimidyl ester moiety for reaction with the cell-binding agent, as well as a maleimido- or haloacetyl-based moiety for reaction with the drug.” *Id.* at [0140].

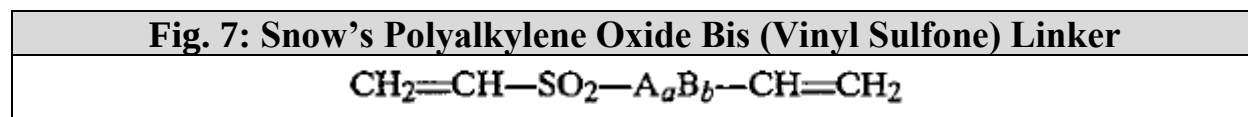
73. Singh further describes a class of maytansinoid drugs having “a non-cleavable thioether moiety that bears a reactive group are compounds of formula (5), D’-Y’—V-Q-W—Z’.” *Id.* at [0187]. Here, Z’ represents a functional group that reacts with the cell-binding agent including N-succinimidyl esters, N-sulfosuccinimidyl esters, pentafluorophenyl ester, tetrafluorosulfophenyl, and nitrophenyl ester. *Id.* Additionally, Singh discloses a method of preparation for cell-binding maytansinoid drug conjugates. Singh discloses that “sulfhydryl-bearing maytansinoids are covalently linked via a non-cleavable thioether bond to a heterobifunctional crosslinker that bears a reactive group and isolated prior to conjugation with a cell binding agent.” *Id.*

E. Snow (EX1010)

74. Snow (EX1010) is a U.S. Patent titled, “Vinyl sulfone coupling of Polyoxyalkylenes to Proteins” that issued on May 9, 1995. Snow is directed to protein conjugates and discloses a class of polyalkylene oxide vinyl sulfone polymers structures, including methods for preparation, for conjugation to proteins. EX1010 at Abstract. Compared to other protein conjugates, Snow discloses

polymer-protein conjugates that are more stable against hydrolysis, exhibit increased circulating half lives in the blood, and demonstrate reduced antigenicity. *Id.* at 4:45-50. The disclosed protein conjugates may be used for the treatment of disease although Snow does not specifically disclose attachment of a separate drug compound to the protein conjugate. *Id.* at 4:29-32.

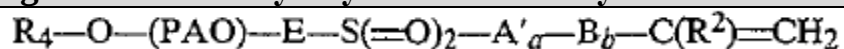
75. In one example, Snow discloses a polymeric linker containing bis(vinyl sulfone) represented by the formula shown in Fig. 7 below. *Id.* at 7:14-27. Here, A is an alkylene radical of 1 to 8 carbon atoms which, may be saturated or unsaturated and which may contain one or more heteroatoms, such as an ether group; B is a sulfoxide or a sulfone group; a and b are zero or one. *Id.*



76. In another example, Snow discloses a polymeric linker having the formula shown in Fig. 8 below. *Id.* at 8:1-10. Here, A is “an alkylene radical of 1 to 8 carbon atoms which may be saturated or unsaturated and which may contain one or more heteroatoms, such as an oxygen atom preferably in the form of an ether group.” *Id.* at 7:20-24. A’ is “an alkylene radical of 1 to 8 carbon atoms which may be saturated or unsaturated and which may contain one or more heteroatoms such as an oxygen atom in the form of an ether, or a sulfur atom in the form of a sulfoxide group.” *Id.* at 8:6-10. B is a sulfur atom, a sulfone group, or a sulfoxide group; a

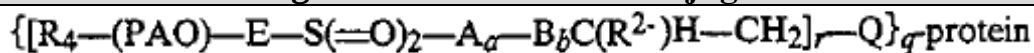
and b are either zero or one. E may be hydrogen, an alkylene group of 1 to 8 carbons, or an alkylene group of 2 to 8 carbons, preferably an ethylene group. *Id.* at 5:61-63. R₄ is “H or an alkyl or an aralkyl group of 1 to 8 carbon atoms which may be substituted with an alkoxy group of 1 to 3 carbon atoms,” while PAO is a polyalkylene oxide having an “average molecular weight in the range of 250 to 200,000 daltons.” *Id.* at 7:58-63.

Fig. 8: Snow’s Polyalkylene Oxide Vinyl Sulfone Linker



77. Snow discloses a “polypeptide or protein is bonded to one or more polyalkylene oxide moieties through a sulfone containing group.” *Id.* at 10:7-11. In one embodiment, the protein conjugate has the structural formula shown in Fig. 9 below. Here, “Q is a sulfur atom or nitrogen atom that is attached to the protein; q is a positive integer; r is one when Q is sulfur, and r is one or two when Q is nitrogen; R₄ is H or an alkyl or an aralkyl group of 1 to 8 carbon atoms which may be substituted with an alkoxy group of 1 to 3 carbon atoms; PAO is a polyalkylene oxide having an average molecular weight in the range of 250 to 200,000 daltons; E is an alkylene group of 1 to 8 carbons, or an alkylene group of 2 to 8 carbons, preferably an ethylene group,” and A may be an arylene or aralkylene group, an alkylene radical of 1 to 8 carbon atoms, a sulfide, a sulfone, a sulfoxide, an amide or heteroaromatic ring containing nitrogen. *Id.* at 10:18-31.

