

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

Patent No. 10,131,682

Ex Parte Reexamination Certificate Issued: January 4, 2021

Title: HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF
DRUGS TO A CELL BINDING MOLECULES

Inter Partes Review No. IPR2022-01531

**PETITION FOR *INTER PARTES* REVIEW
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 *ET. SEQ.***

TABLE OF CONTENTS

TABLE OF AUTHORITIES	v
EXHIBIT LIST.....	vii
I. INTRODUCTION	1
II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8.....	1
A. Real-Party-In-Interest.....	1
B. Notice of Related Matters	1
C. Lead and Backup Counsel	2
D. Service Information.....	2
III. REQUIREMENTS FOR IPR UNDER 37 C.F.R. §42.104.....	2
A. Grounds for Standing.....	2
B. Identification of Challenge	2
IV. STATE OF THE ART	4
A. Technical Introduction	4
B. Harris.....	5
C. Morales-Sanfrutos	7
D. Straus.....	9
E. Singh	10
F. Bhakta	15

G.	Snow.....	17
V.	LEVEL OF SKILL IN THE ART	18
VI.	THE '682 PATENT.....	19
A.	Prosecution History Overview.....	19
B.	Reexamination Summary.....	20
C.	Claims Summary.....	21
D.	Claim Construction	24
VII.	CLAIM-BY-CLAIM EXPLANATION OF GROUNDS OF UNPATENTABILITY	24
A.	Ground 1: Claims 1-3, 6, 24-25, and 33 Are Anticipated by Morales-Sanfrutos as Evidenced by Straus	24
1.	Claim 1.....	25
2.	Claim 2.....	32
3.	Claims 3 and 24	32
4.	Claims 6, 25, and 33	36
B.	Ground 2: Claims 1, 20-21, and 29-31 are anticipated by or obvious in view of Harris.....	37
1.	Claim 1.....	38
2.	Claims 20-21, and 29-31	40

C.	Ground 3: Claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31 are obvious over Singh in view of Harris	44
1.	Claims 1-2.....	44
2.	Claims 20-21 and 29-31	53
3.	Claims 3-8, 10-12, 14-17, 24, and 26	61
D.	Ground 4: Claims 9 and 13 are obvious over Singh in view of Harris and Bhakta.....	70
E.	Ground 5: Claims 2, 25 and 32-34 are obvious over Singh in view of Harris and Snow.....	73
F.	There is no evidence of secondary considerations	77
VIII.	THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION	78
A.	The Board Should Not Deny Review Under §314(a).....	78
B.	The Board Should Not Deny Review Under §325(d)	78
	CONCLUSION	80

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Amneal Pharms. v. Supernus Pharms.</i> , IPR2013-00368 (PTAB Dec. 17, 2013)	77
<i>Apple Inc. v. Fintiv, Inc.</i> , IPR2020-00019, Paper 11 (PTAB March 20, 2020)	78
<i>AVX Corp. v. Greatbatch, Ltd.</i> , IPR2014-00697, Paper 60 (PTAB Jan. 11, 2016)	18
<i>Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.</i> , 289 F.3d 801 (Fed. Cir. 2002)	25, 26, 33
<i>Custom Accessories, Inc. v. Jeffrey-Allan Indus.</i> , 807 F.2d 955 (Fed. Cir. 1986)	18
<i>Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha</i> , IPR2016-01357, Paper 19 (PTAB Sept. 6, 2017).....	78
<i>Kayak Software Corp. v. IBM Corp.</i> , CBM 2016-00075, Paper 16 at 11, (PTAB 2016)	79
<i>KSR Int’l Co. v. Teleflex</i> , 550 U.S. 398 (2007).....	18
<i>In re Paulson</i> , 30 F.3d 1475 (Fed. Cir. 1994)	25
<i>Kennametal, Inc. v. Ingersoll Cutting Tool Co.</i> , 780 F.3d 1376, 1381, (Fed. Cir. 2015)	38
<i>Pitney Bowes v. Hewlett-Packard Company</i> , 182 F.3d 1298 (Fed. Cir. 1999)	26
<i>In re Schreiber</i> , 128 F.3d 1473 (Fed. Cir. 1997)	26
<i>Oticon Medical AB v. Cochlear Ltd.</i> , IPR2019-00975 (PTAB Oct. 16, 2019)	80

<i>Teva Pharmaceuticals USA, Inc. v. Sandoz Inc.</i> , 810 F.Supp.2d 578 (2011)	25
--	----

Statutes

35 U.S.C. §102(a)(1).....	3,5,8,10,15,17
35 U.S.C. §102.....	24
35 U.S.C. §103.....	44
35 U.S.C. §103(a)	3,4
35 U.S.C. §§ 311-19.....	1
35 U.S.C. §314(a)	3, 78

Other Authorities

37 C.F.R. §42.8	1
37 C.F.R. § 42.100 <i>et seq.</i>	1
37 C.F.R. §42.104.....	2

EXHIBIT LIST

Ex. #	Exhibit
EX1001	U.S. Patent No. 10,131,682 (“the ’682 Patent”)
EX1002	Ex Parte Reexamination Certificate for the U.S. Patent No. 10,131,682 (“the ’862 REC”)
EX1003	Declaration of Dr. Ravi Chari
EX1004	Curriculum Vitae of Dr. Ravi Chari or ’682 PHE
EX1005	Morales-Sanfrutos <i>et al.</i> , "Vinyl sulfone bifunctional tag reagents for single-point modification of proteins." <i>The Journal of Organic Chemistry</i> 75, no. 12 (2010): 4039-4047 (“Morales-Sanfrutos”)
EX1006	Straus & Keller, “Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells,” <i>Histochemistry</i> 85, July 1986, pages 277-285 (“Straus”)
EX1007	International Publication No. WO 1995/013312 (“Harris”)
EX1008	U.S. Patent Publication No. 2010/0129314 (“Singh”)
EX1009	U.S. Patent No. 5,208,020 (“Chari”)
EX1010	U.S. Patent No. US 5,414,135 (“Snow”)
EX1011	U.S. Patent Application Publication No. 2011/0301334 (“Bhakta”)
EX1012	Declaration of Dr. James Mullins
EX1013	Curriculum Vitae of Dr. James Mullins
EX1014	Thomas <i>et al.</i> , “Application of Strain-Promoted Azide-Alkyne Cycloaddition and Tetrazine Ligation to Targeted Fc-Drug Conjugates,” <i>Bioconjug Chem.</i> , 23(10), October 2012, pages 2007–2013 (“Thomas”)
EX1015	Kathrin-Maria Roy <i>et al</i> , <i>Sulfones and Sulfoxides</i> , Ullmann's Encyclopaedia of Industrial Chemistry, Vol. 34, page 571 (2003) (“Roy”)

Ex. #	Exhibit
EX1016	Zhao et al., Synthesis and Evaluation of Hydrophilic Linkers for Antibody_Maytansinoid Conjugates, J. Med. Chem. 2011, 54, 3606–3623 (“Zhao”)
EX1017	U.S. Patent No. 6,214,345 (“Firestone”)
EX1018	Prosecution History excerpts for US 10,131,682.
EX1019	Excerpts for File Wrapper of Ex Parte Reexamination No. 90/014,390
EX1020	WTS Scan of Morales-Sanfrutos from WTS
EX1021	Download of Morales-Sanfrutos from Purdue U. Libraries
EX1022	WorldCat entry for Morales-Sanfrutos
EX1023	Download of Linda Hall Library OPAC record for Morales-Sanfrutos
EX1024	Morales-Sanfrutos ACS Digital Publication record
EX1025	WTS Scan of Strauss from Linda Hall Library
EX1026	Download of Strauss from Purdue University Libraries
EX1027	WorldCat entry for Strauss
EX1028	Download of Linda Hall Library OPAC record for Strauss
EX1029	WTS Scan of Thomas from Linda Hall Library
EX1030	Download of Thomas from Purdue University Libraries
EX1031	WorldCat entry for Thomas
EX1032	Download of Linda Hall Library OPAC record for Thomas
EX1033	Thomas ACS Digital Publication record
EX1034	Scan of Roy from Linda Hall Library
EX1035	Screenshot of link to Roy via Purdue University Libraries
EX1036	Download of Roy from Purdue University Libraries
EX1037	WorldCat entry for Roy
EX1038	Monographic record for Roy at Linda Hall Library

Ex. #	Exhibit
EX1039	Roy Digital Publication Record
EX1040	Scan of Zhao from National Library of Medicine
EX1041	Download of Zhao from Purdue University Libraries
EX1042	Download of WorldCat entry for Zhao
EX1043	Download of National Library of Medicine OPAC record for Zhao
EX1044	Zhao ACS Digital Publication record
EX1045	Certified translation of priority French Application No. FR 10/52589, filed 6 April 2010
EX1046	International Publication No. WO2011124571
EX1047	U.S. Patent No. 5,122,614 (“Zalipsky”)
EX1048	Boja & Fales, <i>Anal. Chem.</i> 2001, 73, pages 3576-3582 (“Boja”)
EX1049	Lewis Phillips <i>et al.</i> , <i>Cancer Res</i> (2008) 68 (22): 9280–9290
EX1050	US Patent No. 8,236,319 (“Chari”)
EX1051	Pietersz <i>et al.</i> , <i>Advances in Immunology</i> Vol. 56: 301-387 (1994).
EX1052	Trail & Bianchi, <i>Current Opinion in Immunology</i> 11:584–588 (1999).
EX1053	Ghose <i>et al.</i> , <i>Journal of the National Cancer Institute</i> , Vol. 61(3): 657–676 (1978) (“Ghose”)
EX1054	Panousis & Pietersz, <i>Drugs & Aging</i> 15 (1): 1-13 (1999)
EX1055	Alley <i>et al.</i> , <i>Bioconjug Chem.</i> 2008 Mar;19(3):759-65.
EX1056	Doronina <i>et al.</i> , <i>Nature Biotech</i> 21(7):778-784 (2003) (“Doronina”).
EX1057	Screen capture Wayback Machine Bioconjugate Chemistry

I. INTRODUCTION

SynAffix B.V. (“Petitioner”) requests *inter partes* review of claims 1-17, 20-21, 24-26, and 29-34 (the “Challenged Claims”) of U.S. Patent No. 10,131,682 (“the ’682 patent,” EX1001), assigned to Hangzhou DAC Biotech Co., Ltd. (“Patent Owner” or “DAC”), in accordance with 35 U.S.C. §§ 311-19 and 37 C.F.R. § 42.100 *et seq.*

Claims 1-17, 20-21, 24-26, and 29-34 recite nothing more than conventional hydrophilic linkers that were widely used in industry to produce drug conjugates comprising cell-binding agents (*e.g.*, proteins such as antibodies and enzymes, vitamins, peptides, *etc.*) prior to the effective filing date of the ’682 patent.

II. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

A. Real-Party-In-Interest

The only real-party-in-interest is Petitioner, SynAffix B.V., located at Molenstraat 110, Oss, Netherlands 5342 CC.

B. Notice of Related Matters

The ’682 patent was re-examined as Reexamination Control Number 90/014,390, yielding, *inter alia*, amended claims 1, 3, 20, and new claims 24-26 and 29-34. There are no pending continuation or divisional applications related to the ’682 patent. Petitioner is not aware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

C. Lead and Backup Counsel

Lead Counsel: Michael Houston (Reg. No. 58,486) **Tel:** 312.832.4378

Backup Counsel: Joseph Meara (Reg. No. 44,932) **Tel:** 608.258.4303

Jolene Fernandes (Reg. No. 73,897) **Tel:** 617.571.5261.

Address: Foley & Lardner LLP, 3000 K St NW, Suite 600

Washington, DC 20008 **Fax:** 608.257.5035

D. Service Information

Please address all correspondence to the lead counsel at the address above.

Petitioner consents to electronic service at: 682IPR@foley.com.

III. REQUIREMENTS FOR IPR UNDER 37 C.F.R. §42.104

A. Grounds for Standing

Petitioner hereby certifies that the '682 patent is available for *inter partes* review and that the Petitioner is not barred or estopped from requesting an IPR on the grounds identified herein.

B. Identification of Challenge

Petitioner requests review and cancellation of claims 1-17, 20-21, 24-26, and 29-34 of the '682 patent for the reasons explained in this petition, which are summarized as follows:

Ground	Claims	Basis	References
1	1-3, 6, 24-25, and 33	§102(a)(1)	Morales-Sanfrutos (EX1005) as evidenced by Straus (EX1006)
2	1, 20-21, and 29-31	§102(a)(1)/ §103(a)	Harris (EX1007)
3	1-8, 10-12, 14-17, 20- 21, 24, 26, 29-31	§103(a)	Singh (EX1008) in view of Harris (EX1007)
4	9 and 13	§103(a)	Singh (EX1008) in view of Harris (EX1007) and Bhakta (EX1011)
5	2, 25 and 32-34	§103(a)	Singh (EX1008) in view of Harris (EX1007) and Snow (EX1010)

Per 37 C.F.R. §42.6(d), copies of the references are filed herewith. In support of the proposed grounds, Petitioner includes the Declaration of Dr. Ravi Chari (EX1003), explaining what the art would have conveyed to a person of ordinary skill in the art (“POSA”) as of the priority date of the ’682 patent. EX1003, ¶¶1-13.

A petition for *inter partes* review must demonstrate “a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition.” 35 U.S.C. §314(a). The Petition meets this threshold. EX1003, ¶¶14-15. Each of the elements of challenged claims 1-17, 20-21, 24-26,

and 29-34 of the '682 patent¹ is taught in the prior art as explained below in the proposed grounds of unpatentability. Also, for each ground under 35 U.S.C. §103(a), the reason to combine and the basis for a reasonable expectation of success are established.

IV. STATE OF THE ART

A. Technical Introduction

For over six decades, antibody-drug conjugates (ADCs) have been developed and used as means for selectively targeting cells or tissues expressing target tumor-associated antigens to deliver various cytotoxic anti-cancer agents. EX1009, 1:20-45; EX1003, ¶44. Because ADCs “function as ‘smart bombs’ that allow the toxin to bypass healthy tissue and hit only the targets of interest,” they produce fewer side-effects than administration of unconjugated cytotoxic agents. EX1014, 2007; *see also, e.g.*, EX1009, 4:63-68; EX1003, ¶44. Some early concerns in the clinical use of ADCs included diminished potency, “especially when antigen expression on the target cancer cell is low, or when the target cancer

¹ References to claims 1, 3, 20, 24-26 and 29-34 refer to those from the '390 reexamination, and references to claims 2, 4-17, 21, 24-26 refer to those originally issued in the '682 patent (all of which depend from independent claims newly issued from the '390 reexamination).

cells are resistant to treatment” (EX1008, ¶¶0006]), and “ADC aggregation, loss of affinity for the target antigen, and rapid clearance from circulation” particularly where “both the cytotoxic agent and the linker were hydrophobic.” EX1016, 3607 (citations omitted).

However, well before the ’682 patent’s priority date it was recognized that the linker between the antibody and the cell-killing agent “significantly affects the potency, selectivity and pharmacokinetics of the resulting conjugate.” *Id.*, 3606. Water solubility in particular, was recognized as very useful for overcoming many of the above-identified concerns initially encountered with ADC linkers. EX1008, Abstract, ¶¶[0002], [0009], [0011], [0078]; EX1016, 3607; EX1003, ¶45. As such, well prior to 2012, suitable hydrophilic linkers were developed to create drug conjugates that overcame the foregoing challenges, producing ADCs with better potency and target affinity combined with reduced aggregation and system clearance, as evidenced by the prior art discussed below. EX1003, ¶45.

B. Harris

International Publication No. WO 1995/013312 (“Harris”, EX1007) was first published May 18, 1995, and is prior art under at least §102(a)(1). Harris was not cited during prosecution or reexamination of the ’682 patent.

Harris discloses “water soluble and hydrolytically stable derivatives of poly(ethylene glycol) (‘PEG’) polymers and related hydrophilic polymers having

one or more active **sulfone** moieties.” EX1007, 6:8-11 (emphasis added), 16:14-17 and 24-25, claims 29-30. Harris teaches PEG/sulfone derivatives as useful for conjugating two different biologically-active moieties such as proteins, pharmaceuticals, and vitamins, wherein at least one of the biologically-active moieties has a reactive thiol moiety. *Id.*, claims 33-34, 16:34-17:5, Abstract. Harris’ PEG/sulfone “derivatives are considered infinitely soluble in water or as approaching infinite solubility and can enable otherwise insoluble molecules to pass into solution when conjugated with the derivatives.” EX1007, 19:34-37. These derivatives are thus hydrophilic and serve to link two differing moieties, including, *e.g.*, proteins and drugs. EX1003, ¶¶46-48, 51.

