

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
U.S. Patent No. 10,131,682

**DECLARATION OF LAWRENCE NATHAN TUMEY, Ph.D.,
IN SUPPORT OF PATENT OWNER'S RESPONSE TO PETITION FOR
INTER PARTES REVIEW OF U.S. PATENT NO. 10,131,682**

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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 to request review of claims 1-17, 20-21, 24-26, and 29-34 (“the challenged claims,” attached to this Declaration as **Appendix A**) of the ’682 Patent, which also includes the Declaration of Dr. Ravi Chari (“Chari Declaration” or “Chari Dec.”) (EX1003).

2. For this Declaration, I have been asked to provide certain opinions in support of the Patent Owner’s Response (“POR”), which I understand will be filed concomitantly with this Declaration. Specifically, I have been asked by counsel for DAC to review the Petition and exhibits thereto, including the ’682 Patent itself, the Chari Declaration, and the references cited in the Petition. I have also reviewed the file history of the ’682 Patent, including the reexamination file history, and the materials cited in this Declaration. I have also reviewed the Board’s August 22, 2023 Institution Decision that denied institution (Paper 17), SynAffix’s Request for Director Review (Paper 18), DAC’s Response to SynAffix’s Request for Director

Review (Paper 22), the Board’s Rehearing Decision (Paper 23), the Board’s August 30, 2024 Institution Decision that granted institution (Paper 25), and the transcript (EX2037) and exhibits of the November 14, 2024 deposition of Dr. Ravi Chari. 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 claim 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 been asked to analyze the publications by Morales-Sanfrutos (EX1005), Straus (EX1006), Harris (EX1007), Singh (EX1008), Snow (EX1010), and Bhakta (EX1011), and explain the disclosures therein. Finally, I have been asked to provide my opinions as to the patentability of the challenged claims in view of the Petition and exhibits thereto filed by SynAffix.

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 SynAffix. 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 SynAffix 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 as EX2002 and an updated version is attached to this Declaration as **Appendix B**. 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- θ 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 Associate Professor of Pharmacy and Pharmaceutical Sciences, as well as holding titles of Assistant Graduate Director and Vice Chair of the Department of Pharmaceutical Sciences. In this role, 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 \$4 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 Biosolutions, 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, including those described above in Paragraph 2, 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, accompanying figures, and the reexamination certificate. I have also considered the '682 Patent's claims, as the claims would have been understood by a POSITA at the time of the '682 Patent's earliest possible priority

date, November 24, 2012. I have also reviewed the prosecution history (the “file history”) of the ’682 Patent, including the reexamination file history.

15. In forming my opinions, I have also reviewed technical literature relevant to the field of the ’682 Patent, including the materials cited in this Declaration that are filed as Exhibits in this IPR. 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 (POSITA)

19. I am informed that patent validity is determined from the perspective of a POSITA at the time of the invention. 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 POSITA 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.

C. Prior Art Status

25. I understand that the “priority date” of a patent is the date on which it is filed, or the date on which an earlier-filed patent application is filed if the patentee claims the benefit of priority to that earlier-filed patent application.

26. I understand that a U.S. or foreign patent or patent application qualifies as prior art to a patent being challenged, if the date of issuance or publication of the patent or patent application is prior to the priority date of the challenged patent.

27. I understand that a printed publication, such as an article published in a magazine or trade publication, qualifies as prior art to the challenged patent if the date of publication is prior to the priority date of the challenged patent.

28. I understand that to qualify as prior art to support an anticipation challenged (discussed below), a reference must contain an enabling disclosure that allows one of ordinary skill to practice the reference’s disclosure without undue experimentation.

D. Anticipation

29. I understand that, once the claims of a patent have been properly construed, determining anticipation of a patent claim requires a comparison of the properly construed claim language to the prior art on a limitation-by-limitation basis.

30. I understand that in order for a claim to be anticipated, each and every requirement of the claim must be found, expressly or inherently, in a single prior art reference as recited in the claim.

31. I understand that a prior art reference “inherently” discloses a limitation if that limitation is necessarily present in the prior art reference.

32. I understand that it is impermissible for anticipation to combine multiple, separate embodiments, even if they are described in a single prior art reference.

33. I understand that anticipation must be based on a single prior art reference, not multiple references, but in some cases a patent challenger may point to a second prior art reference to shed light on what the single prior art reference would have meant to a POSITA. But that second reference cannot be used to supply a very specific teaching or a requirement of the claim that is missing in the single prior art reference.

E. Obviousness

34. I understand that a claimed invention is not patentable if the claimed invention would have been obvious to a POSITA in the field of the invention at the time of the invention.

35. I have been informed and understand that the obviousness analysis requires evaluating the claim language as a whole, including comparing each and every limitation of the properly construed claim language to the prior art.

36. I understand that a POSITA provides a reference point from which the prior art and claimed invention should be viewed. This reference point prevents one from using his or her own insight or hindsight in deciding whether a claim is obvious.

37. I understand that in order to show obviousness based on a single reference or a combination of references, a particular motivation to modify the reference or combine the teachings in the references, and a reasonable expectation of success, must be shown.

38. I understand that the obviousness inquiry includes consideration of various factors, such as the scope and content of the prior art, the differences between the prior art and the claims at issue, the knowledge of a POSITA at the time of invention, and any objective factors indicating non-obviousness.

39. I am informed that objective factors indicating non-obviousness, also known as objective indicia, may include (1) a long felt but unmet need in the prior art that was satisfied by the invention of the patent; (2) commercial success or lack of commercial success of process or product covered by the patent; (3) unexpected results achieved by the invention; (4) praise of the invention by others skilled in the art; (5) taking of licenses under the patent by others; and (6) deliberate copying of

the invention by others. I also understand that there must be a relationship or nexus between any such objective indicia and the claimed invention.

40. I understand that in order to rely on a reference for obviousness, the reference must be analogous art. I also understand that to be analogous art, the reference must be either (1) from the same field of endeavor as the claimed subject matter, regardless of the problem addressed, or (2) if not in the same field of endeavor, reasonably pertinent to the particular problem with which the inventor is involved. I am also familiar with the premise that for a reference to be reasonably pertinent, it must have logically presented itself to an inventor's attention at the time of invention.

F. Burden of Proof

41. I understand that the Petition must identify with particularity the grounds on which it is challenging each claim and the evidence that supports each ground.

42. I understand that the Petitioner (SynAffix) bears the burden of showing that it is more likely than not that the challenged claims are unpatentable.

V. PERSON OF ORDINARY SKILL IN THE ART

43. For purposes of this Declaration, I have been asked to apply the following definition of a POSITA, proposed by SynAffix and Dr. Chari, with respect to the '682 Patent as of November 24, 2012.

44. 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.

45. 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 in this and other proceedings.

46. 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

47. 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.

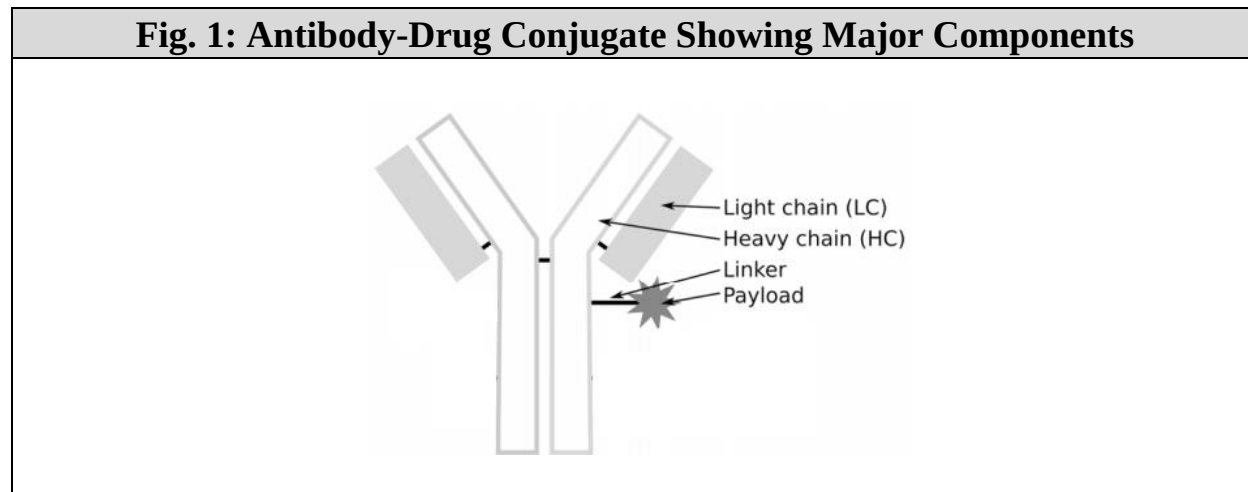
A. Targeted Drug Delivery for Cancer Therapy

48. 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. EX2003 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.*

49. To avoid damaging normal tissues, scientists have endeavored to target cancer selectively. EX2004 at 1191. To this end, certain cancer cells can be identified by unique markers on their surfaces that distinguish them from surrounding tissues. EX2005 at 2528. These markers are called “cell surface antigens.” EX2006 at 397-398. Scientists can design antibodies that bind to these cell surface antigens. *Id.*

50. These cancer-specific antibodies can be used as targeted delivery agents for chemotherapies, including for highly toxic drugs. EX2005 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. EX2007 at 5.



51. 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. EX2005 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). EX2008 at 154, 163.

52. Designing an ADC is a complex process both in synthesis and downstream performance. EX2007 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. EX2008 at 154. The major structural components (antibody, payload, and linker) are discussed in turn below.

1. Antibody

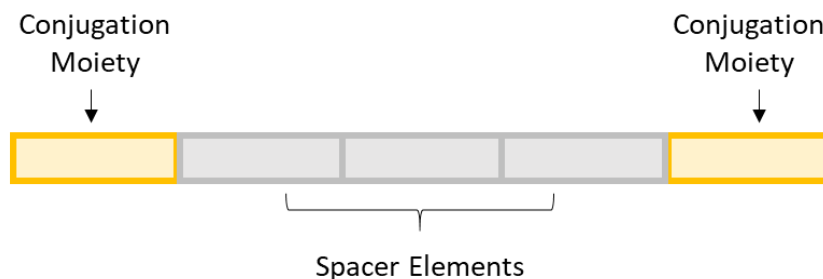
53. Proteins, such as antibodies, are an attractive targeting modality to facilitate cancer treatment. When compared to traditional small molecule drugs, ADC therapies offer a number of advantages including selectivity and favorable therapeutic windows. EX2004 at 1191-1192. However, due to their reliance 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. EX2009 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

54. 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. EX2006 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

55. The linker component of an ADC connects the antibody to the cytotoxic drug via covalent conjugation. EX2008 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.



56. 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.**”

EX2010 at 1313 (emphasis added).

57. The term “spacer element” (or simply “spacer”) is also an art-accepted term 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).

EX2011 at 277 (emphasis added).

58. 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

59. Conjugation moieties are structures on the two terminal ends of the linker that enable reaction with, or linkage to, a reactive site on the antibody or a reactive site on the drug, respectively. Accordingly, a conjugation moiety typically requires chemical functional groups that enable a reaction with the antibody or drug to form a covalent bond. EX2012 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 or drug can enable and drive the reaction to form a new covalent bond with specific functional groups

present on the antibody or 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 to form a covalent bond between the linker and the antibody or drug. *Id.* at 489. The absence of a reactive conjugation moiety means that the conjugation reaction will not take place, a covalent bond will not form, and the linker will not attach to the antibody or drug, respectively.

60. Certain types of conjugation moieties were long known in the art such as N-hydroxysuccinimide (NHS) esters, maleimides, and haloacetates. EX2013 at 305, 307-308; EX2014 at 363. N-hydroxysuccinimide esters are commonly used as conjugation moieties to react with amine functional groups on lysine residues of an antibody. EX2013 at 305. For conjugation to cysteine residues on an antibody, a thiol-reactive maleimide or a bromoacetamide is typically employed as a conjugation moiety. EX2013 at 308; EX2015 at 7064. As I discuss further below, another conjugation moiety is vinyl sulfone. EX2013 at 305.

61. 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. EX2014 at 362-363. 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. EX2015 at 7069.

62. 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. EX2016 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 925-926.

63. As discussed below in Sections VIII and IX, the '682 Patent uses “Y” and “Z” to designate the conjugation moieties on the two ends of its linker, with “Y” defined as “a functional group that enables **reaction**” of the linker “with a cell-binding agent” (*e.g.*, an antibody), and “Z” defined as “a functional group that enables **linkage**” of the linker “to a cytotoxic drug.” The '682 Patent uses different words to describe “Y” and “Z”: Y “enables reaction” and Z “enables linkage.” The different definitions of Y and Z in the '682 Patent indicate that Y and Z serve different functions. For example, as discussed below, during prosecution, the Examiner mapped a vinyl moiety from a prior-art compound containing a vinyl

sulfone group to “Z” and, at the same time, the Examiner and the Applicant mapped an entire reactive N-hydroxysuccinimide (NHS) ester functional group to “Y”.

64. The unsaturated double bond in a vinyl group enables linkage of the linker to a drug because the double bond in the vinyl allows it to be converted to a saturated ethylene linkage to enable the covalent linkage of the linker to a drug. The Examiner mapped vinyl to the “Z” functional group. However, to enable reaction of the linker with a cell-binding agent, the Y conjugation moiety must be a reactive functional group to drive the conjugation reaction, such as the N-hydroxysuccinimide ester the Examiner and the Applicant mapped to Y.

65. As discussed throughout this Declaration, vinyl itself is not a reactive functional group that would enable the reaction and thus cannot serve as “Y”; whereas vinyl sulfone is a reactive functional group that enables reaction of the linker with a cell-binding agent as described in the ’682 Patent. SynAffix’s expert, Dr. Ravi Chari, appears to agree with my opinions stated herein. For example, Dr. Chari testified in deposition that vinyl and vinyl sulfone are different functional groups. EX2037 at 21:4-16. Dr. Chari also testified that vinyl alone cannot enable reaction of a linker with a cell-binding agent. *Id.* at 20:17-21, 52:5-53:1. Dr. Chari explained that the sulfone part of the vinyl sulfone enables the reaction. *Id.* at 21:17-22:9. Dr. Chari also explained, while discussing a prior art compound, that the “vinyl alone will not react”; “the only reactive group” is vinyl sulfone, not vinyl. *Id.*

at 52:16-53:1. Thus, Dr. Chari agrees with my opinions provided herein that vinyl cannot serve as “Y” to enable reaction of the linker with a cell-binding agent.

66. Dr. Chari also testified that “linkage” means “just to connect the link together You could say it’s a covalent bond.” EX2037 at 15:18-16:3. Dr. Chari testified that a “reaction,” in contrast, is the “the process to get that connection together.” EX2037 at 33:6-17; *id.* at 17:23-18:9. Upon reviewing the claims of the ’682 Patent, Dr. Chari agreed that enabling “linkage” and enabling “reaction” are two different requirements of the two different “Z” and “Y” moieties claimed in the ’682 Patent, respectively. EX2037 at 16:20-18:14. This is consistent with how the ’682 Patent describes “Y” and “Z” and the prosecution history of the ’682 Patent, as discussed below in Sections VIII and IX.

(b) Spacer Elements

67. Spacer design depends on the developer’s goal for the ADC. Spacer elements stabilize the ADC by offsetting steric issues created by bulky payloads. EX2012 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.*

68. 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. EX2007 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.*

69. 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.*

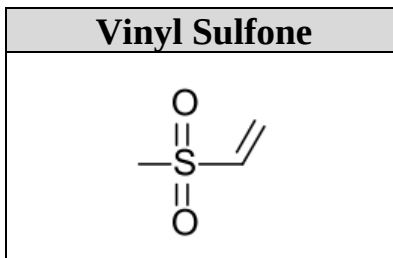
70. In contrast, non-cleavable linkers, such as thioether or maleimidocaproyl, consist of stable bonds among the spacer elements that prevent

proteolytic cleavage and ensure greater plasma stability than their cleavable counterparts. EX2017 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.

71. 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). EX2004 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.*; EX2009 at 700; EX2014 at 362. 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. EX2007 at 13.

(c) Vinyl Sulfone as a Conjugation Moiety

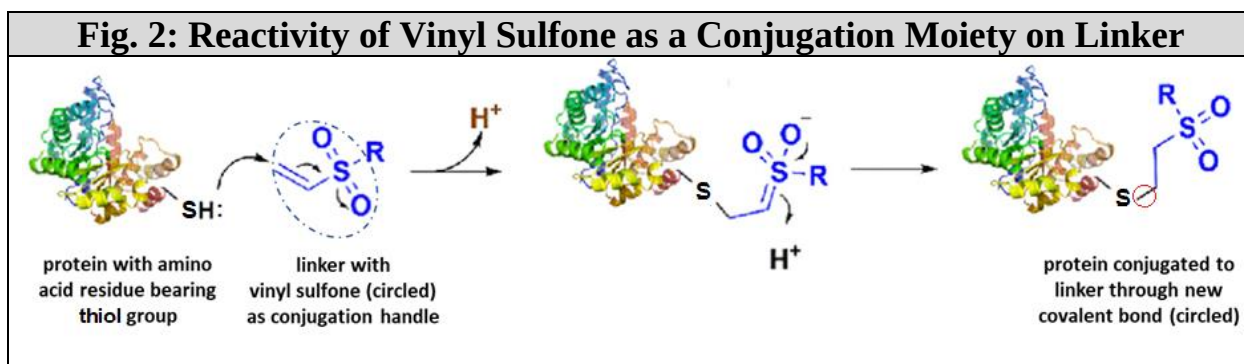
72. The functional group vinyl sulfone ($\text{CH}_2=\text{CH}-\text{SO}_2-$) as shown in the graphic below has long been used in the art as a conjugation moiety. EX2018 at 111, 113.



73. The entirety of the vinyl sulfone functional group acts as a conjugation moiety to enable the conjugation reaction because the whole structure is necessary for the group to react with endogenous amino acids on a protein or protein fragment. EX2012 at 488-489. I explain mechanisms underlying this reactivity in greater detail below. I understand from reviewing the deposition transcript of Dr. Ravi Chari that Dr. Chari agrees with me that the vinyl sulfone functional group as a whole is necessary to enable the conjugation reaction.

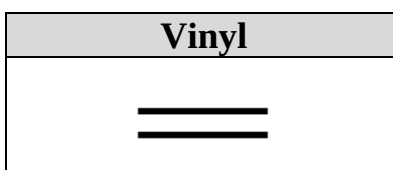
74. Vinyl sulfone is a functional group composed of a vinyl substituent and a sulfonyl (also called sulfone) substituent directly bonded to each other, which has unique properties that cannot be ascribed to its vinyl or sulfonyl components alone. EX2013 at 303-307. Here, an electron withdrawing substituent, 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. EX2012 at 488-489. Here, as an electron withdrawing group, the sulfonyl pulls electrons away from the vinyl group towards its oxygen atoms, leaving the vinyl 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 488-489, 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 that enables the conjugation reaction 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 to enable the reaction. *Id.*



(d) Vinyl Alone Is Non-Reactive as a Conjugation Moiety to Enable Reaction of a Linker with a Protein

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



76. 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. EX2012 at 488-489; EX2019 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 reaction will not take place between the linker and the protein. For this reason, vinyl alone cannot be a conjugation moiety. EX2012 at 491. In other words, vinyl alone lacks the reactive functionality to be a conjugation moiety to enable a conjugation reaction 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 488-489, 491. I understand from reviewing the deposition transcript of Dr. Ravi Chari that Dr. Chari agrees with me that vinyl alone lacks the reactivity to be a conjugation moiety to enable the conjugation reaction.

VII. OVERVIEW OF THE ASSERTED PRIOR ART REFERENCES

A. Morales-Sanfrutos (EX1005)

77. 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, nor cell-binding agents such as antibodies. Instead, Morales-Sanfrutos concerns a reporter system, which is specifically used to observe the activity of biomolecules typically in *in vitro* biological assays and does not disclose any therapeutic system.

78. 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. EX1005 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.

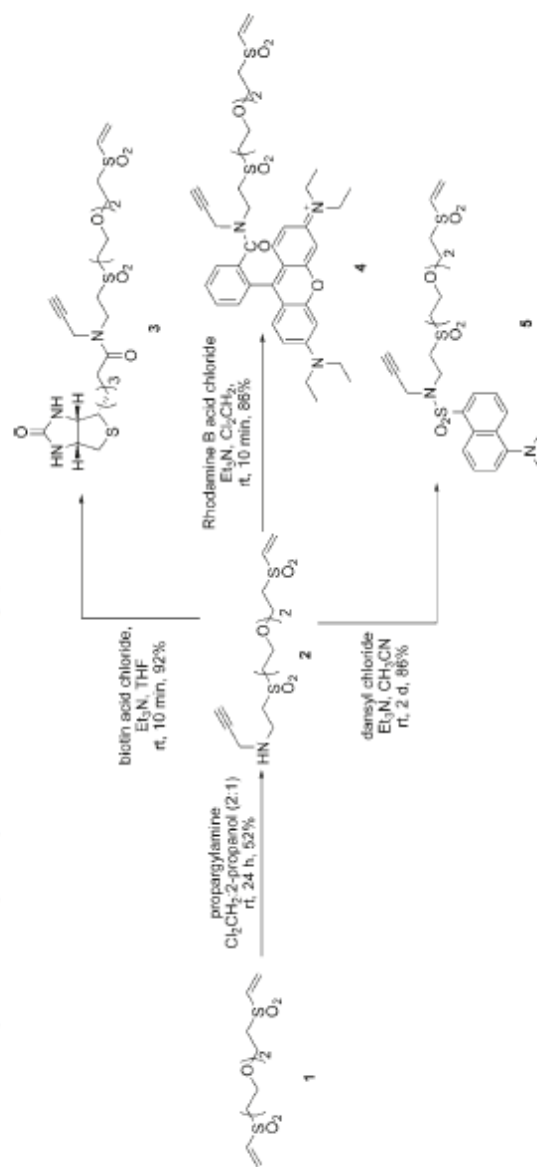
79. Morales-Sanfrutos further discloses conjugation of the disclosed bifunctional tagging compounds to horse radish peroxidase (HRP). According to Morales-Sanfrutos, “because [of] its biotechnological relevance (HRP has been coupled to other molecules to use the peroxidase activity as a reporter).” *Id.* 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.

80. Morales-Sanfrutos uses a vinyl sulfone ($\text{CH}_2=\text{CH}-\text{SO}_2-$) 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)

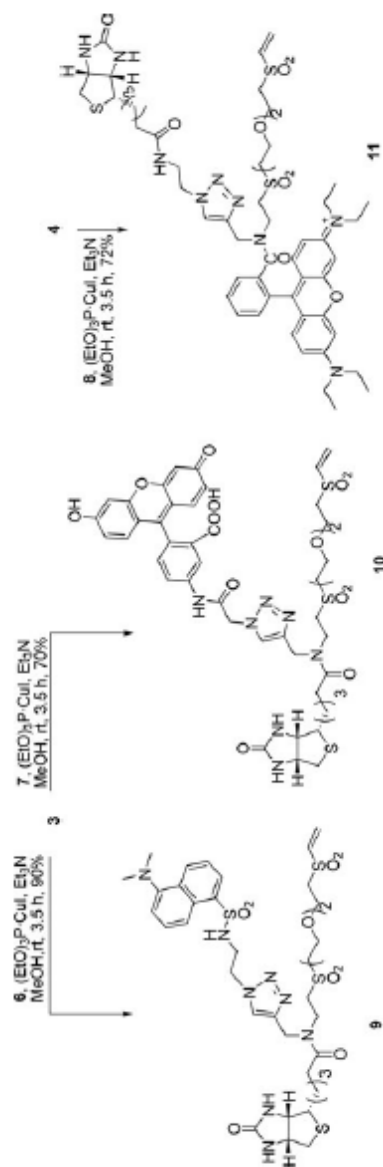
possesses a broad reactivity as it is reactive with amine, thiol, and imidazole groups naturally present in proteins. *Id.* at 4044. Morales-Sanfrutos discloses the vinyl sulfone on compound 11, which is already tagged with a rhodamine label and a biotin label, undergoes reaction with HRP via vinyl sulfone 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, ...) were dialyzed” *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)



81. Further, Morales-Sanfrutos does not disclose binding of any of its compounds to a cell, nor a functional group that enables reaction with any cell-binding agent. Morales-Sanfrutos does not expressly or inherently¹ disclose a “cell-binding agent”. 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. EX2020 at 6.2.1. Thus, cell-binding is not an intrinsic property of HRP.

B. Straus (EX1006)

82. 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 nearly 40 years ago. EX2041 at 1-3; EX2021 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 are not mainstream, well-known, or relied upon. HRP is routinely

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.

used in cell-free assays, usually as a reporter to detect the presence of a protein. EX2020 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.

83. 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 (paragraph 59). 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.

84. Straus states that "binding sites for HRP with **unusual** properties were detected at the surface of cultured and isolated cells after the cells (on cover slips) had been **quickly dried, fixed in cold methanol**, and post-fixed in a paraformaldehyde solution." EX1006 at 277. 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 the “possibility of artifacts” (*id.* at 283), 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.

85. Notably, Straus only described 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)

86. 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, among a wide variety of other possible molecules or materials that can be modified by its PEG derivatives,

stating that “almost any substance could be modified” (EX1007 at 18:34-19:2). Harris 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).

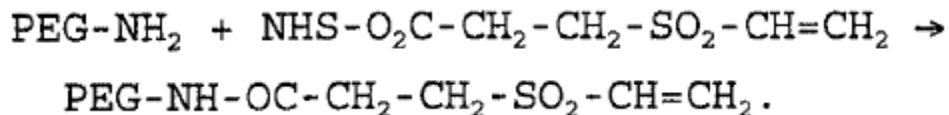
87. Harris discloses a poly(ethylene glycol) (PEG) derivative compound with a vinyl sulfone or haloethyl sulfone moiety that selectively reacts with and attaches to thiol moieties on molecules and surfaces as well as methods for synthesizing the PEG derivative compound and for preparing conjugates. Harris 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 at 6:8-14. Harris does not disclose vinyl or haloethyl alone as having this reactivity. Specifically, Harris discloses water soluble and hydrolytically stable derivatives of PEG polymers having one or more “active sulfone moieties” such as a vinyl sulfone or haloethyl sulfone. *Id.* at 6:8-15. The active 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.