Fig. 9: Snow's Protein Conjugate



F. Bhakta (EX1011)

78. Bhakta (EX1011) is a U.S. Patent Publication published on December 8, 2011 titled, "Cysteine Engineered Antibodies and Conjugates." Bhakta discloses cysteine-engineered antibodies comprising a free cysteine amino acid in the heavy chain or light chain, which are prepared by replacing one or more native amino acids in an antibody with cysteine to encode a cysteine-engineered antibody. EX1011 at Abstract. Bhakta further discloses expressing and isolating the cysteine-engineered antibody and covalently attaching it to a capture label, detection label, drug moiety or solid support. *Id.*

79. Bhakta discloses antibodies engineered with reactive cysteine residues for therapeutic or diagnostic applications. *Id.* at [0002]. These reactive residues enable cysteine-engineered antibodies to be conjugated with chemotherapeutic drugs, toxins, affinity ligands such as biotin, and detection labels, such as fluorophores. *Id.* Bhakta discloses using antibody-drug conjugates (ADCs) for *in vitro*, *in situ*, and *in vivo* diagnosis or treatment of mammalian cells. *Id.*

80. Formula I of Bhakta specifically discloses the following ADC composition: Ab-(L-D)_p, which contains a cysteine-engineered antibody having one or more free cysteines (Ab), a drug moiety (D), and a linker moiety (L) that attaches to the one or more free cysteines on the antibody. *Id.* at [0211]. Bhakta discloses

that p is 1, 2, 3, or 4, thereby limiting the number of drug moieties that may be conjugated via a thiol reactive linker moiety to the cysteine-engineered antibody. *Id.* at [0212].

81. With respect to drug activity, Bhakta discloses that when the drug is not conjugated to an antibody, the drug has a cytotoxic or cytostatic effect for the treatment of cancer. *Id.* at [0213]. Thus, the biological activity of the drug moiety is “modulated by conjugation” to the cysteine-engineered antibody. *Id.* at [0213]-[0215]. To release a drug moiety and thereby activate its therapeutic effect, Bhakta discloses a variety of cleavable linkers. *Id.* at [0244]. For example, a linker may comprise amino acid residues that are susceptible to cleavage by specific enzymes, such as a tumor-associated protease. *Id.* at [0245]. Bhakta also discloses a linker containing a valine-citrulline (val-cit) amino acid residue unit, that serves as the cleavage site for several enzymes, including cathepsin B, C, and D, as well as plasmin protease. *Id.* Following enzyme-catalyzed cleavage, the active drug moiety is liberated from the conjugate and may be internalized by nearby cells to trigger a cytotoxic or cytostatic effect. *Id.* at [0217].

VIII. THE '682 PATENT

A. Claims

82. The '682 Patent contains 34 claims, of which 8 are independent and the remainder dependent. I understand that the dependent claims contain all the

elements of their respective independent claim in addition to the elements recited in the dependent claims.

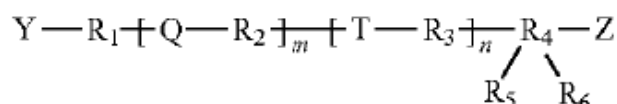
83. I understand that SynAffix challenges claims 1–17, 20–21, 24–26, and 29–34. The independent claims are generally directed to linker structures. The specific formulas corresponding to the challenged claimed linkers of the '682 Patent are shown in Table 1 below. *See* EX1002. In each of these structures, Y serves as the conjugation moiety to enable attachment of the linker to a cell-binding agent (Cb) and Z serves as the conjugation moiety to enable attachment of the linker to a drug. EX1001 at 3:1-23. R₁, R₂, R₃, R₄, R₅, R₆, Q, and T are each spacer elements. *Id.* at 3:14-45. Not each exemplary linker recites a Y structure. However, as recited in the '682 Patent claims and disclosed in the specification, adjacent structures, such as Q, do not take the place of the Y when Y is not present. Rather, the patent discloses that Q is a spacer element in any of the claimed linkers.

Table 1		
Claim	Structure	Formula
1	$Y-R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-Z$ $\swarrow \quad \searrow$ R₅ R₆	I
3, 24, 26	$Cb-\left(R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-\text{Drug} \right)_q$ $\swarrow \quad \searrow$ R₅ R₆	II

20, 29, 30	$Y-R_1-Q-R_2-T-R_3-R_4-\text{Drug}$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	IV
------------	---	----

84. For example, Claim 1 recites:

1. A hydrophilic linker of formula (I)



wherein:

Y represents a functional group that enables reaction of the hydrophilic linker with a cell-binding agent;

Q and T are either $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$;

m and n are integers from 0 to 5, but not 0 at the same time; provided that when $m=1$, $n=0$, Q is not $-P(=O)(OM)-$; when $n=1$, $m=0$, T is not $-P(=O)(OM)-$; and when Q or T is $-S(O_2)-$, m and n are not 0;