One PEG derivative disclosed by Harris “has the basic structure: R-(OCH₂CH₂)_n-Y,” wherein Y represents -SO₂-CH=CH₂ (*i.e.*, vinyl sulfone) or -SO₂-CH₂-CH₂-X where X is a halogen (*i.e.*, a haloethyl sulfone); n is about 5 to 3,000 (including 5 to 2,200, 34 to 1,100, and 45 to 110). R in Harris’ basic structure represents a group that is the same or different from Y and thus can be CH₂=CH-SO₂- or Cl-CH₂-CH₂-SO₂-. EX1007, 19:10-30. Harris therefore discloses PEG derivatives with one or two sulfonyl groups, including PEG bis vinyl sulfone. *Id.*, 18:34-19:2; EX1003, ¶49.

Harris also describes **heterobifunctional** PEG derivatives that can be used “to carry a protein or other biologically active molecule by **sulfone** linkages on one

end and by another linkage on the other end, such as an amine linkage, to produce a molecule having two different activities.” EX1007, 17:24-34. Harris teaches many reactive groups that may be used for heterobifunctional sulfone-activated PEGs, including those for reaction with amino groups such as N-hydroxysuccinimide ester, acyl azide and succinate. *Id.*, 18:5-30; claim 35. The latter are groups known to form amide bonds with amines. EX1003, ¶50. Harris also cites U.S. Patent No. 5,122,614 (Zalipsky, EX1047) as teaching use of, *e.g.*, a PEG-N-succinimide carbonate for formation of a urethane linkage from, *e.g.*, a lysine epsilon –NH₂ group. EX1007, 3:28-35. Harris thus expressly recommends use of vinyl sulfones and other active sulfones in combination with non-sulfone activating groups known in the art on either end of its PEG-based linkers. EX1003, ¶¶50-52.

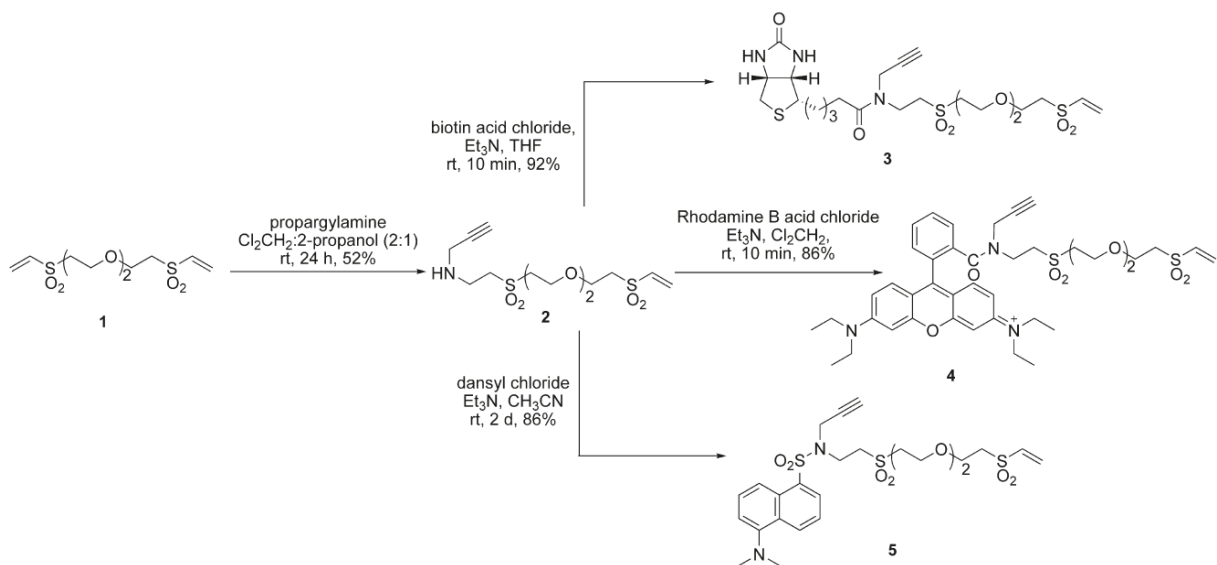
C. Morales-Sanfrutos

Morales-Sanfrutos *et al.*, “Vinyl Sulfone Bifunctional Tag Reagents for Single-Point Modification of Proteins,” *J. Org. Chem.* 75:4039–4047, was first published in May 2010 (“Morales-Sanfrutos,” EX1005). Morales-Sanfrutos was

publicly available in print at least by June 26, 2010. *See* EX1012, ¶¶35-51.² Thus, Morales-Sanfrutos is prior art under at least §102(a)(1). Although Morales-Sanfrutos was submitted in an IDS during reexamination proceedings and appeared on the list of considered references on the face of the Reexamination Control Number 90/014,390, it was not applied or cited in any rejection during reexamination, nor during prosecution of the '682 patent.

Morales-Sanfrutos discloses several examples of alkyne vinyl sulfone derivatized tags (AVSTs) as shown in Scheme 1, reproduced below:

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



² Exhibit 1012 is the Declaration of Dr. James L. Mullins, a professional librarian retained by Petitioner to opine on the authenticity and public availability of certain prior art references relied on herein.

EX1005, 4041.

These bifunctional PEG linker compounds were linked to both horse radish peroxidase enzyme and biotin, among other moieties. *Id.*, 4041, 4044; EX1003, ¶¶53-56. Morales-Sanfrutos further teaches 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,” and that “Michael-type addition between vinyl sulfone and thiols is accepted as a click reaction.” EX1005, 4041, 4044. Finally, Morales-Sanfrutos notes that:

[T]he AVST compounds clearly establish that the vinyl sulfone chemistry is a valuable methodology for the introduction of clickable groups with similar characteristics to other traditional bioconjugation strategies (*i.e.*, activated esters-lysine or maleimide-Cys) used for this same purpose with the major advantage of the vinyl sulfone stability in water over the activation chemistries used on those strategies.

EX1005, 4043-44; EX1003, ¶¶54-57.

D. Straus

Straus & Keller, “Unusual Binding Sites for Horseradish Peroxidase on the Surface of Cultured and Isolated Mammalian Cells,” *Histochemistry* 85:277-285, was first published in July 1986 (“Straus,” EX1006). Straus was publicly available in print at least by November 16, 1986. *See* EX1012, ¶¶52-67. Thus, Straus is

prior art under at least §102(a)(1). Although Straus was submitted in an IDS during reexamination and appeared on the list of considered references, it was not applied or cited in any rejection during reexamination, nor during prosecution of the '682 patent.

Straus discloses that horse radish peroxidase may bind to the surface of a variety of cells, including macrophages, fibroblasts, mast cells and endothelial cells. EX1006, 277; EX1003, ¶¶58-59.

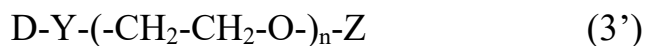
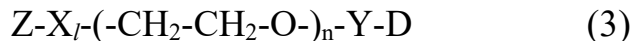
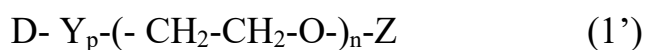
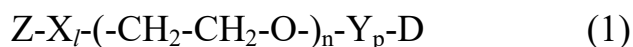
E. Singh

U.S. Patent Application Publication No. 2010/0129314 to Singh (“Singh,” EX1008) was published on May 27, 2010 (also first published as International Publication No. WO 2009/134976 on November 5, 2009) is prior art under at least §102(a)(1). EX1003, ¶60. Although Singh was submitted in an IDS during reexamination and appeared on the list of considered references, it was not applied or cited in any rejection during reexamination, nor during prosecution of the '682 patent.

Singh relates to hydrophilic linkers that “link drugs to cell-binding agents” such as antibodies. The “linker design provides conjugates that are active across a broad spectrum of tumors, particularly in low antigen expressing or drug resistant tumors.” EX1008, ¶¶[0002], [0008]. Singh found that “when traditional linkers...are modified to hydrophilic linkers by incorporating a polyethylene glycol

[PEG_n (-CH₂CH₂O)_n] spacer, the potency or the efficacy of the cell-binding agent-drug conjugates is surprisingly enhanced several fold in a variety of cancer cell types.” *Id.*, ¶¶0009]; EX1003, ¶61.

Singh expressly teaches PEG cross-linkers as compounds of formulas (1), (1’), (3), and (3’):



In each formula, a drug “D” is attached at one end of a PEG chain and a reactive functionality “Z” is attached at the other end. EX1008, ¶¶[0014], [0016], [0080], [0090]. Z “can form an amide or a **thioether bond** with a cell-binding agent.” *Id.* Exemplary reactive functionalities for Z include “amine-reactive functionality, where the functionality could be a reactive carboxylic ester” such as an N-succinimidyl ester “to give an amide bond,” and “thiol-reactive functionality...that could be a maleimide, haloacetamide, or a **vinyl sulfone** to form a thioether bond.” EX1008, ¶[0134] (emphasis added); *see also id.*, ¶[0136], Figs. 4, 13; EX1003, ¶¶62-63.

Singh also teaches PEG cross-linkers where a cell-binding agent such as an antibody (mAb) is attached at one end of a PEG chain and a drug (D) is attached at

the other end (*i.e.*, compounds of formulas (2): $\text{CB}—[\text{X}_l—(\text{—CH}_2\text{—CH}_2\text{—O—})_n\text{—Y}_p\text{—D}]_m$, and (2'): $\text{D—Y}_p—(\text{—CH}_2\text{—CH}_2\text{—O—})_n\text{—CB}$. EX1008, ¶¶ [0137]-[0138], [0219], [0221], Figs. 8, 10, 12, 15, 18, 21. The main difference between each pair of linkers is the direction of the PEG within the linker. For example, the PEG oxygen is adjacent to Y in formulas (1), (2) and (3), and is adjacent to X_l in formulas (1'), (2') and (3'). EX1003, ¶63.

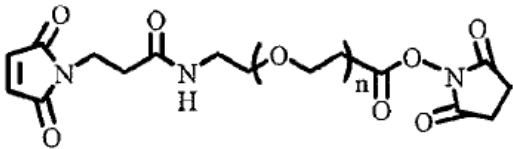
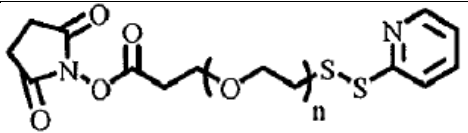
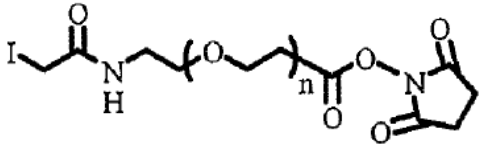
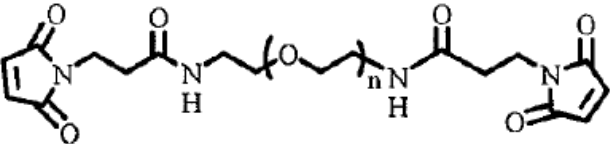
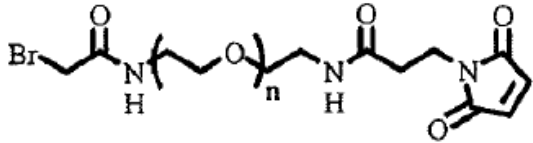
In Singh's formulas (1), (1'), (3), and (3'), l may be 0 or 1. When present (*i.e.*, when $l=1$), X represents an aliphatic, aromatic, or heterocyclic unit attached to the cell-binding agent via a thioether, amide, carbamate, or ether bond. In formulas (1) and (1'), p may be 0 or 1. When present ($p=1$), Y represents an aliphatic, aromatic, or heterocyclic unit attached to the drug via a covalent thioether, amide, carbamate, ether, amine, carbon-carbon, or hydrazone bond. EX1003, ¶64.

In formulas (3) and (3'), Y is always present, and represents an aliphatic, aromatic, or heterocyclic unit attached to the drug via a disulfide bond. Variable n , which pertains to the number of ethyleneoxy subunits present in the PEG group, is an integer from 1 to 2000 in formulas (1) and (1'), but is 1-14 in formulas (3) and (3'). EX1008, ¶¶ [0014], [0080]. Preferred values of n in formulas (1) and (1') are 1-100, 1-14, and most preferred is 1-4. *Id.*, ¶ [0082]. Numerous examples of these

PEG cross-linkers are given in Figs. 4, 5, 6A, 7, 9, 11, 13, 14, 16A, 17, 19A, 20, and Examples II and III of Singh. EX1003, ¶64.

Singh's PEG cross-linkers may be prepared by coupling a "bifunctional PEG-containing cross linker" to a drug or an antibody. EX1008, ¶¶[0136]-[00138], [0217]-[0219], [0221]-[0222]. Examples of Singh's bifunctional PEG cross-linkers are shown in Table A1 below, along with the figures in which they appear. EX1003, ¶65.

Table A1

Entry	Bifunctional PEG Cross-linkers	Figs.
1		4, 8
2		6B, 12
3		10
4		13, 15
5		16B, 18

These bifunctional crosslinkers include “n” PEG subunits, just as in the PEG crosslinker formulas, where n is defined throughout Singh to be an integer of 1-2000, 1-100, 1-14 or 2-8, and most preferably, 1-4. EX1008, ¶¶[0014]-[0017], [0080], [0082], [0084], [0087], [0090]-[0093], [0095]; EX1003, ¶66.

After coupling one end of the bifunctional PEG cross-linker to a drug (to give compounds of formulas (1), (1'), (3), (3')) (*e.g.*, through a maleimide, iodo- or bromoacetamide, or a pyridyldisulfide), the remaining reactive functionality may be coupled to an antibody to form an ADC of formulas (2), (2'), (4) or (4'). The ADCs are prepared, *e.g.*, by modifying the antibody with the PEG crosslinker at a lysine side-chain amino group via an amide bond (*see, e.g.*, Figs. 7, 9, 11) or to a cysteine thiol via a thioether bond (*see, e.g.*, Figs. 14, 17, 20). EX1008, ¶¶[0137], [0209], [0214], [0220], [0221]; EX1003, ¶67. Alternatively, after coupling the bifunctional PEG cross-linker to an antibody at one end (*e.g.*, through a maleimide, iodo- or bromoacetamide, or NHS ester), the remaining reactive functionality may be coupled to a drug to form an ADC. EX1008, ¶¶[0136]-[0137], Figs. 8, 10, 12, 15, 18, 21. The drugs may be part of the crosslinker or subsequently added. *Id.*, ¶[0007], [0014], [0080]; EX1003, ¶68.

Compared to ADCs with traditional hydrophobic linkers, the potency/efficacy of Singh's hydrophilic PEG-containing ADCs was “enhanced several fold in a variety of cancer cell types, including those expressing a low

number of antigens on the cell surface” and “toward cell lines that are resistant to treatment.” EX1008, ¶¶0009]; EX1003, ¶¶69-70.

F. Bhakta

U.S. Patent Application Publication No. US 2011/0301334 to Bhakta (“Bhakta,” EX1011) was first published December 8, 2011, and is prior art under §102(a)(1). Bhakta was not applied or cited in any rejection during reexamination or prosecution of the ’682 patent. Bhakta expressly teaches antibody-drug conjugates (ADCs) comprising:

a cysteine engineered antibody (Ab), and a drug moiety (D) wherein the antibody has one or more free cysteine amino acids, and the antibody is attached through the one or more free cysteine amino acids by a linker moiety (L) to D; the composition having formula I: Ab-(L-D)_p, where p is 1, 2, 3, or 4.

EX1011, ¶¶[0211]-[0212] EX1003, ¶¶71-72.

Bhakta discloses the advantages of including cleavable peptide linker components within ADCs to permit protease-mediated release of active drugs. Specifically, Bhakta teaches that the “linker may comprise amino acid residues which links the antibody (Ab) to the drug moiety (D) of the cysteine engineered antibody-drug conjugate (ADC) of the invention,” and that the “*amino acid residues may form a dipeptide*” as well as longer peptides. Both natural amino

may be used, *e.g.*, val-cit. EX1011, ¶¶[0244]-[0245]; EX1003, ¶73.

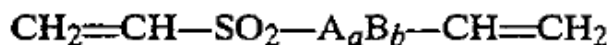
MC-val-cit-PAB

When the val-cit dipeptide is cleaved from the PAB by cathepsins associated with the target cancer cell, the resulting p-aminobenzyloxycarbonyl group falls apart, releasing the drug within the cancer cell. EX1003, ¶¶74-75.

G. Snow

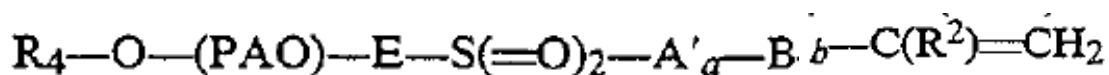
U.S. Patent No. US 5,414,135 to Snow ("Snow," EX1010) was first published May 9, 1995, and is prior art under at least §102(a)(1). Snow was not cited in any rejection during reexamination or prosecution of the '682 patent.