88. Harris discloses PEG groups (rather than the active sulfones moieties) 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.

89. 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. Harris states that, “Y represents $SO_2-CH=CH_2$ or $SO_2-CH_2-CH_2-X$ where X is a halogen,” and “R represents a group that may be the same or different from 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 $CH_2=CH-SO_2-$, $Cl-CH_2-CH_2-SO_2-$, such as is referred to with respect to the above patents and published patent applications.” *Id.* at 19:27-30. And “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.

90. Harris discloses synthesis of another PEG derivative, called an amino activated PEG. An amino activated PEG (PEG-NH₂) is reacted with a small molecule that has a succinimidyl active ester moiety NHS-O₂C- at one terminus and a vinyl sulfone moiety at the other terminus. *Id.* at 15:18-24. 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



91. 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 CH₂=CH-SO₂-(OCH₂CH₂)_n-SO₂-CH=CH₂). *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 an active group “selected from among a wide variety of compounds,” including 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, and **others.**” *Id.* at 18:5-15.

D. Singh (EX1008)

92. 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.

93. Singh discloses the use of hydrophilic polyethylene glycol or polyethylene oxide linkers (CH₂CH₂O)_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] (emphasis added).

Fig. 5: Singh’s Linker Structures with PEG Spacer	
$Z-X_1-(\text{---CH}_2\text{---CH}_2\text{---O---})_n-Y_p\text{-D}$	Formula 1
$D-Y_p-(\text{---CH}_2\text{---CH}_2\text{---O---})_n-X_1-Z$	Formula 1’
$CB-[X_1-(\text{---CH}_2\text{---CH}_2\text{---O---})_n-Y_p\text{-D}]_m$	Formula 2
$[D-Y_p-(\text{---CH}_2\text{---CH}_2\text{---O---})_n-X_1]_m\text{---CB}$	Formula 2’

94. Singh discloses vinyl sulfone, but refers to it only **once** in Singh, as one possible “reactive functionality,” among others. *Id.* at [0134]. Singh defines the term “reactive functionality” as “refer[ring] to an amine-, a thiol- or a hydroxyl-reactive functionality,” i.e., three classes of reactive functionalities, and states that, “for thiol-reactive functionality,” one of the three classes, “the functionality could be a maleimide, a haloacetamide, or a vinyl sulfone to give a thioether bond.” *Id.* at [0134].

95. 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] (emphasis added).

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'

96. 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].

97. Singh further describes a class of maytansinoid drugs having “a non-cleavable thioether moiety that bears a reactive group [that] are compounds of formula (5), D'-Y'-V-Q-W-Z'.” *Id.* at [0187]. Here, Z' represents a functional

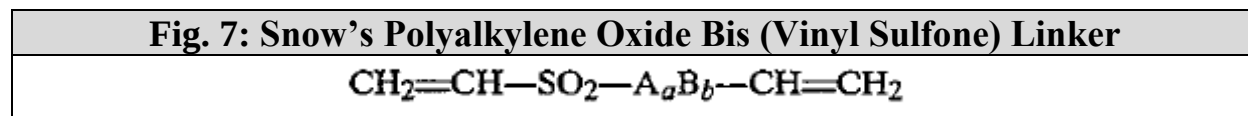
group that reacts with the cell-binding agent including N-succinimidyl esters, N-sulfosuccinimidyl esters, pentafluorophenyl ester, tetrafluorosulfophenyl, and nitrophenyl ester. *Id.* Additionally, Singh discloses a method of preparation for cell-binding maytansinoid drug conjugates. Singh discloses 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)

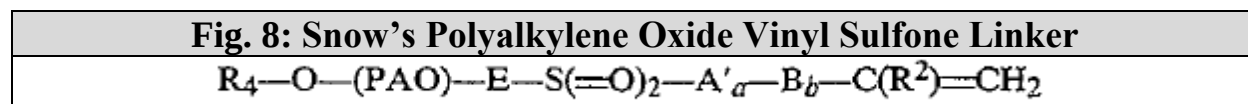
98. Snow (EX1010) is a U.S. Patent titled, “Vinyl Sulfone Coupling of Polyoxyalkylenes to Proteins” that issued on May 9, 1995. Snow is directed to protein conjugates and discloses a class of polyalkylene oxide vinyl sulfone polymers structures, including methods for preparation, for conjugation to proteins to modify the proteins. EX1010 at Abstract. Compared to “unmodified proteins,” Snow discloses that proteins modified by its polymeric reagents are more stable and exhibit increased circulating half lives in the blood, and demonstrate reduced antigenicity. *Id.* at 4:43-50. The disclosed protein conjugates may be used for the treatment of disease although Snow does not specifically disclose attachment of a separate therapeutic drug compound to the protein conjugate. *Id.* at 4:29-32.

99. 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.*



100. 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 in the form of an ether, or a sulfur atom in the form of a sulfoxide group," and "R₄, PAO, E, a, B, b, and R² are as defined above" in the patent. *Id.* at 8:6-10. Thus, B is a sulfur atom, a sulfone group, or a sulfoxide group (*id.* at 6:25-26); a and b are either zero or one (*id.* at 6:24, 6:35). E is hydrogen, or an alkylene group of 1 to 8 carbons, or an alkylene group of 2 to 8 carbons, preferably an ethylene group, or a substituted aryl group of a certain formula provided in the patent that contains additional variants. *Id.* at 5:61-6:10. 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.



101. Snow discloses that 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, or a substituted aryl group” of a certain formula provided in the patent that contains additional variants, “A is an arylene or an aralkylene group of 6 to 8 carbons which may be unsubstituted or substituted with one or more low molecular weight substituents selected from halogen, methyl, methoxy, and trifluoromethyl; or an alkylene radical of 1 to 8 carbon atoms which may be saturated or unsaturated and which may contain one or more heteroatoms selected from an oxygen atom comprised in an ether or an ester group, a sulfur atom comprised in a sulfide or a sulfone or a sulfoxide group, and a nitrogen atom that is part of a heteroaromatic ring or an amide group; a is zero or one; B is a sulfur atom, a sulfone group, or a sulfoxide group; b is zero or one; and R² is selected from H, F, C₁, CF₃ and alkyl groups of 1 to 8 carbon atoms.” *Id.* at 10:11-58.

Fig. 9: Snow's Protein Conjugate
$\{[R_4-(PAO)-E-S(=O)_2-A_\alpha-B_\beta C(R^{2'})H-CH_2]_r-Q\}_q \text{protein}$

F. Bhakta (EX1011)

102. 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.*

103. 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.*

104. 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].

105. 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

106. The '682 Patent contains 34 claims, of which 12 are independent claims (i.e., claims 1, 3, 18, 20, 22, 23, 24, 26, 27, 28, 29, and 30) and the remainder

dependent claims. See EX1001; EX1002. 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.

107. I understand that SynAffix challenges claims 1-17, 20-21, 24-26, and 29-34. The challenged claims are reproduced in **Appendix A** of this Declaration.

108. Among the challenged claims, claims 1, 3, 20, 24, 26, 29 and 30 are independent claims. The independent claims are generally directed to linker structures including related therapeutic drug conjugates. The specific formulas corresponding to the linker structures of the challenged independent claims are shown in Table 1 below. See EX1002.

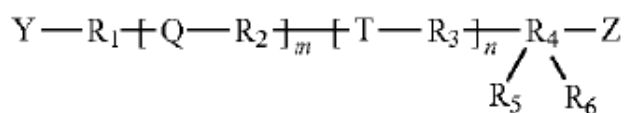
Table 1		
Claim	Structure	Formula
1	$Y-R_1-\text{---}Q-R_2-\text{---}T-R_3-\text{---}R_4-Z$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	I
3, 24, 26	$Cb-\left(R_1-\text{---}Q-R_2-\text{---}T-R_3-\text{---}R_4-\text{Drug}\right)_q$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	II
20, 29, 30	$Y-R_1-\text{---}Q-R_2-\text{---}T-R_3-\text{---}R_4-\text{Drug}$ $\begin{array}{c} \diagup \quad \diagdown \\ R_5 \quad R_6 \end{array}$	IV

109. In these structures, Y serves as the conjugation moiety to enable reaction with a cell-binding agent (Cb) and Z serves as the conjugation moiety to

enable linkage 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 structure recites a Y element. Formula II depicted below has a Cb attached to one end of the linker and a Drug attached to the other end of the linker

110. 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(O₂)—, 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(O₂)—, 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**;

R₁, R₂, R₃, and R₄, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof,

or R₁, R₂, R₃ and R₄ 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 (R₁, R₂, R₃ and R₄), , provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ 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, R₁, R₃ or R₄;

R₅ and R₆, 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.

111. The claim defines the conjugation moieties on the two ends of the linker, Y and Z, by their function, with Y defined as “a **functional group** that **enables reaction with**” a cell-binding agent, and Z defined as “a **functional group** that **enables linkage to**” a cytotoxic drug via certain types of chemical bonds. On the other hand, other elements of the claimed formula, such as the spacer elements embedded in the linker, Q, T, R_1 , R_2 , R_3 , R_4 , R_5 , and R_6 , are defined by their structure, for example, with Q and T defined as $-\text{P}(=\text{O})(\text{OM})-$, $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$.

112. The dependent claims further specify the cytotoxic drug conjugation moiety Z (Claim 2), the spacer elements (Claims 25, 31-34), the cell-binding agent (Claims 6, 7), the drug (Claims 4, 5, 8, 10, 14, 21), or additional structural elements (Claims 9, 12). Dependent claims 15, 16, and 17 are directed to a pharmaceutical composition containing the claimed conjugate. Dependent claims 11 and 13 further specify the properties of the claimed conjugate:

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

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

114. 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 agent drug conjugates such as ADCs with this structure. *Id.*

115. The '682 Patent discloses that although cell-binding agent 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.

116. 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.

117. The '682 Patent discloses hydrophilic linkers possessing discrete subunits, including the Y and Z conjugation moieties at the end of the linker, and spacer elements in between. EX1001 at 7:54-66, 8:12-60. The linker of the '682

Patent uses functional groups having certain specified functions as the Y and Z conjugation moieties. EX1001 at 8:61-67; 9:1-7.

118. The '682 Patent refers to the Y and Z conjugation moieties as a functional group that “enables reaction” of the linker structure with a cell-binding agent on one terminus and a functional group that “enables linkage” of the linker to a drug at the other terminus, respectively, and provide different examples for the Y and Z conjugation moieties. *Id.* at 8:61-67; 9:1-7. The specification of the '682 Patent therefore describes the Y and Z conjugation moieties in terms of their function, as a functional group that enables reaction or linkage, as in the claims.

119. In contrast, the specification describes the spacer elements (Q, T, R₁, R₂, R₃, R₄, R₅, and R₆) located in between the conjugation moieties in terms of their structures, as in the claims. EX1001 at 2:53-55, 3:14-15, 3:24-43, 8:23-24, 8:34-58. For example, the '682 Patent describes that phosphinate, sulfonyl, and/or sulfoxide groups (i.e., -P(=O)(OM)- , $\text{-S(O}_2\text{)-}$, or -S(O)-) are spacer elements designated Q and T in the patent. *Id.* at 13:7-12; *see also id* at 3:5-4:21 (Formulas I-IV).

120. The intervening spacer elements, such as Q, T, R₁, R₂, R₃, R₄, R₅, and R₆, are distinct structural elements that are separate from the Y and Z conjugation moieties. The spacer elements serve different purposes, for example, to increase hydrophilicity, provide stability, and reduce steric effects resulting from the cell-binding agent and drug, as discussed herein.

121. Below, I discuss certain disclosures of the '682 Patent regarding subparts of its claimed linkers.

1. Spacer Elements (*e.g.*, Q, T)

122. The '682 Patent provides hydrophilic linker structures specifically containing one or more phosphinate, sulfonyl, or sulfoxide substituent groups as spacer elements, which are represented as Q and T in Formulas I-IV. EX1001 at 7:58-60. The specification further discloses the significance of these spacer elements during synthesis of the cell-binding drug conjugate. It provides that, “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 “Y” that Enables Reaction with a Cell-Binding Agent

123. In Formulas I and IV, Y serves as the conjugation moiety to enable reaction of the linker with 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.

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

3. Cell-Binding Agents

125. As discussed further in Section IX below, a cell-binding agent 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.” EX1001 at 14:42-44.

126. 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 at 14:42-44. I understand this to mean in the context of the ’682 Patent 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. EX1001 at 14:45-58; *see also id.* at 14:39-28:5.

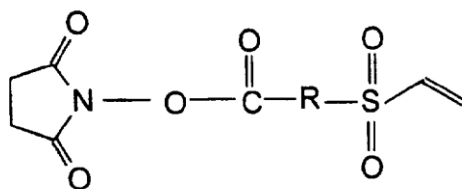
C. Prosecution History and Reexamination

127. 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.

128. Based on my review of the prosecution history of the ’073 Application (EX1018-EX1019, EX2022-EX2032), 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) (EX2023) (*see* Non-Final Office Action dated August 15, 2017 (EX2022)); WO1997/41897 (Lees) (EX2026) (*see* Non-Final Office Action dated March 8, 2018 (EX2025)); and WO2012/145112 (Fishkin) (EX2029) as evidenced by Kovtun et al., Cancer Research (2010), 70: 2528-2537 (EX2005) and Widdison et al., Journal of Medicinal Chemistry (2006), 49:4392-4408 (EX2030) (*see* Final Office Action dated July 10, 2018 (EX2028)). The claims were amended to overcome these rejections. The Examiner subsequently allowed the claims and issued the patent (EX2032).

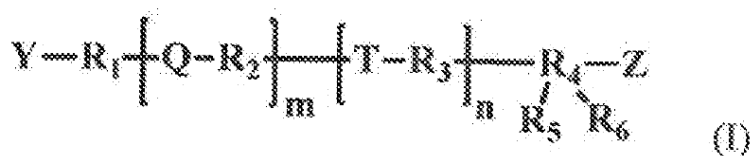
129. In the Office Action dated March 8, 2018, the Examiner rejected the application's claim 1 as anticipated by Lees (EX2026). EX1018 at 42-43. The Examiner cited the following structure from Lees, with N-hydroxysuccinimide (NHS) ester on one end and vinyl sulfone on another end of the linker structure:

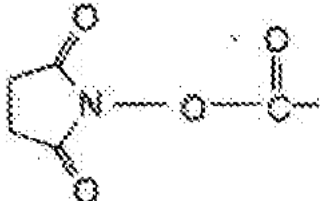


EX2026 at 22. The Examiner stated that in the above structure “the **NHS portion** represents a functional group that **enables reaction** of the linker with a cell binding agent, and the **vinyl group enables linkage** of the linker to a cytotoxic drug” EX1018 at 42-43 (emphasis added). The Examiner therefore mapped the reactive

NHS ester to “Y” as a “functional group that enables reaction ... with a cell binding agent,” and the vinyl group to “Z” as a functional group that “enables linkage ... to a cytotoxic drug.” *Id.*

130. In response to the Office Action, the Applicant amended claim 1, including adding a requirement that “when Q or T is -S(O₂)-, m and n are not 0.” EX1018 at 45. The Applicant noted that the Examiner mapped the above structure from Lees to the formula recited in claim 1:



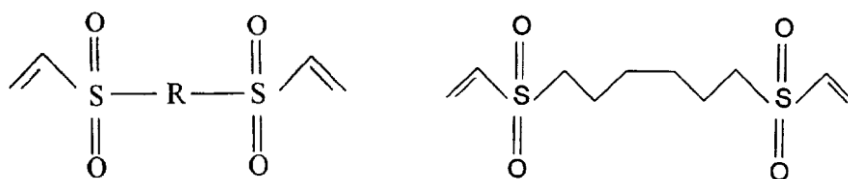
“where Y is , Q (or T) is -S(O₂)-, m (or n) is 1, n (or m) is 0,

R₂(R₃) and R₄-R₆ are absent, and Z is ” EX1018 at 62. The Applicant stated that “claim 1 of the present application recites that when Q or T is -S(O₂)-, m and n are not 0, thereby excluding the above noted compound described in Lees.” *Id.*

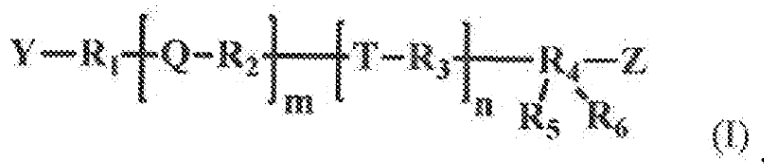
131. Therefore, the Examiner and the Applicant both mapped “Y” to a reactive NHS ester. They did not map “Y” to the vinyl. Notably, the Applicant specifically listed the **entire** active NHS ester, with both the N-hydroxysuccinimide (NHS) portion and the ester portion of the reactive functional group in the response.

This is consistent with the claim's requirement that "Y" be a reactive functional group that enables reaction of the linker to a cell-binding agent.

132. Notably, if Y could be mapped to vinyl only, as SynAffix argues in this IPR, the claim amendment requiring that "when Q or T is -S(O₂)-, m and n are not 0" would not be enough to distinguish the claimed linker over Lees. Specifically, Lees discloses the following two structures on the pages immediately preceding the page cited by the Examiner:



EX2026 at 20-21. If one were to assume that both Y and Z can be vinyl only, without the adjacent sulfone of a vinyl sulfone group, then each of the above two structures of Lees would map to Formula I and meet all other requirements of the claim to anticipate the amended claim 1:

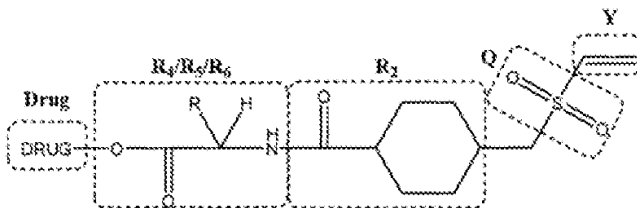


where each of Y and Z is mapped to vinyl only, Q and T are sulfone, m and n are 1 (not 0), R₁ and R₃ through R₆ are absent, and R₂ is either "R" as defined in Lees or the C₆-alkylene linker in the above structures of Lees. EX2026 at 20-21.

133. This portion of the file history therefore shows that, unlike Z (which can be vinyl to enable linkage), Y must be a reactive “functional group that enables reaction of the hydrophilic linker with a cell-binding agent.” This is consistent with Dr. Chari’s testimony in deposition that Y cannot be vinyl alone. EX2037 at 20:17-21, 52:5-53:1.

134. I understand that SynAffix also cited a portion of the reexamination file history to support its argument that “Y” in the claimed Formulas I and IV can be vinyl only, without the adjacent sulfone. Specifically, during reexamination, in response to an office action (EX1019 at 1-44; *id.* at 45-81), the patentee commented on a rejection against independent **claim 3** as follows:

The Examiner appeared to miss a portion in the proposed structure. It is presumed that the following structure was intended:



It is clear that in the above formula, the portion allegedly corresponding to R_2 in formula (II) of claim 3 of the present patent contains a cyclic structure. On the other hand, R_2 as defined in claim 3 of the present patent as amended does not encompass a cyclic structure.

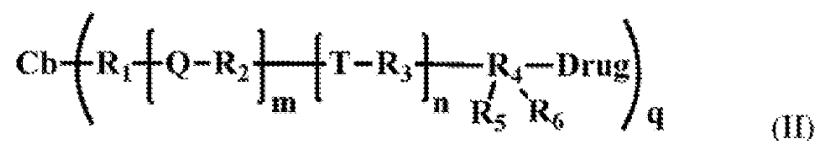
For at least this reason, the above compound of US '053 does not meet all the requirements for formula (II) of claim 3 of the present patent.

EX1019 at 72-73.

135. In my opinion, the above remarks concerning a rejection of independent claim 3, which does not recite any “Y” claim element, do not clearly demonstrate that the “Y” claim element recited by different independent claims (claims 1, 20, 29, and 30) could be mapped to vinyl alone. For example, in the response to the office action, the patentee noted that claim 3 recites the following formula II, which does not include any “Y” element:

II. Independent Claim 3

Claim 3 recites a cell-binding agent-drug conjugate of formula (II):



EX1019 at 68.

136. Moreover, the remarks made by the patentee are vague and ambiguous as to whether the patentee intended to define “Y” differently from how claims other than claim 3 expressly define it. In those remarks, the patentee noted the lack of clarity of the rejection and “presumed” that “[t]he Examiner ... intended” to describe a certain structure, as well as the Examiner’s “alleged[.]” mapping of that presumed structure to R₂ in formula II of claim 3. *Id.* The patentee then noted one of the reasons why the presumed structure does not meet all the requirements of formula II, specifically stating that “[f]or at least this reason,” the prior art “does not meet all the requirements” of the claim. *Id.*

IX. CLAIM CONSTRUCTION

137. Counsel for DAC asked that I provide my opinions regarding the interpretation of two claim terms recited in the '682 Patent claims.

- “Y represents a functional group that enables reaction ...” (claims 1, 20, 29-30, and dependent claims);
- “cell-binding agents” (all claims).

A. “Y represents a functional group that enables reaction ...” (claims 1, 20, 29-30, and dependent claims)

138. 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	$\text{Y} - \text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Z}$ $\text{R}_5 \quad \text{R}_6$	I
20, 29, 30	$\text{Y} - \text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Drug}$ $\text{R}_5 \quad \text{R}_6$	IV

139. **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 20, 29, and 30 similarly require that “Y” “represents **a functional group that enables reaction** of the

compound with a cell-binding agent.” EX1002 at 1:31-32, 4:12-13, 9:64-65, 11:2-3. The term “enables reaction” necessitates that the Y structure by itself allows for the reaction between the linker (or compound) and the cell-binding agent to occur. The claims do not refer to any other claim element, such as Q together with Y, to enable the reaction of the linker (or compound) to a cell-binding agent. A non-reactive chemical functional group (such as vinyl) that cannot enable the reaction to proceed would not satisfy the claims’ express requirement of “Y”.

140. Other structures of the claimed Formulas, including Q and T, are separate and distinct elements from Y. As noted, the claims do not require that Q and Y together “enables reaction” with the cell-binding agent. Instead, the patent defines Q and T to be three particular structures (phosphinate, sulfonyl, or sulfoxide) and Y as the claimed functional group. EX1002 at 1:22-34, 4:3-15, 9:55-67, 10:60-11:5.

141. Further, the claims recite that an optional intervening structure, “R₁,” is located between and therefore physically separate Y from Q. The claims define that “R₁” can be absent or a non-reactive alkyl group, among other non-reactive moieties. EX1002 at 1:46-2:4. When R₁ is present, the Q structure is not directly adjacent to Y and any alleged effect of Q on Y would be eliminated.

142. **Second**, the specification supports my opinion; it reiterates that Y is defined as a functional group that is specifically and independently reactive with

certain chemical groups present on a cell-binding agent. EX1001 at 8:61-67, 13:51-63. The specification consistently defines Y as “a functional group that enables reaction” with a cell-binding agent. EX1001 at 3:12-13, 4:14-15, 8:21-22. The specification also provides examples of reactive functional groups as Y. *Id.* at 8:61-67, 13:51-63, 14:8-10.

143. 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.

144. The '682 Patent further states that “cell-binding agents bearing an amino or hydroxyl substituent can react with cross linkers bearing an N-

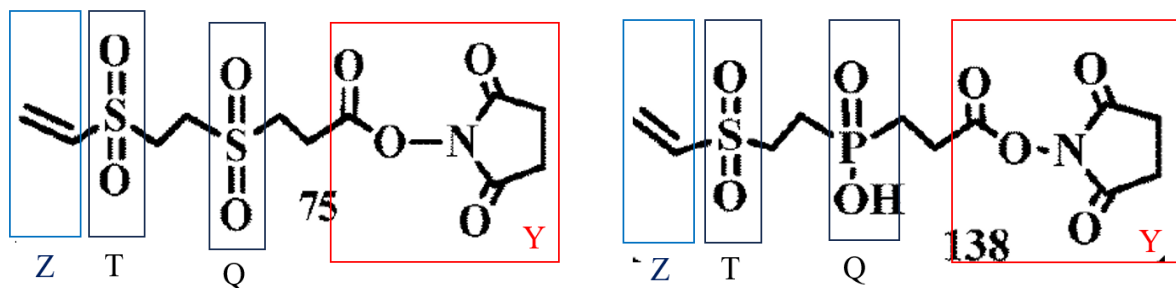
hydroxysuccinimide (NHS) ester, cell-binding agents bearing a thiol substituent can react with cross linkers bearing a maleimido or haloacetyl group. Additionally, cell-binding agents bearing a carbonyl substituent can react with cross linkers bearing a hydrazide or a hydroxylamine.” *Id.* at 13:54-60. “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 13:61-64. Thus, a POSITA would understand that only reactive functional groups that enable reaction of the linker with 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 and described in the specification as “a functional group that enables reaction.” EX1001 at 48:30-43.

145. **Third**, my opinion regarding the meaning of the “Y” claim term is consistent with the prosecution history. As noted in Section VIII.C, when discussing the rejection over Lees, the Examiner and the Applicant only mapped “Z” to vinyl. EX1018 at 42-43, 62. The Examiner and the Applicant mapped the **entire** reactive NHS ester to Y. *Id.* The mapping of vinyl to “Z” does not alter the meaning of “Y”, a distinctly different claim term.

146. As noted above, the claims use different words to define Y and Z: Y is “a functional group that enables **reaction**” of the linker “with a cell-binding agent,” whereas Z is “a functional group that enables **linkage**” of the linker “to a cytotoxic drug” via certain chemical bonds. EX1002 at 1:31-32, 1:40-45 (emphasis added).

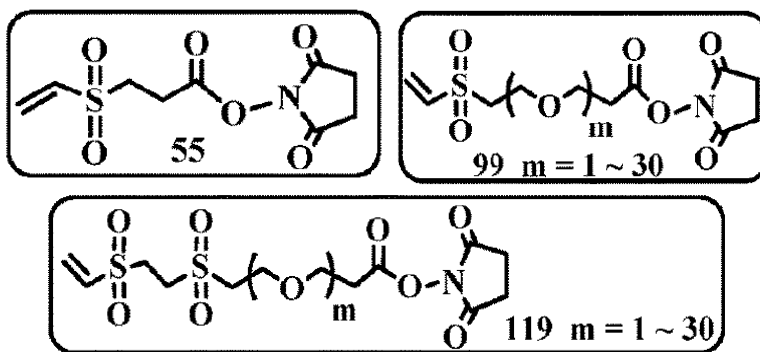
And the specification describes “Y” and “Z” differently. EX1001 at 8:61-67, 9:1-7; *see also* EX2037 at 15:23-16:3, 22:4-9, 33:6-14 (Dr. Chari confirming the different meanings of “linkage” and “reaction”). Thus, the mapping of vinyl to only “Z”, not to a different claim term “Y”, does not change the meaning of “Y”.