Z represents a functional group that enables linkage of the hydrophilic linker to a cytotoxic drug via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

R_1 , R_2 , R_3 , and R_4 , are the same or different and are absent, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $-S(O_2)-$ or $-S(O)-$, R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having 3 to 6 carbon atoms, linear or branched

alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof,

or R_1 , R_2 , R_3 and R_4 are respectively a chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), , provided that when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, R_2 is a straight branched chain of two or more atoms selected from the group consisting of C, N, O, S, Si, and P that covalently connects a cell-surface binding ligand, a phosphinate or sulfonyl group, a conjugated drug, R_1 , R_3 or R_4 ;

R_5 and R_6 , are the same or different and are absent, H, linear alkyl having from 1-6 carbon atoms, branched or cyclic alkyl having from 3 to 6 carbon atoms, linear, branched or cyclic alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt.

85. The dependent claims are generally directed to the structures comprising the cytotoxic drug conjugation moiety Z (Claim 2), spacer elements (Claims 9, 31-34), the cell-binding agent (Claims 6, 7), or drug (Claims 4, 5, 8, 10, 14, 21). Dependent claims 16 and 17 are directed to a pharmaceutical composition containing the claimed conjugate. Certain dependent claims contain functional limitations related to the conjugate. For example:

Claim 11: The conjugate of claim 3, having in vitro, in vivo or ex vivo cell killing activity.

Claim 13: The conjugate of claim 3, wherein the conjugate is cleavable by a protease.

B. Specification

86. The '682 Patent is titled “Hydrophilic Linkers and Their Uses for Conjugation of Drugs to A Cell Binding Molecules.”

87. The '682 Patent discloses that treatment of a wide array of diseases, particularly cancer, often involves systemic delivery of a drug that subsequently targets a specific cell population or tissue. Such targeted therapies aim to “overcome drug resistance” found in certain cell populations as well as reduce or eliminate off-target “unpalatable side effects.” EX1001 at 1:19-26. The '682 Patent discloses that an “ideal” drug delivery system must be non-toxic, biocompatible, non-immunogenic, biodegradable, and avoid detection by the host’s immune surveillance and defense mechanisms. *Id.* at 1:47-52. The structural composition of an exemplary drug delivery system generally includes a targeting moiety that has binding affinity for a molecule expressed on a cell surface (*e.g.*, an antibody, protein or protein fragment), a therapeutic moiety (*e.g.*, a small molecule drug or cytotoxic drug), and a linker connecting the targeting moiety to the therapeutic moiety. *Id.* at 2:54-60. The '682 Patent discloses cell-binding-drug conjugates such as ADCs with this structure. *Id.*

88. The '682 Patent discloses that although cell-binding drug conjugates such as ADCs offer targeted therapeutic potential, their use is often limited by

conjugation methodologies which result in the formation of protein aggregates as the amount of conjugated drug is increased. EX1001 at 2:25-33. The presence of aggregated protein is especially harmful *in vivo* because it is both non-specifically toxic and immunogenic. The '682 Patent thus addresses a “critical need to improve methods for conjugating drugs/cytotoxic drugs to carriers (cell binding molecules) that minimize the amount of aggregation and thereby allow for as high a drug loading as possible through application of a hydrophilic cross-linker.” *Id.* at 2:45-49.

89. The '682 Patent discloses improved targeted drug delivery vehicles through a unique hydrophilic linker structure that is used to connect a cell-binding agent (targeting moiety) to a drug payload (therapeutic moiety). The specification discloses a variety of functions associated with the claimed linkers, including: reducing the aggregation of the conjugates in water-based media, enabling higher drug-per-cell binding molecule-ratio conjugate, resulting in higher potency, and facilitating retention inside the target cell after the drug-linker released from the conjugates, which can combat permeability-glycoprotein (Pgp)-expressing multidrug resistant (MDR) cells. EX1001 at 2:60-67.

90. The '682 Patent discloses hydrophilic linkers possessing discrete subunits. EX1001 at 7:54-66. The individual subparts of these linkers can be classified by their overall roles in the linker structure as either a spacer element or a conjugation moiety as exemplified in Fig. 10 below.

“advantageously, because the phosphinate groups and sulfonyl groups on the hydrophilic linkers are soluble in water or require only a small percentage of organic solvent to maintain solubility in aqueous solution, the reaction between the cell-binding agent and the cross-linker can be conducted in aqueous solution.” *Id.* at 13:7-12. Accordingly, based on the disclosures of the ’682 Patent, these substituents increase hydrophilicity of the linker, thereby improving stability, decreasing aggregation, reducing immunogenicity, and improving *in vivo* therapeutic safety and efficacy of the overall cell-binding drug conjugate. *Id.* at 2:25-67.