Snow teaches the bis(vinyl sulfone) reagent



where A is an alkylene radical of 1-8 carbon atoms, a is 1; B is a sulfoxide or a sulfone group; and b is 1. EX1010, 7:14-27; EX1003, ¶¶76-77.

Snow further discloses a class of polyalkylene oxide vinyl sulfone reagents that are useful for generating protein conjugates, are hydrolytically stable, and react with proteins in aqueous media. *Id.*, abstract, 4:36-42. Snow expressly discloses polyalkylene oxide bis(vinyl sulfone) reagents represented by the formula:



where R₄ is H, PAO is a polyalkylene oxide having an average molecular weight in the range of 250-200,000 daltons, E is alkylene group of 1-8 carbons or an alkylenyl group of 2-8 carbons, A is an alkylene radical of 1-8 carbon atoms which may be saturated, a is 1, B is a sulfoxide group, b is 1, and R² is H. *Id.*, claim 1, 7:51-65, 5:61-63; EX1003, ¶78.

Snow teaches that its polyalkylene oxide-vinyl sulfone reagents can react with accessible sulfhydryl groups on proteins at a faster rate than the rate of addition to amino groups. *Id.*, 9:58-63; EX1003, ¶¶78-79.

V. LEVEL OF SKILL IN THE ART

A person of ordinary skill in the art (hereinafter “POSA”) would “be aware of all the pertinent prior art” at the time of the alleged invention (*Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 963 (Fed. Cir. 1986)), including specialized knowledge applicable to various aspects of the claimed invention. *See, e.g., AVX Corp. v. Greatbatch, Ltd.*, IPR2014-00697, Paper 60 at 3 (PTAB Jan. 11, 2016). A POSA is also a person of ordinary creativity, not an automaton, and thus is able to make inferences from the art. *KSR Int’l Co. v. Teleflex*, 550 U.S. 398, 420–21 (2007); EX1003, ¶¶16-17.

As supported by the testimony of Dr. Chari (EX1003, ¶¶23, 44-79), a POSA in the field of the ’682 patent as of November 24, 2012, would have had highly specialized knowledge in the field of linkers and conjugates for biologically-active molecules. This would entail 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. Alternatively, a POSA 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.

As evidenced by the prior art cited herein, such a person would have been familiar with protein/drug conjugates, including antibody-drug conjugates, the use of antibodies to selectively target cells and tissues associated with various diseases and conditions, linker design and selective attachment of the linker to proteins/antibodies and drugs, including targeted release of the drugs, as well as the need for water soluble conjugates for use with hydrophobic drugs, and methods for enhancing the potency of the protein/antibody-drug conjugates. EX1003, ¶¶23, 44-79.

VI. THE '682 PATENT

A. Prosecution History Overview

The '682 patent issued from USSN 14/432,073, filed March 27, 2015 and claiming priority to International Application PCT/IB2012/056700, filed November 24, 2012, which is the earliest possible priority date of the '682 patent.

During prosecution of the '073 application, the Office issued three office actions. EX1018. In each OA, DAC faced a novelty rejection and/or various rejections under §112. The Examiner never made any obviousness rejections.

In the first OA (dated 8/15/2017), claims 1-12 and 14-20 were pending, but only claims 1-7 (directed to formulas (I), (II) and (IV) at issue in this proceeding)

were rejected over US 5,094,848 (“Brixner”) for lack of novelty. EX1018, 11. Brixner discloses conjugates including a diphosphate in the linker. *Id.* While DAC overcame Brixner by amendment, Brixner is not relevant to this proceeding as no ground relies on Brixner or any phosphate-containing linker.

Another non-final OA (dated 3/8/2018) rejected various claims again for §112 issues and claim 1 for lack of novelty over WO 1997/041897 (“Lees”). EX1018, 42. Lees discloses N-hydroxysuccinimide/vinyl sulfone linkers to link a derivatized polysaccharide with a protein. *Id.* DAC overcame Lees by specifying that when Q or T is -S(O)₂-, m and n are not zero (*i.e.*, both Q and T must be present). Further amendments expanded claim scope by allowing R₁-R₆ to be absent in some embodiments and added claims 22-24. *Id.*, 45.

A Final OA (dated 7/10/2018) included further 112 rejections and a novelty rejection of claim 2 and its dependent claims over WO 2012/145112 (“Fishkin”) as evidenced by two additional references. *Id.*, 75. DAC amended claim 2 to add the same proviso from claim 1 described above. EX1018, 81. An NOA subsequently issued without any consideration of prior art disclosing bis-sulfonyl linkers or conjugates, or any obviousness rejections.

B. Reexamination Summary

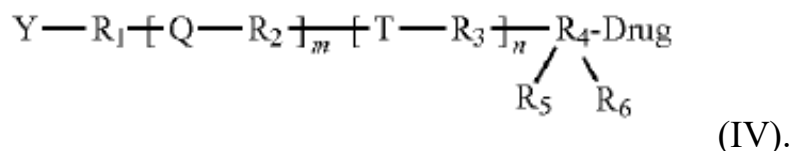
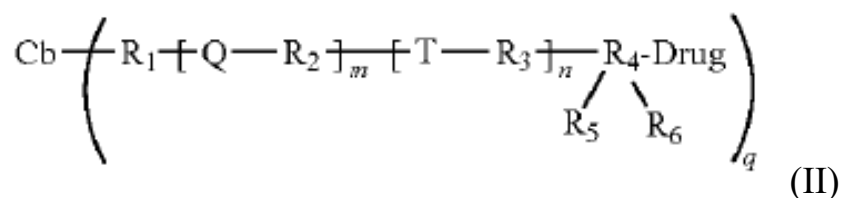
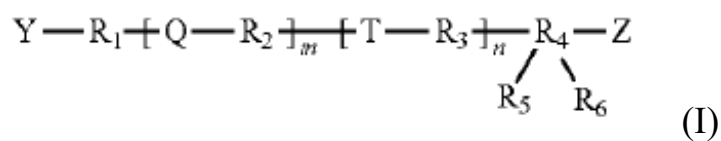
A third-party *ex parte* reexamination of the ’682 patent (Control No. 90/014,390) was filed October 16, 2019. The reexamination involved various

novelty and obviousness challenges on different grounds than presented herein. Ultimately, a Reexamination Certificate issued (EX1002) only after all independent claims were amended and 13 new claims added. All claims challenged in this petition were either amended during reexam or newly added to require R_2 to be absent or acyclic “when Q and T are each independently $-S(O_2)-$ or $-S(O)-$ ” such that none of the claims have ever been challenged by a third party. Moreover, none of the claims have been examined in view of prior art disclosing ADC and ADC precursors comprising acyclic bis-sulfonyl linkers, as herein.

C. Claims Summary³

The '682 patent discloses a vast array of hydrophilic linkers containing phosphinate, sulfonyl, and/or sulfoxide groups, and cell-binding agent-drug conjugates comprising the same. EX1001, 2:53-55; EX1003, ¶¶24-43. The challenged claims are directed to a bifunctional hydrophilic linker of formula (I) (claims 1-2), a cell-binding agent-drug conjugate of formula (II) (claims 3-17, 24-26, and 33), and a drug conjugated monofunctional linker compound of formula (IV) (claims 20-21, 29-32, and 34), reproduced below:

³ The complete set of challenged claims are attached to EX1003 as an appendix.



The Q and T variables of formulas (I), (II), and (IV) are identically defined and are selected from -P(=O)(OM)-, or -S(O₂)-, or -S(O)-. Depending on the values of m and n, one or both of Q and T are present in the claimed linkers. In claims 1, 3, 20, 22, and 29, m and n are integers from 0 to 5, but not 0 at the same time, and provided that (i) when m=1 and n=0, Q is not -P(=O)(OM)-, and (ii) when m=0 and n=1, T is not -P(=O)(OM)-. Certain claims further require that m and n are not 0 when Q or T are -S(O₂)- (claims 1, 22) or -S(O)- (claims 3). Claims 24, 26, and 30 define m and n as integers from 1 to 5.

The Y variable is present in both formulas (I) and (IV) and is defined as a functional group that enables reaction of the hydrophilic linker with a cell-binding agent.

The “Drug” variable is present in both formulas (II) and (IV), defined as 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.

The Z variable of formula (I) represents a functional group that enables linkage 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.

The “Cb” variable of formula (II) represents a cell-binding agent.

Each independent claim provides two broad, overlapping definitions of R₁, R₂, R₃ and R₄ for one of formulas (I), (II) and (IV). In the first definition, R₁-R₄ are the same or different and are absent or selected from specific short hydrocarbon or other chains (*i.e.*, ester, ether or amide) or a polyoxyethylene unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000, or combinations of any of the foregoing. *See, e.g.*, EX1002, 1:46-2:4, 2:37-62, 4:25-50. EX1003, ¶¶24, 30-31. Alternatively, in the second definition, 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, provided that when Q and T are each independently -S(O₂)- or -S(O)-, R₂ is a straight or branched chain. The second definition also specifies connections among the groups and the rest of the linker. *Id.*

R₅ and R₆ are defined identically in formulas (I), (II) and (IV) as being the same or different, and are absent, H, or selected from many of the same groups appearing in the first definition of R₁-R₄. *Id.*

Although the specification provides thirty Examples (EX1001, 36:55-47:14), most are syntheses of compounds of formula (I) or its precursors. The '682 patent discloses only a single working example preparing and testing *in vitro* a compound of formula (II), namely compound 86. *Id.*, Examples 29-30, Fig. 21. Thus, the '682 claims are not commensurate in scope with the limited actual working examples provided in the specification. Moreover, the examples within the application fail to demonstrate that the claimed compositions exhibit any surprising or unexpected effects whatsoever. EX1003, ¶¶42-43.

D. Claim Construction

Petitioner does not currently believe that any claim terms require construction for purposes of deciding this Petition, but reserves the right to rebut any subsequent Patent Owner claim construction argument. EX1003, ¶18.

VII. CLAIM-BY-CLAIM EXPLANATION OF GROUNDS OF UNPATENTABILITY

A. Ground 1: Claims 1-3, 6, 24-25, and 33 Are Anticipated by Morales-Sanfrutos as Evidenced by Straus

Anticipation under 35 U.S.C. §102 requires that every element of the claimed invention be disclosed expressly or inherently in a single prior art

reference. *In re Paulson*, 30 F.3d 1475, 1478–79 (Fed. Cir. 1994); EX1003, ¶19.

Morales-Sanfrutos (EX1005) anticipates claims 1, 3, 6, 24-25, and 33 of the '682 patent, as evidenced by Straus (EX1006). EX1003 ¶¶80-99.

1. Claim 1

Claim 1 begins with the phrase “[a] hydrophilic linker of formula (I).” This preamble is not limiting, but is nonetheless taught by Morales-Sanfrutos.

a. Preamble is non-limiting, and disclosed by Morales-Sanfrutos

Formula (I) defines an organic compound with sulfones, sulfoxides and other functional groups, whereas “hydrophilic linker” refers to a property of the compound (hydrophilic) and the intended use for the compound (linking).

EX1003, ¶81. In claim 1, as in many pharmaceutical patents, the word “of” serves as the transitional phrase. *Teva Pharmaceuticals USA, Inc. v. Sandoz Inc.*, 810 F.Supp. 2d 578, 585 (2011) (noting that terms “like ‘composed of’ and ‘of’ are ‘transition phases’”). The term “hydrophilic linker” therefore is part of the preamble and does not further limit the composition because the body of the claim recites a structurally complete composition in formula (I). *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808-809 (Fed. Cir. 2002).

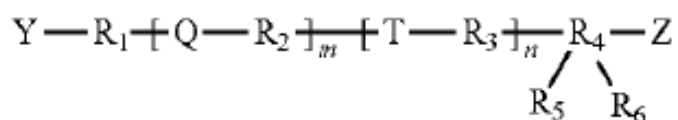
Although “hydrophilic linker” also appears in the body of the claim, it places no further restriction on the inherent hydrophilicity of the compounds represented by formula (I) such as specific water solubility levels. EX1003, ¶¶80-81. Further,

recitation of an intended purpose in the body of a claim is likewise non-limiting. *In re Schreiber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Because the phrase “hydrophilic linker” does not recite an essential structure or impose additional limitations of any kind on the compound of formula (I), it fails to further limit the claim. *Catalina Mktg.* at 808; *Pitney Bowes v. Hewlett-Packard Company*, 182 F.3d 1298, 1305 (Fed. Cir. 1999).

Even if “hydrophilic linker” were deemed to be limiting, it fails to define any level of hydrophilicity beyond what is inherent to the structure of formula (I). Hence, any prior art compound that teaches formula (I) must by definition be a hydrophilic linker. As discussed below, Morales-Sanfrutos discloses each element of formula (I), and thus discloses the claimed hydrophilic linkers. EX1003, ¶¶82-85.

b. Morales-Sanfrutos discloses every element of claim 1

Claim 1’s formula (I) is depicted below, with each variable taken from a vast array of possible choices (*supra* §VI.C):



Morales-Sanfrutos teaches at least four bifunctional vinyl sulfone PEG derivatives falling within formula (I). EX1005, 4041 (Scheme I), 4044 (Scheme

4). These disclosed compounds are shown in Table B1:

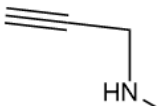
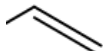
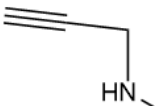
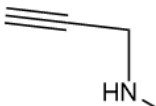
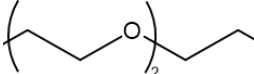
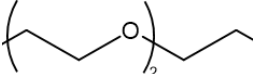
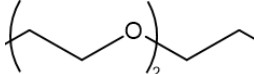
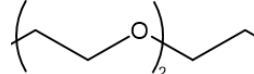
Table B1

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

⁴ The rhodamine group in compound 4 and the dansyl group in compound 5 will be abbreviated, respectively, “Rhod.” and “Dns.” to simplify their representations.

As explained by Dr. Chari (EX1003 ¶83) and shown in Table B2, each of the four compounds tracks with the variables defining the compound of formula (I) in claim 1. Indeed, formula (I) of the '682 patent is so broad that the compounds of Morales-Sanfrutos satisfy its variables in more than one way, only a few of which are shown in Table B2.

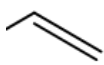
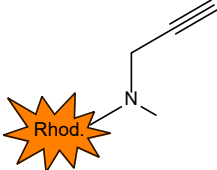
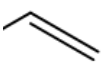
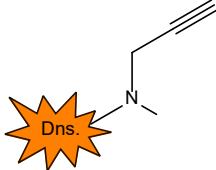
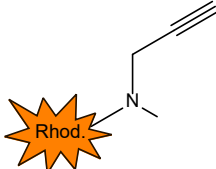
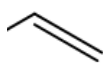
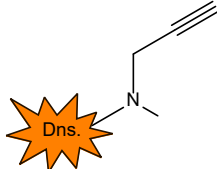
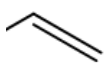
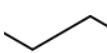
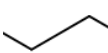
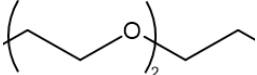
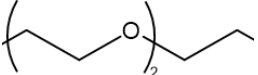
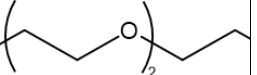
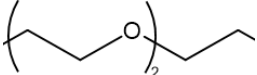
Table B2

	Morales-Sanfrutos' Compounds 1-2 (Table B1)			
'682 (I)	Compound 1	Compound 2		
		(a)	(b)	(c)
Y				
Z				
R₁	absent ⁵	absent	absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₂				
p	2	2	2	2

⁵ Any or all of R¹-R⁴ may be absent and still meet the limitations of claim 1.

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

Table B2 (continued)

'682 (I)	Compound 4		Compound 5	
	(a)	(b)	(a)	(b)
Y				
Z				
R₁	absent		absent	
m	1	1	1	1
Q	-SO ₂ -	-SO ₂ -	-SO ₂ -	-SO ₂ -
R₂				
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

To illustrate, comparing Claim 1's formula (I) and one embodiment of Morales-Sanfrutos' compound 2 shown in column 2(a) of Table B2 above, Y is vinyl ($-\text{CH}=\text{CH}_2$), R₁ is absent, m = 1, Q is sulfonyl ($-\text{S}(\text{O}_2)-$), R₂ is ethylene in combination with two PEG units $(\text{OCH}_2\text{CH}_2)_2$ (referred to hereinafter as "the ethylene-bis-ethyleneoxy group"), where p=2. Further, n=1, T is sulfonyl ($-\text{S}(\text{O}_2)-$), R₃ is ethylene, $-\text{R}_4(\text{R}_5)(\text{R}_6)-$ is absent, and Z is the alkynyl group indicated in Table B2. EX1003, ¶¶82-84. The ethylene-bis-ethyleneoxy group in compound 2 falls within the part of R₂'s definition that allows for a combination of a linear C₁₋₆ alkyl and PEG having 1-1000 ethylene-oxy subunits. EX1003, ¶84. The remaining ethylene group falls within the definitions of R₃ or R₄, or, as shown in column 2(b), one methylene group is assigned to each of R₃ and R₄, since both variables may be C₁₋₆ alkyl. *Id.*

Alternatively, as shown in column 2(c), Morales-Sanfrutos' compound 2 maps to claim 1 starting from the other end of the linker, wherein Y is the alkynyl group, Z is the vinyl group, R₁ is ethylene, and R₃ and R₄ are absent; the remaining variables (m, Q, R₂, p, and n) are the same as before. EX1003, ¶84.