147. My proposed construction of “Y” does not exclude the embodiments disclosed in the ’682 Patent. For example, during prosecution, the Applicant cited Examples 75 and 138, among other examples, as support for the amendments made to claim 1. EX1018 at 59. As shown below, claim 1 covers both Examples 75 and 138 under my proposed construction of “Y” to require a functional group that independently enables reaction with a cell-binding agent, where Y is an NHS ester highlighted in red box below. As noted above, the Examiner mapped vinyl to “Z” (highlighted in blue box below). As also shown below, both Q and T are present (i.e., m and n are not zero) in Examples 75 and 138, as required by claim 1.



148. Additionally, Examples 55, 99, and 119 of the ’682 Patent, shown in the patent’s figures, have a vinyl as the Z that can be linked to a drug, and an NHS ester as the Y that can react with a cell-binding agent. For similar reasons provided

above for Examples 75 and 138, Example 119, with an additional sulfone in the linker structure, is covered by claim 1. On the other hand, Examples 55 and 99, each with a vinyl sulfone on the left and an NHS ester on the right, **without** an additional sulfone in the linker (unlike Examples 75, 119, and 138), are not covered by claim 1, because the claim requires that both m and n are not zero. As noted in Section VIII.C, the Applicant made remarks during prosecution that a compound such as Example 55 is not covered by claim 1. EX1018 at 62. Thus, my proposed construction is consistent with the prosecution history.



149. As also discussed in Section VIII.C, the patentee's remarks during reexamination regarding the rejection of independent claim 3 that does not even recite "Y"—including the remarks concerning the "presumed" structure that the Examiner might have "intended" when rejecting claim 3—were vague and ambiguous and do not clearly alter the meaning of "Y" as defined in different independent claims of the patent.

150. **Fourth**, other evidence also supports my proposed construction. For example, Dr. Chari at deposition agreed with a definition of “functional group” as “a specific identifiable group of atoms within a molecule that directly contributes to its characteristic chemical properties and reactivity.” EX2037 at 10:5-11. This definition of “functional group” is similar to and consistent with the definitions in technical dictionaries:

- “[A] group of atoms that reacts as a single unit and determines the properties and structure of a class of chemicals.” Dictionary of Science & Technology (2007), at 266 (EX2042).
- “The functional group is an atom (or a group of atoms) that has similar chemical properties whenever it occurs in different compounds. It defines the characteristic physical and chemical properties of families of organic compounds.” Encyclopedia of Chemistry (2005), at 113 (EX2043).
- “An atom or group of atoms, acting as a unit, that has replaced a hydrogen atom in a hydrocarbon molecule and whose presence imparts characteristic properties to this molecule.” McGraw-Hill Dictionary of Scientific and Technical Terms (2003), at 865 (EX2044).
- “The group of atoms responsible for the characteristic reactions of a compound.” A Dictionary of Science (2010), at 339 (EX2045).

151. The above definitions of “functional group” demonstrate that a POSITA would understand that as a “**functional group** that enables reaction” with

a cell-binding agent, “Y” as a single unit must be capable of and responsible for the recited reaction.

152. As Dr. Chari testified at deposition, a POSITA would understand that vinyl and vinyl sulfone are different functional groups with different properties, and vinyl sulfone is “much more reactive” than vinyl. EX2037 at 19:15-17, 21:11-16. As Dr. Chari testified, vinyl “won’t react by itself” because it is “not reactive,” and “you need” the “sulfone” moiety to “activate the vinyl sulfone” to “enable[e] the reaction” because “vinyl alone will not react.” *Id.* at 19:18-21:3, 21:17-22:9, 52:16-53:1. Dr. Chari consistently identified the more reactive vinyl sulfone, not just vinyl, as the “Y” functional group. *Id.* at 48:6-49:12, 52:5-53:1.

B. “cell-binding agent” (all claims)

153. 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 at 14:43-44.

154. I understand that in the Institution Decision, the Board adopted DAC’s proposed construction of “cell-binding agent” 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.” Paper 25 at 20-21.

155. 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 at 14:42-44; *see also id.* at 14:45-15:32 (disclosing “large molecular weight proteins” and a variety of other biological and chemical molecules, preferably monoclonal antibodies).

156. 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 at 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”). 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.

157. Such broad interpretation of “cell-binding agent” incorrectly detached from the patent’s definition and context is reflected in SynAffix’s reliance on Straus (EX1006). As discussed in Sections VII.B and X.A, Straus discloses “unusual binding sites” on certain cultured and isolated 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 ’682 Patent.

X. SYNAFFIX FAILS TO PROVE UNPATENTABILITY

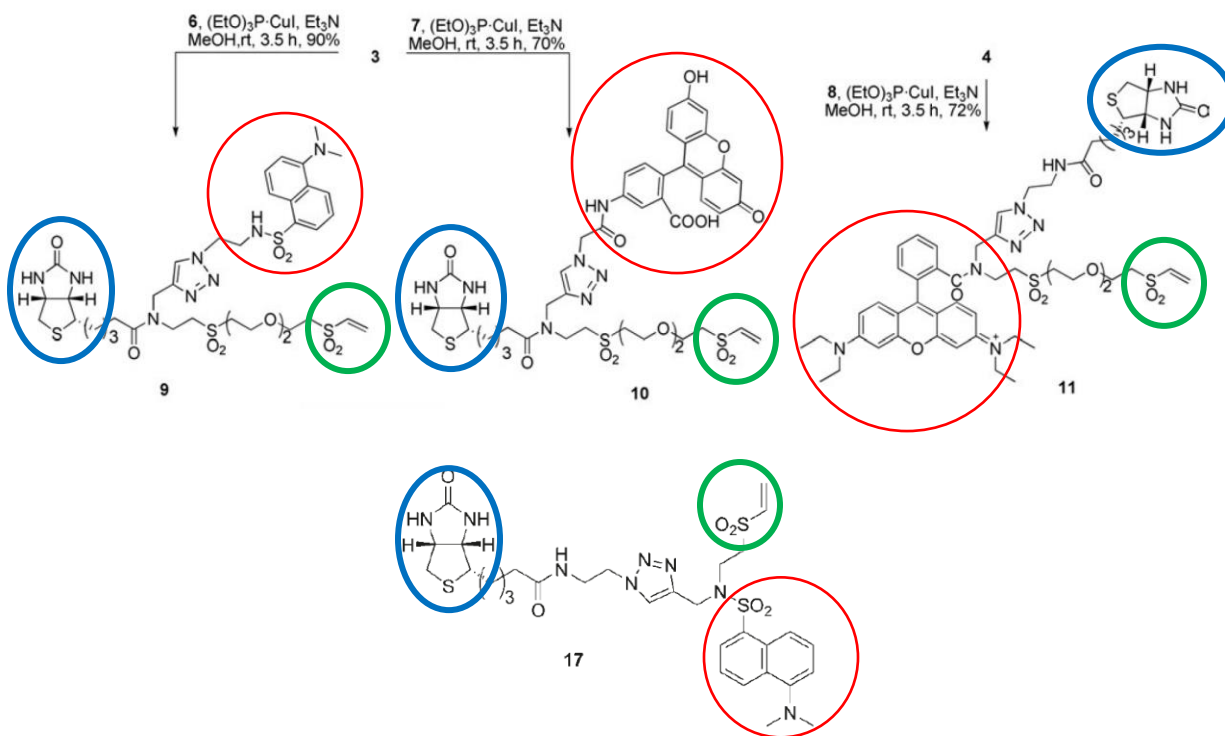
158. Counsel for DAC asked that I provide my opinions regarding whether SynAffix has demonstrated that the challenged claims are anticipated or obvious for the reasons provided in the Petition and its exhibits. In my opinion, SynAffix has failed to prove anticipation or obviousness of the challenged claims.

A. Ground 1: SynAffix Fails to Show Morales-Sanfrutos and Straus Anticipate Claims 1-3, 6, 24-25, and 33.

1. Morales-Sanfrutos (EX1005)

159. In my opinion, Morales-Sanfrutos does not disclose the hydrophilic linker or cell-binding agent-drug conjugate of claims 1-3, 6, 24, 25, and 33.

160. As discussed in Section VII.A, Morales-Sanfrutos discloses a reporter system, which is a tool for visualizing the activity of biomolecules in *in vitro* assays. Morales-Sanfrutos describes “bifunctional tag single attachment point reagents (BTSAP),” such as compounds **9-11** and **17** (reproduced below), which include a biotin tag (annotated below with blue circles), a fluorescent tag (annotated below with red circles), and an “electrophilic vinyl sulfone group” that “function[s] as a reactive linking group” (annotated below with green circles). EX1005 at 4039-4040.

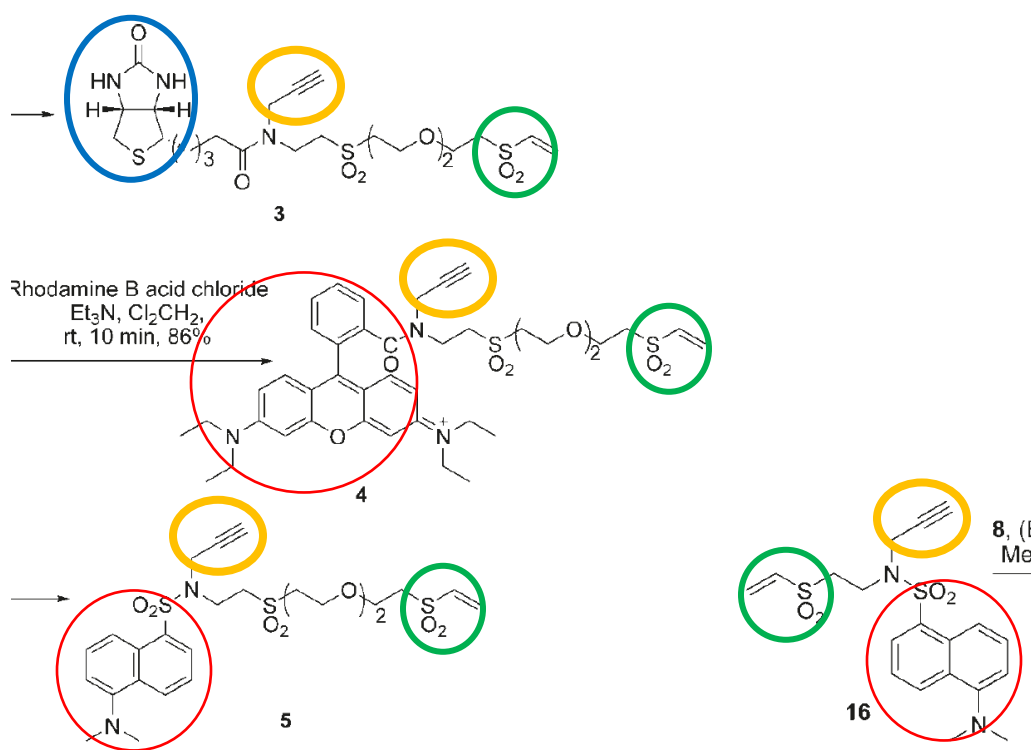


EX1005 at 4041-4042.

161. Morales-Sanfrutos discloses that vinyl sulfone—not vinyl alone—is a reactive functional group that enables reaction of its compound with a protein. For example, Morales-Sanfrutos explains that vinyl sulfone “is an appealing function for

protein conjugation through the Michael-type addition with the amine and thiol groups present in the proteogenic residues under mild conditions that are compatible with their biological function.” EX1005 at 4040.

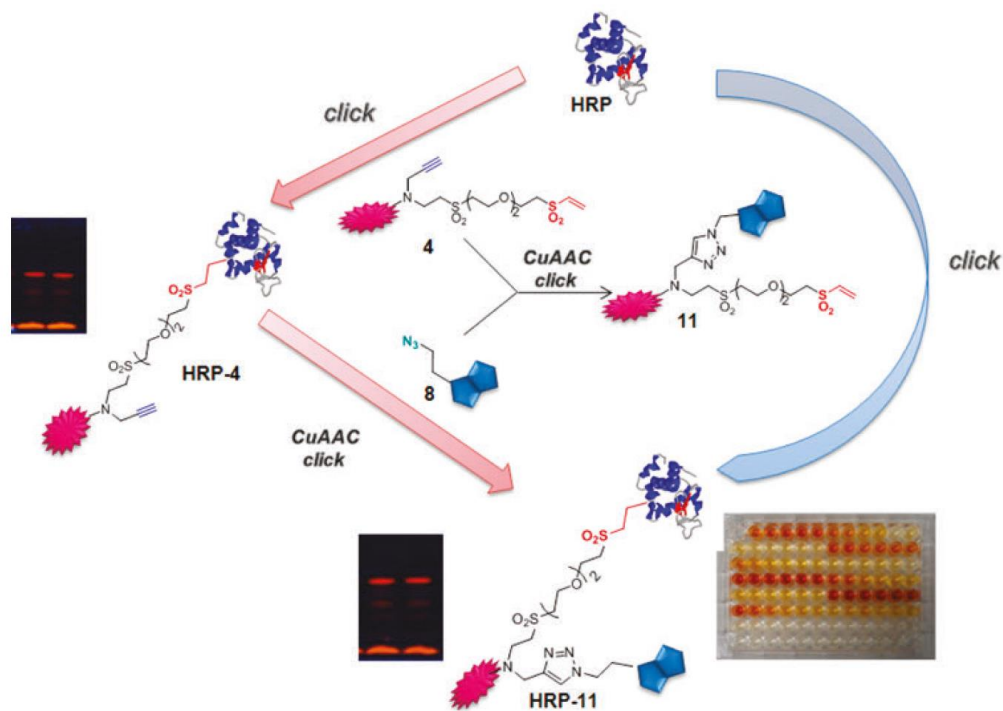
162. Morales-Sanfrutos describes the chemical synthesis of the BTSAP reagents from “alkyne vinyl sulfone derivatized tags (AVST),” such as compounds **3-5** and **16** (reproduced below), containing a vinyl sulfone (annotated with green circles) and a terminal alkyne group (annotated with orange circles) that may react with an azide moiety from another compound via a copper-catalyzed reaction for “click CuAAC attachment of a second azide functionalized tag.” EX1005 at 4039-4040.



EX1005 at 4041-4042 (Schemes 1-3 depicting copper-catalyzed reactions of AVST compounds).

163. Morales-Sanfrutos emphasizes that “copper catalyst is toxic for living organisms and induces degradation of the structures of the biomolecule in vitro.” EX1005 at 4040; *id.* at 4043 (“the problem of the use of copper in bioconjugation whose toxicity for living organisms and potential to induce degradation of the structure of the biomolecule in vitro are important drawbacks”). Morales-Sanfrutos describes the alkyne in its AVST compounds as reacting only to a small-molecule “azide derivative of a second tag,” not to any protein or biomolecule, “while leaving unreacted the vinyl sulfone group for the ulterior coupling with biomolecules.” EX1005 at 4040; *id.* at 4041-4042 (Schemes 2-3).

164. Morales-Sanfrutos does not disclose any chemical group other than vinyl sulfone as a functional group enabling reaction with a peroxidase enzyme, horseradish peroxidase (“HRP”). For example, in Scheme 4 (reproduced below), Morales-Sanfrutos discloses the reaction of HRP with compound **4** having both vinyl sulfone and alkyne that yielded a labeled **HRP-4** as the product, with vinyl sulfone enabling the reaction of compound **4** with HRP, while leaving the terminal alkyne group intact for a subsequent reaction with compound **8**, a small-molecule azide-labeled biotin:



EX1005 at 4044.

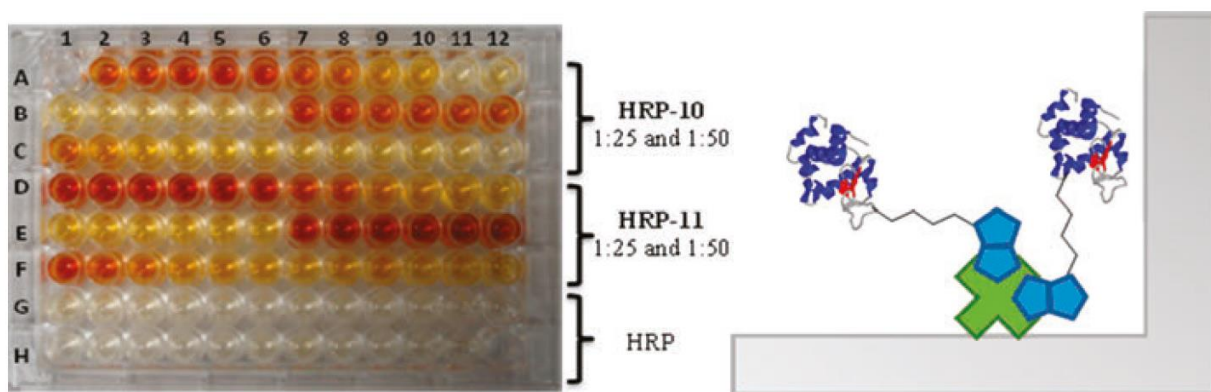
165. Moreover, Morales-Sanfrutos does not disclose that the alkyne in the AVST compounds, or in HRP-4 (shown above), enables any reaction with a protein, such as HRP. Morales-Sanfrutos only discloses the **vinyl sulfone** group as enabling the reaction to HRP. EX1005 at 4040 (“vinyl sulfone is an appealing function for protein conjugation through the Michael-type addition with the amine and thiol groups present in the proteogenic residues under mild conditions that are compatible with their biological function”). Indeed, Dr. Chari testified that Morales-Sanfrutos does not disclose reacting the alkyne group in its compounds to any cell-binding agent. EX2037 at 30:5-32:2. Moreover, while in the “Introduction” section, Morales-Sanfrutos states that the drawbacks of copper catalysts “have been

overcome by developing copper-free azide alkyne cycloaddition strategies,” citing literature publications (EX1005 at 4040), such copper-free reactions would require more complex alkyne moieties (such as a compound with a strained alkyne group that is destabilized by the structural strain to facilitate the copper-free reaction). All of the alkyne-containing compounds disclosed in Morales-Sanfrutos have a simple terminal alkyne group and would require a copper catalyst to catalyze their reaction with an azide.

166. Morales-Sanfrutos also does not disclose a “cell-binding agent,” either under my proposed construction of that term (discussed above) or under SynAffix’s broad interpretation of that term. SynAffix argues that HRP is a cell-binding agent. But Morales-Sanfrutos describes labeling the peroxidase enzyme HRP with its BTSAP reagents “to generate a dual **reporter group** (i.e., fluorescence and **peroxidase activity**) that may be also coupled to any recognition system” via the biotin tag. EX1005 at 4042 (emphasis added). Morales-Sanfrutos refers to the labeled HRPs as a “dual reporter” with “fluorescence and peroxidase activity,” meaning the HRP functions as a reporter through its peroxidase activity, not through binding to any specific cell populations. *Id.* at 4039, 4043.

167. For example, Figure 2 of Morales-Sanfrutos (reproduced below) illustrates the use of the biotin-tagged HRP reporter. EX1005 at 4043. The biotin tag (depicted in blue shape) binds to a commercial “avidin” (depicted as green cross)

that “was immobilized onto the surface of ELISA plate wells,” which anchors the conjugated peroxidase reporter within the wells. *Id.* After washing the unbound peroxidase reporter molecules from the wells, the “**peroxidase activity**” of HRP enzyme present in the wells was assayed. *Id.* (emphasis added). Wells with stronger color (from the product of the oxidation reaction) indicate the presence of a larger amount of HRP reporter in the wells. Thus, HRP is a reporter in *in vitro* assays based on its peroxidase enzymatic activity.



EX1005 at 4043 (Figure 2).

168. Therefore, a POSITA would not understand HRP to be a cell-binding agent; rather, a POSITA would understand HRP to be a reporter as disclosed by Morales-Sanfrutos and used by scientists. *See also* EX1005 at 4041 (“HRR has been coupled to other molecules to **use the peroxidase activity as a reporter**”) (emphasis added). As explained above in Section VII.A-B, HRP is a peroxidase enzyme that catalyzes oxidation of organic substrates by hydrogen peroxide, and it is widely

utilized in cell-free biochemistry assays (*e.g.*, western blotting, ELISA) to detect proteins, not as a cell-binding agent.

2. Straus (EX1006)

169. In my opinion, Straus does not establish that the HRP disclosed in Morales-Sanfrutos is a cell-binding agent, either under my proposed construction of that term (discussed above) or under SynAffix's broad interpretation of that term.

170. As discussed in Section VII.B, Straus describes cytochemical studies of potential binding of HRP to previously dried and cold-methanol-treated cells under highly artificial conditions. For example, Straus discloses that “[b]inding sites for horseradish peroxidase (HRP) with **unusual** properties, were detected on the surface of cultured and isolated cells after the cells (**on the cover slips**) had been **quickly dried, fixed in cold methanol, and post-fixed in a paraformaldehyde solution.**” EX1006 at 277 (emphasis added). Straus repeatedly emphasizes the “[i]mportance” of the “**initial treatment of dried cells with cold methanol,**” which it describes as “**essential** to attain a strong binding of HRP to the cell surface.” *Id.* at 279 (emphasis added); *id.* at 282 (“The **initial treatment of dried cells with cold methanol was essential** to obtain a strong binding of HRP to the plasma membrane and to prevent a significant ‘background’ adsorption of HRP.”). Straus reports that in cells “without having been first dried, the reaction for the surface-bound HRP was relatively weak.” *Id.* As Dr. Chari admitted, drying cells and treating them with

methanol would cause the cells to die. EX2037 at 24:22-27:3. Such conditions are not the conditions for cell-binding as contemplated by the '682 Patent.

171. The binding studies conducted under the unusual conditions of Straus do not establish that HRP would necessarily bind to cells under normal physiological conditions. Moreover, as discussed in Section IX.B, the '682 Patent defines a “cell-binding agent” 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.**” EX1001 at 14:39-44. Straus does not demonstrate HRP as having the ability to target or bind specific cell populations to allow the therapeutical or biological modification of such cells.

172. Straus merely states that “[b]inding sites for [HRP], with **unusual properties**, were detected on the surface of cultured and isolated cells” that were previously dried, treated with methanol, and fixed in a paraformaldehyde solution, EX1006 at 277 (emphasis added), indicating that HRP’s ability to bind cells is atypical and unusual. As discussed above in Section VII.B, Straus also describes various limitations of its study, including the presence of artifacts, which further demonstrate the uncertainty of its conclusions. EX1006 at 283-284. As discussed above in Section VII.B, Straus’s teachings regarding HRP’s purported cell-binding activity are not mainstream, well-known, or relied upon; rather, as illustrated by

Morales-Sanfrutos, HRP is routinely used as a reporter to detect the presence of a protein, *e.g.*, in cell-free assays.

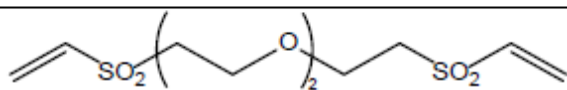
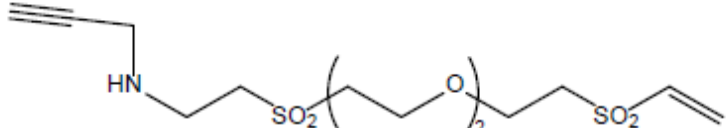
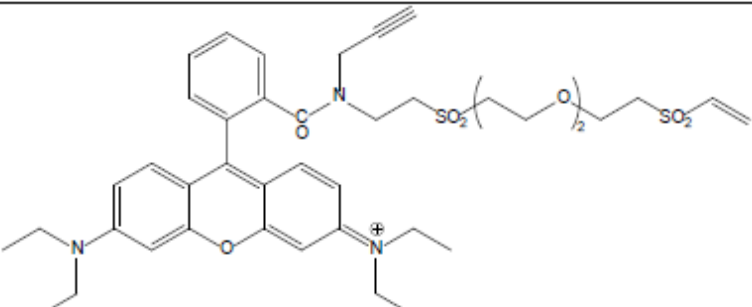
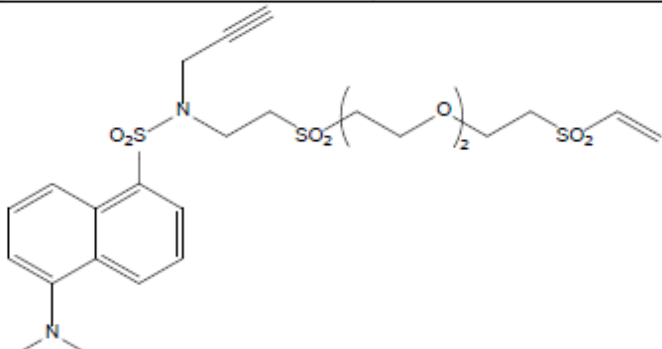
3. Claim 1

173. In my opinion, Morales-Sanfrutos and Straus do not anticipate claim 1.

Claim 1 claims a hydrophilic linker of Formula I:

Structure	Formula
$Y-R_1-T-Q-R_2-T-T-R_3-T-R_4-Z$ $\begin{matrix} \diagup \\ R_5 \end{matrix}$ $\begin{matrix} \diagdown \\ R_6 \end{matrix}$	I

174. SynAffix argues that each of four compounds (compounds 1, 2, 4, and 5 in Table B1, reproduced below) disclosed in Morales-Sanfrutos anticipates claim 1. Petition at 27. I disagree.