2. Conjugation Moiety for Attachment of Cell-binding Agent (Y).

95. In Formulas I and IV, Y serves as the conjugation moiety to attach the linker to a cell-binding agent. According to the specification, “examples of the functional group, Y, that enables reaction with a cell-binding agent include amine reacting agents such as but not limited to N-hydroxysuccinimide esters, p-nitrophenyl esters, dinitrophenyl esters, pentafluorophenyl esters; thiol reactive agents such as but not limited to pyridyldisulfides, nitropyridyldisulfides, maleimides, haloacetates and carboxylic acid chlorides.” EX1001 at 8:61-67. The specification further provides:

“The hydrophilic cross-linkers described herein have diverse functional groups that can react with any cell-binding agent that possesses a suitable substituent. For example cell-binding agents bearing an amino or hydroxyl substituent can react with cross linkers bearing an N-

hydroxysuccinimide (NHS) ester, cell-binding agents bearing a thiol substituent can react with cross linkers bearing a maleimido or haloacetyl group. Additionally, cell-binding agents bearing a carbonyl substituent can react with cross linkers bearing a hydrazide or a hydroxylamine. One skilled in the art can readily determine which linker to use based on the ***known reactivity of the available functional group on the cell-binding agent.***” *Id.* at 13:51-63 (emphasis added).

96. A vinyl sulfone group can act as a conjugation moiety Y because it is also thiol reactive as explained above. See Section VI.A.3(c).

3. Conjugation Moiety for Attachment of Drug (Z).

97. In Formula I, Z serves as the conjugation moiety to attach the linker to a cytotoxic drug. According to the specification, “examples of the functional group, Z, which enables linkage of a cytotoxic drug, include groups that enable linkage via an either disulfide, or thioether, thioester, peptide, hydrazone, ester, carbamate, carbanate, alkoxime or amide bond. Such functional groups include, but are not limited to, thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines, and hydroxy.” EX1001 at 9:1-7. The specification further explains how specific functional groups on a drug can react with certain conjugation moieties on the linker:

“For example a thiol-containing drug can be reacted with the cross linker of formula (I) bearing a maleimido substituent at neutral pH in aqueous buffer to give a drug connected to the hydrophilic linker via

thioether linkage. A thiol-containing drug can undergo disulfide exchange with a hydrophilic linker bearing a pyridyldithio moiety to give a modified drug attached via a disulfide bond to the hydrophilic cross linker. A drug bearing a hydroxyl group can be reacted with a cross linker bearing a halogen, in the presence of a mild base, to give a modified drug bearing an ether link. A hydroxyl group containing drug can be condensed with a cross linker of formula (I) bearing a carboxyl group, in the presence of a dehydrating agent, such as EDC or dicyclohexylcarbodiimide (DCC), to give an ester link. A drug bearing a thiol group can be reacted with a cross linker bearing a malimido or a vinylsulfonyl, or a haloacetyl group, to give a modified drug bearing thioether link. An amino group containing drug can similarly undergo condensation with a carboxyl group on the hydrophilic cross linker of formula (I) to give an amide bond.” *Id.* at 14:14-34.

4. Cell-Binding Agents

98. A cell-binding agent included in the conjugate disclosed by the '682 Patent is defined as “a molecule that binds to, complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.” *Id.* at 14:42-44.

99. In defining cell-binding agent, the specification discloses that the cell-binding agent “complexes with or reacts with a moiety of a cell population sought to be therapeutically or otherwise biologically modified.” EX1001, 14:42-44. I understand this to mean that a cell-binding agent is a molecule that can be used to

selectively target a cell population of interest, such as cancer cells, in order to deliver drug only to that cell population. *See* Section VI. If a cell-binding agent lacked this targeting capability, it would not be therapeutically useful and may instead result in off-target toxicity that can be harmful to a patient. *See id.* The patent language is consistent with my explanation. The '682 Patent explains that cell-binding agents include, but are not limited to, large molecular weight proteins such as, for example, full length antibodies (polyclonal antibodies, monoclonal antibodies, dimers, multimers, multi-specific antibodies), single chain antibodies; and antibody fragments that bind an cell surface antigen. *Id.* at 14:45-58. *See also id.* at 14:39-28:5.

5. Drugs

100. The '682 Patent discloses “drugs that can be conjugated to a cell-binding molecule in the present invention are small molecule drugs including cytotoxic agents, which can be linked to or after they are modified for linkage to the cell-binding agent.” *Id.* at 29:43-46. Small molecule drug generally refers to an organic, inorganic, or organometallic compound with a molecular weight between 100 to 1800 daltons. *Id.* at 29:46-50. In certain embodiments, the drug “can be any of many small molecule drugs, including, but not limited to, tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 analogs, morpholinos doxorubicins, taxanes, cryptophycins, epothilones, and benzodiazepine dimers (*e.g.*,

dimmers of pyrrolobenzodiazepine (PBD) or tomaymycin), indolinobenzodiazepines, imidazobenzothiadiazepines, or oxazolidino benzodiazepines).” *Id.* at 11:58-65; *see also id.* at 29:46-36:31.