Table B2 shows that Morales-Sanfrutos' disclosed compounds 1, 4, and 5

likewise fall within claim 1's broad scope—sometimes in multiple different ways (e.g., columns 4(a)-(b) and 5(a)-(b))—with each being equally anticipatory. EX1003, ¶¶84-85.

Notably, Claim 1 ***does not require*** actual conjugation to a cell-binding agent; rather it requires only that Y be a functional group that ***enables*** reaction of the formula (I) compound with a cell-binding agent. Vinyl groups adjacent to a sulfone moiety are known in the art to react with functional groups present in cell-binding agents (e.g., at thiol groups). EX1003, ¶86; EX1005, 4043-4044. Indeed, the '682 patent discloses exemplary formula (I) compounds that contain a vinyl functional group located adjacent a sulfone moiety, and shows their reaction with a thiol (–SH) functional group. EX1001, Figs. 7-10 (showing compound 75, compound 99, compound 119 and compound 138, respectively).

Claim 1 likewise does not require conjugation of the formula (I) compound to a cytotoxic drug, but rather requires only that Z be a functional group that ***enables*** reaction with a cytotoxic drug via any one of the many identified bond types, including thioether and heteroaromatic bonds. Claim 1 places no other limits on the size or nature of the Z group, and the specification does not define the Z group further.

Alkynyl functionalities are known in the art as able to react with an N₃ (azide) group to form a heteroaromatic bond, and Morales-Sanfrutos discloses an

alkynyl used to link biotin (an example of a drug) to a sulfone-containing linker. EX1005, 4041 (Scheme 1), 4043-4044 (Scheme 4); EX1003, ¶87. Notably, the '682 patent discloses a formula (I) compound containing an azide that reacts with an alkynyl on a drug to form the exact same heteroaromatic bond disclosed years before in Morales-Sanfrutos. EX1001, Fig. 13 (compound 166); EX1003, ¶87.

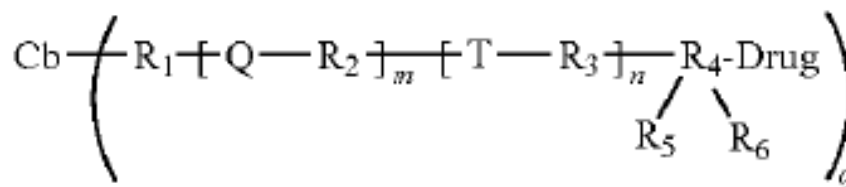
Accordingly, Morales-Sanfrutos discloses all elements of independent claim 1. EX1003, ¶88.

2. Claim 2

Claim 2 further specifies that Z comprise various groups, *e.g.*, an **amino** group. As shown in Table B1, Morales-Sanfrutos' compound 2 has an amino group. Morales-Sanfrutos shows that the drug biotin may be attached to this amino group via an amide bond, meeting claim 2's definition of Z. EX1005, 18:5-15. Morales-Sanfrutos thus anticipates claim 2. EX1003, ¶¶87-88.

3. Claims 3 and 24

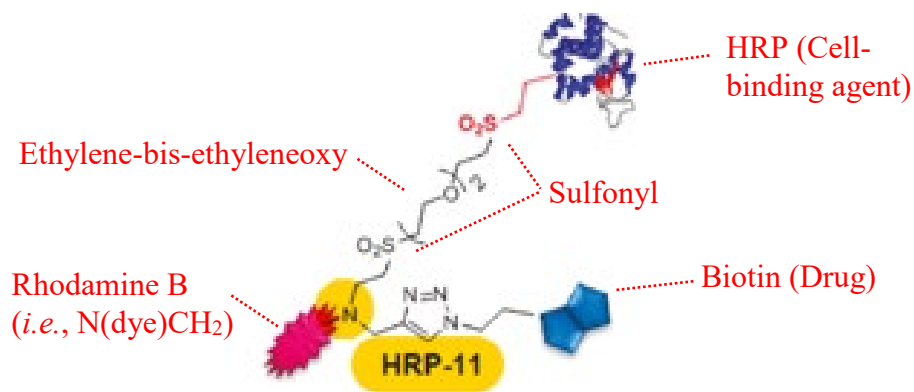
Independent claims 3 and 24 are directed to the cell-binding agent-drug conjugate of formula (II):



Formula (II) defines an organic compound with sulfones, sulfoxides and other functional groups. EX1003, ¶89. Claims 3 and 24 are nearly identical, differing slightly in scope of variables m, n, and R₂.

Similar to claim 1, the preamble term “cell-binding agent-drug conjugate” of claims 3 and 24 is again not limiting. The bodies of claims 3 and 24 recite the structurally complete composition of formula (II), which formula requires a cell-binding agent and a drug covalently linked to each other as a conjugate. The preamble “cell-binding agent-drug conjugate” fails to recite any essential structure not found in formula (II) or impose additional limitations on the compound of formula (II). It therefore fails to limit independent claims 3 and 24. *Catalina Mktg.* at 808-809. Nonetheless, should Patent Owner argue that the preamble is limiting, Morales-Sanfrutos teaches a cell-binding agent-drug conjugate, as described below.

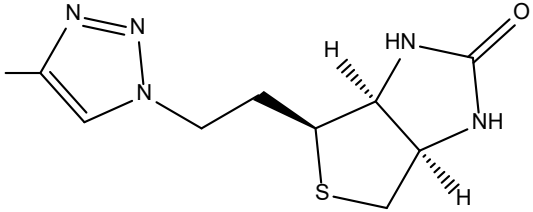
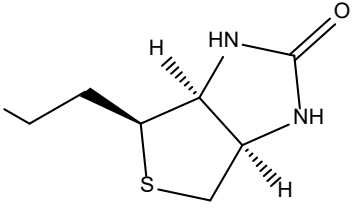
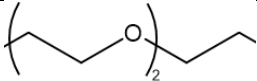
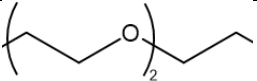
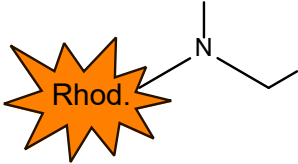
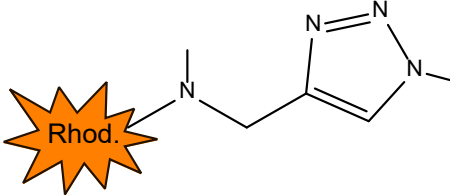
Morales-Sanfrutos teaches every element of claims 3 and 24, including the non-limiting preamble, in disclosing the HRP-11 conjugate (EX1005, 4044), a species encompassed by the claimed genus of formula (II). EX1003, ¶91. Morales-Sanfrutos’ HRP-11 conjugate has the following structure, where the jagged oval represents the fluorescent dye rhodamine B, and the bicyclic structure represents biotin:



As explained by Dr. Chari (EX1003, ¶¶90-94) and shown in Table B3 below, each part of the HRP-11 conjugate tracks with the sub-elements defining the scope of the formula (II) compounds. Specifically, in the HRP-11 conjugate, Cb is horseradish peroxidase (HRP), q is 1, R₁ is ethylene, Q is sulfonyl (–S(O₂)–), R₂ is ethylene in combination with two PEG units (OCH₂CH₂)₂ (*a.k.a.*, ethylene-bis-ethyleneoxy), m is 1, T is sulfonyl (–S(O₂)–), R₃ is ethylene, and n is 1. Further, R₄ is –N(dye)CH₂–, R₅ and R₆ are absent, and Drug is biotin linked to the rest of the conjugate via a heteroaromatic bond. EX1045, 4:11-26; EX1003, ¶¶90-94.

Alternatively, because the scope of R₄ and Drug in formula (II) is so vast, R₄ maps to –N(dye)–CH₂–(triazole)–, with R₅ and R₆ absent as before, and Drug is biotin linked to the cell-binding agent via a heteroaromatic bond that is formed via the heterocyclic triazole function of R₄. EX1003, ¶94. These two applications of Morales-Sanfrutos’ HRP-11 conjugate to formula (II) of claims 3 and 24 are delineated in Table B3 below:

Table B3

	HRP-11 Conjugate	
'682 (II)	A	B
Cb	HRP	HRP
q	1	1
Drug		
R ₁		
m	1	1
Q	-SO ₂ -	-SO ₂ -
R ₂		
p	2	2
n	1	1
T	-SO ₂ -	-SO ₂ -
R ₃		
R ₄		

While claims 3 and 24 call for “chain of two or more atoms” in broadly

defining R₁-R₄, the '682 patent neither defines this term nor limits it to any particular type of chain (*e.g.*, it is not limited to acyclic chains). Hence, a POSA would appreciate the broad coverage of this limitation, and would understand it to encompass each of the ethylene groups (R₁ and R₃), ethylene-bis-ethyleneoxy group (R₂), and the N(dye)CH₂ group with or without the triazole in the HRP-11 conjugate, since each of R₁-R₄ may be a chain of *two or more atoms selected from the group consisting of C, N, O, S, Si, and P* that are covalently connected to a cell-surface binding ligand, a sulfonyl group, a drug and among themselves (R₁, R₂, R₃ and R₄). EX1003, ¶95.

HRP is a known cell-binding agent, as evidenced by Straus. EX1006, 277; EX1003, ¶¶59, 90. The specification teaches that “drugs that can be conjugated to a cell-binding molecule in the present invention are small molecule drugs including cytotoxic agents” and defines “small molecule drug” as “an organic, inorganic, or organometallic compound that may have a molecular weight of for example 100 to 1800, more suitably from 120 to 1400.” EX1001, 29:43-54. Biotin (which is part of Morales-Sanfrutos' HRP-11) falls within the scope of the recited term “Drug.” EX1003, ¶¶90, 94 (citing to EX1045, 4:11-26). Morales-Sanfrutos thus discloses all elements of independent claims 3 and 24, anticipating them. EX1003, ¶¶96, 99.

4. Claims 6, 25, and 33

Dependent claim 6 further specifies that the cell-binding agent is selected

from various groups, including proteins. As discussed above, Morales-Sanfrutos' HRP-11 conjugate comprises HRP, a protein well-known for its cell-binding properties. EX1003, ¶¶59, 90, 98; EX1006, 277. Morales-Sanfrutos thus anticipates claim 6.

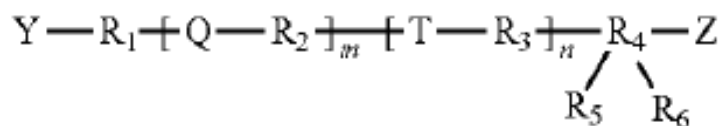
Dependent claims 25 and 33 further specify that when Q and T are each independently $-S(O_2)-$ (*i.e.*, sulfonyl) or $-S(O)-$, at least one of R_1 - R_4 comprises the polyethyleneoxy unit of formula $(OCH_2CH_2)_p$; and each of remaining R_1 , R_2 , R_3 and R_4 comprises an alkyl or $(OCH_2CH_2)_p$. These requirements are satisfied by Morales-Sanfrutos because, as discussed above, in the HRP-11 conjugate with m and n being 1, Q and T are sulfonyl, R_1 and R_3 are ethylene (*i.e.*, an alkyl group), R_2 is ethylene in combination with two PEG units $(OCH_2CH_2)_2$, and R_4 is $-N(\text{dye})CH_2-$ or $-N(\text{dye})CH_2(1,4 \text{ triazole})-$, which comprises a methyl (*i.e.*, alkyl) group. EX1003, ¶97. Morales-Sanfrutos thus anticipates claims 25 and 33. EX1003, ¶99.

B. Ground 2: Claims 1, 20-21, and 29-31 are anticipated by or obvious in view of Harris

Harris (EX1007) anticipates or renders obvious claims 1, 20-21, and 29-31 of the '682 patent. EX1003, ¶¶19-22, 100-114.

1. Claim 1

Independent claim 1 is directed to the hydrophilic linker of formula (I):



For the reasons discussed above in §VII.A.1, claim 1's preamble is not limiting. In any event, Harris expressly teaches a hydrophilic linker satisfying formula(I).

As explained by Dr. Chari (EX1003, ¶¶101-103), Harris' basic structure, R-(OCH₂CH₂)_n-Y, discloses PEG derivatives comprising **two** sulfone moieties and tracks with the variables defining the compound of formula (I) claimed in the '682 patent. *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381, (Fed. Cir. 2015) (disclosed genus in reference anticipates a claim "if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination") (quoting *In re Petering*, 301 F.2d 676, 681(CCPA 1962)). Specifically, when R and Y in Harris are vinyl sulfone and/or halo-ethyl sulfone (*see, e.g.*, EX1007, 19:10-15 and 24-30), this aligns with Y of formula (I) in the '682 patent being vinyl (-CH=CH₂) or halo-ethyl (-CH₂-CH₂-X), R₁ being absent, Q being sulfonyl, R₂ being (OCH₂CH₂)_n (where n is disclosed to have typical values of 5, 34, 45 and 110), m and n each being 1, T being sulfonyl, R₃ and -R₄(R₅)(R₆)- being absent, and Z being vinyl (-CH=CH₂) or halo-ethyl (-CH₂-

CH₂-X). EX1003, ¶103. Vinyl and halo-ethyl groups located adjacent to a sulfone moiety are well-known in the art as functional groups that selectively react with thiol moieties present in cell-binding agents (*e.g.*, antibodies) or cytotoxic drugs to form thioether linkages. *Id.*, ¶104.

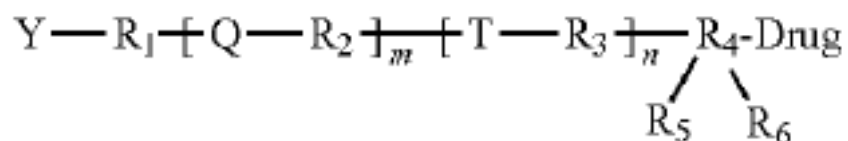
Thus, the vinyl and halo-ethyl groups located adjacent to sulfone moieties in Harris are equivalent to Y or Z of formula (I) because they are known in the art as functional groups that react with thiol moieties, which are present in both cell-binding agents (*e.g.*, antibodies) and cytotoxic drugs, and react to form thioether linkages. EX1003, ¶104. Additionally, Harris discloses PEG groups of the basic structure that expressly fall within the claimed range of formula (I) of the ‘682 patent with 5, 34, 45, and 110 ethyleneoxy subunits. EX1007, 19:10-23. Accordingly, Harris discloses all elements of independent claim 1.

Claim 1 is also obvious over Harris, because Harris’ basic structure suggests each element of formula (I) of claim 1 as described above. A POSA would have been motivated to prepare PEG bis vinyl sulfones having, *e.g.*, 5, 34, 45 or 110 ethyleneoxy subunits because Harris teaches that such bifunctional PEGs are water soluble, hydrolytically stable, selective for coupling with thiol moieties, and form stable thioether linkages with proteins and pharmaceuticals. EX1007, 6:8-21, 6:28-33, claim 34. Furthermore, the PEG groups may be linear or branched. EX1007, 19:10-23; 17:9-20. A POSA would have had a reasonable expectation of

success in making a PEG bis vinyl sulfone as Example 1 of Harris expressly show how to prepare terminal PEG vinyl sulfone derivatives. Harris also demonstrates their aqueous stability (Example 3) and use by coupling to thiol-containing compounds, including proteins (Examples 2, 4). Accordingly, Harris renders claim 1 obvious. EX1003, ¶105.

2. Claims 20-21, and 29-31

Independent claims 20 and 29-30 are directed to a compound of formula (IV):



Each of independent claims 20 and 29-30 include overlapping definitions of the variables in formula (IV) as noted above in §VI.A. Harris teaches or suggests all of these. EX1003, ¶106.

Harris, as described above (§IV.B), discloses bifunctional PEG derivatives useful for generating conjugates linking two different biologically-active moieties such as proteins and pharmaceuticals, wherein at least one of the biologically-active moieties has a reactive thiol moiety. EX1007, claims 33-34, 16:34-17:5, 7:23-28; Abstract; EX1003, ¶107. Harris further teaches that “**Pharmaceuticals**

from aspirin to penicillin can be usefully modified by attachment of active sulfone polymer derivatives if these pharmaceuticals are **modified to contain thiol moieties.**” EX1007, 6:28-31 (emphasis added). Hence, Harris teaches conjugates where pharmaceuticals containing thiols are attached to its PEG derivatives via reaction with a vinyl sulfone to provide a drug PEG linker containing one or two sulfones. EX1003, 107.

