

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

PETITIONER'S SUR-SUR-REPLY TO PATENT OWNER'S SUR-REPLY

I. INTRODUCTION

Pursuant to the Board's Order (Paper 40, 2), Petitioner hereby submits this Sur-Sur-Reply to Patent Owner DAC's Sur-Reply (Paper 44; "POSR").

In the POR (Paper 31), despite the DRP having ruled unequivocally that the vinyl of vinyl sulfone can meet the Y "enabling reaction" limitation of claim 1 (Paper 23, 16), DAC continued to attempt to import a limitation into the claims, arguing that Y must "independently" enable reaction to a cell binding agent. POR, §V.B. While Petitioner refuted any such construction on numerous grounds (Pet. Reply (Paper 36), §II.A), it was also shown that vinyl can indeed independently react in the presence of light to link to cell-binding agents (CBAs) (*id.*, 14-15 (citing Ex. 1076, ¶¶5-10, Ex. 1064 ("Dondini"), 11447)).

In its sur-reply, DAC attacked this evidence on the grounds that (1) disulfide bridge cleavage allegedly leads to unstable proteins, and (2) the reaction is not "independent" because of the presence of light and a photoinitiator. POSR, 13-16. Both arguments are without merit.

II. ARGUMENT

A. Thiol-ene coupling is a recognized approach for coupling to CBAs

DAC's expert's position (Ex. 2047, ¶27) that a POSA would not apply Dondoni's photoinduced thiol-ene coupling (TEC) reaction to Morales-Sanfrutos' vinyl sulfone chemistry due to "unexpected side reactions such as cleavage of disulfide bonds in proteins" is unsubstantiated. Specifically, Dr. Tumey alleges that

“when disulfide bridges are cleaved local rigidity is lost, the protein . . . can undergo partial unfolding, and enzymatic activity may be altered.” *Id.*, ¶11.

However, Dr. Tumey’s position is undermined by the fact that antibody drug conjugate (ADC) generation routinely involves the cleavage of disulfide bridges within monoclonal antibodies (mAbs) with reducing agents (*e.g.*, dithiothreitol (DTT)) to expose free thiol groups for the purpose of coupling to drug-linker compounds. Ex. 1090, ¶136 (“The maleimide conjugation is performed by reduction of the disulfide bridges between heavy and light chains of the antibody facilitated by addition of relevant reducing agents.”). Indeed, during cross-examination, Dr. Tumey admitted that “antibodies have four disulfide bridges” and that a “frequently used way to conjugate molecules to antibodies is by cleaving those disulfide bridges to form thiols.” Ex. 1091, 12:16-21. He further conceded that a “range of two up to eight thiol residues” are created when mAbs are treated with DTT, and that this “Antibody + DTT” scheme is taught by the ’682 patent. *Id.*, 11:7-15:15; Ex. 1001, Fig. 15.

In fact, the ’682 patent reports attachment of up to 20 linkers to thiol groups on antibodies, implying that up to 10 disulfide bridges can be cleaved in a mAbs protein (to form the 20 thiol groups). Ex. 1001, Fig. 15 (compounds 195 and 196); Ex. 1091, 15:16-17:18. Thus, even DAC’s patent was not concerned with any potential negative effects of cleaving up to 10 disulfide bridges on ADC stability or

activity. Accordingly, DAC's alleged concern over Dondoni's reported cleavage of just 3 disulfide bridges as part of its thiol-ene coupling reaction is both unsubstantiated and contradicted by the '682 patent itself.

Lastly, Dr. Tumey acknowledges that Dondoni's TEC reaction was conducted with UV light at 365 nm wavelength in DMSO/pH 7.4 phosphate buffer, "an *aqueous solution at physiological pH* eventually diluted with salts." Ex. 2047, ¶¶7,10. Dondoni further states that UV light at 365 nm "is known to cause minimum photodamage to the living cells and organism," further undercutting DAC's expert's concerns regarding the protein structure or folding after the photoinduced TEC reaction. Ex. 1064, 11447.