C. Prosecution History and Reexamination

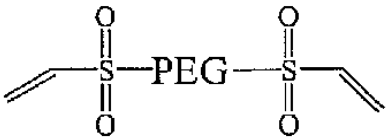
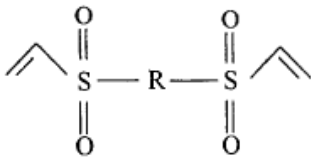
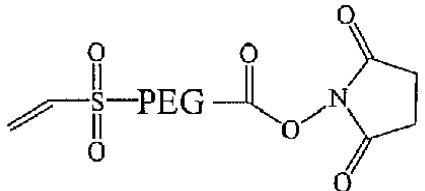
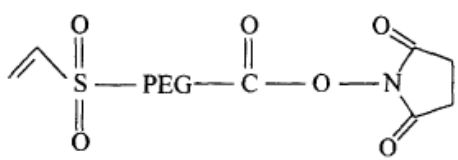
101. U.S. Patent Application No. 14/432,073 (“the ’073 Application”) filed March 27, 2015 and claiming priority to PCT/IB2012/056700 filed November 24, 2012 ultimately issued as the ’682 Patent.

102. Based on my review of the prosecution history of the ’073 Application (EX.2022-EX.2032), it is my understanding that the Examiner relied on the following references in making rejections under 35 U.S.C. § 102: U.S. Patent No. 5,094,848 (Brixner) (EX.2023) (*see* Non-Final Office Action dated August 15, 2017 (EX.2022)); WO1997/41897 (Lees) (EX.2026) (*see* Non-Final Office Action dated March 8, 2018 (EX.2025)); and WO2012/145112 (Fishkin) (EX.2029) as evidenced by Kovtun et al., *Cancer Research* (2010), 70: 2528-2537 (EX.2005) and Widdison et al., *Journal of Medicinal Chemistry* (2006), 49:4392-4408 (EX.2030) (*see* Final Office Action dated July 10, 2018 (EX.2028)). The claims were amended to overcome these rejections. The Examiner subsequently allowed the claims and issued the patent (EX.2032).

103. In Grounds 1, 2, 3, and 5 of the Petition, Petitioner contends that certain structures disclosed by Harris, Snow and Morales-Sanfrutos are invalidating—*e.g.*,

linkers containing vinyl sulfone groups. Petition at 27, 41, 42, 49, 74 . Based on my review of references cited during prosecution and reexamination, however, identical structures were considered by the Examiner.

104. For example, Lees discloses identical structures to Harris on which SynAffix is relying for Grounds 2-3 as shown in Fig. 11 below.

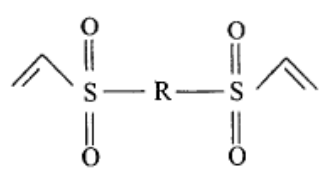
Fig. 11: Identical Linkers Disclosed in Harris and Lees	
Harris	Lees
 Homobifunctional sulfone linker structure	 Homobifunctional sulfone linker structure
 Heterobifunctional linker structure comprising vinyl sulfone and NHS	 Heterobifunctional linker structure comprising vinyl sulfone and NHS

105. Lee discloses that for the homobifunctional divinyl sulfone linker structure shown above, “R may be polyethylene glycol.” EX.2026 at 20:10-19. Lees’ homobifunctional divinyl sulfone is exactly the same structure as Harris’ bifunctional variation of a linear PEG derivative with bis vinyl sulfone that SynAffix relies upon in Grounds 2-5. EX1007 at 16:37-17:5 (“A linear PEG with active hydroxyls at each end can be activated at each end with vinyl sulfone ... to become

bifunctional. The bifunctional structure, PEG bis vinyl sulfone, for example, is sometimes referred to as a dumbbell structure...”).

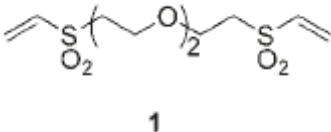
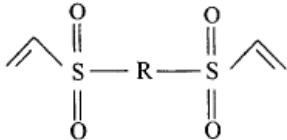
106. As shown in Fig. 11 above, Lees also discloses a heterobifunctional vinyl sulfone PEG linker containing N-hydroxysuccinimide (NHS) on one end and vinyl sulfone on the other end as shown above, which is identical to Harris’ heterofunctional variation of a linear PEG derivative with vinyl sulfone that SynAffix relies upon in Ground 2. *Compare* EX.2026 at 23:9-15 with EX1007 at 18:11-13 (“[T]he substituents would typically be selected from reactive moieties typically used in PEG chemistry to activate PEG such as ... n-hydroxylsuccinimide ester ...”).

107. Notably, Lees’ homobifunctional sulfone (Fig. 11 above) is also identical to Snow’s polymeric bis vinyl sulfone linker shown below in Fig. 12 below wherein A is PEG and B is a sulfone group. EX1010, 7:14-27.