As explained by Dr. Chari, the basic structure $R-(OCH_2CH_2)_n-Y$ disclosed in Harris teaches PEG derivatives having **two sulfones** and these derivatives track with the variables defining the compound of formula (IV) of the '682 patent. EX1007, 16:34-17:5; 19:10-12, 24-30. Specifically, with respect to the basic structure disclosed in Harris, for each of claims 20, 29 and 30, Y of formula (IV) described in the '682 patent is $-CH=CH_2$ or $-CH_2-CH_2-X$ where X is a halogen; R_1 is absent; $m=1$, Q is $-SO_2-$, R_2 is $(OCH_2CH_2)_n$ (a PEG having any of 5, 34, 45, or 110 ethyleneoxy subunits); $n=1$, and T is $-SO_2-$ for the same reasons given in §VI.B.1 above with respect to formula (I) of claim 1. Drug is a pharmaceutical linked via a thioether linkage to an ethylene group resulting from reaction of the thiol-containing drug with the vinyl sulfone. EX1003, ¶108. The ethylene group serves as R_3 and/or $R_4(R_5)(R_6)$: *e.g.*, R_3 is methylene and $R_4(R_5)(R_6)$ is methylene. Alternatively, one of R_3 and $R_4(R_5)(R_6)$ is absent and the other is ethylene. The ethylene group in the basic structure of Harris respectively meet the definitions of

R₃ and R₄(R₅)(R₆) in formula (IV) as each of these groups may be C₁₋₆ alkylene or absent. *Id.*

Additionally, Harris' also discloses heterobifunctional PEG derivatives comprising a **single sulfone** moiety that track with the variables defining the compound of formula (IV) of the '682 patent. Specifically, with respect to formula (IV), Harris' basic structure discloses a linker where Y of formula (IV) is N-hydroxysuccinimide (NHS) ester; R₁ is (OCH₂CH₂)_n (PEG having about 5, 34, 45 or 110 ethyleneoxy subunits); Q and R₂ are absent and m is 0; T is -SO₂-, R₃ is methylene, and n is 1; R₄(R₅)(R₆) is methylene; and Drug is a pharmaceutical linked via a thioester or thioether linkage. The PEG and methylene groups in the basic structure of Harris respectively meet the definitions of PEG in R₁ and C₁₋₆ alkylene in R₃ and R₄, respectively. EX1003, ¶109. N-Hydroxysuccinimide (NHS) ester is known in the art for its ability to react with cell-binding agents comprising a reactive amine group (*e.g.*, a lysine epsilon amino in antibodies). EX1003, ¶110; *see, e.g.*, EX1008, FIGs. 7-12. Accordingly, Harris discloses all elements of independent claims 20, and 29-30.

In the alternative, independent claims 20, 29 and 30 would also have been obvious over Harris. Harris' teachings concerning bifunctional and heterobifunctional sulfone-containing PEG derivatives as disclosed above are relied on to teach each element of formula (IV). To the extent that a POSA would

need to select and/or combine teachings within Harris to arrive at the claimed drug-linkers of formula (IV), the POSA would have been motivated to do so and would have had a reasonable expectation of success for the same reasons given in §VII.B.1. Additionally, with respect to heterobifunctional linkers, a POSA would have been motivated to select NHS and reasonably expect to succeed in preparing such derivatives as NHS is an example of the “reactive moieties typically used in PEG chemistry to activate PEG” and is known to form a “stable amine linkage,” *i.e.*, an amide, that could be attached, *e.g.*, to a lysine group in proteins. EX1007, 17:34-18:15; EX1003, ¶111.

Dependent claim 21 requires in relevant part that the drug is derived from a drug containing a –SH ... or –NHR", wherein R" is H. Harris teaches this limitation as it discloses that drugs “from aspirin to penicillin” can be modified to contain thiol (*i.e.*, –SH) moieties. EX1007, 6:28-31. Indeed, modifying drugs to include a thiol moiety was performed on a regular basis in the industry prior to November 24, 2012. *See, e.g.*, EX1009, Fig. 3; EX1008, ¶[0144], FIGs. 46-52 (describing ADCs including the maytansinoid DM1, a maytansine modified to have a free thiol group). Harris thus anticipates or renders obvious dependent claim 21. EX1003, ¶113.

Dependent claim 31 further specifies that when Q and T are each independently –S(O₂)– or –S(O)–, ***at least one*** of R₁ , R₂, R₃ and R₄ comprises the

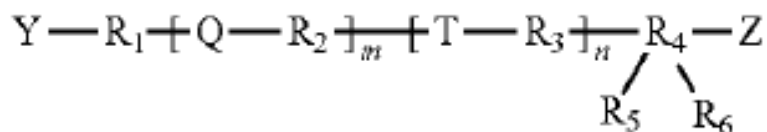
polyethyleneoxy unit of formula $(\text{OCH}_2\text{CH}_2)_p$. As discussed above, Harris teaches PEG derivatives comprising two sulfone moieties, wherein R_2 is $(\text{OCH}_2\text{CH}_2)_n$. EX1003, ¶112. The additional limitations of claim 31 are thus expressly taught and anticipated or rendered obvious by Harris.

C. Ground 3: Claims 1-8, 10-12, 14-17, 20-21, 24, 26, and 29-31 are obvious over Singh in view of Harris

In addition to claims 1-2, 20-21, and 29-31 being anticipated by Harris (Ground 2), these claims are also obvious under 35 U.S.C. §103 over Singh in view of Harris. Additionally, claims 3-8, 10-12, 14-17, 24 and 26 would also have been obvious to a POSA over Singh in view of Harris. EX1003, ¶¶115-177. Harris' teaching of the elements of claims 1-2, 20-21, and 29-31 from Ground 2 (*supra* §§VII.B.1-B.2) are reincorporated here, and are further supplemented as described below.

1. Claims 1-2

As noted above, claims 1 and 2 are directed to hydrophilic linkers of formula (I) (*supra* §§VII.A.1-2.)



Singh discloses bifunctional PEG cross-linkers containing each element of claim 1, save Q and T (which must be $-\text{P}(=\text{O})(\text{OM})-$, or $-\text{S}(\text{O}_2)-$, or $-\text{S}(\text{O})-$). For the

reasons given below, it would have been obvious to modify Singh's cross-linkers to incorporate the water soluble, sulfonyl ($-S(O_2)-$) moieties present in the PEG derivatives as taught by Harris. EX1003, ¶¶116-117.

As Dr. Chari explains, the bifunctional PEG cross-linkers disclosed in Singh (*supra* Table A1) track closely with the variables defining the compound of formula (I) in claim 1. EX1003, ¶118. This may be clearly seen in Table C1, below. The Singh cross-linkers include a reactive functionality on each end of the linker. At one end, the reactive functionality comprises maleimide, iodo- or bromo-acetamide, and NHS ester groups. EX1008, ¶¶[0134], [0136], Figs. 4, 8, 10, 13, 15, 16A. These functional groups “enable reaction of the hydrophilic linker with a cell-binding agent” and therefore meet the definition of Y in formula (I) of the '682 patent. EX1008, ¶[0136] (indicating that bifunctional PEG-containing cross-linkers contain a reactive functionality for reaction with a cell-binding agent); EX1003, ¶119.

At the other end of Singh's cross-linkers, the reactive functionality comprises pyridyldisulfide, maleimide, iodo- or bromoacetamide, or NHS ester groups. EX1008, ¶[0136], Figs. 4, 6B, 8, 12-13, 15, 16B; *see also* ¶[0134] (defining such groups as reactive functionalities); EX1003, ¶120. These functional groups “enable linkage of the hydrophilic linker to a cytotoxic drug” via, *inter alia*,

a disulfide, thioether, or amide bond and therefore meet the definition of Z in formula (I) of the '682 patent. EX1003, ¶120.

Singh's bifunctional PEG cross-linkers meet the definitions of R₁-R₄ as well. As permitted by claim 1, R₁ and R₃ are absent but PEG and atoms linked to the PEG meet the definitions of R₂ and R₄. EX1003, ¶121. Specifically, claim 1, provides that R₂ may be a "polyethyleneoxy unit of formula (OCH₂CH₂)_p, wherein p is an integer from 1 to about 1000," or one of various short carbon chains, "or combination thereof." EX1001, claim 1; EX1003, ¶121. Singh's bifunctional cross-linkers each include (OCH₂C₂)_n, where Singh's variable "n" meets the definition of "p" since n can be any integer within the disclosed ranges of 1-2000, 1-100, 1-14, and 1-4. EX1008, ¶¶[0082], [0087]; EX1003, ¶121.

Atoms between the PEG group and the second reactive functionality (serving as Z) in Singh's linkers meet the definition of R₄, which is defined similarly to R₂. For linkers where PEG is directly linked to the second reactive functionality, R₄ is then absent as claim 1 permits. EX1003, ¶122; *see* Table C1.

Table C1 below shows how the bifunctional PEG cross-linkers of Singh meet each element of formula (I) in claim 1 of the '682 patent aside from Q and T. Indeed, claim 1's formula (I) is so broad that the cross-linkers of Singh satisfy its elements in multiple ways (*e.g.*, starting from either end of the linker), only a few of which are shown below (EX1003, ¶123):

Table C1

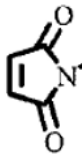
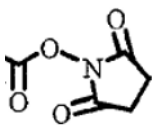
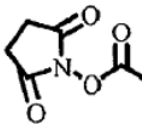
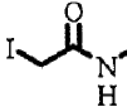
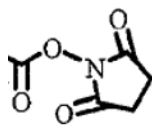
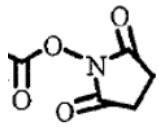
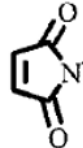
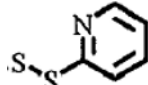
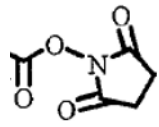
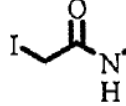
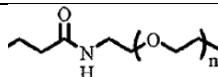
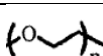
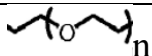
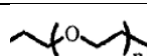
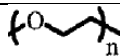
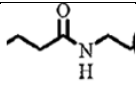
	Singh's Compounds (Table A1)				
'682 (I)	1		2	3	
	(a)	(b)		(a)	(b)
Y					
Z					
R₁	absent	absent	absent	absent	absent
R₂					
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-14	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	absent	absent	absent	absent
R₄	absent		absent	absent	

Table C1 (continued)

	Singh's Compounds (Table A1)			
'682 (I)	4		5	
	(a)	(b)	(a)	(b)
Y				
Z				
R₁	absent	absent	absent	absent
R₂				
p	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4	n=1-2000, 1-100, 1-14, 1-4
R₃	absent	absent	absent	absent
R₄				

Although Singh's expressly shown PEG cross-linkers lack sulfonyl groups, Singh expressly suggests the use of vinyl sulfones as a thiol-reactive functionality and teaches their equivalence to maleimide and haloacetamides for this purpose. EX1008, ¶[0134]; EX1003, ¶124. Therefore, 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. EX1003, ¶125. Such substitutions, as expressly taught by Singh, would thereby fully satisfy claim 1's formula I. *Id.*

In addition, a POSA would have been further motivated to incorporate vinyl sulfones into Singh's bifunctional PEG cross-linkers (providing Q and/or T) and reasonably expect success in doing so in view of Harris. As discussed above in §IV.B and §VII.B.1, the basic structure $R-(OCH_2CH_2)_n-Y$ disclosed in Harris encompasses hydrophilic PEG derivatives comprising one or two sulfone moieties that are useful for conjugating two biologically-active molecules (*e.g.*, proteins, pharmaceuticals), where at least one of the biologically-active molecules *has a reactive thiol moiety*. EX1007, claims 33-34, 3:28-35, 16:34-17:5, 18:5-30, 19:10-15, 24-30, Abstract; EX1003, ¶126. A POSA would have appreciated that Harris' vinyl sulfone-containing PEG derivatives are nearly identical to the bifunctional PEG cross-linkers of Singh and serve the same purpose: to link two biologically-active molecules with a hydrophilic linker that imparts good water solubility to the resulting conjugate. EX1003, ¶127.

A POSA would have appreciated numerous advantages offered by Harris' sulfonyl-containing PEG derivatives. First, as taught by Harris, PEG-containing

“polymer derivatives with active sulfone moieties are highly selective for coupling with thiol moieties instead of amino moieties on molecules,” and the “selectivity of PEG vinyl sulfone for thiols means that PEG can be selectively attached to cysteine units, thus preserving protein activity for specific proteins and controlling the number of PEG molecules attached to the protein.” EX1007, 6:12-15, 26:11-15; EX1003, ¶128. Second, Harris further teaches that sulfonyl-containing PEG derivatives “are considered *infinitely soluble* in water or as approaching infinite solubility and can enable *otherwise insoluble molecules* to pass into solution when conjugated with the derivative.” EX1007, 19:34-37 (emphasis added); EX1003, ¶128. Third, while the “utility of many PEG derivatives is limited because they react rapidly with water, thus interfering with attempts to attach the [PEG] derivative to molecules and surfaces under aqueous conditions,” PEG vinyl sulfone and PEG chloroethyl sulfone are stable in water. EX1007, 28:29-34.

A POSA would therefore have been motivated to incorporate Singh’s/Harris’ vinyl sulfones and related sulfonyl functionality—which are reactive functionalities that can form a thioether bond—into Singh’s expressly shown ADC linkers to obtain their aforementioned known benefits. A POSA would have appreciated that the resulting PEG linkers would (i) provide active sulfone moieties that are hydrolytically stable, (ii) enable water-insoluble molecules (*e.g.*, hydrophobic drugs) to be dissolved in water, (iii) promote

selective attachment to cysteine units on proteins, and (iv) preserve activity for specific proteins. *See* EX1007, 6:8-15, 19:31-37, 26:11-15; EX1003, ¶129. A POSA would have been further motivated to substitute vinyl sulfones reactive functionalities into Singh's haloacetamide ADCs because, in contrast, haloacetamides cross-react with amino groups on proteins and require prolonged reaction times at high pH, which are less desirable if not unsuitable for conjugation reactions. EX1003, ¶129.

A POSA would have also expected that combining the teachings of Singh and Harris would successfully yield hydrophilic ADC linkers having desirable functional properties. For example, Singh teaches attaching PEG linkers to -SH groups on drugs via a bis-maleimide containing PEG linker, and that maleimide and haloacetamide moieties are functionally equivalent to vinyl sulfone for the purpose of forming thioether bonds. EX1008, ¶[0134], FIGs. 50-51. Examples 1 and 2 of Harris describe how to synthesize a PEG linker comprising a terminal vinyl sulfone or chloro-ethyl sulfone group and how to couple these sulfone containing PEG linkers to molecules comprising free -SH groups, respectively. EX1007, 21:26-28:28. Thus, a POSA would understand how to achieve these substitutions. EX1003, ¶130.

Moreover, Harris teaches that the vinyl sulfone PEG linkers are highly water soluble, hydrolytically stable and show selective reactivity with -SH groups

relative to amino groups, especially at pHs of about 9 or less. EX1007, 14:1-7, 19:31-36, 27:21-28:28, and 29:1-22. Indeed, Example 4 of Harris validates the preferential attachment of the vinyl sulfone PEG linker to –SH groups in cysteine residues (instead of the –NH₂ group on lysine) in protein conjugation experiments. EX1007, 30:3-29; EX1003, ¶130.

Singh teaches that hydrophilic PEG linkers enhance the potency and efficacy of cell-binding agent-drug conjugates several-fold compared with traditional linkers (*e.g.* SMCC, SIAB). EX1003, ¶130; EX1008, ¶¶[0009], [0221]. Additionally, “incorporation of hydrophilic linkers allowed the conjugation of up to 15 molecules of a drug per antibody molecule with high yield and no aggregation or precipitation” and these conjugates “bound with high affinity to target antigen (similar to that of unmodified antibody).” EX1008, ¶[0011]. EX1003, ¶130.

Thus, modifying the PEG-containing ADC linkers of Singh to *include* vinyl sulfones or related sulfonyl derivatives as a reactive functionality that can form a thioether bond with a cell-binding agent or drug would be expected to have comparable, *if not higher*, hydrophilicity, and such conjugates would be expected to exhibit the same advantageous properties (enhanced potency, less precipitation) already recognized by Singh for its ADC linkers. EX1003, ¶131.

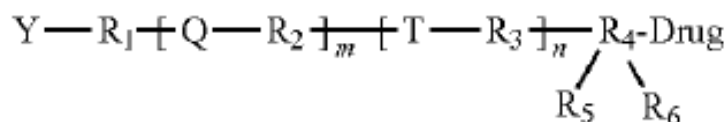
Because a POSA would have understood that Singh and Harris relate to substantially similar subject matter and that the PEG-containing linkers of each are hydrophilic and are being used for their known purposes, a POSA would have reasonably expected success in combining the teachings of Singh and Harris in the manner claimed. EX1003, ¶132.