Cmpd	Bifunctional PEG Cross-linkers
1	
2	
4 ⁴	
5 ³	

(a) “Y” and “Q”

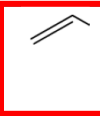
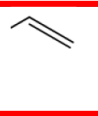
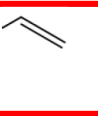
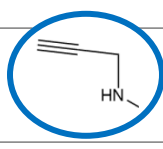
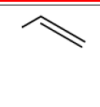
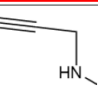
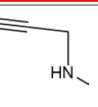
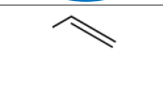
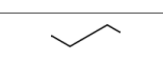
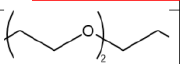
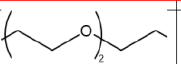
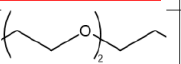
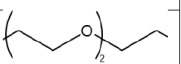
175. In my opinion, SynAffix incorrectly maps each of the above four compounds to the elements of Formula I. See Petition at 28-30 (Table B2).

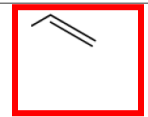
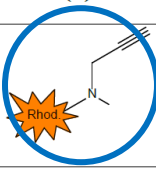
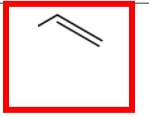
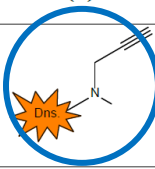
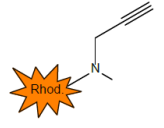
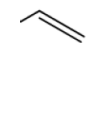
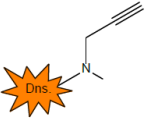
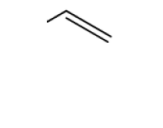
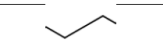
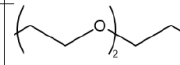
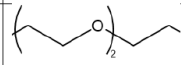
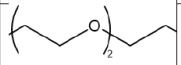
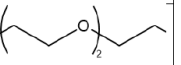
176. For example, SynAffix splits the vinyl sulfone in Morales-Sanfrutos’ compounds in half—mapping the vinyl to Y and the sulfone to Q. As discussed above in Section IX.A, the claimed “Y” group must be a **functional group** that independently **enables reaction** with a cell-binding agent. As Dr. Chari testified, vinyl itself cannot enable reaction with a cell-binding agent and it does not meet the

“Y” limitation; rather, the entire vinyl sulfone group must be mapped to “Y” as a functional group that enables reaction. *See* EX2037 at 19:15-22:9, 48:12-49:12, 52:16-53:1; EX1003 at ¶¶103, 107 (Dr. Chari relying on “vinyl sulfone”).

177. Once the entire vinyl sulfone is mapped to Y as required by the claim’s definition of Y, Morales-Sanfrutos does not disclose any compound with a separate sulfone that can be mapped to Q. Claim 1 requires that when Q or T is -S(O)₂- (sulfone), “m and n are not 0.” EX1002 at 1:38-39. At least one of Q and T is missing from the compounds of Morales-Sanfrutos. The same sulfone from a single vinyl sulfone of Morales-Sanfrutos cannot be mapped to both Y and Q.

178. Therefore, SynAffix’s mapping of 1, 2(a), 2(b), 4(a), and 5(a) in its Table B2 (reproduced below) fail at least because vinyl does not meet the claim’s requirement for Y and, once the entire vinyl sulfone is mapped to Y, the claim element Q would be missing in each compound, as highlighted in red boxes below. Notably, SynAffix acknowledges that the sulfone group in Compound 5 that belongs to a “dansyl” group is irrelevant to this analysis. *See* Petition at Tables B1-B2.

Morales-Sanfrutos' Compounds 1-2 (Table B1)				
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				
R ₁	absent ⁵	absent	absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R ₂				
p	2	2	2	2
n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R ₃	absent		CH ₂	absent
R ₄	absent	absent	CH ₂	absent

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				
R ₁	absent		absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R ₂				
p	2	2	2	2

n	1	1	1	1
T	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₃		absent	absent	absent
R₄	absent	absent		absent

179. SynAffix's mapping of 2(c), 4(b), and 5(b) in its Table B2 (shown above) also fail. In each of 2(c), 4(b), and 5(b), SynAffix maps a moiety containing an **alkyne** group (shown above, highlighted with blue circles) to Y. But, as discussed in Sections VII.A and X.A.1, Morales-Sanfrutos does not disclose the terminal alkyne group in its compounds reacting with any biomolecule (such as HRP), much less any cell-binding agent. Morales-Sanfrutos only discloses the alkyne reacting with small-molecule azide-containing tags (such as biotin or fluorescence tags) in the presence of a copper catalyst. As Dr. Chari testified, Morales discloses reaction of the alkyne only with an azido (*viz.* azide) group in biotin and other small molecules that are **not** cell-binding agents. EX2037 at 30:5-32:2.

180. For example, Morales-Sanfrutos describes the reaction of alkyne in its compounds to a small-molecule "azide derivative of a second tag," not to any biomolecule (*e.g.*, HRP), "while leaving unreacted the vinyl sulfone group for the ulterior coupling with biomolecules." EX1005 at 4040; *id.* at 4041-4042 (Schemes 2-3). In Scheme 4, Morales-Sanfrutos discloses the reaction of HRP with compound **4** (having both vinyl sulfone and alkyne) that yielded compound **HRP-4**, with vinyl

sulfone enabling the reaction of compound **4** with HRP, while leaving the alkyne intact for a subsequent reaction with compound **8**, an azide-labeled biotin.

181. Additionally, as discussed above in Sections VII.A and X.A.1, the alkyne in Morales-Sanfrutos' compounds is designed to react with an azide in another molecule, which must be catalyzed by a copper catalyst. Yet Morales-Sanfrutos repeatedly emphasizes that "copper catalyst is toxic for living organisms and induces degradation of the structures of the biomolecule in vitro." EX1005 at 4040; *id.* at 4043 ("the problem of the use of copper in bioconjugation whose toxicity for living organisms and potential to induce degradation of the structure of the biomolecule in vitro are important drawbacks"). Dr. Chari confirmed that a POSITA was moving away from copper catalysts due to their toxicity. EX2037 at 33:18-34:8. In my opinion, mapping the alkyne in Morales-Sanfrutos' compounds to Y for reaction with a cell-binding agent (*e.g.*, a biomolecule), as SynAffix has done in its tables, is contrary and opposite to Morales-Sanfrutos' teachings.

182. Furthermore, as discussed above in Sections VII.A and X.A.1, Morales-Sanfrutos does not disclose any biomolecule, let alone any cell-binding agent, that can react with the terminal alkyne group in the compounds disclosed in Morales-Sanfrutos (*e.g.*, an azide group that can react with an alkyne). HRP does not naturally contain any azide group. In my opinion, the HRP disclosed in Morales-

Sanfrutos does not contain any azide that can react with the alkyne moiety in Morales-Sanfrutos' compounds.

183. Morales-Sanfrutos does not disclose any compound using alkyne as the functional group that enables reaction with any cell-binding agent.

(b) **“Cell-Binding Agent”**

184. In my opinion, Morales-Sanfrutos and Straus do not disclose any “cell-binding agent” as required by claim 1, either under my proposed construction of that term (discussed above) or under SynAffix's broad interpretation of that term.

185. SynAffix argues that claim 1 does not require a cell-binding agent because the claim “does not require actual conjugation” to this agent. Petition at 31. I disagree. Claim 1 requires that Y be “a **functional group that enables reaction** of the hydrophilic linker **with a cell-binding agent.**” The prior art reference must disclose or identify “a cell-binding agent” with an appropriate chemical group that can react with the claimed “Y”. Absent such disclosure, the claim limitation is not met by the prior art to establish anticipation.

186. As discussed above in Sections VII.A-B and X.A.1-2, neither Morales-Sanfrutos nor Straus discloses HRP as a cell-binding agent. Morales-Sanfrutos does not disclose any “cell-binding agent” as it does not disclose or even suggest that HRP binds to any cells. Rather, as discussed above, Morales-Sanfrutos specifically

describes HRP as a reporter that functions through its peroxidase enzymatic activity, **not** through binding to any cells. EX1005 at 4039, 4043.

187. SynAffix relies on Straus for alleged prior-art teaching of HRP as a “cell-binding agent.” Petition at 36. But, as noted above, Morales-Sanfrutos expressly describes HRP as a peroxidase reporter for *in vitro* biological assays, not for binding to any cells. In contrast, as discussed above, Straus describes “unusual” binding of HRP to previously dried and methanol-treated cells under highly artificial conditions. The disclosures of Morales-Sanfrutos and Straus are unrelated to each other. SynAffix does not use Straus to confirm the teachings of Morales-Sanfrutos, but instead relies on Straus to supply the missing claim limitation of “cell-binding agent.”

188. SynAffix fails to show that the HRP in Morales-Sanfrutos is a cell-binding agent, under *either* my construction *or* SynAffix’s broad interpretation of that claim term. Regarding “cell-binding agent,” SynAffix asserts in a single sentence that “HRP is a known cell-binding agent,” citing page 277 of Straus and paragraphs 59 and 90 of the Chari declaration. Petition at 36. Paragraph 90 of the Chari Declaration repeats the same sentence as the Petition, EX1003 at ¶90. Paragraph 59 of the declaration merely states that “Straus discloses that the [HRP] enzyme **may** bind to the surface of a variety of cells, including macrophages, fibroblasts, mast cells and endothelial cells,” citing page 277 of Straus without

further explanation. EX1003 at ¶59. The cited page (page 277) of Straus states that “[t]he occurrence of mannose-specific binding sites for horseradish peroxidase (HRP) in macrophages, fibroblasts, mast cells and endothelial cells of rat tissues has been demonstrated earlier by a **cytochemical method**,” and that “[i]n the present **cytochemical study**, binding sites for HRP with unusual properties were detected at the surface of cultured and isolated cells.” EX1006 at 277 (emphasis added).

189. Straus does not provide detailed information on those earlier studies, including whether the cells were treated and/or studied under artificial conditions. For the “present” study, as discussed above in Sections VII.B and X.A.2, Straus describes a cytochemical method that involves highly artificial conditions, such as drying the cells, treating them with cold methanol, and fixing them in a paraformaldehyde solution. Straus does not establish that HRP is a cell-binding agent under normal physiological conditions. Rather, Straus emphasizes the “[i]mportance” of the “initial treatment of dried cells with cold methanol.” EX1006 at 279, 282. Those disclosures of Straus demonstrate the opposite—that HRP does not necessarily and inherently bind cells under normal physiological conditions. Moreover, in view of the highly artificial conditions used by Straus, a POSITA would not have looked to Straus to inform their understanding of Morales-Sanfrutos regarding HRP.

4. Claim 2

190. In my opinion, Morales-Sanfrutos and Straus do not anticipate claim 2 at least for the reasons provided above for claim 1, and for additional reasons below.

191. For claim 2, SynAffix cites Morales-Sanfrutos' compound 2 and argues that compound 2 has an **amino** group that can be mapped to Z, and that "biotin may be attached to this amino group **via an amide bond.**" Petition at 32 (emphasis added). As discussed above for claim 1, SynAffix's mapping of 2(a) and 2(b) in its table corresponds a group containing amino and alkyne to "Z". Petition at 28. But this mapping in 2(a) and 2(b) is incorrect at least because vinyl does not meet the claim's requirement for Y (as discussed above) and, once the entire vinyl sulfone is mapped to Y, Q would be missing in compound 2.

192. In addition, as the Board noted (Paper 25 at 41-42), SynAffix's analyses of claim 1 and claim 2 are internally inconsistent. For claim 1, it argues that "Z is the **alkynyl** group" in compound 2 (Petition at 30) (emphasis added), and that the alkynyl can react with an azide group in biotin to form a linkage (Petition at 31-32). For claim 2, it argues that the **amino** group in compound 2 is mapped to Z, and that biotin is attached to that **amino** via an amide bond (Petition at 32). Because claim 2 depends from claim 1, SynAffix should analyze the two claims consistently but it has failed to do so.

5. Claims 3, 6, 24, 25, and 33

193. Independent claims 3 and 24 recite cell-binding agent-drug conjugates of Formula II, and claims 6, 25, and 33 each depend from one of these claims.

Structure	Formula
$\text{Cb} - \left(\text{R}_1 - \text{Q} - \text{R}_2 - \text{T} - \text{R}_3 - \text{R}_4 - \text{Drug} \right)_q$ R_5 R_6	II

194. In my opinion, Morales-Sanfrutos and Straus do not anticipate each of claims 3, 6, 24, 25, and 33. SynAffix argues that **HRP-11**—a compound containing a modified HRP—discloses every limitation of this formula. Petition at 33-36. SynAffix maps HRP-11 to the elements of Formula II, arguing that the HRP moiety in HRP-11 is a cell-binding agent. *Id.* This argument fails at least because, as discussed above for claim 1, Morales-Sanfrutos and Straus do not disclose any cell-binding agent under either my construction or SynAffix’s construction of that term.

B. Ground 2: SynAffix Fails to Show Harris Anticipates or Renders Obvious Claims 1, 20-21, and 29-31.

195. In my opinion, SynAffix fails to show that Harris anticipates or renders obvious claims 1, 20-21, and 29-31 for at least the same reasons discussed above for Ground 1 and for the following reasons.

1. Harris (EX1007)

196. In my opinion, Harris does not disclose or render obvious the hydrophilic linker or related compounds of claims 1, 20-21, and 29-31.

197. As discussed in Section VII.C, Harris discloses poly(ethylene glycol) (PEG) derivatives “**activated with a sulfone moiety** for selective attachment to thiol moieties on molecules and surfaces,” and “[t]he PEG derivative is useful for modifying the characteristics of substances including modifying biologically active molecules and surfaces for biocompatibility.” EX1007 at Abstract (emphasis added). Harris discloses that the **active sulfone** moieties such as vinyl sulfone and haloethyl sulfone—not just vinyl or haloethyl without an adjacent sulfone—have the reactivity to allow reaction of the PEG linkers with thiol moieties. In my opinion, as discussed above and further discussed below, Harris’ active sulfone moieties as a whole (such as vinyl sulfone or haloethyl sulfone, as a whole) are the functional groups that enable the conjugation reaction.

198. For example, Harris discloses:

Specific sulfone moieties for the activated polymers of the invention are those having at least two carbon atoms **joined to the sulfone group -SO₂-** with a reactive site for thiol specific coupling reactions on the second carbon from the sulfone group. ... [T]he **active sulfone moieties** comprise **vinyl sulfone**, the active ethyl sulfones, including the **haloethyl sulfones**, and the thiol-specific active derivatives of these sulfones....

EX1007 at 7:3-22; *id.* at 9:37-10:1 (“active sulfone functional group”); *id.* at 11:8-17 (defining “functional group”). Thus, Harris identifies the entire vinyl sulfone and haloethyl sulfone as the reactive groups, and discusses them together as examples of active sulfone moieties.

199. Indeed, Harris specifically explains that haloethyl sulfone is in fact a **precursor** of vinyl sulfone in the thiol-coupling reaction:

[B]ased on the observable reaction kinetics as shown in Example 3, ... the chloroethyl and other activated ethyl sulfones and reactive derivatives are **converted to PEG vinyl sulfone**, and ... **it is the PEG vinyl sulfone or derivative thereof that is actually linked to the thiol moiety.**

EX1007 at 14:15-21; *id.* at 17:21-23. In other words, Harris teaches that haloethyl sulfone is converted to vinyl sulfone, which then reacts with the thiol moiety on another molecule. The presence of sulfone facilitates both reactions, the elimination of the halo to form the vinyl sulfone and the Michael addition reaction of the vinyl sulfone with the thiol moiety. Haloethyl alone would not achieve these reactivities necessary for the selective reaction with the thiol moiety described in Harris.

200. As discussed above for Ground 1, vinyl alone does not satisfy “Y”; the entire vinyl sulfone functional group should be mapped to Y. In view of Harris’ disclosures, including its disclosures that haloethyl sulfone is a precursor of vinyl sulfone, and its consistent usage of the phrase “**active sulfone** moieties” to describe

the functional group responsible for driving the reaction with the thiol moiety, a POSITA would understand that haloethyl sulfone (not just haloethyl) would be mapped to Y, similar to the mapping of the entire vinyl sulfone to Y, as required by the claims.

201. Accordingly, when the vinyl sulfone or haloethyl sulfone is mapped to Y, SynAffix's arguments fail because the claimed "Q" is then absent in Harris, for similar reasons discussed above for Ground 1.

202. As for its obviousness challenge, Harris is not from the same field of endeavor as the '682 Patent's inventions and does not qualify as relevant art. Harris does not relate to the field of therapeutic drug conjugates. Rather, Harris "relates to active derivatives of poly(ethylene glycol) and related hydrophilic polymers and to methods for their synthesis for **use in modifying the characteristics of surfaces and molecules.**" EX1007 at 1:2-6 (emphasis added). Harris' isolated disclosure about pharmaceuticals is general and non-specific, where it also states that "almost any substance could be modified":

It should be apparent to the skilled artisan that the dumbbell structures discussed above could be used to carry **a wide variety of substituents and combinations of substituents.** Pharmaceuticals such as aspirin, vitamins, penicillin, and others too numerous to mention; polypeptides or proteins and protein fragments of various functionalities and molecular weights; cells of various types; surfaces for biomaterials, **almost any substance could be modified.**

EX1007 at 18:31-19:2. Notably, Harris does not specifically teach conjugation of a drug to an antibody or other cell-binding agent for treating diseases. It only generally states that its linkers maybe used to link a wide variety of different materials or substrates, without specifically teaching the conjugation of a drug and a protein, much less the conjugation of a drug and a cell-binding agent. In my opinion, Harris relates to a different field of endeavor.

203. In addition, Harris is not reasonably pertinent to the problem facing the '682 Patent's inventor. As described in the '682 Patent, "there is 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." EX1001, 2:45-49. Because Harris does not teach linkers for use in therapeutic drug conjugates, nor any linkers that solve the identified need, it is not reasonably pertinent to this problem facing the inventor here.

2. Claim 1

204. In my opinion, Harris does not anticipate claim 1, nor does it render claim 1 obvious. Claim 1 recites a Formula I linker.

Structure	Formula
$Y-R_1-Q-R_2-T-R_3-R_4-Z$ $\begin{matrix} \diagup \\ \diagdown \end{matrix}$ $\begin{matrix} R_5 \\ R_6 \end{matrix}$	I

(a) **Anticipation**

205. SynAffix argues that claim 1 is anticipated by “Harris’ basic structure” of $R-(OCH_2CH_2)_n-Y$, where R and Y are “vinyl sulfone and/or halo-ethyl sulfone,” and Harris “discloses PEG derivatives comprising **two** sulfone moieties.” Petition at 38 (emphasis in original). SynAffix maps “vinyl” or “halo-ethyl” to “Y” of the claimed formula I, and “sulfonyl” of the same active sulfone moiety of Harris to “Q” of the claimed formula I. Petition at 38-39. Again, SynAffix incorrectly maps a single active sulfone moiety described in Harris (*e.g.*, vinyl sulfone or haloethyl sulfone) to two separate and distinct claim elements (Y and Q), when the claim expressly requires that Y be a “functional group that enable reaction” of the linker.

206. As discussed above in Sections VII.C and X.B.1, Harris identifies vinyl sulfone and haloethyl sulfone (not just vinyl and haloethyl) as the reactive functional group for the conjugation reaction with thiol moieties of another molecule. For example, Harris discloses that coupling the “**active sulfone moieties**” to the PEG linker allows the linker to “coupl[e]” with thiol moieties in other molecules. EX1007 at 6:8-14. Thus, Harris’ active sulfone moieties (vinyl sulfone or haloethyl sulfone) are the claimed “Y” group and necessary to enable the conjugation reaction. Harris’ active sulfone moieties cannot be divided and then mapped separately to Y (as vinyl or haloethyl) and Q (as sulfone). Doing so would contradict the disclosures of Harris and the requirements of the ’682 Patent claims.

207. For similar reasons discussed above for Ground 1, once the entire active sulfone moiety of Harris is mapped to Y, then there is no sulfone moiety in Harris' compounds to be mapped to Q (or T) to meet the claim's requirement that both Q and T must be present (i.e., m and n are not zero). Harris merely discloses PEG linkers without any sulfone as spacer elements, and with "one or more active sulfone" conjugation moieties incorporated at the end of the linker for reacting with thiol in other molecules. EX1007 at 6:11. Harris therefore does not disclose all elements of the claimed formula including the claimed Q (or T) element. Ground 2 fails for the same reasons discussed above for Ground 1.

208. SynAffix's Ground 2 arguments also fail for two other reasons.

209. **First**, Harris' disclosure of its "basic structure" $R-(OCH_2CH_2)_n-Y$, which allows R to be a wide variety of different activating groups, is exceedingly broad. Harris states that in the above structure:

Y represents $-SO_2-CH=CH_2$ or $-SO_2-CH_2-CH_2-X$ where X is a halogen.
R represents a group that **may be the same or different from Y**. 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 $CH_2=CH-SO_2-$, $Cl-CH_2-CH_2-SO_2-$, such as is referred to with respect to the above patents and published patent applications.**

EX1007 at 19:24-30. Thus, Harris discloses a broad genus in which R can be "a **polymer activation group other than**" vinyl sulfone or haloethyl sulfone, meaning

that R could be all possible activation groups. *Id.*

210. Regarding linking two different molecules to the linker, Harris states that “**more typically**, a heterobifunctional PEG derivative” with an active sulfone moiety on one end and a different activating moiety on the other end are used “to produce a molecule having two different activities.” EX1007 at 17:24-18:4. Thus, Harris teaches that R being different from Y is “more typical[,]” especially when linking two different molecules using its linker.

211. Harris also discloses that “[o]ther active groups for heterobifunctional sulfone-activated PEGs can be selected from among **a wide variety of compounds.**” EX1007 at 18:5-30. And on page 18, Harris lists a broad range of different active groups that could possibly be R, including active groups disclosed in literature references and patent publications cited in Harris. EX1007 at 18:5-30. Indeed, Dr. Chari testified that Harris’ disclosure is “broad,” and that Dr. Chari did not even calculate the total number of possible linkers disclosed by Harris’ broad disclosure. EX2037 at 35:11-36:7, 40:15-22, 43:7-44:1. Harris’ broad genus disclosure of R-(OCH₂CH₂)_n-Y does not anticipate the claimed formula with specific combination of the claimed elements because a POSITA would not readily envision the claimed combination of elements from reading Harris.

212. **Second**, Harris does not disclose any “cell-binding agent” as required by claim 1, either under my proposed construction or SynAffix’s broad interpretation

of that term. SynAffix does not attempt to demonstrate otherwise, as it does not argue that Harris invalidates claims 3, 24, and 26 and their dependent claims.

213. As discussed in Ground 1 for claim 1 (Section X.A.3), the asserted prior art must disclose or identify “a cell-binding agent” that can react with Y. This requirement applies not only to claim 1, but also to claims 20-21 and 29-31 (analyzed below in this Declaration) that each expressly recite “Y” as “a functional group that **enables reaction** of the compound **with a cell-binding agent**.” In the absence of any disclosure of “cell-binding agent” in the asserted prior art, the claim limitation is not fully met to establish anticipation. Here, Harris at best discloses unspecified biologically active molecules and proteins, which are not necessarily antibodies or cell-binding agents. EX1007 at 17:28-34.

214. For at least the above reasons, SynAffix’s anticipation arguments fail.

(b) **Obviousness**

215. SynAffix’s obviousness arguments in a single paragraph also fail. Petition at 39-40. To the extent SynAffix’s obviousness argument is similar to its anticipation argument, its obviousness argument fails for the same reasons discussed above, including its incorrect mapping of the active sulfone moieties of Harris to the claimed formula and the lack of any disclosure of a cell-binding agent.

216. Additionally, as discussed above in Sections VIII and IX, the Y conjugation moiety and the Q spacer element are separate and distinct components

of the claimed linker serving different purposes. SynAffix does not explain how any alleged prior-art teachings of the reactive Y conjugation moiety (*e.g.*, vinyl sulfone or haloethyl sulfone) and the hydrophilic Q spacer element (*e.g.*, sulfone) would be combined to achieve the claimed linker. For example, SynAffix does not identify any reason from the prior art to use sulfones (or other claimed spacer structures) as spacer elements. Besides pointing to sulfone-based **conjugation moieties** from the prior art, SynAffix has not identified any motivation to incorporate sulfone groups (or any other claimed Q/T groups) as **spacer elements** in the linker. In fact, Dr. Chari testified that there would be no reason to add sulfone-based spacers when PEG was already present. EX2037 at 39:14-40:5, 41:16-42:2. SynAffix also fails to explain why a POSITA would have been motivated to combine prior-art elements in a manner as claimed in the claimed formula.

3. Claims 20-21 and 29

217. Claims 20 and 29 recite a compound of Formula IV that is identical to Formula I except for the substitution of a “Drug” for the Z group. Claim 21 depends from claim 20. In my opinion, Harris does not anticipate claims 20-21 and 29, nor render these claims obvious for similar reasons discussed above for claim 1.

Structure	Formula
$Y-R_1-\text{---}Q-R_2-\text{---}_m-\text{---}T-R_3-\text{---}_n-\text{---}R_4-\text{Drug}$ $\swarrow \searrow$ $R_5 \quad R_6$	IV

218. **First**, SynAffix maps “Y” of Formula IV to only vinyl or haloethyl of the active sulfone moieties of Harris. Petition at 41. But neither vinyl nor haloethyl is “a functional group that enables reaction of the compound with a cell-binding agent” as discussed above for claim 1.

219. **Second**, a POSITA would not readily envision the claimed combination of the elements of Formula IV from reading Harris’ disclosure of $R-(OCH_2CH_2)_n-Y$, which allows R to be a wide variety of activating groups as discussed above for claim 1. This problem applies not only to SynAffix’s arguments regarding PEG derivatives having two sulfones (Petition at 41), which fail for the same reasons discussed above for claim 1, but also to its arguments regarding Harris’ alleged teachings of heterobifunctional PEG derivatives having an active sulfone moiety on one end and an NHS ester on the other end (Petition at 42).

220. As discussed above for claim 1, Harris discloses a wide variety of activating groups that may be used in heterobifunctional PEG derivatives. EX1007 at 18:5-30. From Harris’ broad disclosure of numerous possible activating groups, a POSITA would not readily envision a PEG derivative having an active sulfone moiety on one end and an NHS ester on another end.

221. **Third**, for the same reasons discussed above for claim 1, claims 20-21 and 29 require a “cell-binding agent” that can react with “Y”, but Harris does not disclose any “cell-binding agent” that can react with Y, as required by the claims.