Fig. 12: Identical Linkers Disclosed in Snow and Lees	
Snow	Lees
$\text{CH}_2=\text{CH}-\text{SO}_2-\text{A}_a\text{B}_b-\text{CH}=\text{CH}_2$ Polyalkylene Oxide Bis (Vinyl Sulfone) Linker	 Homobifunctional sulfone linker structure

108. Morales-Sanfrutos and Straus were cited in an IDS form and appeared on the list of considered references by the Examiner (EX.2033) during

reexamination of the '682 Patent (Control No. 90/014,390). Additionally, Singh substantially overlaps in its disclosure with related PCT Publication No. WO2009/134976 (Singh '976) (EX.2034), which was cited in an IDS form and appeared on the list of considered references by the Examiner (EX.2033). Again, Lees' homobifunctional divinyl sulfone (see Fig. 13 below) is also exactly the same as compound 1 disclosed by Morales-Sanfrutos (EX1005 at Fig. 2, p. 4041).

Fig. 13: Identical Linkers Disclosed in Morales-Sanfrutos and Lees	
Morales-Sanfrutos	Lees
 Compound 1	 Homobifunctional sulfone linker structure

IX. CLAIM CONSTRUCTION

109. Below, I offer my opinions regarding certain terms recited in the '682 Patent claims.

A. “Y” (Claims 1, 20, 29, 30)

110. In my opinion, based on my review of the '682 Patent and its file history, a POSITA would understand the term “Y” as requiring that Y, as a functional group distinct from Q/T (and other claimed elements of the linker), independently enable the reaction of the linker with a cell-binding agent.

Claim	Structure	Formula
1	$\text{Y} - \text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Z}$ $\swarrow \searrow$ $\text{R}_5 \quad \text{R}_6$	I
20, 29, 30	$\text{Y} - \text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Drug}$ $\swarrow \searrow$ $\text{R}_5 \quad \text{R}_6$	IV

111. First, the claim language supports my opinion. For example, claim 1 recites that “Y” “represents *a functional group that enables reaction* of the hydrophilic linker with a cell-binding agent.” Claims 2, 29, and 30 similarly require that “Y” “represents *a functional group that enables reaction* of the compound with a cell-binding agent.” The term “enables reaction” necessitates that the Y structure by itself allows for the reaction between the linker (compound) and cell-binding agent to occur.

112. Other structures of the claimed Formulas, including Q and T, are separate and distinct elements from Y. In part, this is because the claims do not require that Q and Y together “enables reaction” with the cell-binding agent. Instead, the intrinsic evidence defines Q and T to be three particular structures and Y as the functional element. Further, the claims recite that an optional intervening structure, “R1,” (see Section VIII.B), can be located between and therefore physically separate Y from Q. When that happens, the Q structure is not directly adjacent to Y and any alleged effect of Q on Y would be attenuated or eliminated.

113. *Second*, the specification supports my opinion; it reiterates that Y is defined as a structure that is specifically and independently reactive with certain chemical groups present on a cell-binding agent. EX1001, 8:61-67, 13:51-63.

114. For Formulas I and IV, the specification provides examples of the reactivity of Y with certain functional groups (substituents) on a cell-binding agent. In particular, Y can be reactive with (1) an amine substituent, (2) a thiol substituent, (3) a hydroxyl substituent, or (4) a carbonyl substituent. *See id.* at 13:54-60. The specification provides examples of functional groups that possess this reactivity and discloses amine reactive agents (*e.g.*, N-hydroxysuccinimide esters, p-nitrophenylesters, dinitrophenyl esters, pentafluorophenyl esters), thiol reactive agents (*e.g.*, pyridyldisulfides, nitropyridyldisulfides, maleimides, haloacetates and carboxylic acid chlorides), carbonyl reactive agents (*e.g.*, hydrazide or hydroxylamine), or hydroxyl reactive agents (*e.g.*, N-hydroxysuccinimide esters) (*See id.* at 8:61-67, 13:54-60.) In each of these cases, the Y group is independently sufficient for reactivity with the cell-binding agent – and does not in any way depend on the presence or absence of a Q or T.

115. The '682 Patent further states that “cell-binding agents bearing an amino or hydroxyl substituent can react with cross linkers bearing an N-hydroxysuccinimide (NHS) ester, cell-binding agents bearing a thiol substituent can react with cross linkers bearing a maleimido or haloacetyl group. Additionally, cell-

binding agents bearing a carbonyl substituent can react with cross linkers bearing a hydrazide or a hydroxylamine.” *Id.* “One skilled in the art can readily determine which linker to use based on the known ***reactivity of the available functional group*** on the cell-binding agent.” EX1001, 13:61-64 (emphasis added). Thus, A POSITA would understand that only functional groups that enable binding of the linker structure to a “cell-binding agent” fall within the scope of Y and that Y is distinct from the other linker components. Y, not Q or T, is claimed as “a functional group.” EX1001, 48:30-43.

116. In my opinion, a POSITA would read Claims 1, 20, 29, and 30 each as a whole, including the claimed structures of Formulas I and IV, and the requirements for spacer elements (R1-R6, Q, and T) and conjugation moieties (Y and Z). In doing so, it is clear that regardless of the identities of the spacer elements (R1-R6, Q, and T), which serve a distinct purpose as described in Section VI.A.3(b) and VIII.B.1, Y, as a conjugation moiety, must be a functional group that, on its own, is specifically and independently capable of enabling reactivity.