For the reasons given above, claim 1 of the '682 patent would have been obvious to a POSA as of November 24, 2012, over Singh in view of Harris. EX1003, ¶134.

Dependent claim 2 of the '682 patent specifies that Z comprises a thiol, disulfide, amino, carboxy, aldehydes, maleimido, haloacetyl, hydrazine or hydroxyl group. Both Singh and Harris teach that Z can be maleimide or haloacetyl, as set forth in Table C1 and §VII.B.1, respectively, as required by claim 2. Accordingly, claim 2 would also have been obvious over Singh in view of Harris for the same reasons as discussed above for claim 1. EX1003, ¶¶133-134.

2. Claims 20-21 and 29-31

Claims 20-21 and 29-31 are directed to the compound of formula (IV):



In addition to Harris teaching each of the elements of claims 20-21 and 29-31 as set forth in §VII.B.2, claims 20-21 and 29-31 were also obvious over Singh in view of Harris. EX1003, ¶¶135-136.

Singh discloses formula (1), $Z-X_1-(CH_2-CH_2-O)_n-Y_p-D$, and related formulas⁶ which, like '682's formula (IV), are PEG drug linkers that may be attached to a cell binding agent to provide conjugates. EX1008, ¶¶[0014], [0080]. Singh also discloses examples of formula (1) as shown in Table C2, below. As explained by Dr. Chari, Singh's formula (1) and its related formulas overlap with and suggest compounds of formula (IV). EX1003, ¶¶137-151.

For example, in Singh's formula (1) compound, Z is "a reactive functionality that can form an *amide or a thioether* bond with *a cell-binding agent*" and therefore meets the definition of Y of formula (IV) in the '682 patent, which "represents a functional group that enables reaction of the compound with a cell-binding agent." EX1003, ¶138.

Singh's Z group also meets at least the Q variable of '682's formula (IV) because Singh discloses vinyl sulfone—a reactive functionality that forms thioether bonds—as one of only three such groups (along with haloacetamide and maleimide). EX1008, ¶[0134]. In this case, Y of formula (IV) is vinyl, Q is

⁶ Formulas (1'), (3), and (3'). *Supra*, §IV.E.

sulfonyl, $m=1$ and, as permitted by the claims, R_1 is absent from Singh's compound of formula (1). EX1003, ¶138.

The PEG group of formula (1) (*i.e.*, $(OCH_2CH_2)_n$ where n is any of 1-2000, 1-100, 1-14, 1-4) meets the '682's definition of R_2 , which can include a “polyethylene oxy unit of formula $(OCH_2CH_2)_p$, wherein p is an integer from 1 to about 1000.” EX1008, ¶[0082]. Claim 20 further requires one of R_1 - R_4 to comprise PEG when Q and T are each SO_2 , and Singh's PEG group meets this requirement too. EX1003, ¶139.

Singh's formula (1) compound optionally contains an X group linking the PEG to the Z group. When present (*i.e.*, Singh's X_l where $l=1$), the X group is also part of R_2 as an “aliphatic ... group attached to the cell-binding agent via a thioether bond, an amide bond, a carbamate bond, or an ether bond” (EX1008, ¶¶[0014], [0080]) because R_2 's definition permits combinations of PEG with “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.” EX1003, ¶139. Although claims 29 and 30, impose additional restrictions on R_2 (*e.g.*, if present, alkyl is branched having 3-6 carbons) when Q and T are both SO_2 , the rest of R_2 definition remains unchanged and is still met by Singh's PEG and X groups in formula (1). EX1003, ¶140.

In embodiments of Singh's formula (1) having only one sulfone (*e.g.*, those that meet the definitions of Q and R₂), R₃ is absent (n=0) as permitted by the claims. EX1003, ¶140. Alternatively, in such embodiments, Q and R₂ are absent (m=0), T is present and (OCH₂CH₂)_n and X meet the definition of R₃ (n=1), which is defined even more broadly than R₂. EX1003, ¶140.

The Y group of Singh's formula (1) compound, when present (*i.e.*, p=1) as an aliphatic or heterocyclic group ***attached to the drug*** via a thioether or amide bond, a carbamate bond, an ether bond, or an amine bond, meets the definition of R₄ (which definition is identical to R₁ and R₃), with R₅ and R₆ as H or absent. D of formula (1) is a drug and meets formula (IV)'s definition of Drug. EX1003, ¶141.

Singh's Y group in formula (I) can also provide a first or second sulfonyl group because in order to provide a thioether bond to the drug, the precursor (*i.e.*, the bifunctional PEG crosslinker discussed in the previous section) must include thiol reactive moieties which Singh discloses as including vinyl sulfones. For at least the same reasons discussed above (*supra* §VII.C.1), a POSA would have been motivated to incorporate vinyl sulfones as the Z group in formula (I) of Singh and/or attach the drug using a vinyl sulfone in view of Harris and would have had a reasonable expectation of success in doing so. EX1003, ¶142.

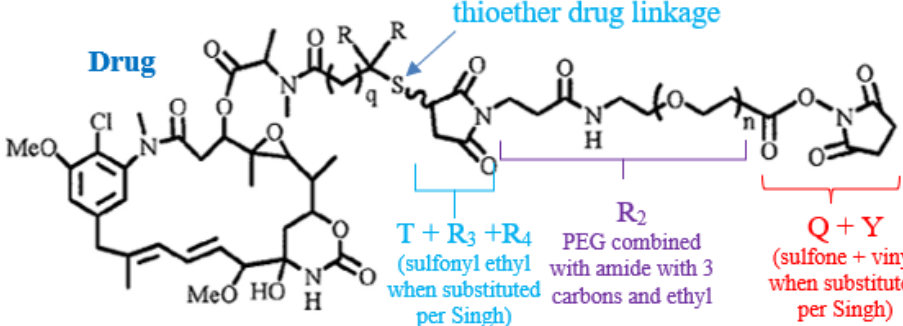
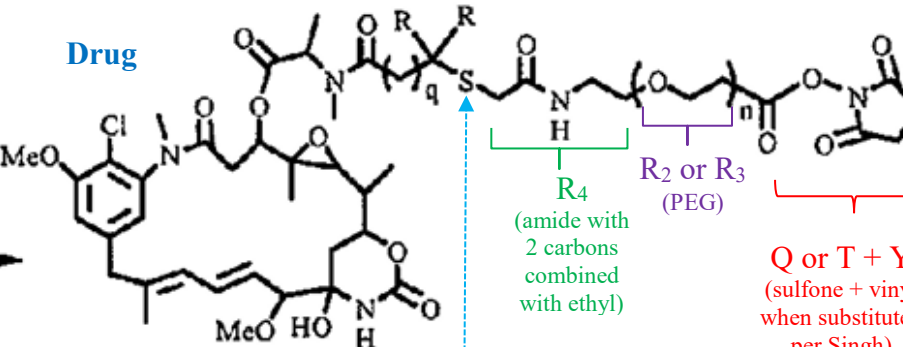
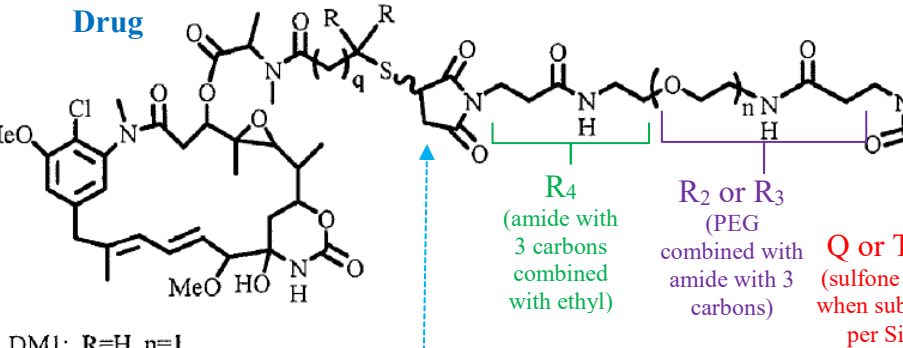
Claims 20 and 29 encompass drug-linkers with only a single sulfonyl group and require that the Y group of formula (IV) be selected from common activating

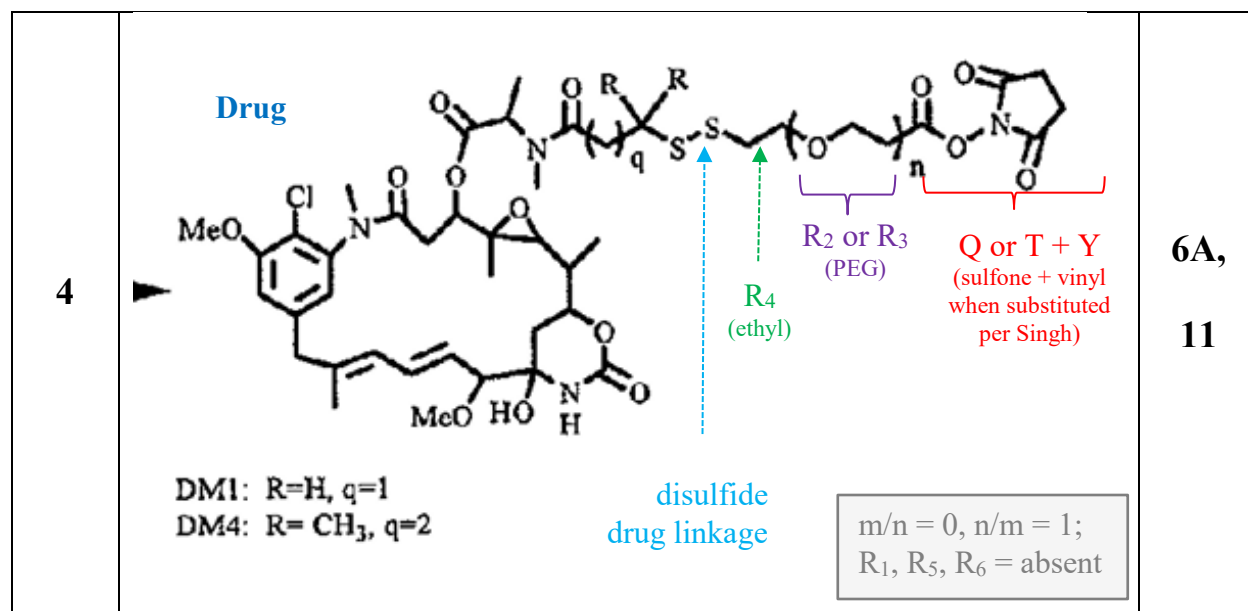
groups such as NHS ester. Singh's formula (1) suggests such embodiments as well. As noted above, when Y of Singh's formula (1) is sulfonyl ethyl with a thioether link to the drug, Singh's Z may be reactive functionalities that form a thioether or **amide** bond. EX1008, [0080]. Singh discloses that NHS is not only an amide bond forming reactive functionality, but employs it in a number of Drug linker conjugates reproduced in Table C2, below. *Id.*, ¶[0134]; EX1003, ¶143.

In addition to compounds of formula (1)/(1') and (3)/(3'), Singh discloses examples of such PEG drug crosslinkers in Figs. 4, 5, 6A, 13 and 16A and the accompanying text. As shown in Table C2 below, these compounds also map to and suggest compounds of '682's formula (IV). EX1003, ¶¶143-149.

Table C2

Entry	Singh's PEG Drug Crosslinkers	FIGs.
1	DM1: R=H, q=1 DM4: R= CH₃, q=2 m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	4, 7

1	 thioether drug linkage Drug DM1: R=H, q=1 DM4: R=CH₃, q=2 $m = 1, n = 1$; $R_1, R_5, R_6 = \text{absent}$	4, 7
2	 thioether drug linkage Drug DM1: R=H, q=1 DM4: R=CH₃, q=2 $m/n = 0, n/m = 1$; $R_1, R_5, R_6 = \text{absent}$	5, 9
3	 Cycloheteroalkane drug linkage Drug DM1: R=H, n=1 DM4: R=CH₃, n=2 $m/n = 0, n/m = 1$; $R_1, R_5, R_6 = \text{absent}$	13, 14



Each crosslinker compound in Table C2 includes a maytansinoid (DM1 or DM4), a cytotoxic anticancer drug, at one end of the crosslinker. Each maytansinoid is attached to the rest of the cross-linker via a thioether bond (compounds 1-3) or a disulfide bond (compound 4), and each crosslinker includes at its other end an NHS ester or maleimide derivative that can form, respectively, an amide or a thioether bond with a cell-binding agent (*i.e.*, antibody) to form an ADC. EX1008, Figs. 4-6A, 14, 16A, 19A; EX1003, ¶144.

The exemplary PEG drug linker compounds of Singh differ from the '682's formula (IV) only in that Q and T are absent, where claims 20 and 29 require the presence of at least one of Q and T while claim 30 requires the presence of both Q and T.

For the same reasons given above (*supra* §VII.C.1), a POSA would have been motivated to substitute thiol reactive groups that can react with a cysteine in a cell-binding agent (*e.g.*, the maleimide in compound 3) and/or the reactive functionality forming the thioether bond (*e.g.*, maleimide, iodo- or bromo-acetamide) to the drug (Y in Singh's formulas (1), (1'), (3) and (3')) with vinyl sulfone or other sulfones as taught by Harris. A POSA would also have been motivated to replace the amide bond forming groups (such as N-hydroxysuccinimide in compounds 1, 2, and 4) with vinyl sulfones because i) Singh itself suggests thiol-reactive groups such as vinyl sulfones may be used as Z groups in compounds of formulas (1)/(1') and (3)/(3') and ii) Harris discloses several advantages for doing so as previously explained. *Supra*, §VII.C.1; EX1003, ¶¶148-149.

Also as previously described (*supra*, §VII.C.1), a POSA would have had a reasonable expectation of success that combining the teachings of Singh and Harris would successfully yield hydrophilic PEG drug crosslinkers having desirable functional properties and that could be used to prepare ADCs by reacting the crosslinkers with suitable antibodies. EX1003, ¶150.

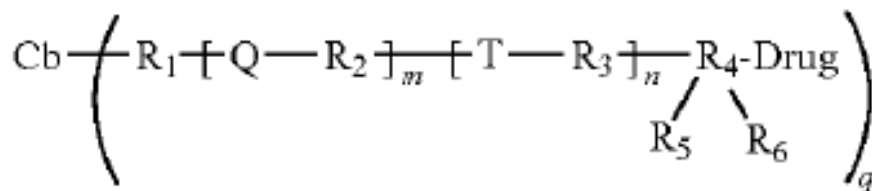
Accordingly, claims 20, and 29-30 would have been obvious over Singh in view of Harris.

Dependent claim 21 also would have been obvious over Singh in view of Harris for at least two reasons. First, for the reasons explained in §VII.B.2, Harris discloses that drugs modified to contain thiol moieties react with vinyl sulfones. EX1007, 6:28-31; EX1003 ¶151. Second, Singh also discloses that its PEG spacers may be reacted with “a thiol-containing maytansinoid drug” or “an amine-containing maytansinoid.” EX1008, ¶¶[0136], [0139]. Indeed, a POSA will understand that the drug in each of compounds 1-5 in Table C2 was derived from a drug containing a –SH. EX1003, ¶¶151, 153.

Dependent claim 31 further specifies 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. As shown in Table C2 and discussed with respect to claims 20 and 29, each of Singh’s PEG-drug linkers comprise PEG matching R₂ and/or R₃. As such, dependent claim 31 would have been obvious over Singh in view of Harris. Accordingly, claims 20-21 and 29-31 would have been obvious in view of Harris in view of Singh. EX1003, ¶¶152-153.

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

As noted above, §VI.A, independent claims 3, 24 and 26 are directed to a cell-binding agent (“Cb”)-drug conjugate of formula (II):



The primary differences between formula (II) and formula (IV) are that Cb replaces Y at one terminus of the drug-linker and Cb can have multiple drug linkers (*i.e.*, $q=1-20$) attached to it. Claims 3 and 24 largely overlap but, as explained in §VI.A, the definitions of m and n differ slightly between them. As set forth below, claims 3 and 24 would have been obvious over Singh in view of Harris. EX1003, ¶¶154-155.

As explained in §VII.A.1 above, the preamble “cell-binding agent-drug conjugate” is not limiting. Nevertheless, the combination of Singh and Harris teaches this limitation because it merely refers to compounds of formula (II) and fails to further limit the scope of the claims. EX1003, ¶156-157.