222. **Lastly**, SynAffix’s obviousness arguments in a single paragraph rely on similar rationales for claim 1. Petition at 42-43. Those arguments fail for similar reasons provided above for claim 1 and/or for addressing SynAffix’s anticipation challenges of claims 20, 21, and 29.

4. Claims 30-31

223. In my opinion, Harris does not anticipate claims 30-31, nor does it render these claims obvious for similar reasons discussed above for claims 1, 20-21, and 29, and for additional reasons below.

224. Claim 30 requires that “m and n are integers from 1 to 5.” EX1002 at 11:6. Claim 31, which depend from claim 30, also includes that requirement. Thus, claims 30-31 require that Q and T must both be present. SynAffix overlooks this requirement of the claims in its analysis regarding Harris’ purported teachings of heterobifunctional PEG derivatives having an active sulfone moiety and an NHS ester group. In its analysis, SynAffix admits that “Q and R₂ are absent and m is 0.” Petition at 42. Thus, the heterobifunctional PEG derivatives do not anticipate or render obvious claims 30-31, for the additional reason that they lack the requisite Q and R₂ moieties required by claims 30-31.

C. Ground 3: SynAffix Fails to Show Singh in View of Harris Renders Obvious Claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31.

1. Singh (EX1008)

225. As discussed in Section VII.D, Singh discloses PEG linkers that may be conjugated to maytansinoid drugs. In a single sentence, Singh states that vinyl sulfone may serve as a “reactive functionality” for conjugation with thiol moiety, without mentioning vinyl sulfone again elsewhere, nor disclosing any compound containing vinyl sulfone. EX1008 at ¶[0134]. For example, none of the exemplified compounds disclosed in Singh’s figures contains any sulfone group. EX1008. As SynAffix admits, “Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, **save Q and T** (which must be $-P(=O)(OM)-$, or $-S(O_2)-$, or $-S(O)-$.” Petition at 44. SynAffix admits that Singh does not teach either Q or T.

226. Dr. Ravi Chari, one of the named inventors of Singh, testified that Singh “doesn’t include sulfones.” EX2037 at 38:15-39:1. Dr. Chari also testified that the inventors of Singh found that polyethylene glycol (PEG) led to increased hydrophilicity of the linker, *id.* at 36:12-21, that those inventors found it sufficient to use PEG alone to achieve the hydrophilicity, and that “there was no reason to add anything else,” *id.* at 39:14-40:5, 41:16-42:2. Thus, a POSITA would not have had a reason to modify Singh because, as Dr. Chari testified, Singh discloses that PEG had already achieved the desired properties, and there was no need to add other elements to Singh’s compounds.

2. Claim 1

227. In my opinion, claim 1 would not have been obvious over Singh in view of Harris for several reasons.

228. **First**, as in Grounds 1-2, SynAffix misreads the challenged claims and prior-art disclosures and incorrectly maps a single reactive vinyl sulfone functional group, allegedly taught by Singh and Harris, onto both Y and Q.

229. Singh discloses PEG linkers that SynAffix admits do not contain the claimed Q or T spacer element. Petition at 44, 46 (“Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, **save Q and T.**”) (emphasis added). Because Singh does not disclose the Q or T spacer element, SynAffix argues that a POSITA would have modified one or both of Singh’s reactive functionalities with vinyl sulfone.

230. SynAffix points to Singh’s disclosures of vinyl sulfone as one of several “reactive functionalities” and argues that a POSITA would have been motivated to incorporate vinyl sulfone in Singh’s linkers. Petition at 48-49 (citing EX1008 at [0134]). Singh defines “reactive functionality” as set forth below:

As used herein, the term “reactive functionality” refers to an amine-, a thiol- or a hydroxyl-reactive functionality. In other words, the **reactive functionality can react with amine, sulfhydryl(thiol), or hydroxyl group present on cell binding agent.** For example ... for thiol-reactive functionality, **the functionality could be** a maleimide, a halo

acetamide, or **a vinyl sulfone to give a thioether bond ...**

EX1008 at [0134].

231. SynAffix argues that “a POSA would have been motivated to replace one or both of the reactive functionalities in Singh’s bifunctional PEG cross-linkers with a vinyl sulfone group, resulting in Q or Q and T each being a sulfone group, and Y, or Y and Z, each being a vinyl group.” Petition at 48-49. But this mapping of the same vinyl sulfone to Y and Q is incorrect, as explained above for Grounds 1-2 in Sections X.A-B.

232. Singh teaches that vinyl sulfone possesses the “reactive functionality,” and Dr. Chari admits that it is the sulfone in the vinyl sulfone that enables the linker’s reaction. EX2037 at 22:1-3. Singh or Harris does not teach that vinyl alone has this capability. SynAffix’s mapping strategy is contrary to the meaning of the “Y” claim term and the prior-art disclosures.

233. **Second**, SynAffix argues that it would have been obvious to modify Singh’s linkers to incorporate “vinyl sulfones and related sulfonyl functionality” taught in Harris. Petition at 44. This argument fails for the same reasons discussed above for Harris in Ground 2 and discussed above for Singh in this Ground.

234. Additionally, SynAffix admits that “Harris’ vinyl sulfone-containing PEG derivatives are **nearly identical** to the bifunctional PEG cross-linkers of Singh and serve the same purpose.” Petition at 49. SynAffix does not argue why it would

have been obvious to modify the Singh structure with the “nearly identical” Harris structure, or what additional benefits that including Harris’ active vinyl sulfone groups (conjugation moieties) would confer to a Singh linker that already comprises vinyl sulfone (conjugation moieties). Indeed, as Dr. Chari testified, the inventors of Singh found that **polyethylene glycol (PEG)** led to increased hydrophilicity of the linker, EX2037 at 36:12-21, that the inventors found it sufficient to use PEG alone to achieve the hydrophilicity, and that “there was no reason to add anything else,” *id.* at 39:14-40:5, 41:16-42:2.

235. **Third**, SynAffix fails to show any motivation to achieve the claimed invention. The claimed invention comprises separate and distinct Y and Q elements. Vinyl sulfone was recognized in the art, including in Morales-Sanfrutos, Harris, and Singh, discussed above, as a reactive functional group. Even if a POSITA were motivated to add vinyl sulfone to a linker to serve as a Y group (*e.g.*, as a conjugation moiety at the end of the linker that enables reaction with a cell-binding agent), SynAffix fails to demonstrate any motivation in Singh or Harris to add sulfonyl groups to **a different part of the linker to achieve Q or T, the novel claimed spacer elements**. If a POSITA were motivated to add vinyl sulfone to the linker, the vinyl sulfone would be added to the **end** of the linker for the conjugation reaction, not as a spacer element in the middle between the two ends. SynAffix points to Harris’ methods of synthesizing linkers that comprise sulfone groups at the ends of

linkers—*i.e.*, to serve as conjugation moieties. Petition at 51 (“Examples 1 and 2 of Harris describe how to synthesize a PEG linker comprising a **terminal** vinyl sulfone or chloro-ethyl sulfone group...”), 52 (“modifying ... Singh to include vinyl sulfones ... as a reactive functionality that can form a thioether bond with a cell-binding agent or drug”). But these substitutions do not achieve a linker with sulfone group(s) as the Q or T spacer element.

236. As noted, SynAffix argues that the vinyl group is Y. Petition at 49. But, even assuming Y can be vinyl (as discussed above, this is incorrect), SynAffix fails to identify any motivation whatsoever to add **vinyl** alone to a linker to serve as a separate, distinct functional group that enables the linker to react with a cell-binding agent. As discussed above, and as SynAffix and its expert Dr. Chari admit, vinyl cannot enable reaction. The sulfone in the vinyl sulfone is what enables the reaction. EX2037 at 22:1-3. Vinyl alone would be ineffective. Thus, a POSITA would not have been motivated to select vinyl as the Y conjugation moiety.

3. Claim 2

237. In my opinion, Singh in view of Harris does not render claim 2 obvious at least for the same reasons provided above for claim 1, and for additional reasons below.

238. SynAffix argues that “Singh and Harris teach that Z can be maleimide or haloacetyl ... as required by claim 2.” Petition at 53. But keeping Z as maleimide

or haloacetyl as SynAffix argues for dependent claim 2 is inconsistent with its arguments for independent claim 1 to substitute the Z conjugation moiety with vinyl sulfone in order to supply a sulfone moiety to be mapped to T. Because claim 2 depends from claim 1, SynAffix should analyze the two claims consistently but it has failed to do so.

4. Claims 3-8, 10-12, 14-17, 24, and 26

239. For similar reasons discussed above for claim 1, claims 3-8, 10-12, 14-17, 24, and 26 would not have been obvious over Singh and Harris.

5. Claims 20-21 and 29

240. For similar reasons discussed above for claims 1, 3, 24, and 26, claims 20-21 and 29 would not have been obvious over Singh and Harris.

6. Claims 30-31

241. Singh in view of Harris does not render claims 30-31 obvious at least for the same reasons provided above for claims 1-2, 20-21, and 29, and for additional reasons below.

242. As discussed above in Section X.B.4, claims 30-31 require that Q and T must both be present (m and n are not zero). As also discussed above throughout this Declaration, “Y” in claims 30-31 must be mapped to a reactive functional group, such as vinyl sulfone, not just vinyl. SynAffix overlooks these limitations in its analysis regarding claims 30-31. Even assuming a POSITA were to modify Singh’s

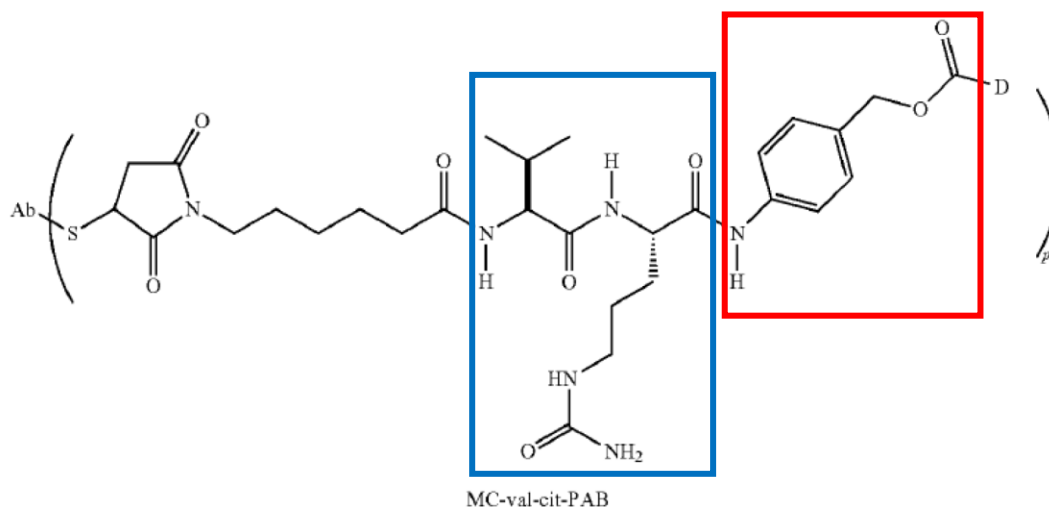
linker to incorporate **two** vinyl sulfone conjugation moieties at the two ends of the linker, one vinyl sulfone must be mapped entirely to Y (as discussed above). That leaves only one sulfone group (from the second vinyl sulfone) for potential mapping to Q or T. Thus, one of Q and T would be missing. And, as discussed above, SynAffix fails to demonstrate that Singh in view of Harris would have motivated a POSITA to incorporate any Q or T spacer element, without its flawed reliance on vinyl sulfone as a conjugation moiety.

D. Ground 4: SynAffix Fails to Show Singh in View of Harris and Bhakta Renders Obvious Claims 9 and 13.

1. Claims 9 and 13

243. Claims 9 and 13 depend from claim 3. In my opinion, claims 9 and 13 would not have been obvious over Singh in view of Harris and Bhakta for reasons discussed above in Ground 3 and for additional reasons below.

244. SynAffix argues Bhakta discloses the following structure with a dipeptide val-cit (highlighted in blue box) and a para-aminobenzylcarbamoyl (PAB) group (highlighted in red box). Petition at 71-72.



245. SynAffix argues that “[a] POSA would have been motivated to use the well-known val-cit-PAB linker of Bhakta to replace, e.g., the disulfide linkage of Singh.” Petition at 72. SynAffix, however, does not explain which “disulfide linkage of Singh” is being replaced, which specific compound of Singh it is referring to as the starting point for the structural modification, and whether the modified compound would still meet all the elements of claim 9 and 13, including the Q, T, m, n, and R₁ through R₆ elements in the claimed Formula II. SynAffix also does not explain **how** a POSITA would have allegedly combined the prior-art teachings to arrive at the claimed conjugate (*e.g.*, how to modify any particular compound from Singh to allegedly incorporate the val-cit-PAB linker of Bhakta), and whether a POSITA would have had a reasonable expectation of success in doing so.

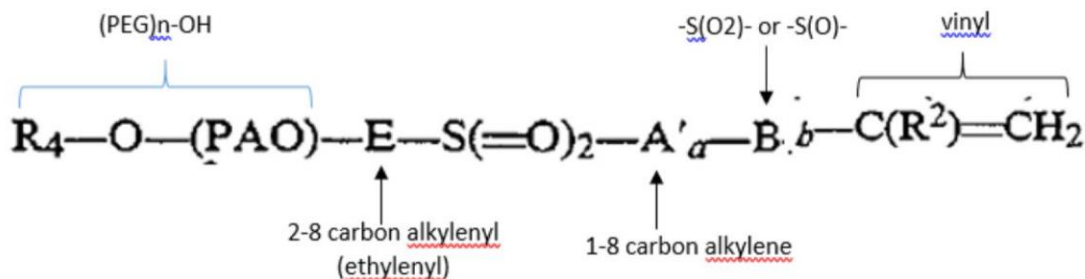
E. Ground 5: SynAffix Fails to Show Singh in View of Harris and Snow Renders Obvious Claims 2, 25, and 32-34.

246. Claim 2 depends from claim 1. Claim 25 depends from claim 24. Claim 32 depends from claims 30 and 31. Claim 33 depends from claim 3. Claim 34 depends from claim 20.

247. In my opinion, claims 2, 25, and 32-24 would not have been obvious over Singh in view of Harris and Snow for the same reasons set forth above for Ground 3 with respect to the corresponding independent claims, and for the additional reasons set forth below.

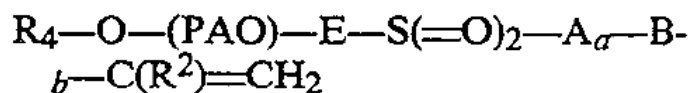
1. Claims 2, 25, and 32-34

248. SynAffix argues that Snow allegedly discloses the following structure:



Petition at 73-74 (citing EX1010 at 7:51-65). SynAffix argues that “a POSA would have been motivated to replace at least one of the maleimide-containing arms in Singh’s bifunctional bis-maleimide PEG crosslinking agent with the bis-vinyl sulfone group of Snow because such substitution would further enhance the hydrophilicity of the PEG linkers” Petition at 74. I disagree for several reasons.

249. **First**, while Snow discloses the above genus structure, it defines the elements of that structure as **broad** genus groups, not the limited choices SynAffix depicts above. EX1010 at 7:51-65 (defining R₄ as broad genus (not just H), and E, A, a B, b, and R₂ as “defined above”); *see also id.* at 5:61-6:10, 6:12-35, 6:56-57 (defining each of E, A, B, and R₂ as broad genus, which are referenced at 7:65 as “defined above”). Specifically, Snow discloses that in the structural formula depicted at 7:54-56:



- “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” (*id.* at 7:58-60);
- “E, A, a B, b, and R₂ are defined above” (*id.* at 7:65), and Snow further discloses in preceding paragraphs that:
- “E is hydrogen, or an alkylene group of 1 to 8 carbons, or an alkylenyl group of 2 to 8 carbons, preferably an ethylenyl group, or a substituted aryl group of the formula



where:

G is a leaving group, preferably, a nitro group or a halogen such as fluorine or bromine or chlorine, or G is a vinyl group, or a haloalkyl group such as a chloromethyl or bromomethyl group, or a vinyl sulfone group, each R¹ is an electron withdrawing group

independently selected from fluorine, trifluoromethyl, nitro, and functional equivalents thereof;

i is 0 or an integer from 1 to 4; and

h is (4-i)” (*id.* at 5:61-6:10);

- “A is an arylene or an aralkylene group of 6 to 8 carbons which may be unsubstituted or substituted with one or more low molecular weight substituents such as a halogen, methyl, methoxy, trifluoromethyl, and the like; or 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 that is comprised in an ether or an ester group, or a sulfur atom that is comprised in a sulfide or a sulfone or a sulfoxide group, or a nitrogen atom as part of a heteroaromatic ring or an amide group” (*id.* at 6:12-23);
- “a is zero or one” (*id.* at 6:24);
- “B is a sulfur atom, a sulfone group, or a sulfoxide group” (*id.* at 6:25-26);
- “b is zero or one” (*id.* at 6:27); and
- “R² is selected from H, F, C₁, CF₃ and alkyl groups of 1 to 8 carbon atoms” (*id.* at 6:56-57).

250. SynAffix does not explain how and why a POSITA would have selected the specific structural elements it depicts in the Petition (at 73-74) from the broad genus groups actually disclosed by Snow.

251. **Second**, SynAffix does not explain why a POSITA would have selected the above genus structure over other structures disclosed in Snow. Snow discloses

a series of “preferred,” “more preferred,” and “even more preferred” embodiments. EX1010 at 7:66-9:48 (using the word “preferred” **eleven** times to describe such preferred embodiments). SynAffix does not explain why a POSITA would not have instead looked to the more preferred embodiments of Snow.

252. **Third**, SynAffix argues, without any support, that “bis-vinyl sulfone linkers of Snow impart higher water solubility.” Petition at 75. But Snow does not disclose anything about its linkers’ solubility or hydrophilicity. It appears that the reason SynAffix has to rely on Snow for the dependent claims at issue is because when it mapped Singh’s compounds to the claimed formula, many of the R₁, R₂, R₃, and R₄ groups are “absent.” Petition at 57-59, 65-66. SynAffix combination of Singh and Snow allows it to assemble a compound with the R groups being alkyl, rather than absent, in order to meet the limitations of the dependent claims. Such structural changes to **add** several alkyl groups to a molecule would likely decrease the hydrophilicity of the molecule.

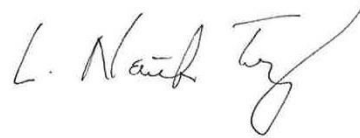
253. **Lastly**, with respect to claim 2, SynAffix argues that it “specifies that Z comprises a maleimido group, among other options.” Petition at 73. As discussed above in Section X.C.3, keeping Z as maleimide as SynAffix argues for claim 2 is inconsistent with its arguments for claim 1 to substitute the Z conjugation moiety with vinyl sulfone in order to supply a sulfone moiety to be mapped to T.

XI. CONCLUSION

254. 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 6th day of December, 2024, at Binghamton, New York.

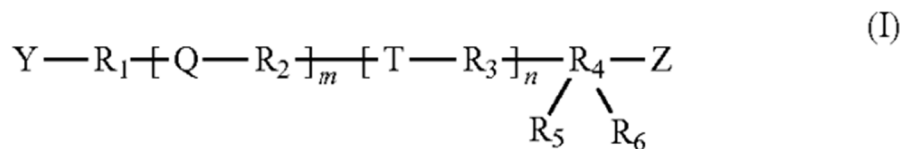
A handwritten signature in cursive script, appearing to read "L. Nathan Tumey". The signature is written in dark ink and is positioned above a horizontal line.

Dr. L. Nathan Tumey

Appendix A

IPR2022-01531 – CHALLENGED CLAIMS

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 $\text{—S(O}_2\text{)—}$, 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 $\text{—S(O}_2\text{)—}$, 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

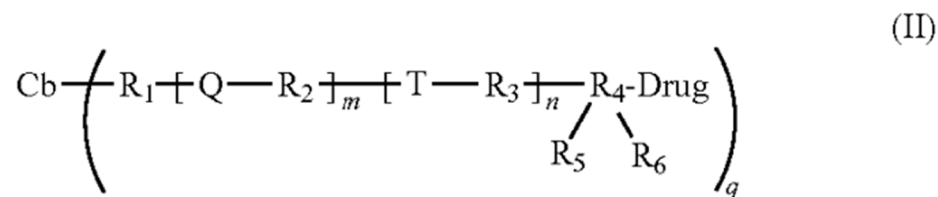
(OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently —S(O₂)— or —S(O)—, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof,

or R₁, R₂, R₃ and R₄ 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 (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently —S(O₂)— or —S(O)—, R₂ is a straight or 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, R₁, R₃, or R₄;

R₅ and R₆, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt.

2. The hydrophilic linker of claim 1, wherein Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group.
3. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$;

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)— , m and n are not 0;

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 $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $\text{—S(O}_2\text{)—}$ or —S(O)— , R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 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 $\text{—S(O}_2\text{)—}$ or —S(O)— , R_2 is a straight or 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 $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof; M is H, or Na, or K, or $N^+R_1R_2R_3$ or a pharmaceutical salt; provided that:

when Q and T are each independently $—S(O_2)—$, or $—S(O)—$, at least one of R_1 , R_2 , R_3 and R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$, and

when (i) Q is $—S(O_2)—$, m is 1, and n is 0, or (ii) T is $—S(O_2)—$, n is 1 and m is 0, R_1 is not a chain of three atoms selected from the group consisting of C and S.

4. The conjugate of claim 3, wherein the Drug is selected from the group consisting of
 - 1) therapeutic agents comprising

a). Alkylating agents comprising chlorambucil, chlornaphazine, cyclophosphamide, dacarbazine, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, mannomustine, mitobronitol, melphalan, mitolactol, pipobroman, novembichin, phenesterine, prednimustine, thiotepa, trofosfamide, uracil mustard, CC-1065 adozelesin, carzelesin, bizelesin, duocarmycin, KW-2189, CBI-TMI, pyrrolobenzodiazepine dimers, tomaymycin dimers, indolinobenzodiazepine dimers, imidazobenzothiadiazepine dimers, oxazolidinobenzodiazepine dimers, carmustine, lomustine, chlorozotocin, fotemustine, nimustine, ranimustine, busulfan, treosulfan, improsulfan piposulfan, Triazenes, dacarbazine, carboplatin, cisplatin, oxaliplatin, benzodopa, carboquone, meturedopa, uredopa, altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate or trimethylolomelamine;

b). Plant Alkaloids comprising vincristine, vinblastine, vindesine, vinorelbine, navelbin, paclitaxel, docetaxol, Maytansinoids comprising DM1, DM2, DM3, DM4, DM5, DM6, or DM7, maytansine, ansamitocins, cryptophycin 1, cryptophycin 8, epothilones, eleutherobin, discodermolide, bryostatins, dolostatins, auristatins, tubulysins, cephalostatins, pancratistatin, sarcodictyin A or spongistatin;

- c). DNA Topoisomerase Inhibitors comprising 9-aminocamptothecin, camptothecin, crisnatol, daunomycin, etoposide, etoposide phosphate, irinotecan, mitoxantrone, novantrone, retinoic acids, retinols, teniposide, topotecan, 9-nitrocamptothecin, or mitomycins;
- d). Anti-metabolites comprising methotrexate, trimetrexate, denopterin, pteropterin, aminopterin, mycophenolic acid, tiazofurin, ribavirin, EICAR, hydroxyurea, deferoxamine, ancitabine, azacitidine, 6-azauridine, capecitabine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, 5-Fluorouracil, floxuridine, ratitrexed, cytarabine, cytosine arabinoside, fludarabine, azathioprine, fludarabine, mercaptopurine, thiamiprine, thioguanine, and a folic acid replenisher;
- e). Hormonal therapies comprising Receptor antagonists comprising Anti-estrogen selected from the group consisting of megestrol, raloxifene, and tamoxifen; LHRH agonists comprising goserelin, and leuprolide acetate; Anti-androgens comprising bicalutamide, flutamide, calusterone, dromostanolone propionate, epitiostanol, goserelin, leuprolide, mepitiothane, nilutamide, testolactone, and trilostane;
- f). Vitamin D3 compounds comprising CB 1093, EB 1089 KH 1060, cholecalciferol, or ergocalciferol;

g). Photodynamic therapies comprising verteporfin, phthalocyanine, photo sensitizer Pc4, or demethoxy-hypocrellin A;

h). Cytokines comprising Interferon-alpha, Interferon-gamma, tumor necrosis factor (TNFs), or human proteins containing a TNF domain;

i). Kinase inhibitors comprising, imatinib, gefitinib, pegaptanib, sorafenib, dasatinib, sunitinib, erlotinib, nilotinib, lapatinib, axitinib, pazopanib, vandetanib, mubritinib, ponatinib, bafetinib, bosutinib, cabozantinib, vismodegib, iniparib, ruxolitinib, CYT387, axitinib, tivozanib, sorafenib, or ispinesib;

j). antibiotics comprising calicheamicin $\gamma 1$, $\delta 1$, $\alpha 1$ or $\beta 1$, dynemicin A, deoxydynemicin, esperamicin, kedarcidin, C-1027, maduropeptin, neocarzinostatin chromophore, chromoprotein enediyne antiobiotic chromomophores, aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabycin, carminomycin, carzinophilin; chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, deoxydoxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, nitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin,

quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, or zorubicin;

k). Polyketides comprising bullatacin or bullatacinone; gemcitabine, epoxomicins, bortezomib, thalidomide, lenalidomide, pomalidomide, tosedostat, fosbretabulin, vemurafib, gentespib, tecemotide, Isoprenylation inhibitors, Dopaminergic neurotoxins, Cell cycle inhibitors, Actinomycin D, bleomycin A2, bleomycin B2, peplomycin, daunorubicin, adriamycin, idarubicin, epirubicin, pirarubicin, zorubicin, mtoxantrone, MDR inhibitors, Ca.sup.+2 ATPase inhibitors, Vorinostat, Romidepsin, Panobinostat, Valproic acid, Mocetinostat, Belinostat, PCI-24781, Entinostat, SB939, Resminostat, Givinostat, AR-42, CUDC-101, sulforaphane, Trichostatin A, Celecoxib, glitazones, epigallocatechin gallate, Disulfiram, Salinosporamide A, aminoglutethimide, mitotane, trilostane; aceglatone, aldophosphamide glycoside; aminolevulinic acid, amsacrine, arabinoside, bestrabucil, bisantrene, edatraxate, defofamine, demecolcine, diaziquone, eflornithine, elformithine, elliptinium acetate, etoglucid, gallium nitrate, gacytosine, hydroxyurea, ibandronate, lentinan, lonidamine, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone; 2,2',2''-trichlorotriethylamine,