B. “Z” (Claim 1)

117. In my opinion, based on my review of the ’682 Patent and its file history, a POSITA would understand the term “Z” term to mean a component distinct and separate from the other recited components, including “Q” and “T”, of the claimed linkers of Formula I (claim 1).

118. Additionally, the “Z” term a POSITA would understand that Z, as a functional group separate from Q or T (and other claimed elements of the linker), independently enables the reaction of the claimed linker with a cytotoxic drug, specifically.

119. *First*, the claim language supports my opinion. For example, claim 1 recites that “Z” “represents a ***functional group that enables linkage*** of the hydrophilic linker ***to a cytotoxic drug.***” The term “cytotoxic drug” means that Z enables attachment of the linker to a particular class of cell-killing compounds. Additionally, the term “enables reaction” necessitates that the Z structure by itself allows for the reaction between the linker (compound) and cytotoxic drug to occur. The claim language also specifically defines the type of chemical linkage between the claimed linker and cytotoxic drug, which must occur “via a disulfide, thioether, thioester, hydrazone, ether, ester, carbamate, carbonate, secondary, tertiary, or quaternary amine, imine, cycloheteroalkane, heteroaromatic, alkoxime or amide bond.”

120. Other structures of the claimed Formula I, including Q and T, are separate and distinct elements from Z. In part, this is because the claims do not require that T and Z together “enables reaction” with a cytotoxic drug. Instead, the intrinsic evidence defines Q and T to be three particular structures and Z as the functional element. Further, the claims include optional intervening structures, such

as “R3” and “R4,” (see Section VIII.B), which can be located between and therefore physically separate Z from T. When that happens, the T structure is not directly bonded to Z and any potential effect of T on Z would be attenuated or eliminated.

121. *Second*, the specification supports my opinion. The specification discloses that Z is defined as a structure that is specifically and independently reactive with certain chemical groups present on a cytotoxic drug. EX1001, 8:61-67, 13:51-63.

122. In Formula I, Z alone must enable reaction with specific functional groups (substituents) present on a cytotoxic drug. Due to this functional requirement, only a limited pool of structures are within the scope of Z. The specification provides the following examples:

“[A] thiol-containing drug can be reacted with the cross linker of formula (I) bearing a maleimido substituent at neutral pH in aqueous buffer to give a drug connected to the hydrophilic linker via a thioether link.

A thiol-containing drug can undergo disulfide exchange with a hydrophilic linker bearing a pyridyldithio moiety to give a modified drug attached via a disulfide bond to the hydrophilic cross linker.

A drug bearing a hydroxyl group can be reacted with a cross linker bearing a halogen, in the presence of a mild base, to give a modified drug bearing an ether.

A hydroxyl group containing drug can be condensed with a cross linker of formula (I) bearing a carboxyl group, in the presence of a dehydrating agent, such as EDC or dicyclohexylcarbodiimide, to give an ester link.

A drug bearing a thiol group can be reacted with a cross linker bearing a malimido or a vinylsulfonyl, or a haloacetyl group, to give a modified drug bearing thioether link.

An amino group containing drug can similarly undergo condensation with a carboxyl group on the hydrophilic linker of formula (I) to give an amide bond.” EX1001 at 14:15-34.

123. The '682 Patent also discloses various cytotoxic drugs that can be attached to the claimed linkers, including “analogs of tubulysins, calicheamicins, maytansinoids, auristatins, doxorubicin, daunorubicin, CC-1065, [and] pyrrolobenzodiazepine dimmers.” EX1001, 5:60-62; *see also id.* at 28:6-20; 33:39-36:19. The specification further states that cytotoxic drugs bearing thiol, amino, or hydroxyl substituents can react with Z structures, including “thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazines, and hydroxy” functional groups. EX1001, 9:1-7; 14:15-34. Z, not Q or T, is claimed as “a functional group.” EX1001, 48:30-43. Finally, the specification discloses the type of resulting covalent bond formed between the claimed cytotoxic drug and linker consistent with the claim language. *Id.* at 14:15-34. Therefore, a POSITA would understand that only functional groups that enable binding of the linker structure with specific substituents on a cytotoxic drug to form a covalent bond fall within the scope of Z, and that Z is different from other linker components.

124. In my opinion, a POSITA would read Claim 1 as a whole, including the claimed structure of Formula I, and the requirements for spacer elements (R_1 - R_6 , Q,

and T) and conjugation moieties (Y and Z). In doing so, it is clear that regardless of the identities of the spacer elements (R₁-R₆, Q, and T), which serve a distinct purpose, Z, as a conjugation moiety, must be a functional group that, on its own, is specifically and independently capable of enabling reaction with a substituent present on a cytotoxic drug.

C. “Q” and “T” (Claims 1, 3, 20, 24, 26, 29, and 30)

125. In my opinion, based on my review of the '682 Patent and its file history, and to the extent not covered by the construction of claim elements above, a POSITA would understand the terms “Q” and “T” as each being (—P(=O)(OM)-, —S(O₂)—, or —S(O)—), and a claim element separate from Y and Z (as well as other claimed elements of the linker). A POSITA would not interpret either “Q” or “T” in a manner to allow for overlap with other structures in the claim, including Y and Z. This is consistent with a POSITA’s understanding of familiar conjugation moieties at end and spacers in between. *See* Sections VI.A.3(a)-VI.A.3(b) above.