Singh teaches cell-binding drug conjugates in its formulas (2)/(2') and (4)/(4') (EX1008, ¶¶[0015], [0017], [0084], [0093]) and provides examples of each in Figs. 1-3, 7-12, 14-15, 17-18, and 20-21 and accompanying text. EX1008, ¶¶[0136]-[0138], [0214], [0218]-[0221]. As with the '682 formulas (II) and (IV), the primary differences between Singh's formulas (2)/(2') and formulas (1)/(1') are that a cell-binding agent CB is present in formulas (2)/(2') in place of Z and that it

is bound to m (=2-15) drug-linkers.⁷ Singh's disclosure of D, Y, p, n, X, and l for formulas (2)/(2') is identical to its disclosure of those variables for formulas (1)/(1'). EX1003, ¶157 (comparing EX1008, ¶¶[0014], [0080] to ¶¶[0015], [0084]). Hence, Singh in combination with Harris is relied on for the reasons given above (*supra*, §§VII.C.1-VII.C.2) to teach or suggest all variables in common between formulas (II) and (IV) of the '682 patent, including sulfonyl groups meeting the definition of Q and T. Additionally, a POSA would understand that the cell-binding agent and variable m of Singh's formulas (EX1008, ¶¶[0146]-[0156]) teach the cell binding agent and q as defined in claims 3, 24 and 26 of the '682 patent. EX1003, ¶158. Hence. Claims 3, 24, and 26 would have been obvious over the compounds of formulas (2)/(2') and (4)/(4') of Singh in view of its and Harris' teachings concerning vinyl sulfones based on the same motivation to combine and reasonable expectation of success detailed above in §§VII.C.1-2.

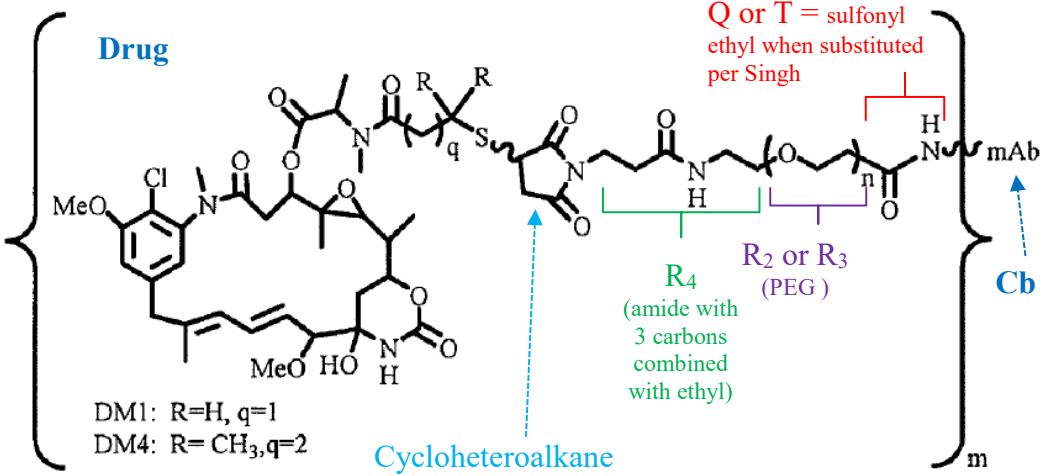
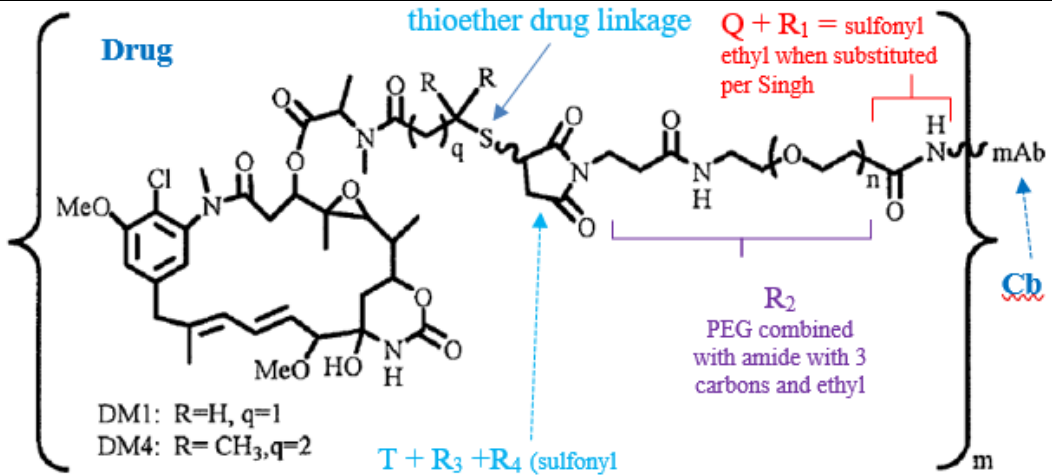
Singh's exemplary compounds of formulas (2)/(2') and (4)/(4'), further demonstrate the obviousness of the formula (II) compounds in claims 3 and 24. Specifically, Singh's compounds are ADCs in which a PEG-containing linker is

⁷ Similarly, formulas (4)/(4') are identical to formulas (3)/(3') except a cell-binding agent CB is present in formula (4)/(4') instead of Z, and CB is attached to m (2-15) drug-linkers. EX1008, [0016]-[0017], [0090]-[0095]; EX1003, ¶157.

conjugated to an antibody via an amide or thioether bond and to a drug via a thioether or disulfide bond. EX1008, Figs.1-3, 14, 17, 20; EX1003, ¶165. As shown in Table C3 below, the exemplary drug linker compounds of Singh differ from formula (II) of claims 3, 24, and 26 only in that Q and T are absent. EX1003, ¶¶157-168.

Claims 24 and 26 of the '682 patent differ from claim 3 because they require the presence of both Q and T in the conjugates. Nonetheless, for the same reasons given in §§VII.C.1-2 above, a POSA would have been motivated to prepare ADCs with one or two sulfones using vinyl sulfones as the reactive groups based on Singh's exemplary compounds in view of Singh itself and Harris' disclosed advantages of sulfonyl-containing linkers. In particular, a POSA would have been motivated to substitute the sulfonyl ethyl group in for either the linking moiety to the antibody and/or the linking moiety to the drug. EX1003, ¶169.

Table C3

No.	Antibody Drug Conjugates of Singh	FIG.
1	 Drug Q or T = sulfonyl ethyl when substituted per Singh R₄ (amide with 3 carbons combined with ethyl) R₂ or R₃ (PEG) Cycloheteroalkane drug linkage DM1: R=H, q=1 DM4: R=CH₃, q=2 m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	1, 7-8
1	 Drug thioether drug linkage Q + R₁ = sulfonyl ethyl when substituted per Singh R₂ PEG combined with amide with 3 carbons and ethyl T + R₃ + R₄ (sulfonyl ethyl when substituted per Singh) DM1: R=H, q=1 DM4: R=CH₃, q=2 m = 1, n = 1; R₅, R₆ = absent	1, 7-8

2	Drug DM1: R=H, n=1 DM4: R=CH₃, n=2 Cycloheteroalkane drug linkage R₄ (amide with 3 carbons combined with ethyl) R₂ or R₃ (PEG combined with amide with 3 carbons) Q or T = sulfonyl ethyl when substituted per Singh mAb Cb m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	14, 15
3	Drug DM1: R=H, q=1 DM4: R=CH₃, q=2 disulfide drug linkage R₄ (ethyl) R₂ or R₃ (PEG) Q or T = sulfonyl ethyl when substituted per Singh mAb Cb m/n = 0, n/m = 1; R₁, R₅, R₆ = absent	3, 11, 12

Further, a POSA would have expected that combining the teachings of Singh and Harris would lead to the successful generation of ADCs with enhanced potency/cytotoxicity. Singh teaches that its hydrophilic PEG-containing linkers improves the “potency or efficacy of the cell-binding agent-drug conjugates” in various “cancer cell types, including those expressing a low number of antigens on the cell” and that its hydrophilic linkers allowed the conjugation of up to 15

molecules of a drug per antibody molecule with high yield and no aggregation or precipitation. EX1008, ¶¶[0009], [0011]. A POSA would have expected that ADCs that include the hydrophilic vinyl sulfone or related sulfone moieties of Harris would exhibit *improved solubility*, and thus enhanced therapeutic properties (enhanced cytotoxicity/potency and high number of drug molecules (1-15) per antibody molecule *etc.*) as the PEG-containing ADCs of Singh. EX1003, ¶170.

Because the hydrophilic properties of the PEG-containing ADCs of Singh are correlated with the enhanced cytotoxicity/potency in target cancer cells (EX1008, ¶¶[0009], [0011]), and PEG spacers including sulfonyl moieties are highly water-soluble (EX1007, 19:34-37), a POSA would have had both a motivation and a reasonable expectation of success in combining the teachings of Singh and Harris in the manner claimed. Thus, independent claims 3, 24 and 26 would have been obvious over Singh in view of Harris. EX1003, ¶¶171, 177.

Dependent claims 4-5, 8 and 10 further define the “Drug” of formula (II) as being selected from various classes and groups of therapeutic agents. Singh teaches a number of the same drugs for use in its conjugates, including maytansinoids, DNA-binding drugs such as CC-1065, calicheamicins, doxorubicin, vinca alkaloids, cryptophycins, dolastatin, auristatin, tubulysin, epothilones, taxoids and siRNA. EX1008, ¶¶[0165]-[0167]; EX1003, ¶172. Accordingly, claims 4-5, 8 and 10 would likewise have been obvious over Singh in view of

Harris since Singh expressly discloses drugs satisfying the added limitations of these claims for combination with Singh's linkers.

Dependent claims 6-7 and 14 further specify a cell-binding agent selected from, *e.g.*, antibodies, proteins, peptides, hormones, vitamins, growth factors, lymphokines, and colony stimulating factors. Singh defines cell-binding agents as "proteins (*e.g.*, immunoglobulin and non-immunoglobulin proteins) that bind specifically to target antigens on cancer cells." Singh's examples of cell-binding agents include antibodies, epitope binding fragments of antibodies such as sFv, Fab, Fab', and F(ab')₂, Ankyrin repeat proteins, interferons, lymphokines, hormones, vitamins, growth factors and colony-stimulating factors. EX1008, ¶¶[0120], [0146]-[0156]; EX1003, ¶173. Harris likewise discloses that its PEG sulfonyl conjugates may include proteins. EX1007, 6:31-7:2. Thus, claims 6-7 and 14 would likewise have been obvious over Singh in view of Harris since both Singh and Harris expressly disclose cell-binding agents satisfying the added limitations of these claims for combination with the disclosed linkers.

Claims 11, 12, 14, each depend from claim 3. Claim 11 specifies that the conjugate of claim 3 has in vitro, in vivo or ex vivo cell killing activity; claim 12 specifies that the conjugate comprises, *e.g.*, a **thioether** unit; and claim 14 alternatively recites that in the conjugate, the "Drug is derived from a drug containing a —SH, ... or —NHR", wherein R" is H, CH₃, Et, Pr, Bu, or Ph."

Regarding claim 11, Singh teaches that cell-binding agent-drug conjugates bearing PEG spacers exhibit a “superstoichiometric increase in cytotoxicity toward target cancer cells by as much as a 260-650 fold enhancement in potency...as compared to traditionally prepared conjugates with similar drug loads.” EX1008, ¶[0078]; EX1003, ¶174. A POSA would have expected at least as good if not better performance when incorporating one or two vinyl sulfones given their impartation of even better water solubility. *Supra* §VII.C.1; EX1003, ¶174.

Regarding claims 12 and 14, Singh teaches ADCs in which the drug (containing a **thiol**) may be attached to a Y group by a **thioether bond** and/or the cell binding agent (bearing a cysteine thiol or lysine amine) may be attached to, an X group by a **thioether bond or an amide bond**. EX1008, ¶¶[0015], [0017], [0084]-[0085], [0093], Figs. 1-2, 7-9, 14, 17-18, 21; EX1003, ¶175. Likewise, Harris discloses that drugs “from aspirin to penicillin” can be modified to contain thiol moieties. EX1007, 6:28-31; EX1003, ¶175. As such, claims 11-12 and 14 would also have been obvious over Singh in view of Harris, since both Singh and Harris expressly disclose the added limitations of these claims. EX1003, ¶¶174-175, 177.

Dependent claims 15-16 overlap in that both recite pharmaceutical compositions comprising the conjugate of claim 3 and a pharmaceutically acceptable carrier. Claim 15 also alternatively includes a pharmaceutically

acceptable salt, diluent, or excipient. Dependent claim 17 recites 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.” Regarding claims 15-16, Singh teaches that “cell-binding agent drug conjugates (*e.g.*, immunoconjugates) can be used with as pharmaceutically acceptable carriers, diluents, and/or excipients, which are well known, and can be determined, by one of skill in the art as the clinical situation warrants,” and as a pharmaceutically acceptable salt. EX1008, ¶[0174], claim 13. Regarding claim 17, Singh discloses that “cell-binding agent drug conjugates (*e.g.*, immunoconjugates) of this invention can also be used in combination with chemotherapeutic agents.” EX1008, ¶[0171]; EX1003, ¶176. Accordingly, claims 15-17 would also have been obvious over Singh in view of Harris since Singh expressly discloses the added limitations of these claims in combination with Singh’s linker compounds. For at least the foregoing reasons, claims 3-8, 10-12, 14-17, 24, and 26 would have also been obvious in view of Harris in view of Singh. EX1003, ¶¶157-177.

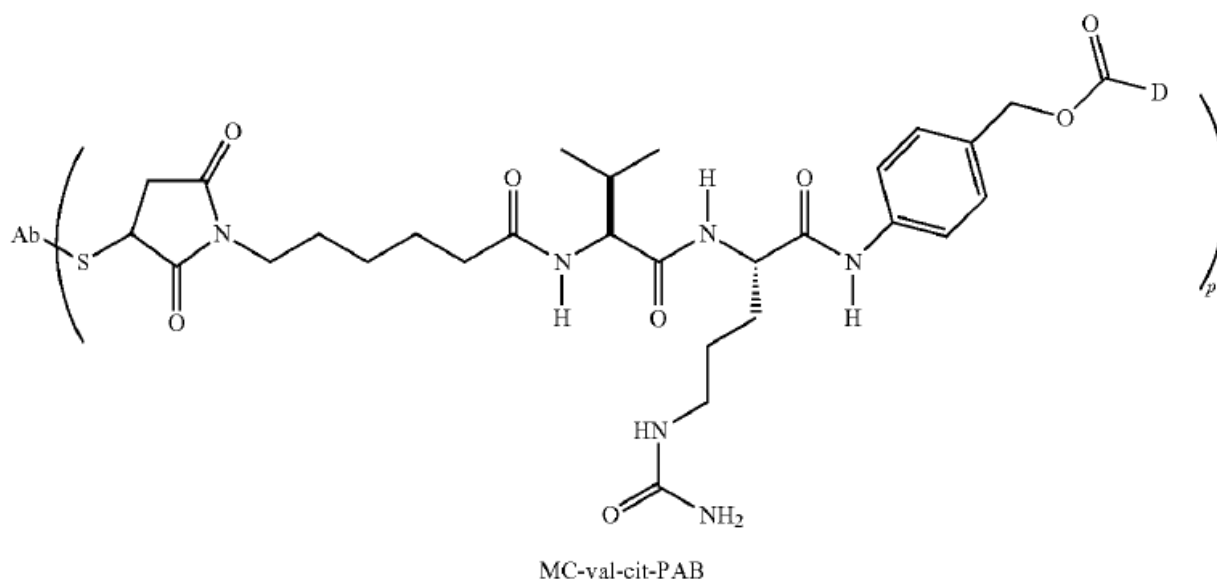
D. Ground 4: Claims 9 and 13 are obvious over Singh in view of Harris and Bhakta

Claims 9 and 13 of the ’682 patent would have been obvious over Singh in view of Harris and Bhakta for the reasons set forth in detail below. Singh and

Harris are relied on to teach the various elements of claims 3-8 as set forth in §VII.C.2 above.

Dependent claim 9 adds “wherein the conjugate comprises one or more linker components of...**valine-citrulline**, alanine-phenylalanine,...and (4-acetyl)aminobenzoate,” whereas claim 13 requires the conjugate to be “cleavable by a protease.” EX1003, ¶178. As shown by Bhakta, by 2012, valine-citrulline was a well-known cleavable dipeptide used to link drugs in ADCs, just as disulfide bonds were.

Bhakta expressly teaches ADCs comprising a cysteine engineered antibody and a drug moiety, wherein the antibody has one or more free cysteine amino acids that attach via a linker to the drug moiety. EX1011, ¶¶[0211]-[0212]. Bhakta’s linkers may further comprise amino acid residues linking the antibody to the drug moiety of the cysteine engineered ADC, where the amino acid residues can be “optimized in their selectivity for enzymatic cleavage by...for example, a tumor-associated protease to liberate an active drug moiety.” EX1011, ¶¶[0244]-[0245]. The valine-citrulline (“val-cit”) dipeptide is highlighted and can be cleaved by cathepsin B, C and D, or a plasmin protease. *Id.* It was also known to use combinations of the dipeptide val-cit with para-aminobenzylcarbamoyl (PAB) as shown in the structure below from Bhakta. EX1011, ¶[0250]; EX1003, ¶¶179-180.