T-2 toxin, verrucarin A, roridin A, anguidine, urethane, siRNA, or antisense drugs;

2). Anti-autoimmune disease agents comprising cyclosporine, cyclosporine A, aminocaproic acid, azathioprine, bromocriptine, chlorambucil, chloroquine, cyclophosphamide, amcinonide, betamethasone, budesonide, hydrocortisone, flunisolide, fluticasone propionate, fluocortolone danazol, dexamethasone, Triamcinolone acetonide, beclometasone dipropionate, DHEA, enanercept, hydroxychloroquine, meloxicam, methotrexate, mofetil, mycophenylate, prednisone, sirolimus, or tacrolimus;

3). Anti-infectious disease agents comprising amikacin, astromicin, netilmicin, sisomicin, isepamicin, hygromycin B, arbekacin, bekanamycin, dibekacin, tobramycin, framycetin, paromomycin, ribostamycin, spectinomycin, streptomycin, verdamicin, azidamfenicol, chloramphenicol, florfenicol, thiamphenicol, geldanamycin, herbimycin, biapenem, doripenem, ertapenem, imipenem, meropenem, panipenem, carbacephem, cefacetrile, cefaclor, cefradine, cefadroxil, cefalonium, cefaloridine, cefalotin, cefalothin, cefalexin, cefaloglycin, cefamandole, cefapirin, cefatrizine, cefazaflur, cefazedone, cefazolin, cefbuperazone, cefcapene, cefdaloxime, cefepime, cefminox, cefoxitin, cefprozil, cefroxadine, ceftazolidime, cefuroxime, cefixime, cefdinir, cefditoren, cefepime, cefetamet,

cefmenoxime, cefodizime, cefonicid, cefoperazone, ceforanide, cefotaxime, cefotiam, cefozopran, cephalixin, cefpimizole, cefpiramide, cefpirome, cefpodoxime, cefprozil, cefquinome, cefsulodin, ceftazidime, cefteram, ceftibuten, ceftiolene, ceftizoxime, ceftobiprole, ceftriaxone, cefuroxime, cefuzonam, cefotetan, cefmetazole, flomoxef, and latamoxef, bleomycin, vancomycin, teicoplanin, ramoplanin, Glycylcyclines, penam clavam, clindamycin, and lincomycin, daptomycin, A54145, calcium-dependent antibiotics, azithromycin, cethromycin, clarithromycin, dirithromycin, erythromycin, flurithromycin, josamycin, ketolide, midecamycin, miocamycin, oleandomycin, rifamycins, rokitamycin, roxithromycin, spectinomycin, spiramycin, troleandomycin, telithromycin, aztreonam, tigemonam, Oxazolidinones, amoxicillin, ampicillin, azidocillin, azlocillin, benzylpenicillin, benzathine benzylpenicillin, benzathine phenoxymethylpenicillin, clometocillin, procaine benzylpenicillin, carbenicillin, cloxacillin, dicloxacillin, epicillin, flucloxacillin, mecillinam, mezlocillin, meticillin, nafcillin, oxacillin, penamecillin, penicillin, pheneticillin, phenoxymethylpenicillin, piperacillin, propicillin, sulbenicillin, temocillin, ticarcillin, bacitracin, colistin, polymyxin B, alatrofloxacin, balofloxacin, ciprofloxacin, clinafloxacin, danofloxacin, difloxacin, enoxacin, enrofloxacin, floxin, garenoxacin, gatifloxacin,

gemifloxacin, grepafloxacin, kano trovafloxacin, levofloxacin, lomefloxacin, marbofloxacin, moxifloxacin, nadifloxacin, norfloxacin, orbifloxacin, ofloxacin, pefloxacin, trovafloxacin, grepafloxacin, sitafloxacin, sparfloxacin, temafloxacin, tosufloxacin, trovafloxacin, pristinamycin, quinupristin/dalfopristin, mafenide, prontosil, sulfacetamide, sulfamethizole, sulfanilimide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sulfamethoxazole, Steroid antibacterials, doxycycline, chlortetracycline, clomocycline, demeclocycline, lymecycline, meclocycline, metacycline, minocycline, oxytetracycline, penimepicycline, rolitetracycline, tetracycline, annonacin, arspenamine, bactoprenol inhibitors, DADAL/AR inhibitors, dictyostatin, discodermolide, eleutherobin, epothilone, ethambutol, etoposide, faropenem, fusidic acid, furazolidone, isoniazid, laulimalide, metronidazole, mupirocin, mycolactone, NAM synthesis inhibitors, nitrofurantoin, paclitaxel, platensimycin, pyrazinamide, rifampin, tazobactam tinidazole, or uvaricin;

4). Anti-viral drugs comprising aplaviroc, maraviroc, vicriviroc, enfuvirtide, PRO 140, raltegravir, elvitegravir, globoidnan A, bevirimat, vivecon, oseltamivir, zanamivir, peramivir, abacavir, aciclovir, adefovir, amdoxovir, apricitabine, brivudine, cidofovir, clevidine, dexelvucitabine, didanosine, elvucitabine, emtricitabine, entecavir, famciclovir, fluorouracil, 3'-fluoro-

2',3'-dideoxythymidine and 3'-fluoro-2',3'-dideoxyguanosine, fomivirsen, ganciclovir, idoxuridine, lamivudine, β -1-thymidine, β -1-2'-deoxycytidine, penciclovir, racivir, stampidine, stavudine, taribavirin, telbivudine, tenofovir, trifluridine valaciclovir, valganciclovir, zalcitabine, zidovudine amantadine, ateviridine, capravirine, diarylpyrimidines, delavirdine, docosanol, emivirine, efavirenz, foscarnet, imiquimod, interferon alfa, loviride, lodenosine, methisazone, nevirapine, NOV-205, peginterferon alfa, podophyllotoxin, rifampicin, rimantadine, resiquimod, tromantadine; amprenavir, atazanavir, boceprevir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, pleconaril, ritonavir, saquinavir, telaprevir, tipranavir, umifenovir, calanolide-a, ceragenin, cyanovirin-n, epigallocatechin gallate, foscarnet, griffithsin, hydroxyurea, KP-1461, miltefosine, pleconaril, ribavirin, or seliciclib;

5). a radioisotopes of ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{64}Cu , ^{68}Ga , ^{86}Y , ^{99}Tc , ^{111}In , ^{123}I , ^{124}I , ^{125}I , ^{131}I , ^{133}Xe , ^{177}Lu , ^{211}At , or ^{213}Bi ; and

6) the pharmaceutically acceptable salts or acids of any of the above drugs.

5. The conjugate of claim 3, wherein Drug is selected from the group consisting of tubulysins, calicheamicins, auristatins, maytansinoids, CC-1065 compounds, morpholinos doxorubicins, taxanes, cryptophycins,

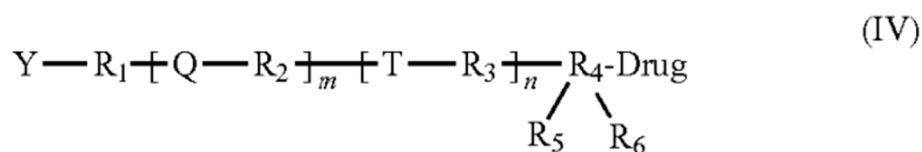
epothilones, and benzodiazepine dimers, siRNA or a combination thereof, and pharmaceutically acceptable salts or acids of any of the above.

6. The conjugate of claim 3, wherein the cell binding agent is selected from the group consisting of antibodies, proteins, vitamins, peptides, polymeric micelles, liposomes, lipoprotein-based drug carriers, nano-particle drug carriers, dendrimers, and combination thereof.
7. The conjugate of claim 3, wherein the cell-binding agent is an antibody, a single chain antibody, an antibody fragment that binds to a target cell, a monoclonal antibody, a single chain monoclonal antibody, or a monoclonal antibody fragment that binds the target cell, a chimeric antibody, a chimeric antibody fragment that binds to the target cell, a domain antibody, a domain antibody fragment that binds to the target cell, a resurfaced antibody, a resurfaced single chain antibody, or a resurfaced antibody fragment that binds to the target cell, a humanized antibody or a resurfaced antibody, a humanized single chain antibody, or a humanized antibody fragment that binds to the target cell, a lymphokine, a hormone, a vitamin, a growth factor, a colony stimulating factor, or a nutrient-transport molecule.

8. The conjugate of claim 3, wherein the drug is selected from the group consisting of a toxin, a chemotherapeutic agent, a drug moiety, an antibiotic, a radioactive isotope, and a nucleolytic enzyme.
9. The conjugate of claim 3, wherein the conjugate comprises one or more linker components of 6-maleimidocaproyl, maleimidopropanoyl, valine-citrulline, alanine-phenylalanine, p-aminobenzyloxycarbonyl, 4-thio-pentanoate, 4-(N-maleimidomethyl)cyclohexane-1-carboxylate, 4-thio-butyrates, maleimidoethyl, 4-thio-2-hydroxysulfonyl-butyrates and (4-acetyl)aminobenzoate.
10. The conjugate of claim 3, wherein Drug is selected from the group consisting of tubulysins, maytansinoids, taxanoids, CC-1065 compounds, daunorubicin and doxorubicin compounds, benzodiazepine dimers, calicheamicins and the enediyne antibiotics, actinomycin, azaserines, bleomycins, epirubicin, tamoxifen, idarubicin, dolastatins/auristatins, duocarmycins, thiotepa, vincristine, hemiasterlins, and esperamicins.

11. The conjugate of claim 3, having in vitro, in vivo or ex vivo cell killing activity.
12. The conjugate of claim 3, wherein the conjugate comprises either a peptide of 1-20 units of natural or unnatural amino acids, or a p-aminobenzyl unit, or a 6-maleimidocaproyl unit, or a disulfide unit, or a thioether unit, or a hydrozone unit, or an alkoxime unit.
13. The conjugate of claim 3, wherein the conjugate is cleavable by a protease.
14. The conjugate of claim 3, wherein the drug is derived from a drug containing a —SH, —CONHNH₂, —≡, —COR'' or —NHR'', wherein R'' is H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.
15. A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 3, and a pharmaceutically acceptable salt, carrier, diluent, or excipient therefor.

16. A pharmaceutical composition comprising the conjugate of claim 3, and a pharmaceutically acceptable carrier.
17. A pharmaceutical composition comprising a therapeutically effective amount of the conjugate of claim 3, and a chemotherapeutic agent, radiation therapy agent, immunotherapy agent, autoimmune disorder agent, or anti-infectious agent.
20. A compound of formula (IV):



wherein:

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

Q and T are either —P(=O)(OM)— , or $\text{—S(O}_2\text{)—}$, 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)— ; and when $n=1$, $m=0$, T is not —P(=O)(OM)— ;

“Drug” represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, 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 from 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 $(OCH_2CH_2)_p$, 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 $-(O_2)-$ [*sic*] or $-S(O)-$, R_2 is a straight or

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, R₁, R₃, or R₄;

R₅ and R₆, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H or Na, or K or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that:

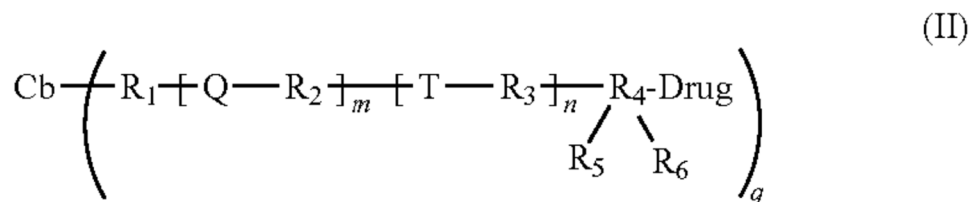
when Q and T are each independently —S(O₂)— or —S(O)—, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p, and

when (i) Q is —S(O₂)—, m is 1, and n is 0, or (ii) T is —S(O₂)—, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

- 21.** The conjugate of claim 20, wherein the drug is derived from a drug containing a —SH, —CONHNH₂, —≡, —COR'' or —NHR'', wherein R'' is

H, CH₃, Et, Pr, Bu, or Ph; and/or the cell-binding agent is an antibody or protein.

24. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either —P(=O)(OM)—, or —S(O₂)—, or —S(O)—;

m and n are integers from 1 to 5;

R₁, R₂, R₃, and R₄, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination

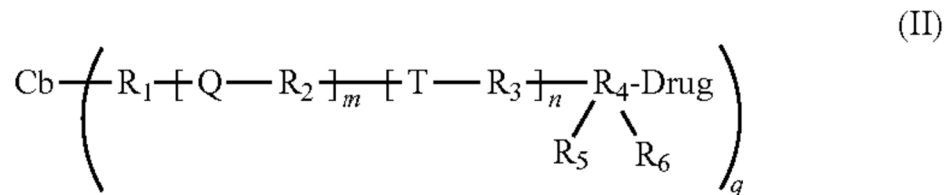
thereof provided that when Q and T are each independently —S(O₂)— or —S(O)—, R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 3 to 6 carbon atoms, linear or branched alkenyl or alkynyl, or ester, ether or amide having 2-6 carbon atoms, or polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof,

or R₁, R₂, R₃, and R₄ 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 (R₁, R₂, R₃, and R₄), provided that when Q and T are each independently —S(O)— [*sic*] or —S(O)—, R₂ is a straight or 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, R₁, R₃, or R₄, provided that when Q and T are each independently —S(O₂)— or —S(O)—, at least one of R₁, R₂, R₃, and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p,

R₅ and R₆ 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.

25. The cell-binding agent-drug conjugate of claim 24, wherein when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, at least one of R_1 , R_2 , R_3 , and R_4 comprises the polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$; and each of remaining R_1 , R_2 , R_3 , and R_4 comprises an alkyl or $(\text{OCH}_2\text{CH}_2)_p$.
26. A cell-binding agent-drug conjugate of formula (II):



wherein:

Cb represents a cell-binding agent;

Drug represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, cycloheteroalkane, heteroaromatic, alkoxime or amide bond;

q is an integer from 1 to 20; Q and T are either —P(=O)(OM)— , or $\text{—S(O}_2\text{)—}$, or —S(O)— ;

m and n are integers from 1 to 5;

R₁, R₂, R₃, and R₄, 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 $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof, provided that when Q and T are each independently $\text{—S(O}_2\text{)—}$ or —S(O)— , R₂ is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 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 R₁, R₂, R₃, and R₄ 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 (R₁, R₂, R₃ and R₄), provided that when Q and T are each independently $\text{—S(O}_2\text{)—}$ or —(O)— [*sic*], R₂ is a straight or 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, R₁, R₃ or R₄;

R₅ and R₆, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

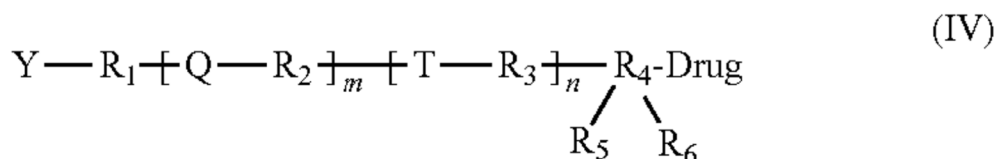
M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently —S(O₂)— or —S(O)—,

m is 1 and n is 1, R₂ is absent, branched alkyl having from 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof, or R₂ is a

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, R₃ or R₄.

29. A compound of formula (IV):



wherein:

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

Q and T are either —P(=O)(OM)— , or $\text{—S(O}_2\text{)—}$, 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)— ; and when $n=1$, $m=0$, T is not —P(=O)(OM)— ;

“Drug” represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, 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 $(\text{OCH}_2\text{CH}_2)_p$, wherein p is an integer from 1 to about 1000, or combination thereof provided that when Q and T are each independently $\text{—S(O}_2\text{)—}$ or —S(O)— , R_2 is absent, linear alkyl having from 1-6 carbon atoms, branched alkyl having from 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 or 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;

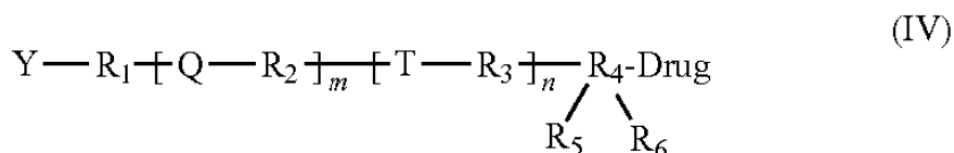
M is H, or Na, or K, or $\text{N}^+\text{R}_1\text{R}_2\text{R}_3$ or a pharmaceutical salt,

provided that:

when Q and T are each independently $-\text{S}(\text{O}_2)-$ or $-\text{S}(\text{O})-$, m is 1 and n is 1, R_2 is absent, branched alkyl having from 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof or R₂ is a 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, R₃ or R₄; and when (i) Q is —S(O₂)—, m is 1, and n is 0, or (ii) T is —S(O₂)—, n is 1 and m is 0, Y is an N-hydroxysuccinimide (NHS) ester, p-nitrophenyl ester, dinitrophenyl ester, pentafluorophenyl ester, pyridyldisulfide, nitropyridyldisulfide, maleimide, haloacetate, carboxylic acid chloride, hydrazide or hydroxylamine.

30. A compound of formula (IV):



wherein:

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

Q and T are either either —P(=O)(OM)—, or —S(O₂)—, or —S(O)—;

m and n are integers from 1 to 5;

“Drug” represents a drug linked to the cell-binding agent via the hydrophilic linker by a disulfide, thioether, thioester, peptide, hydrazone, ether, ester, carbamate, carbonate, 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 from 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 $(OCH_2CH_2)_p$, 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 $-S(O_2)-$ or $-S(O)-$, R_2 is a straight or 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, R₁, R₃ or R₄;

R₅ and R₆, 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof;

M is H, or Na, or K, or N⁺R₁R₂R₃ or a pharmaceutical salt,

provided that when Q and T are each independently —S(O₂)— or —S(O)—, m is 1 and n is 1, R₂ is absent, branched alkyl having from 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 (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combination thereof or R₂ is a 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, R₃ or R₄.

- 31.** The compound of claim 30, wherein when Q and T are each independently —S(O₂)— or —S(O)—, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p.
- 32.** The compound of claim 31, wherein when Q and T are each independently —S(O₂)— or —S(O)—, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.
- 33.** The conjugate of claim 3, wherein when Q and T are each independently —S(O₂)— or —S(O)—, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.
- 34.** The compound of claim 20, wherein when Q and T are each independently —S(O₂)— or —S(O)—, at least one of R₁, R₂, R₃ and R₄ comprises the polyethyleneoxy unit of formula (OCH₂CH₂)_p; and each of remaining R₁, R₂, R₃ and R₄ comprises an alkyl or (OCH₂CH₂)_p.

Appendix B

CURRICULUM VITAE

L. NATHAN TUMEY, PH.D.

Associate Professor
Binghamton University
School of Pharmacy and Pharmaceutical Sciences
P.O. Box 6000, Binghamton NY 13902
Email: ntumey@binghamton.edu
Website: www.Tumeylab.com
Phone: 607-777-5844

EDUCATION

Duke University, Durham, NC.

Ph.D., Organic chemistry, December 2001.

- Dissertation research with Professor Michael Pirrung.
- Certificate in Biological Chemistry (program emphasis)
- Dissertation title: "Medicinal chemistry and high throughput synthesis of inhibitors of lipid A biosynthesis."

King College, Bristol, TN.

B.S., *Summa cum laude*, May 1997. Double major, Chemistry and Biology. Minor, Computer Science.

PROFESSIONAL EXPERIENCE

2022-present	Associate Professor , Binghamton University School of Pharmacy and Pharmaceutical Sciences, Binghamton, NY -Vice Chair, Dept. of Pharmaceutical Sciences (2024-present) -Assistant Graduate Director (2022-present) -Courtesy appointment in Chemistry Dept. (2021-present) -Courtesy appointment in Biomedical Engineering (2018-present)
2017-2022	Assistant Professor , Binghamton University School of Pharmacy and Pharmaceutical Sciences, Binghamton, NY
2010-2017	Associate Research Fellow , Pfizer, Groton, CT
2005-2010	Principal Research Scientist , Wyeth Research, Pearl River, NY
2002-2005	Senior Scientist , Athersys Inc., Cleveland, OH
2000-2001	Organic Chemistry Instructor , Kaplan MCAT prep class, Durham, NC
1997-2001	Graduate Assistant , Mentor: Dr. Michael Pirrung, Duke University Department of Chemical Sciences, Durham NC

CONSULTING, ADVISORY, AND LEADERSHIP EXPERIENCE

Expert Witness and Legal Consulting:

Quinn Emmanuel LLP (2021-present)

Latham and Watkins LLP (2021-present)

Professional consulting work:

Heidelberg Pharma (2022-present)

OnCusp Therapeutics (2022-present)

Ardeagen (2021-present)

Bighat Biosciences (2021-2022)

Iksuda Therapeutics (2021-2022)

Synthesis Inc (2019-present)

Loxo Oncology / Eli Lilly (2020-present)

Takeda Pharmaceuticals (2017-2021)

ImmuNext Biopharma (2018-2019)

Cue Biopharma (2018-2019)

Vertex Pharmaceuticals (2019)

Angiex Pharmaceuticals (2018-2020)

GIMV NV (2019)

Pontifax (2019-2020)

Scientific advisory board member,

Araris Biotech AG (2019-present)

Manhattan Biosolutions (2022-present)

Awards/Scientific leadership roles:

2024-2027, standing member NIH Drug and Biologic Therapeutic Delivery (DBTD) review panel. (07/01/2024 - 06/30/2027)

2023, NIH review panel, Drug and Biologic Therapeutic Delivery (DBTD), Oct. 17-18 2023; Feb. 1-2, 2024.

2023, Outstanding Academic Investigator Award, World ADC Awards, Oct. 18, 2023.

2023, Provost's Award for Excellence in Undergraduate Research Mentoring

2022, chair, "Next Generation Payloads" symposium at ADC World Summit.

2022, NIH grant review panel, Gene and Drug Delivery (GDD), ad hoc member. (Oct 25-26, 2022)

2020, NIH grant review panel, Synthetic and Biological Chemistry A (SBCA), ad hoc member. (October 13-14, 2020)

2014-2017, Bioconjugation Network Leadership Team (Pfizer, Inc)

2014, Co-chair, Bioconjugation Summit (Pfizer, Inc)

2015, Chair, Bioconjugation Summit (Pfizer, Inc)

2014-2017, Bioconjugation Network Leadership Team (Pfizer, Inc)

RESEARCH INTERESTS

Targeted drug delivery; Antibody-drug conjugates (ADCs); Auto-immune disease; Oncology medicinal chemistry; Small molecule drug discovery; Immuno-oncology; Drug metabolism/DMPK; Bioanalytical chemistry; Mass spectroscopy.

PRIVATE SECTOR (PHARMACEUTICAL) WORK EXPERIENCE

Associate Research Fellow, Pfizer, Groton, CT (March 2010-January 2017)

Oncology Medicinal Chemistry, ADC bioconjugation.

- Led a small team of synthetic and bioanalytical scientists that design and synthesize antibody-drug conjugates for use in oncology applications. Prepared bioconjugates for *in vitro* and *in vivo* evaluation.
- Optimized conjugation conditions in order to result in conjugates with minimal aggregation and maximal drug-loading. Developed a variety of bioanalytical methods to assess the purity, identity, and stability of preclinical antibody-drug-conjugates in the Pfizer portfolio. Coordinated across sites and departments to harmonize analytical methods and analytical requirements in order to facilitate technology transfer and data analysis.
- Developed patenting strategies to protect key inventions while simultaneously building the visibility of the team through aggressive external publication and presentation strategies.
- Implemented the use of site-specific conjugation techniques to solve metabolic, synthetic, analytical, and stability issues. Worked with biochemists, biologists, and DMPK scientists to better understand the impact of conjugation site on efficacy and PK.
- Served as the chemistry team leader on multiple ADC programs. Worked with key members of the team to decide on ADCs for advancement into PK, efficacy, and toxicology studies.
- Worked with a small team of scientists and IT specialists to establish an informatics system to track ADCs across Pfizer.
- Mentored three direct reports (2 PhD and 1 MS) and a summer intern (BS).

Principal Research Scientist, Wyeth Research, Pearl River, NY (2005-2010)

Chemistry team leader (2008-2009), IRAK4 kinase program (inflammation)

Chemistry team member (2005-2008), PKC θ (inflammation)

- Coordinated efforts of multiple medicinal chemists across two sites ensuring that each individual had an adequate understanding of the project and had appropriate molecular targets/goals. Directly supervised the synthetic chemistry efforts of three chemists and led an outsourced team of five chemists.
- Responsible for managing and prioritizing all secondary assay requests including DMPK studies, *in vivo* efficacy studies, pharmaceutical properties screening, and selectivity screening.
- Worked with team members to identify strategies to address issues with kinase selectivity, DNA binding, pgp efflux, permeability, *in vitro* metabolism, and drug physical properties. Collaborated with scientists from enzymology, analytical chemistry, DMPK, and pharmaceutical profiling in order to study these issues.
- Represented the project to the management team. Responsible for maintaining project timelines and ensuring the meeting of key deliverables.
- Responsible for establishing and maintaining an intellectual property (IP) position around each lead series. Worked with company attorneys and research librarians in order to evaluate related prior art.

Senior Scientist, Athersys Inc., Cleveland, OH (2002-2005)

- Designed two novel series of CRTH2 antagonists based on literature precedent and competitor's compounds. Synthesized numerous analogs and libraries in order to establish key SAR. Lead inventor on two patent applications claiming these series.
- Designed and synthesized selective agonists of 5HT2C for use in obesity and related disorders resulting in multiple patent applications. Established SAR that led to agonists with excellent selectivity (>100x) over 5HT2A/2B and exhibited good oral bioavailability.
- Responsible for hit-to-lead evaluation, lead-optimization, and molecular design/synthesis.
- Directly supervised two associate chemists.