126. *First*, the claim language supports my opinion. The claim language itself states that Q and T are distinct claim elements from others (*e.g.*, Y and Z). In contrast to Y and Z, the claims define Q and T in terms of specific structures (*i.e.*, —P(=O)(OM)-, —S(O₂)—, or —S(O)—), as opposed to their function. As described above, Y and Z, not Q or T, is claimed as a “a functional group.”

127. *Second*, the specification supports my opinion as it defines Q and T in terms of these specific structures. EX1001, 3:14-15, 8:23-24. As disclosed in the '682 Patent, and as a POSITA would recognize, Q and T serve a different purpose in the claimed linker than Y and Z—*i.e.*, Q and T are each spacer elements, not a conjugation moiety.

128. Q and T are not described by the '682 Patent as reactive functionalities used to form new covalent bonds. The specification instead discloses the significance of these spacer elements during synthesis of the cell-binding drug conjugate, stating “advantageously, because the phosphinate groups and sulfonyl groups on the hydrophilic linkers are soluble in water or require only a small percentage of organic solvent to maintain solubility in aqueous solution, the reaction between the cell-binding agent and the cross-linker can be conducted in aqueous solution.” EX1001 at 13:7-12.

129. In summary, it is my opinion that Q and Y are mutually exclusive and T and Z are mutually exclusive in the claimed linker formulas of the '682 Patent. As such, any functional group mapped to Q or T cannot also map to Y or Z, respectively.

D. “cell-binding agent” (Claims 3, 24, 26)

130. In my opinion, based on my review of the '682 Patent and its file history, a POSITA would understand the term “cell-binding agent” as it is defined

in the specification: “a molecule that binds to, complexes with or reacts with a moiety ***of a cell population sought to be therapeutically or otherwise biologically modified.***” EX1001, 14:43-44 (emphasis added). Here, the “cell-binding agent” is a molecule that is used to selectively target (modify) a specific population of cells, such as for therapeutic applications. See Section VI.A.1. The specification defines “cell-binding agent” in terms of its ability to interact with specific cell-associated molecules (*e.g.*, “a moiety of a cell population”) that are intended to be targeted with the claimed linker conjugate (*e.g.*, “sought to be therapeutically or otherwise biologically modified”). EX1001, 14:42-44; *see also id.* 14:45-15:32 (disclosing “large molecular weight proteins” and a variety of other biological and chemical molecules, preferably monoclonal antibodies).

131. The claims further support the specification’s definition. In particular, it is my opinion that a POSITA would recognize from the term “agent” that the cell-binding “agent” is a molecule that is intended to be used to achieve a specific purpose—*e.g.*, binding a specific cell population as disclosed in the patent.

132. The specification is consistent with the interpretation, showing that a cell-binding agent is selected for conjugation to a claimed linker of the ’682 Patent because the cell-binding agent is intended to bind to an antigen expressed on a target cell surface. *Id.* at 14:42-44. The ’682 Patent also discloses that the linkers of its invention are linkers that target specific cell populations, particularly for therapeutic

purposes. *See generally* EX1001, 1:5-2:67; 1:7-9 (“The present invention relates to the preparation of novel hydrophilic linkers used for the conjugation of a drug, in particular, a cytotoxic agent to a biological molecule”) (emphasis added). Indeed, the specification discloses hundreds of different therapeutic antibodies that may be attached to the claimed linkers. *Id.* at 14:39-28:5. Thus, a “cell-binding agent” does not include any and all structures that could have the property of binding to other molecules that may be on the surfaces of cells. Such an interpretation effectively renders the “agent” term superfluous and reduces the cell-binding agent to a moiety that is not used to target cell populations, contrary to the claim language, specification and undermining the overall purpose of the linker and conjugate.

133. This broad interpretation divorced from the patent’s definition and context is reflected in Petitioner’s reliance on Straus. Straus discloses “unusual binding sites” on cells for an enzyme (HRP) that is only used in the art as a reporter and not once as a cell-targeting agent as contemplated by the patent. *See* Section VII.B *supra*.

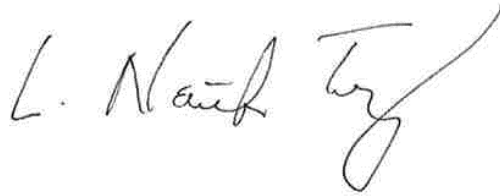
X. CONCLUSION

134. In signing this Declaration, I recognize that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place

within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

I declare under penalty of perjury under the laws of the State of New York that the foregoing is true and correct to the best of my knowledge.

Executed on this 26th day of May, 2023, at Binghamton, New York.

A handwritten signature in black ink, appearing to read "L. Nathan Tumey". The signature is written in a cursive style with a large, sweeping flourish at the end.

Dr. L. Nathan Tumey