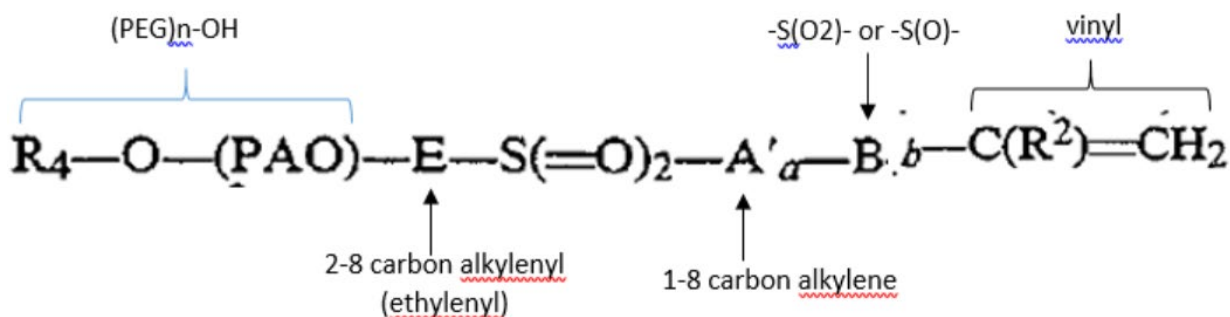
ADCs utilizing the disulfide linkages of Singh were previously found to exhibit reduced efficacy, greater off target toxicity and poor serum stability. EX1049, abstract. A POSA would have been motivated to use the well-known val-cit-PAB linker of Bhakta to replace, *e.g.*, the disulfide linkage of Singh, in order to obtain more selective and efficient release of the Drug at target cancer cells because, for example, when the val-cit dipeptide is cleaved from the PAB by cathepsins associated with the target cancer cell, the ester linkage to the drug subsequently hydrolyzes as well and releases the drug within the cancer cell. A POSA would have had a reasonable expectation of success because the chemistry of this linker was well established and proven in human patients, well before the priority date. EX1017, 101:1-104:43. Accordingly, dependent claims 9 and 13 are obvious over Singh in view of Harris and Bhakta. EX1003, ¶¶181-182.

E. Ground 5: Claims 2, 25 and 32-34 are obvious over Singh in view of Harris and Snow

Singh and Harris are relied on to teach the various elements of claims 1, 3, 20, 24 and 30-31, directed to compounds of formulas (I), (II) or (IV), as set forth in §§VII.C.1-VIIC.3 above.

Claim 2 (which depends from claim 1) specifies that Z comprises a maleimido group, among other options. Claim 25 (dependent on claim 24), claim 32 (dependent on claim 30), claim 33 (dependent on claim 3) and claim 34 (dependent on claim 20) each recite “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.” EX1003, ¶183.

Snow discloses vinyl sulfone linkers containing PEG polymers ranging from 250-100,000 daltons (EX1010, 7:51-65), which overlap with the genus of water soluble sulfone-containing PEG polymers disclosed in Harris. EX1007, 19:10-17 and 24-30. In particular, Snow contemplates polyalkylene oxide bis-vinyl sulfone linkers represented by the formula:



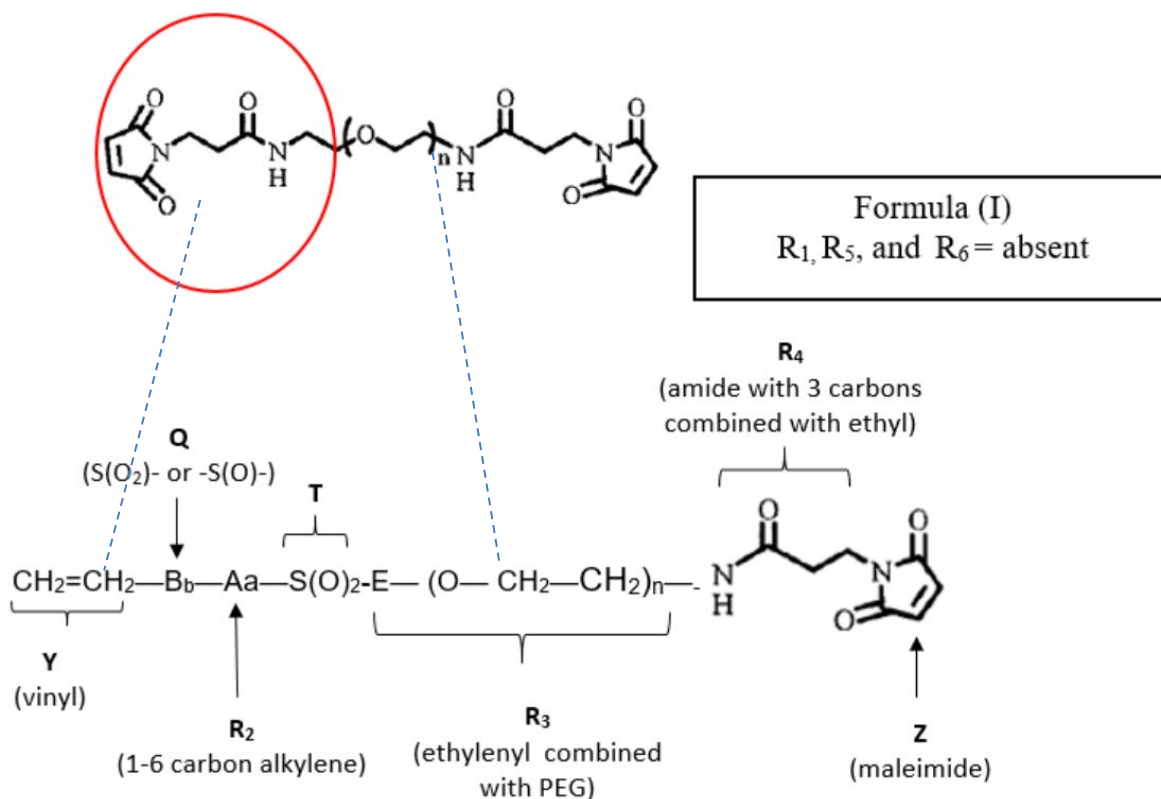
Like Harris, Snow teaches that its polyalkylene oxide vinyl sulfone reagents show preferential reactivity with accessible sulfhydryl groups on proteins.

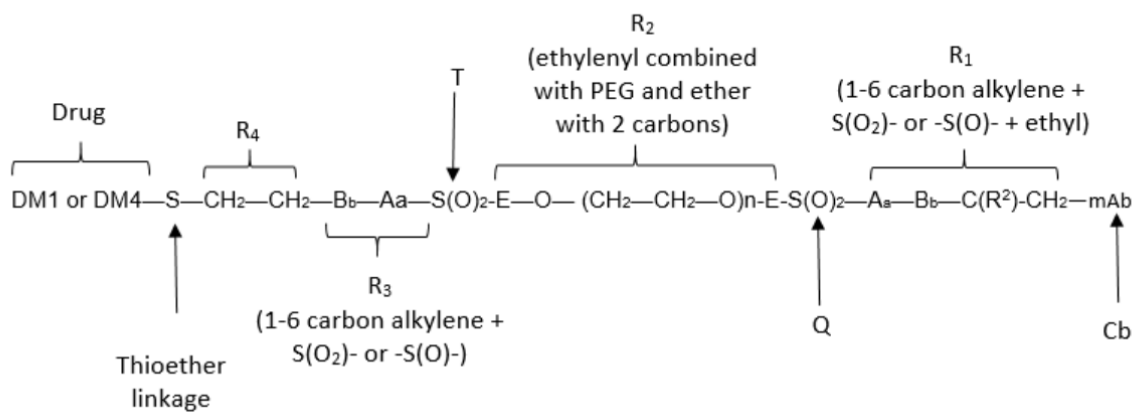
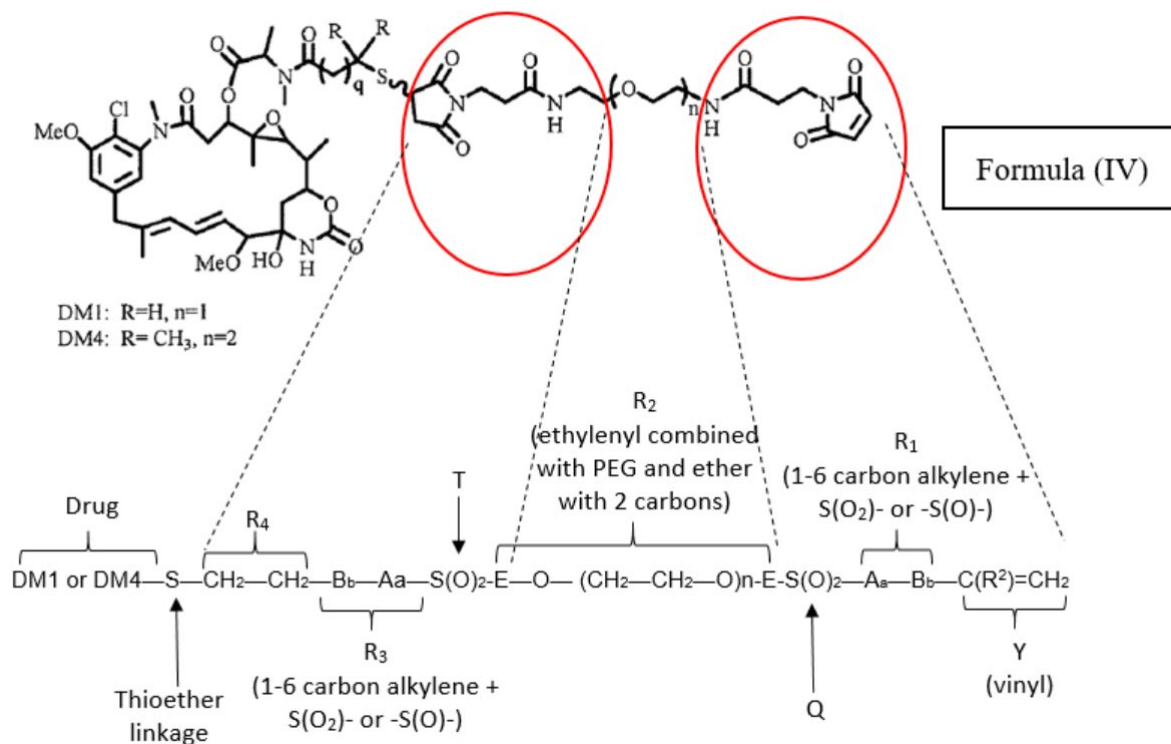
EX1010, 9:58-63; EX1007, 6:12-15, 26:11-15; EX1003, ¶¶184-185.

As shown in Tables A1 and C2, Singh discloses a bifunctional bis-maleimide PEG crosslinker that can be conjugated to a thiol-bearing maytansinoid drug (DM1 or DM4). *Supra*, §§IV.E & VII.C.1-VII.C.2. A POSA would be motivated to further improve the solubility of ADC linkers that are conjugated to exceptionally hydrophobic drugs like maytansinoids, at high drug loads, where they are prone to aggregation/precipitation. *Supra*, §§VII.C.1-§VII.C.3; *see also* EX1050, 2:19-25, 10:20-25, 64:59-67 (teaching the need to increase hydrophilicity of maleimide ADC linkers); EX1003, ¶186.

As such, 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 substitutions would further enhance the hydrophilicity of the PEG linkers conjugated to exceptionally hydrophobic drugs. A POSA would have had a

reasonable expectation of success because bis-vinyl sulfone linkers of Snow impart higher water solubility, and thus enhance cytotoxicity when conjugated to a high load of exceptionally hydrophobic drugs. The diagrams below show how the modified linkers match up with claimed linkers. *Id.* Accordingly, dependent claims 2, 25 and 32-34 would have been obvious over Singh in view of Harris and Snow. EX1003, ¶187-189.





F. There is no evidence of secondary considerations

Patent Owner did not make any arguments or present any evidence during prosecution concerning any secondary considerations of patentability supporting the '682 claims; nor is Petitioner aware of any.

Nothing in the '682 patent demonstrates that the claimed compositions exhibit surprising or unexpected effects. Rather, the '682 patent merely touts the advantage that “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.” Yet, the use of sulfone groups and PEG to impart water solubility to conjugates had been known for at least 22 years before the '682 patent. EX1003, ¶¶43, 186. Further, the examples within the application provide no data on which an assertion of surprising and unexpected results could be based.

To the extent Patent Owner argues denial of institution in its Preliminary Response based on secondary considerations for any ground of obviousness herein, the Board should nevertheless institute trial to permit Petitioner to respond to such arguments that it has never seen before and to allow the parties to develop a complete record concerning the secondary considerations. *Amneal Pharms. v. Supernus Pharms.*, IPR2013-00368, Paper 8 at 12-13 (PTAB Dec. 17, 2013).

VIII. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION

A. The Board Should Not Deny Review Under §314(a)

The Board has discretion whether to institute IPR under §314(a) and can deny review where other petitions challenge the same claims (*Gen. Plastic Indus. Co. v. Canon Kabushiki Kaisha*, IPR2016-01357, Paper 19 at 15-16 (PTAB Sept. 6, 2017) (precedential)) or where a parallel district court proceeding is at an advanced stage (*Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB March 20, 2020)). The '682 patent is not involved in any other proceeding challenging the patentability of the claims. Therefore the Board should not deny institution under §314(a).

B. The Board Should Not Deny Review Under §325(d)

The Board should not deny review under §325(d) because the Patent Office has not previously considered the present grounds of invalidity. This is the first challenge of any kind to the **amended** '682 patent claims (*i.e.*, those newly-issued from the reexamination), and the prior art relied upon herein was not substantively considered during prosecution or reexamination, or in the light presented herein.

Neither Harris nor Snow were cited during prosecution or reexamination, and were never considered by the Examiner. Harris and Snow are not cumulative of the prior art references previously disclosed to the Office because these references expressly disclose hydrophilic PEG linkers comprising bis-vinyl sulfone

or related sulfonyl derivatives, which anticipate/render obvious the amended '682 claims covering linkers and drug-linker compounds encompassed by formulas (I) and (IV). Likewise, Bhakta was never cited or considered by the Examiner during prosecution or reexamination.

While Morales-Sanfrutos, Straus, and Singh were listed on IDSes submitted to the Office, this is, at best, cursory consideration that weighs against discretionary denial. *Kayak Software Corp. v. IBM Corp.*, CBM 2016-00075, Paper 16 at 11, (PTAB 2016). Here, the Examiner failed to identify the anticipatory structures of Morales-Sanfrutos that are encompassed by the broad genus of linkers and conjugates recited in the amended '682 claims. Moreover, Singh was not considered during prosecution or *ex parte* re-examination proceedings. Specifically, the Examiner never acknowledged Singh's teachings that vinyl sulfone is equivalent to maleimide and haloacetamide moieties for thiol-reactive functionality. EX1008, ¶[0134]; EX1003, ¶¶124,130,169. Nor has the Office considered how a POSA would have been motivated to replace one or both reactive functionalities in Singh's bifunctional PEG cross-linkers with vinyl sulfone due its superior properties (*e.g.*, hydrolytic stability, high water solubility), or that such modifications would result in ADCs with enhanced potency/cytotoxicity. *See, e.g., supra* §§VII.C.1-VII.C.3.

Thus, none of the grounds that Petitioner relies on herein have ever been substantively considered by the Office, and discretionary denial is unwarranted.

Oticon Medical AB v. Cochlear Ltd., IPR2019-00975 (PTAB Oct. 16, 2019) (Paper 15) (precedential as to §§II.B-C).

CONCLUSION

For the foregoing reasons, Petitioner respectfully requests that Trial be instituted and that Claims 1-17, 20-21, 24-26, and 29-34 be canceled.

Respectfully submitted,

Dated: February 9, 2023

By: /Joseph P. Meara/

Joseph Meara
Reg. No. 44,932
Counsel for Petitioner

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing Petition complies with the requirements of 37 C.F.R. § 42.24. Excluding the portions exempted by 37 C.F.R. § 42.24(a) (a table of contents, a table of authorities, a listing of facts which are admitted, denied, or cannot be admitted or denied, a certificate of service or word count, or appendix of exhibits), the Petition contains 13,970 words as counted by the word processing system used to prepare it.

By: /Joseph P. Meara/

Joseph Meara
Reg. No. 44,932
Counsel for Petitioner

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review together with all exhibits and other papers filed therewith were caused to be deposited in a Federal Express Box on February 9, 2023, directed to the attorneys of record for the patent at the following address:

Fang Liu, Ph.D.
HANGZHOU DAC BIOTECH CO.,
Buchanan Ingersoll & Rooney PC
1737 King Street, Suite 500
Alexandria, VA 22314
fang.liu@bipc.com

By: /Joseph P. Meara/

Joseph P. Meara
Reg. No. 44,932
Counsel for Petitioner