GRANT FUNDING (active) –

BigHat Biopharma

9/1/2024-8/30/2025

“Fluticasone-based ADCs for the treatment of IBD”

Total direct costs: \$94,720 (+\$47,978 indirect)

Role: PI

Binghamton Excellence in Entrepreneurship and Discovery (ART) Accelerating Research Translation

2/1/24-1/31/26

ADC Translational Research

Total direct costs: \$150,000

Role: PI

SUNY Research seed grant

8/1/2024-8/1/2025

Total direct costs: \$40,000

Role: PI

SUNY Technology Accelerator Fund

8/1/2024-3/1/2025

Validation of Novel ADCs for Treatment of Cancer

Total direct costs: \$50,000

Role: PI

Heidelberg Pharma

12/2022-12/2024

“Optimization of TLR7 Agonist ADCs for the treatment of Cancer”

Total direct costs: \$285,075 (+\$162,493 indirect)

Role: PI

NIH R01 GM144450-01

02/2022-12/2025

“Legumain to the rescue: A new ADC linker strategy to address the limitations of cathepsin cleavage”

Total direct costs: \$800,000 (+\$412,224 indirect)

Role: PI (collaboration with Tracy Brooks)

NIH R01 GM140026-01A1

08/2021-08/2025

“Exploiting the Hydrophobic Glycosyl Pocket of IgG1 for Imaging and Drug Delivery Applications”

Total direct costs: \$800,000 (+\$434,112 indirect)

Role: PI (collaboration with Tracy Brooks and Fake Lu)

NIH R15 CA249793-01, NIH/NCI

07/2020-07/2023

“Synthesis and optimization of antibody:DNAi conjugates targeting the MYC G4”

Total direct costs: \$300,000 (+\$171,000 indirect)

Role: Co-I (PI is Tracy Brooks)

GRANT FUNDING (completed)

NIH R03 AI156696-01A1

06/2021-06/2023

“Molecular whack-a-mole: Targeting transmembrane-TNFα for the delivery of anti-inflammatory drugs.”

Total direct costs: \$100,000. (+\$57,000 indirect)

Role: PI (sole investigator)

NIH R15 AI149755-01

01/2020-01/2023

“Cell-specific blockage of TLR activation: A new strategy for addressing inflammatory disorders.”

Total direct costs: \$300,000 (+\$150,480 indirect)

Role: PI (sole investigator)

Binghamton University XCEED Technology Accelerator (ED19HDQ0200038)

09/2021-12/2021

“Development of TLR-activating ADC technology”

Total direct costs: \$24,000.

Role: PI

Synthis Inc., Award 90784

04/2021-07/2021

“Analysis of cell lysate” (testing agreement)

Total direct costs: \$13,816 (+\$3,454 indirect)

Role: PI (sole investigator)

Takeda Pharmaceuticals, Award 83181

11/2018-04/2020

“The identification of lysosomal-selective proteolytically cleavable linkers”

Total direct costs: \$162,217 (+\$95,251 indirect)

Role: PI (sole investigator)

Binghamton University Translational Areas of Excellence.

06/2018-06/2019

“Understanding Antibody-Drug Conjugate (ADC) Internalization Via Stimulated Raman Scattering (SRS) Imaging of Alkyne-Tags in Live Cancer Cells”.

Total direct costs: \$10,000

Role: Co-I (collaboration with Fake Lu / BME)

ORIGINAL ARTICLES, REVIEWS, AND BOOK CHAPTERS

***Indicates corresponding author**

BOOK CHAPTERS

- “ADC Linker Strategies for the Release of Alcohol-Containing Payloads”, Miller, Jared T., **Tumey, L. Nathan***, Chemical Linkers in Antibody-Drug Conjugates (ADCs); Royal Society of Chemistry; **2021**, pg 232-262.
- “The design and development of antibody-drug conjugates (ADCs) for the treatment of cancer”, **Tumey, L. Nathan***, Burger’s Medicinal Chemistry, Drug Discovery and Development; Wiley Publishing, **2021**.
<https://doi.org/10.1002/0471266949.bmc283>
- “An overview of the current ADC discovery landscape”, **Tumey, L. Nathan***, Methods in Molecular Biology, Springer Publishing, **2019**, 1-22.
- “Detection and Removal of Small-Molecule and Endotoxin Contaminants in ADC Preparations”, Casavant, Jeffery*; Ratnayake, Anokha S.; Puthenveetil, Sujiet; **Tumey, L. Nathan**, Methods in Molecular Biology, Springer Publishing, **2019**, 291-299.
- “Next generation payloads for ADCs” (book chapter), **L. Nathan Tumey***, Springer Publishing, “Innovations for Next-Generation Antibody-Drug Conjugates”, **2018**.

PEER REVIEWED PUBLICATIONS

2024

- “A comparison of the activity, lysosomal stability, and efficacy of legumain-cleavable and cathepsin cleavable ADC linkers”, Meghan E. Gray, Karina M. Zielinski, Fanny Xu, Kayla K. Elder, Steven J. McKay, Victor T. Ojo, Samantha R. Benjamin, Aiman A. Yaseen, Tracy A. Brooks, L. Nathan Tumey*, *Xenobiotica*, **2024**, in press. doi: 10.1080/00498254.2024.235205

2023

- “ValCitGlyPro-Dexamethasone Antibody Conjugates Selectively Suppress the Activation of Human Monocytes”, Justin M Howe, Siteng Fang, Kelsey A. Watts, Fanny Xu, Samantha R Benjamin and **L. Nathan Tumey***, *RSC Medicinal Chemistry*, **2023**, 14, p2348.
<https://pubs.rsc.org/en/content/articlelanding/2023/md/d3md00336a>
- “Synthesis and Optimization of 1-Substituted Imidazo[4,5-c]quinoline TLR7 Agonists”, Emma G. DeYoung, Justin M. Howe, Siteng Fang, Mullapudi Mohan Reddy, Jillian P. Handel, Jared T. Gillen Miller, Daniel R. Wheeler, and **L. Nathan Tumey***, *ACS Med. Chem. Lett.*, **2023**, 14, 10, 1358-68.
<https://doi.org/10.1021/acsmmedchemlett.3c00260>
- “Visualizing drug-induced lipid accumulation in lysosomes of live cancer cells with stimulated Raman imaging”, Yuhao Yuan, Emmanuel O. Olawode, **L. Nathan Tumey**, and Fake Lu; *Biomedical Optics Express*, **2023**, 14(6), pp. 2551-2564;
<https://doi.org/10.1364/BOE.487527>

2022

- “Evaluation of an ester-linked immunosuppressive payload: A case study in understanding the stability and cleavability of ester-containing ADC linkers”, Courtney P. Jackson, Siteng Fang, Samantha R. Benjamin, Tchilabalo Alayi, Yetrib Hathout, Sarah M. Gillen, Jillian P. Handel, Brittany M. Brems, Justin M. Howe, **L. Nathan Tumey***; *Bioorganic and Medicinal Chemistry Letters*, 75, **2022**. DOI: 10.1016/j.bmcl.2022.128953

“Design and Characterization of Immune-Stimulating Imidazo[4,5-c]quinoline Antibody-Drug Conjugates”, Siteng Fang, Brittany M Brems, Emmanuel O Olawode, Jared T Miller, Tracy A Brooks, **L Nathan Tumey***; Molecular Pharmaceutics, 2022, 19, 9, 3228–3241.

<https://doi.org/10.1021/acs.molpharmaceut.2c00392>

“Indoloquinoline-Mediated Targeted Downregulation of KRAS through Selective Stabilization of the Mid-Promoter G-Quadruplex Structure”, AM Psaras, RK Carty, JT Miller, LN Tumey, TA Brooks; Genes **2022**, 13 (8), 1440

2021

“Enzyme-Agnostic Lysosomal Screen Identifies New Legumain-Cleavable ADC Linkers”, Jared T Miller, Caitlin N Vitro, Siteng Fang, Samantha R Benjamin, **L Nathan Tumey***; Bioconjugate Chemistry, **2021**, 32, 4, 842-858. DOI: <https://doi.org/10.1021/acs.bioconjchem.1c00124>

“Development of Highly Optimized Antibody–Drug Conjugates against CD33 and CD123 for Acute Myeloid Leukemia”, Yoon-Chi Han, Jennifer Kahler, Nicole Piché-Nicholas, Wenyue Hu, Stephane Thibault, Fan Jiang, Mauricio Leal, Madan Katragadda, Andreas Maderna, Russell Dushin, Nadira Prashad, Manoj B Charati, Tracey Clark, **L Nathan Tumey**, Xingzhi Tan, Andreas Giannakou, Edward Rosfjord, Hans-Peter Gerber, Lioudmila Tchistiakova, Frank Loganzo, Christopher J O'Donnell, Puja Sapra, Clinical Cancer Research, **2021**, 27(2), 622-631. DOI: 10.1158/1078-0432.CCR-20-2149

“Chemical and Physical Stability of an Admixture Containing Cefepime and Vancomycin in Lactated Ringer Solution”, Pegah Shakeraneh, Risako Robinson, Wesley D Kufel, L Nathan Tumey, Samantha R Benjamin, Christopher D Miller, William Darko, Luke A Probst, Robert W Seabury; Hospital Pharmacy; 2021; <https://doi.org/10.1177/0018578719901278>.

2020

“PF-06804103, A Site-specific Anti-HER2 Antibody–Drug Conjugate for the Treatment of HER2-expressing Breast, Gastric, and Lung Cancers”; Edmund I Graziani, Matthew Sung, Dangshe Ma, Bitha Narayanan, Kimberly Marquette, Sujiet Puthenveetil, **L Nathan Tumey**, Jack Bikker, Jeffrey Casavant, Eric M Bennett, Manoj B Charati, Jonathon Golas, Christine Hosselet, Cynthia M Rohde, George Hu, Magali Guffroy, Hadi Falahatpisheh, Martin Finkelstein, Tracey Clark, Frank Barletta, Lioudmila Tchistiakova, Judy Lucas, Edward Rosfjord, Frank Loganzo, Christopher J O'Donnell, Hans-Peter Gerber, Puja Sapra; Molecular Cancer Therapeutics, **2020**, 19, 10, 2068-2078. DOI: 10.1158/1535-7163.MCT-20-0237

“Expanding the Versatility of Microbial Transglutaminase Using α -Effect Nucleophiles as Noncanonical Substrates.” Tak Ian Chio; Breanna R. Demestichas; Brittany M. Brems; Susan L. Bane*; **L. Nathan Tumey***, Angew. Chemie, 59, 13814–13820 **2020**. (co-corresponding authors) DOI: 10.1002/anie.202001830

2019

“Case report: Albendazole associated psychosis”, Doughty, Bennett; **Tumey, L. Nathan**; Williams, Karen; Mental Health Clinician, November 2019, 9, 6, 397-400. DOI: 10.9740/mhc.2019.11.397

- “Thiolation of Q295: Site-specific conjugation of hydrophobic payloads without the need for genetic engineering”, Benjamin, Samantha R.; Jackson, Courtney P.; Fang, Siteng; Carlson, Dane P.; Guo, Zhongyuan; **Tumey, L. Nathan***, *Molecular Pharmaceutics*, 2019, 16,6, 2795-2807. DOI: 10.1021/acs.molpharmaceut.9b00323
- “Site-Specific Bioconjugation and Multi-Bioorthogonal Labeling via Rapid Formation of a Boron–Nitrogen Heterocycle”, Choi, Tak Ian; Gu, Han; Mukherjee, Kamalika; Tumey, **L. Nathan Tumey***; Bane, Susan L. * (co-corresponding authors), *Bioconjugate Chemistry*, 2019, 30, 5, 1554-1564. DOI: 10.1021/acs.bioconjchem.9b00246
- “Natural Product Bis-Intercalator Depsipeptides as a New Class of Payloads for Antibody-Drug Conjugates”, Ratnayake, Anokha S.*; Chang, Li-ping; **Tumey, L. Nathan**; Loganzo, Frank; Chemler, Joseph A.; Wagenaar, Melissa; Musto, Sylvia; Li, Fengping; Janso, Jeffrey E.; Ballard, T. Eric; Rago, Brian; Steele, Greg L.; Ding, WeiDong; Feng, Xidong; Hosselet, Christine; Buklan, Vlad; Lucas, Judy; Koehn, Frank E.; O'Donnell, Christopher J.; Graziani, Edmund I., *Bioconjugate Chemistry*, 2019, 30(1), 200-209. DOI:10.1021/acs.bioconjchem.8b00843
- “Novel PIKK inhibitor antibody-drug conjugates: Synthesis and anti-tumor activity”, Zhou, Dahui*; Casavant, Jeffrey; Graziani, Edmund I.; He, Haiyin; Janso, Jeffrey; Loganzo, Frank; Musto, Sylvia; **Tumey, Nathan**; O'Donnell, Christopher J.; Dushin, Russell, *Bioorganic & Medicinal Chemistry Letters*, 2019, 29(7), 943-957. DOI:10.1016/j.bmcl.2019.01.009

2017

- “Thinking Small and Dreaming Big: Medicinal Chemistry Strategies for Designing Optimal ADCs”, **L. Nathan Tumey***, *Medicinal Chemistry Reviews*, Chapter 19, 2017, 52, 363-379.
- “Site selection: A case study in the identification of optimal cysteine engineered ADCs.”, **L. Nathan Tumey***, Fengping Li, Brian Rago, Xiaogang Han, Frank Loganzo, Sylvia Musto, Edmund I. Graziani, Sujiet Puthenveetil, Jeffrey Casavant, Kimberly Marquette, Tracey Clark, Jack Bikker, Eric M. Bennett, Frank Barletta, Nicole Piche-Nicholas, Amy Tam, Christopher J. O'Donnell, Hans Peter Gerber, and Lioudmila Tchistiakova; *AAPS Journal*, 2017, 19(4), 1123-1135.
- “Quantitative Conjugated Payload Measurement Using Enzymatic Release of Antibody-Drug Conjugate with Cleavable Linker.”, Brian Rago, **L. Nathan Tumey**, Cong Wei, Frank Barletta, Tracey Clark, Steve Hansel, and Xiaogang Han*; *Bioconjugate Chemistry*, 2017, 28(2), 620-626.
- “ADME Considerations for the Development of Biopharmaceutical Conjugates Using Cleavable Linkers”, **L. Nathan Tumey*** and Sean Han, *Current Topics in Medicinal Chemistry*, 2017, 17(32), 3444-3462.
- “Multivalent peptidic linker enables identification of preferred sites of conjugation for a potent thialanstatin antibody drug conjugate”, Puthenveetil, Sujiet*; He, Haiyin; Loganzo, Frank; Musto, Sylvia; Teske, Jesse; Green, Michael; Tan, Xingzhi; Hosselet, Christine; Lucas, Judy; **Tumey, L. Nathan**; Sapra, Puja; Subramanyam, Chakrapani; O'Donnell, Christopher J.; Graziani, Edmund I,

2016

“Optimization of Tubulysin Antibody-Drug-Conjugates: A Case Study in Addressing ADC Metabolism”, **L. Nathan Tumey***, Carolyn A. Leverett, Beth Vetelino, Fengping Li, Brian Rago, Xiaogang Han, Frank Loganzo, Sylvia Musto, Guoyun Bai, Sai Chetan K. Sukuru, Edmund I. Graziani, Sujiet Puthenveetil, Jeffrey Casavant, Anokha Ratnayake, Kimberly Marquette, Sarah Hudson, Venkata Ramana Doppala-pudi, Joseph Stock†, Lioudmilla Tchistiakov, Andrew J. Bessire, Tracey Clark, Judy Lucas, Christine Hosselet, Christopher J. O'Donnell, and Chakrapani Subramanyam; *ACS Medicinal Chemistry Letters*, 2016, 7(11), 977-982. **[Selected as cover article for November 2016 edition]**

“Calculated conjugated payload from immunoassay and LC-MS intact protein analysis measurements of antibody-drug conjugate”, Brian Rago, Tracey Clark, Lindsay King, Jenny Zhang, **L. Nathan Tumey**, Fengping Li, Frank Barletta, Cong Wei, Mauricio Leal, Steve Hansel*, & Xiaogang Han; *Bioanalysis*, 2016, 8(21), 2205-2217.

“Natural Product Splicing Inhibitors: A New Class of Antibody-Drug Conjugate (ADC) Payloads”, Puthenveetil, Sujiet*; Loganzo, Frank; He, Haiyin; Dirico, Ken; Green, Michael; Teske, Jesse; Musto, Sylvia; Clark, Tracey; Rago, Brian; Koehn, Frank; Veneziale, Robert; Falahaptisheh, Hadi; Han, Xiaogang; Barletta, Frank; Lucas, Judy; Subramanyam, Chakrapani; O'Donnell, Christopher J.; **Tumey, L. Nathan**; Sapra, Puja; Gerber, Hans Peter; Ma, Dangshe; Graziani, Edmund I; *Bioconjugate Chemistry*, 2016, 27(8), 1880-1888.

“Where Did the Linker-Payload Go? A Quantitative Investigation on the Destination of the Released Linker-Payload from an Antibody-Drug Conjugate with a Maleimide Linker in Plasma”, Wei, Cong*; Zhang, Guodong; Clark, Tracey; Barletta, Frank; **Tumey, L. Nathan**; Rago, Brian; Hansel, Steven; Han, Xiaogang; *Analytical Chemistry*, 2016, 88(9), 4979.

“Development of Solid-Phase Site-Specific Conjugation and Its Application toward Generation of Dual Labeled Antibody and Fab Drug Conjugates”, Puthenveetil, Sujiet*; Musto, Sylvia; Loganzo, Frank; **Tumey, L. Nathan**; O'Donnell, Christopher J.; Graziani, Edmund; *Bioconjugate Chemistry*, **2016**, 27(4) 1030.

2015

“In vivo biotransformations of antibody-drug conjugates”, **Tumey, L. Nathan**; Rago, Brian; Han, Xiaogang*; *Bioanalysis*, 2015, 7(13), 1649.

2014

“Mild method for succinimide hydrolysis on ADCs: Impact on ADC potency, stability, exposure, and efficacy”, **L. Nathan Tumey***, Manoj Charati, Tao He, Eric Sousa, Dangshe Ma, Xiaogang Han, Tracey Clark, Jeff Casavant, Frank Loganzo, Frank Barletta, Judy Lucas, and Edmund I. Graziani; *Bioconjugate Chemistry*, 2014, 25(10), p1871-1880.

“Identification and optimization of indolo[2,3-c]quinoline inhibitors of IRAK4” **Tumey, L. Nathan***; Boschelli, Diane H.; Bhagirath, Niala; Shim, Jaechul; Murphy, Elizabeth A.; Goodwin, Deborah; Bennett, Eric M.; Wang, Mengmeng; Lin, Lih-

Ling; Press, Barry; Shen, Marina; Frisbie, Richard K.; Morgan, Paul; Mohan, Shashi; Shin, Julia; Rao, Vikram R., *Bioorganic and Medicinal Chemistry Letters*, 2014, 24, 2066-2072.

2013

“Recent advances in antibody-drug conjugates” Graziani, Edmund I.*; **Tumey, L. Nathan**, *RSC Drug Discovery Series*, 2013, 36 (Biotherapeutics), 145-175.

2012

“CRTH2 antagonists” **Tumey, L. Nathan*** *RSC Drug Discovery Series*, 2012, 26 (Anti-Inflammatory Drug Discovery), 104-134.

2009

“5-Vinyl-3-pyridinecarbonitrile inhibitors of PKC θ : Optimization of enzymatic and functional activity.”, **Tumey, L. Nathan***; Bhagirath, Niala; Brennan, Agnes; Brooijmans, Natasja; Lee, Julie; Yang, Xiaoke; Boschelli, Diane H., *Bioorg. Med. Chem.*, 2009, 17, 7933-7948.

“First generation 5-vinyl-3-pyridinecarbonitrile PKC- θ inhibitors”, Niu, Chuansheng; Boschelli, Diane H.; **Tumey, L. Nathan**; Bhagirath, Niala; Subrath, Joan; Shim, Jaechul; Wang, Yan; Wu, Biqi; Eid, Clark; Lee, Julie; Yang, Xiaoke; Brennan, Agnes; Chaudhary, Divya, *Bioorg. Med. Chem. Lett.*, 2009, 19(20), 5829-5832.

2008

“2-Alkenylthieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKC- θ ”, **Tumey, L. Nathan***; Boschelli, Diane H.; Lee, Julie; Chaudhary, Divya. *Bioorg. Med. Chem. Lett.*, 2008, 18(15), 4420-4423.

“A facile, scalable preparation of 4-oxo-4,7-dihydrothieno[2,3-b]pyridine-5-carbonitriles”, **Tumey, L. Nathan**; Bhagirath, Niala; Wu, Biqi; Boschelli, Diane H., *Tetrahedron Lett.*, 2008, 49(48), 6850-6852.

2005

“Isosteric ramatroban analogs: selective and potent CRTH-2 antagonists.”, Robarge, Michael J.; Bom, David C.; **Tumey, L. Nathan**; Varga, Norbert; Gleason, Elizabeth; Silver, Daniel; Song, Jianping; Murphy, Steven M.; Eckema, George; Doucette, Chris; Hanniford, Doug; Palmer, Marc; Pawlowski, Gary; Danzig, Joel; Loftus, Margaret; Hunady, Karen; Sherf, Bruce A; Mays, Robert W; Stricker-Krongrad, Alain; Brunden, Kurt R; Harrington, John J; Bennani, Youssef L, *Bioorg. Med. Chem. Lett.* 2005, 15(6), 1749-1753.

“The identification and optimization of a N-hydroxy urea series of flap endonuclease 1 inhibitors”, **Tumey, L. N.***; Bom, D.; Huck, B.; Gleason, E.; Wang, J.; Silver, D.; Brunden, K.; Boozer, S.; Rundlett, S.; Sherf, B.; Murphy, S.; Dent, T.; Leventhal, C.; Bailey, A; Harrington, J; Bennani, Y. L.”, *Bioorg. Med. Chem. Lett.* 2005, 15(2), 277-81.

2004

“The identification and optimization of 2,4-diketobutyric acids as flap endonuclease 1 inhibitors”, **Tumey, L.N.***; Huck, B.; Gleason, E.; Wang, J.; Silver, D.; Brunden,

K.; Boozer, S.; Rundlett, S.; Sherf, B.; Murphy, S.; Bailey, A.; Dent, T.; Leventhal, C.; Harrington, J.; Bennani, Y.L., *Bioorg. Med. Chem. Lett.*, 2004, 14(19), 4915-8.

2003

“High-Throughput Catch-and-Release Synthesis of Oxazoline Hydroxamates. Structure-Activity Relationships in Novel Inhibitors of *Escherichia coli* LpxC: In Vitro Enzyme Inhibition and Antibacterial Properties”, Pirrung, M. C.; **Tumey, L. N.**; McClerren, A. L.; Raetz, C. R. H., *J. Am. Chem. Soc.*, 2003, 125 (6), 1575-1586.

2002

“Inhibition of the antibacterial target UDP-(3-O-acyl)-N-acetylglucosamine deacetylase (LpxC): isoxazoline zinc amidase inhibitors bearing diverse metal binding groups”, Pirrung, M.C.; **Tumey, L.N.**; Raetz, C.R.; Jackman, J.E.; Snehalatha, K.; McClerren, A.L.; Fierke, C.A.; Gantt, S.L.; Rusche, K.M., *J. Med. Chem.*, 2002, 45(19), 4359-70.

“19F-Encoded Combinatorial Libraries: Discovery of Selective Metal Binding and Catalytic Peptoids”, Michael C Pirrung; Kaapjoo Park; L Nathan Tumey, *J. Comb. Chem.*, **2002**, 4, 4, 329-344.

2000

“Antibacterial agents that target lipid A biosynthesis in gram-negative bacteria. Inhibition of diverse UDP-3-O-(r-3-hydroxymyristoyl)-n-acetylglucosamine deacetylases by substrate analogs containing zinc binding motifs.”, Jackman JE; Fierke CA; Tumey LN; Pirrung M; Uchiyama T; Tahir SH; Hindsgaul O; Raetz CR., *J. Biol. Chem.*, **2000**, 275(15), 11002-9.

“Oxazoline Synthesis from Hydroxyamides by Resin Capture and Ring-Forming Release”, Michael C. Pirrung; L. Nathan Tumey, *J. Comb. Chem.*, **2000**, 2, 6, 675-680.

EDITORIAL / PEER REVIEW / REFEREE EXPERIENCE

Book Editor:

Springer, Method in Molecular Biology, “Antibody-Drug Conjugates: Methods and Protocols”. Publishing date: Fall 2019. Served as lead editor for this 26-chapter volume. Authored two of the chapters.

Referee service: (typically ~10 per year)

ACS Medchem Letters,
Bioconjugate Chemistry
Protein Engineering, Design, and Selection
Molecular Cancer Therapeutics
Analytical Chemistry
Pharmaceutical Medicine
ACS Omega
Currents in Pharmacy Teaching and Learning (CPTL)
Angewandte Chemie

External examiner, PhD thesis Committee (outside of Binghamton University)

S. R. Shindi, external examiner (thesis committee) – PhD pharmaceutical sciences, 2022, University of Kwazulu-Natal (Nigeria)

PROFESSIONAL AFFILIATIONS

American Chemical Society (1995-present)
American Association of Pharmaceutical Sciences (2017-present)
American Associate of Colleges of Pharmacy (2017-2019)
Society for the Immunotherapy of Cancer (SITC) (2022-present)

TEACHING EXPERIENCE

PHRM501 “Foundations of Pharmacology”. Delivered ~15 hours of lectures plus one group “case study” and multiple review sessions. Content: Medicinal chemistry, drug design, drug metabolism.

Delivered: Fall 2017, Fall 2018, Fall 2019, Fall 2020, Fall 2021

PHRM515 “Pharmaceutics II: Dosage Forms and Drug Delivery”. Delivered 9 hours of lectures plus 3h of review sessions. Content: Parenteral drug delivery, dispersed systems.

Delivered: Spring 2018

PHRM522 “Integrated Pharmacotherapy IV: Endocrine, Renal and Reproductive Health”. Delivered ~7 hours of lectures plus various review sessions. Content: Medicinal chemistry of diabetic drugs, glucocorticoids, mineralocorticoids, diuretics, birth control, PBH, and erectile dysfunction.