For all these reasons, a POSA would not have been concerned about or dissuaded from implementing Dondini's reaction scheme to attach linkers to protein CBAs using just the vinyl moiety from a vinyl sulfone group.

B. Vinyl Groups Enable "Independent" Reaction with a CBA

Dr. Tumey also claims that Dondoni does not show vinyl enabling *independent* reaction with a CBA, allegedly because "the reaction requires both UV light and DPAP [a photoinitiator] to generate the free radicals required to enable the reaction." Ex. 2047, ¶20. This position is again contradicted by both the '682 patent and the art.

The '682 patent expressly teaches that when Y is a hydroxylamine group, it reacts with CBAs bearing a carbonyl group, and also depicts a mAb-linker (compound 196) having a hydroxylamine Z group reacting with a carbonyl on a drug in the presence of hydrochloric acid ("HCl") to form an alkoxime bond. Ex. 1001, 13:58-60, Fig. 15 (compound 196→195); Ex. 1091, 17:20-18:6, 21:21-22:1. And DAC's own expert acknowledges that the "HCl protonates the carbonyl, making it more electrophilic and allowing the hydroxylamine to attack," which "can be referred to as an *acid-catalyzed* reaction." Ex. 1091, 24:16-25:10. Because Y is broader than Z (Pet. Reply, 4), this reaction scheme applies equally when Y is a hydroxylamine as well, as the '682 patent itself says Y can be (Ex. 2047, ¶21).

Yet Dr. Tumey tried to deny the feasibility of this acid-catalyzed reaction scheme when mAbs are reacting or even just present, stating "that's not the way this reaction is done with a monoclonal antibody." Ex. 1091, 22:2-26:2. However, Dr. Tumey's testimony is clearly undercut by not only the '682 patent itself (*e.g.*, Fig. 15, compound 196→195), but also the art, which expressly teaches *acid-catalyzed* reactions between hydroxylamine-functionalized linkers and mAbs at an elevated temperature of 37 degrees. Ex. 1089, Fig. 1A; Ex. 1091, 26:17-27:18, 28:10-30:12. A POSA thus appreciated that these oxime reactions are both acid-catalyzed and assisted by elevated temperatures, contrary to Dr. Tumey's claims that Y group hydroxylamines must react "independently."

Further, when Dr. Tumey was asked whether he was aware of other catalysts besides acids (like HCl) that could catalyze this reaction, he said he could not think of any. Ex. 1091, 31:19-32:7. Yet the art expressly teaches that oxime ligation reactions between mAbs and hydroxylamine-functionalized drug linker compounds may be alternatively catalyzed with acetic hydrazide, at 28 degrees. Ex. 1090, ¶¶[00102], [00132]-[00133] (Table 1), [00163]; Ex. 1091, 33:13-37:5.

Taken together, the '682 patent expressly discloses hydroxylamine as exemplary Y reactive groups, which enable reaction via acid-catalyzed reactions (*cf.*, Ex. 1001, Fig. 15 (reaction scheme for compounds 195-196)), and the art likewise confirms that such reactions are catalyzed by an acid (e.g., HCl) or acetic hydrazide, at elevated temperatures (Ex. 1089, Fig. 1A; Ex. 1090, ¶[00163]). These catalysts and elevated temperatures for the very hydroxylamine reaction scheme depicted in the '682 patent are no different than using light and a photoinitiator such as is taught for Dondini's thiol-ene coupling to a vinyl group, where light mimics elevated temperature and the photoinitiator mimics the acid/catalyst.

Accordingly, a POSA would recognize that thiol-ene ligation represents a safe and acceptable means for conjugating to proteins having thiol groups, in which vinyl serves as "a functional group that enables reaction . . . with a cell binding agent," as required by claims 1 and 20. This reaction is no less "independent" than the '682 patent's reported reaction involving hydroxylamine.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing
PETITIONER'S SUR-SUR-REPLY TO PATENT OWNER'S SUR-REPLY is
being served on counsel for Patent Owner by electronic mail this 16th day of May,
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