Delivered: Fall 2018, Fall 2019 [*co-coordinator*], Fall 2020

PHRM524 “Integrated Pharmacotherapy VI: Infections Diseases”. Delivered ~15 hours of lecture and active learning activities. Content: Medicinal chemistry and pharmacology of antiviral agents, antifungal agents, and antibacterial agents.

Delivered: Spring 2019, spring 2020, spring 2021

PHRM523 “Integrated pharmacotherapy V: Neurology, Psychiatry, Anesthesiology”. Delivered ~2 hours of lectures. Content: Medicinal chemistry of drugs for multiple sclerosis and Alzheimer’s disease.

Delivered: Spring 2019

PHRM542 “Integrated Pharmacotherapy VIII: Hematology / Oncology / Autoimmune Diseases” Delivered ~13 hours of lectures plus various review sessions. Content: Medicinal chemistry of immunomodulating agents and chemotherapeutic agents.

Delivered: Fall 2019, Fall 2020, Fall 2021

PHRM580E “Drug discovery and development”. *Course designer / coordinator*.

Content: Delivered ~15h of lectures and active learning. Coordinated all guest lectures, exams, and projects. Instructor of record.

Delivered: Fall 2020

UNIV101S “Science, Faith, and Ethics”. [Class delivered for Harpur College] Delivered ~15 hours of lectures and class activities. Content: Philosophy of science, ethical theories, and history of science and faith. *Course designer / coordinator*.

Delivered: Fall 2019

BME442/542 “Nanotechnology and Drug Delivery” [Class in Watson], delivered ~5h of lectures each year on pharmacokinetics and pharmacodynamics. *Guest lecturer*.

Delivered: Fall 2020, Fall 2021

MENTORSHIP OF STUDENTS AND POSTDOCTORAL FELLOWS [BINGHAMTON]

Year	Name	Program of study	Outcome / current position
2017-2019	Courtney Jackson	-Undergraduate independent study -Completed honors thesis -Pharmacy School Summer Intern Program (full time)	PharmD candidate, UNC Chapel Hill
2017-2020	Tak Ian Choi	PhD student (co-mentor)	Postdoctoral fellow, U. Penn.
2018	Zhongyuan “Lenny” Guo	Postdoctoral Fellow	Postdoctoral fellow, Harvard School of Public Health
2018-2019	Dane Carlson	MS Student (BME)	R&D associate, Regeneron Pharmaceuticals
2018-2020	Emanuel Oladwode	Postdoctoral Fellow	Assistant Professor of Pharmaceutical Sciences
2018-2020	Kelsey Watts	Undergraduate independent study	Scientific writer, Regeneron Pharmaceuticals
2018-2021	Jared Miller	-Undergraduate independent study -Completed honors thesis -Summer researcher (full time)	PhD candidate at Scripps Research Institute
2018-2024	Siteng Fang	PhD Student, BME	PhD student. Dissertation title “STRATEGIES FOR OPTIMIZING AND EVALUATING IMMUNE-REGULATING ANTIBODY-DRUG CONJUGATES”
2019-2021	Caitlin Vitro	-Undergraduate independent study -Completed honors thesis -Summer researcher (full time)	PhD candidate at UNC Chapel Hill
2019-2021	Brittany Bremms	-Undergraduate independent study -Completed Honors thesis	PhD candidate at Northeastern University

		-Summer researcher (full time)	
2019-2021	James “JP” Maher	PharmD student researcher	PharmD graduate
2019	Sarah Gillen	NSF REU student	Engineer at MedTronic
2019	Jared Frick	Undergraduate independent study	Medical Student at Albany College of Medicine
2020-2021	Rhea Johns	MS Student (BME)	PhD candidate, Virginia Tech
2020-2022	Katherine J Leong	-Undergraduate independent study -Pharmacy School Summer Intern Program (full time)	Researcher at New York Blood Center
2020-present	Samantha Benjamin	PhD Student, Chemistry	Current student
2021-2022	Daniel Wheeler	-Undergraduate independent study -Summer researcher (full time) -Summer Scholars and Artists Program (2021)	Current student
2021-2022	Caleb Manheim	Undergraduate independent study	MS student at Binghamton University
2021-present	Emma DeYoung	-Undergraduate independent study -Summer researcher (full time)	Current student
2020-2022	Justin M Howe	-Undergraduate independent study -Summer researcher (full time) -Summer Scholars and Artists Program (2020)	Medical student at Virginia Tech Carilion School of Medicine
2021	Sophia Cook	NSF REU student	Student at Rowan University
2021-2022	Jillian P. Handel	-Undergraduate independent study	MS Student at Binghamton University (PharmSci)
2022	Karina Zielenski	-Undergraduate independent study	Current student
2022	Steven McKay	-Undergraduate independent study	PhD student at Binghamton University

2022	Victor Ojo	-PhD candidate	Current student
2022	Megan Grey	-PharmD student (research track)	Current student
2022	Nicholas Bianchi	-Undergraduate independent study	Current student
2023	Lina Wu	-Undergraduate independent study	Current student
2023	Mohan Mullapudi	Postdoctoral Fellow	Current fellow
2023	Mohammad Asikur Rahman	Postdoctoral Fellow	Current fellow

Graduate Student Committee Service, not listed above:

- **Julien Avelino Viel**, external examiner (thesis committee) – PhD Chemistry, 2021
- **Laura Zielewicz**, external examiner (thesis committee) – PhD Chemistry, 2021
- **Soujanya Karantha**, external examiner (thesis committee) – PhD Biomedical Engineering, 2021
- **Victor Wamboa**, external examiner (thesis committee) – PhD Chemistry, 2020
- **Yuhao Yuan**, thesis committee member, Biomedical Engineering. (completed comprehensive exam and prospectus. Expected graduation ~2022)
- **Stephanie Zhang**, thesis committee member, Biomedical Engineering. (completed comprehensive exam and prospectus. Expected graduation ~2022)
- **Yundi Chen**, MS/PhD defense committee, Biomedical Engineering, 2020-2022.
- **Saptarshi Ghosh**, external examiner (thesis committee) – PhD Chemistry, 2020
- **S. R. Shindi**, external examiner (thesis committee) – PhD pharmaceutical sciences, 2022, University of Kwazulu-Natal (Nigeria)

Faculty mentorship, not listed above:

- Tony Davis, 2020-present. (SOPPS faculty mentorship committee member)
- Tracy Brooks, 2022-present. (SOPPS faculty mentorship committee member)

MANAGERIAL EXPERIENCE (direct reports, full time)

Fanny Xu (2021-present) – Research technician, Binghamton University
Jared Miller (2020-2021) – Research technician, Binghamton University
Samantha Benjamin (2017-2020) – Research technician, Binghamton University
Jeff Casavant (2013-2017) – Associate Scientist, Pfizer Inc.
Anokha Ratneyake, PhD (2015-2017) – Senior Scientist, Pfizer Inc.
Sujiet Puthenveetil, PhD (2013-2017) – Senior Scientist, Pfizer Inc.
Niala Bhagirath (2006-2010) - Assistant Research Scientist, Wyeth Pharmaceuticals
Joan Subrath (2008-2010) - Assistant Research Scientist, Wyeth Pharmaceuticals
Elizabeth Gleason (2002-2006) – Research Associate, Athersys Inc.

INVITED SEMINARS / ORAL PRESENTATIONS

- 2024 “Optimizing the Efficacy and PK of Immune Stimulating Antibody Conjugates”, Protein Engineering Summit (PEGS), May 17, 2024, Boston MA.
- 2024 “ADC Training Workshop”, Protein Engineering Summit (PEGS), May 14-15, 2024, Boston MA.
- 2024 “Next-generation topoisomerase ADC technology”, DAVA oncology 2024 Antibody Drug Conjugates and Bispecifics Think Tank, March 15-17 2024, Victoria BC.
- 2024 “The promise and the risk of TLR7 stimulating ADCs”, DAVA oncology 2024 Antibody Drug Conjugates and Bispecifics Think Tank, March 15-17 2024, Victoria BC.
- 2024 “ADC technology: How did we get here and where are we going?”, Lotte Biopharma, Syracuse NY, March 6th, 2024.
- 2024 “Precision Therapeutics: Using Chemistry to Supercharge Antibodies”, Feb. 6th, 2024, Houghton University, Caneadea NY.
- 2023 Bristol-Myers Squibb invited presentation, July 17, 2023. “Lessons in ADC design: Conjugation, Linkers, and Payloads”
- 2023 Hanson-Wade Linker and Conjugation Summit, August 22nd 2023. “Delving Into Site-Specific Conjugations to Create Homogenous ADCs” – Workshop leader.
- 2023 Hanson-Wade Linker and Conjugation Summit, August 23rd 2023. “Looking Beyond Cathepsins: Understanding & Optimizing Legumain-Cleavable ADC Linkers”
- 2023 PEGS, May 15-19, Boston MA. “Dual-function antibody conjugates: Combining multiple modes of action to maximize ADC efficacy”
- 2022 Northeast Regional ADC Meeting (NERM), October 4 2022. Rochester, NY; “Design, synthesis, and evaluation of anti-inflammatory antibody-drug-conjugates (ADCs) that target monocytes and macrophages”
- 2022 ADC World Summit, San Diego, CA, September 6, 2022 “New Strategies for the Design of TLR7 Agonist ADCs”
- 2021 ADC World Summit, October 14-15 2021, “Design & Optimization of TLR-activating ADCs for Use in Cancer & Infectious Diseases”
- 2021 Loxo Oncology, invited lecture, February 12 2021, “Challenges and opportunities in the design of antibody-drug conjugates”
- 2021 Bighat Biosciences, ADC workshop leader. April 16, April 29, May 13. Led a 4.5 hour training workshop on antibody-drug-conjugate design.

- 2021 PEGS 2021 Protein Engineering and Cell Therapy Summit, May 13, 2021. "Alternatives to ValCitPABC: New Cleavable Linker and Self-Immolation Strategies for ADCs"
- 2020 Takeda Pharmaceutical Company, invited lecture, October 19, 2020. "New proteolytic linker strategies for ADCs"
- 2020 European Antibody Congress, Oct. 22 2020. "New proteolytic linker strategies for ADCs"
- 2019 Wells College, Nov. 8, 2019. "Macromolecular Medicinal Chemistry: Strategies for Optimizing Antibody-Drug-Conjugates"
- 2018 Binghamton University, Department of Chemistry, March 9, 2018. "Macromolecular Medicinal Chemistry."
- 2018 Takeda Pharmaceutical Company, invited lecturer, May 22nd, 2018. "Macromolecular Medicinal Chemistry."
- 2018 "Bioanalysis on a Budget", L. Nathan Tumey, ADC World Summit, San Diego, CA, November 2018.
- 2017 University of Buffalo, School of Pharmacy, Sept. 14, 2017. "Dreaming Big and Thinking Small: Medicinal Chemistry Strategies for the Optimization of Antibody Drug Conjugates."
- 2017 Binghamton University, Biomedical Engineering, Sept. 26, 2017. "Dreaming Big and Thinking Small: Medicinal Chemistry Strategies for the Optimization of Antibody Drug Conjugates."
- 2017 Binghamton University, Department of Pharmacy and Pharmaceutical Sciences, Oct. 19, 2017. "Macromolecular Medicinal Chemistry."
- 2016 "Site-specific Conjugation for the Advancement of New Linker-Payloads", ADC World Summit, Berlin, Germany, February 2016.
- 2016 "Dreaming Big and Thinking Small: Applying Medicinal Chemistry Strategy to Antibody-Drug-Conjugates", ACS Webinar, June 2016. *[Recording available upon request]*
- 2015 "ADC Biotransformation: Metabolism of ADC Linkers & Payloads in vitro and in vivo", WRIB, Miami, FL, March 2015.
- 2014 "Metabolism of ADC linkers and payloads – how in vivo and in vitro stability data is used to advance decision making", ADC World Summit, San Diego, CA, October 26-29, 2014.
- 2014 "In Vivo ADC Stability", Hanson-Wade webinar, June 3rd, 2014. *[Recording available upon request]*

- 2013 “An Approach For Assessing and Optimizing ADC Linker Stability”, Boston, MA; PEGS; May 2, 2013.
- 2013 “The Impact of Conjugation and Linker Chemistry on ADC Stability”, Frankfurt, GE; ADC World Summit; February 27, 2013.
- 2011 “Identification and optimization of a series of indolo[2,3-c]quinoline IRAK4 inhibitors”, Anaheim, CA; 241st ACS National Meeting & Exposition, MEDI-3, March 27, 2011.
- 2004 “The identification and optimization of a N-hydroxy urea series of flap endonuclease 1 inhibitors,” *Gordon Conference on Medicinal Chemistry*, August 2004.

POSTERS / ABSTRACTS

- 2024 “Investigating Factors Impacting TLR7 Immunostimulatory ADC pharmacokinetics and pharmacodynamics”, Samantha R. Benjamin, Siteng Fang, Mohammad A. Rahman, Kayla K. Elder, Tracy A. Brooks, Tao Zhang, Lawrence N. Tumey, Protein Engineering Summit (PEGS), May 15-17, 2024, Boston, MA.
- 2024 “Optimization and Evaluation of Legumain-Cleavable Topoisomerase-1 Inhibitor ADCs in a Pancreatic Cancer Model”, Victor T. Ojo, Nicholas A. Bianchi, Kayla K. Elder, Michele Yi, , Mohammed A. Rahman, Tracy A. Brooks and L. Nathan Tumey, Protein Engineering Summit (PEGS), May 15-17, 2024, Boston, MA.
- 2024 “Identification of a Novel Trop2-Targeting Immune Stimulating Antibody Conjugate (ISAC) with Efficacy in a Model of Pancreatic Cancer”, Mohan Reddy Mullapudi, Victor T. Ojo, Anqi Zhang, Steven J. McKay, Tracy A. Brooks, L. Nathan Tumey, Protein Engineering Summit (PEGS), May 15-17, 2024, Boston, MA.
- 2024 “Design and preparation of TLR7 agonist antibody-conjugates for oncology and immunology applications”, Siteng Fang, Samantha R. Benjamin, Mohammad Asikur Rahman, Mohan R. Mullapudi, Justin M. Howe, Anqi Zhang, Emma G. DeYoung, Tao Zhang, Tracy A. Brooks and L. Nathan Tumey, TOLL2024, April 17-20, 2024, Rotterdam, Netherlands.
- 2024 “Quantifying Lipid Droplet Metabolic Activities in Ovarian and Cervical Cancer Cells using Stimulated Raman Scattering (SRS) Microscopy with Deuterium Labeling”, Ryan Pierson, Shovit A. Gupta, Mingyuan Zhang, Nathan Tumey, and Fake Lu; 3rd BME Research Exposition Conference 2024 at Binghamton University, March 15, 2024, Binghamton NY.
- 2024 “Exploring the effects of Lactic Acid on Ovarian Cancer Cells using Stimulated Raman Imaging”, Jack Cox, Ryan Pierson, L. Nathan Tumey, and Fake Lu; 3rd BME Research Exposition Conference 2024 at Binghamton University, March 15, 2024, Binghamton NY.
- 2024 “Novel Dual-loaded ADC elicits both cytotoxic and immune-modulating effects in in-vitro pancreatic cancer model”, Victor Ojo and L. Nathan Tumey; Binghamton Biomedical Research Conference, April 4, 2024.
- 2023 “Synthesis and Opitmization of DNAi Conjugates Targeting the MYC G4” Samantha R. Benjamin, Alexandra Maria Psaras, ade Tiszler, Daniel Watson, Katherine J. Leong, L. Nathan

- Tumey, and Tracy A. Brooks. GRC Nucleosides, Nucleotides and Oligonucleotides - June, 2023.
- 2023 “Pharmacology of Legumain-Cleavable MMAE Containing ADC Linkers”, Meghan Gray, Jared Miller, Karina Zielinski, Steven McKay, Kayla Elder, Dr. Tracey Brooks, Dr. L. Nathan Tumey; Protein Engineering Summit (PEGS), Boston MA, May 15th-19th 2023.
- 2023 “Using Conjugation Technology to Increase the Efficacy and Specificity of a MYC-Inhibiting Oligonucleotide”, Samantha R. Benjamin, Alexandra Maria Psaras, Daniel Watson, Tracy A. Brooks, and L. Nathan Tumey; Protein Engineering Summit (PEGS), Boston MA, May 15th-19th 2023.
- 2023 “Design, Evaluation, and Optimization of Immune Stimulating Antibody-Drug Conjugates for Cancer Treatment”, Siteng Fang, Victor Ojo, Kayla Elder, Tracy A. Brooks, and L. Nathan Tumey; Protein Engineering Summit (PEGS), Boston MA, May 15th-19th 2023.
- 2023 “Novel Dual-loaded ADC elicits both cytotoxic and immune-modulating effects in in-vitro pancreatic cancer model”, Victor Ojo and L. Nathan Tumey; Protein Engineering Summit (PEGS), Boston MA, May 15th-19th 2023.
- 2023 “Design, Evaluation, and Optimization of Immune Stimulating Antibody-drug Conjugates for Cancer Therapy”, Siteng Fang, Brittany Brems, Victor Ojo, Tracy A. Brooks, and Lawrence N. Tumey; March 31, 2023, AAPS NERDG meeting, St. Johns University, Queens NY.
- 2023 “Design, Synthesis, and Characterization of MYC-targeting DNAi with Improved Pharmaceutical Properties”, Samantha R. Benjamin, Alexandra Maria Psaras, Daniel Watson, Katherine J. Leong, Tracy A. Brooks, and L. Nathan Tumey; March 31, 2023, AAPS NERDG meeting, St. Johns University, Queens NY.
- 2022 “Visualizing Drug-induced Lipid Accumulation in Lysosomes with Quantitative Stimulated Raman Imaging of Chemical Bonds”, Yuhao Yuan, L. Nathan Tumey, Fake Lu; April 25, 2022; BME Department Research Exposition Conference, Binghamton NY.
- 2022 Abstract #584: “Solid-phase Site-Specific Antibody Conjugation Method Leads to ADCs with Retained Efficacy and Improved Stability.” F. Xu, V.T. Ojo, K.J. Leong, L.N. Tumey; MARM 2022, 6/1/2022, Trenton NJ
- 2022 Abstract #588: “Preparation of indoloquinoline TLR7 agonists with improved potency for use in ADC and targeted delivery applications.” E.G. DeYoung, J.M. Howe, D.R. Wheeler, J.T. Miller, L.N. Tumey; MARM 2022, 6/1/2022, Trenton NJ
- 2022 Abstract #97: “Design, Synthesis, and Characterization of MYC-targeting DNAi with Improved Pharmaceutical Properties. S.R. Benjamin, A.M. Psaras, K.J. Leong, T.A. Brooks, L.N. Tumey”; MARM 2022, 6/1/2022, Trenton NJ

- 2022 “Tumor Targeted Delivery of TLR7 Agonists For The Treatment of Cancer”; Siteng Fang, Brittany Brems, Emmanuel Olawode, and L. Nathan Tumey; Protein Engineering Summit (PEGS), May 2022, Boston, MA.
- 2021 “Design & Optimization of TLR-activating ADCs for Use in Cancer & Infectious Diseases”, L. Nathan Tumey, World ADC Summit, San Diego, Oct. 11, 2021.
- 2021 “Abstract 1246: Anticancer activity of indolo[2,3-c]quinoline stabilization of the KRAS promoter G4mid structure”, Alexandra Maria Psaras, Jared Miller, L. Nathan Tumey, Tracy A Brooks, American Association for Cancer Research, 2021.
- 2021 “Antibody-Mediated Target Delivery of TLR7/8 Agonists”, Siteng Fang and L. Nathan Tumey. PEGS, May 11, 2021.
- 2021 “Design of a Turn-on Fluorescence Assay for the Identification and Application of Improved ADC Linkers”; Caitlin N. Vitro, Samantha R. Benjamin, Jared T. Miller, Siteng Fang, L. Nathan Tumey; PAPER ID: 3554709; ACS National Meeting, Spring 2021. Technical division: MEDI
- 2021 “Targeted Delivery of TLR-Agonists Using ADC Technology”, Brittany Brems, Emmanuel Olawode, Siteng Fang, L. Nathan Tumey; PAPER ID: 3553214; ACS National Meeting, Spring 2021. Technical division: MEDI
- 2021 “GlyPro as a self-immolative spacer for the release of payloads from antibody-drug-conjugates”; Justin M. Howe, Jillian P. Handel, Kelsey A. Watts, Samantha R. Benjamin, Courtney P. Jackson, Brittany Brems, Siteng Fang, Tchilabolo Alayi, Yetrib Hathout, and L. Nathan Tumey. ACS National Meeting, Spring 2021.
- 2020 “New proteolytic linker strategies for ADCs”; L. Nathan Tumey. European Antibody Congress, Fall 2020. (Oct 20th 2020)
- 2020 “ α -Effect nucleophiles as noncanonical substrates for microbial transglutaminase”, Chio, Tak Ian; Demestichas, Breanna R.; Brems, Brittany M.; Bane, Susan L.; Tumey, Lawrence Nathan; From Abstracts of Papers, 259th ACS National Meeting & Exposition, Philadelphia, PA, United States, March 22-26, 2020 (2020), BIOL-0015.
- 2020 “Design and optimization of a turn-on fluorescence assay for the identification of improved ADC linkers”, Vitro, Caitlin N.; Miller, Jared; Benjamin, Samantha Rene; Tumey, Lawrence Nathan; From Abstracts of Papers, 259th ACS National Meeting & Exposition, Philadelphia, PA, United States, March 22-26, 2020 (2020), CHED-0641.
- 2020 “Evaluation of a FRET-based peptide-library aimed at the identification of improved proteolytic substrates for cleavable linkers”, Miller, Jared; Benjamin, Samantha Rene; Tumey, Lawrence Nathan; From Abstracts of Papers, 259th ACS National Meeting & Exposition, Philadelphia, PA, United States, March 22-26, 2020 (2020), CHED-0098.

- 2020 "Optimization of ADC linkers: Design and evaluation of a FRET-based ADC linker-library", Miller, Jared; Benjamin, Samantha Rene; Tumey, Lawrence Nathan; From Abstracts of Papers, 259th ACS National Meeting & Exposition, Philadelphia, PA, United States, March 22-26, 2020 (2020), MEDI-0184.
- 2020 "Optimizing conditions for the conjugation of unusual substrates to IgG1 antibodies using microbial transglutaminase", Brems, Brittany M.; Demestichas, Breanna R.; Chio, Tak Ian; Bane, Susan L.; Tumey, Lawrence Nathan; From Abstracts of Papers, 259th ACS National Meeting & Exposition, Philadelphia, PA, United States, March 22-26, 2020 (2020), CHED-0648.
- 2019 "Bioconjugation via zwitterionic boron-nitrogen heterocycles", Chio, Tak Ian; Gu, Han; Mukherjee, Kamalika; Tumey, L. Nathan; Bane, Susan L.; From Abstracts of Papers, 258th ACS National Meeting & Exposition, San Diego, CA, United States, August 25-29, 2019 (2019), ORGN-0279
- 2019 "Catabolism and Stability of Site-Specific Antibody-Drug Conjugates", Courtney Jackson, Samantha Benjamin, Zhongyuan Guo, and L. Nathan Tumey. Binghamton University Research Days, April 12th, 2019.
- 2019 "Thiolation of Q295: A Simple Strategy for the Site-Specific Conjugation of Hydrophobic Payloads to Native Antibodies"; Samantha R. Benjamin, Courtney P. Jackson, Siteng Fang, Dane P. Carlson, Zhongyuan Guo, L. Nathan Tumey. April 9-11, 2019.
- 2018 "Investigating Non-Canonical Transglutaminase Substrates for Bioconjugate Formation"; Breanna Demestichas, Tak Ian Chio, Dr. Susan Bane, Dr. L. Nathan Tumey; Binghamton University Department of Chemistry Undergraduate Research Conference, November 17th, 2018.
- 2018 "Novel Chemistry for Site-Specific Antibody Bioconjugates", Tak Ian Chio, Han Gu, Kamalika Mukherjee, L. Nathan Tumey, Susan L. Bane; Next Generation Protein Summit, June 10, 2018.
- 2018 "Novel chemistry for site-specific antibody bioconjugates", Chio, Tak; Gu, Han; Mukherjee, Kamalika; Tumey, L. Nathan; Bane, Susan. 256th ACS National Meeting & Exposition, Boston, MA, United States, August 19-23, 2018 (2018), BIOL-33.
- 2009 "SAR of substituted 2-phenyl thieno[2,3-b]pyridine-5-carbonitrile PKC-theta inhibitors", Tumey, L. Nathan; Wu, Biqu; Boschelli, Diane H.; Lee, Julie; Yang, Xiaoke; Brennan, Agnes; Chaudhary, Divya, Medicinal and Bioorganic Chemistry Foundation 9th Winter Conference, Steamboat Springs, CO, January 25-29, 2009.
- 2008 "2-Alkenyl thieno[2,3-b]pyridine-5-carbonitriles: Potent and selective inhibitors of PKC-theta", Tumey, L. Nathan; Boschelli, Diane H.; Chaudhary, Divya; Lee, Julie, 235th ACS National Meeting, New Orleans, LA, United States, April 6-10, 2008, MEDI-036.

PATENTS (FILED)

- 2024 "POTENT FGFR4-TARGETED ANTIBODY-DRUG CONJUGATES AND THEIR USE FOR TREATING CANCERS EXPRESSING FGFR4", Filed 4/5/2024, Javed Khan, Boris Shor, Meijie Tian, Lawrence Nathan Tumey, Placeholder for NIH FGFR4 patent application 63/575,037
- 2024 "TLR7 AND TLR8 AGONISTS FOR THE TREATMENT OF CANCER AND/OR INFECTIOUS DISEASES", Filed 5/14/2024, Lawrence Nathan TUMEY and Mohan Reddy MULLAPUDI, U.S. Application No.: 63/647,200
- 2023 "ANTIBODY-DRUG COMPLEXES WITH TOPOISOMERASE INHIBITORS", Filed, 8/22/2023, L. Nathan Tumey, Victor Ojo, Nicholas Bianchi, U.S. Application No.: 63/520,946
- 2023 "TARGETED DELIVERY OF DUAL PAYLOAD OF MMAF OR MMAE AND TLR7 AGONISTS FOR THE TREATMENT OF CANCER", Filed May 15, 2023. L. Nathan Tumey and Victor Ojo. U.S. Application No.: 63/502,176
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