

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors:	Bedi and Ravi	Art Unit:	1674
Application No.:	18/811,627	Examiner:	KAUFMAN, CLAIRE M
Filing Date:	August 21, 2024	Conf. No.:	5612
Title:	MULTIFUNCTIONAL ANTIBODY-LIGAND TRAPS TO COUNTERACT IMMUNE TOLERANCE		

Mail Stop Amendment

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, Dr. Atul Bedi, declare and state that:

1. I am a named inventor of the subject matter described and claimed in U.S. Patent Application Serial No. 18/811,627, filed on August 21, 2024, entitled, "MULTIFUNCTIONAL ANTIBODY-LIGAND TRAPS TO COUNTERACT IMMUNE TOLERANCE". I am a physician-scientist and medical oncologist, and at the time of the invention, was Associate Professor of Otolaryngology/Head & Neck Surgery and Oncology at the Johns Hopkins University School of Medicine. I am now Chief Scientific Officer at Y-Trap, Inc. My biosketch is attached as Appendix B.

2. I understand that claims 1-4 and 7-12 have been rejected as being obvious given the disclosures of U.S. Patent No. 8,993,524 (hereafter '524) and UChicago Medicine (retrieved online from: <URL:<https://www.uchicagomedicine.org/forefront/news/2015/may/pembrolizumab-shows-real-promise-against-head-and-neck-cancer>> [retrieved on 10/10/2024], 3 pages, 28 May 2015) (hereafter UChicago).

3. I disagree with the Examiner's assertion that '524 and UChicago render the present invention obvious. US 8,993,524 ('524) teaches fusion proteins comprising an anti-EGFR targeting antibody fused to TGFbRII ecd via a flexible linker (anti-EGFR-TGFbRII). However,

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as the Examiner points out, ‘524 does not disclose an the anti-PD1 antibody and specifically does not disclose pembrolizumab. Moreover, ‘524 certainly does not disclose the combination of anti-EGFR-TGFbRII with pembrolizumab for the treatment of cancer.

4. UChicago does disclose the utility of pembrolizumab in the treatment of head and neck cancer. However, as the Examiner notes, UChicago teaches that pembrolizumab alone, an anti-PD1 antibody, is effective in only 25% of patients. Further, the Examiner notes that UChicago teaches that “only 10-13% of patients with head and neck cancer respond to cetuximab as a single agent.” Based on these UChicago teachings, the Examiner states that “anti-EGFR antibody cetuximab was a known antitumor agent” (page 12) and that “anti-PD1 antibody pembrolizumab could be even more effective in that treatment.” The examiner argues that it is obvious to add anti-EGFR-TGFbRII to pembrolizumab, based on certain unsubstantiated assumptions as described below.

5. First, the examiner assumes that it is obvious that an anti-EGFR agent would improve the response to pembrolizumab. However, this assumption is neither obvious nor correct. Indeed, UChicago – which explicitly discusses the possible superiority of pembrolizumab over cetuximab – makes no mention or suggestion of adding cetuximab to pembrolizumab, or that such a combination would have value. If anything, the following reasons would have steered anyone away from even considering the combination of any anti-EGFR agent and pembrolizumab (leave alone conceptualizing and predicting the surprising efficacy of anti-EGFR-TGFbRII + pembrolizumab):

(i) The poor single agent efficacy of cetuximab: it is not approved as a single agent in any indication and is only used in combination with chemotherapy or radiation. Therefore, it would not be an attractive, leave alone obvious, single agent to combine with pembrolizumab.

(ii) even if one had empirically considered adding cetuximab to improve the response rate to pembrolizumab, our data shows that the addition of cetuximab is incapable of

inducing an antitumor response against tumors that resist pembrolizumab, in a human xenograft-bearing model in humanized mice (Appendix A Figure 1).

NSG mice were humanized with 1×10^5 CD34+ hematopoietic stem cells (HSCs). Mice were injected with MDA-MB-231 TNBC cells (1.5×10^6 cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 7 days following tumor cell inoculation, mice were randomized and treated i.p. with 5mg/kg/week with the following (either alone or in combination, as indicated): (i) vehicle control; (ii) cetuximab (anti-EGFR); (iii) pembrolizumab (anti-PD1); (iv) pembrolizumab + cetuximab (anti-PD1 + anti-EGFR). Tumor size was evaluated weekly and tumor volume calculated [length $\times$ width $\times$ height]. None of the treatment groups exhibited a significant reduction in tumor volume compared to vehicle control.

(iii) The addition of cetuximab to pembrolizumab fails to add clinically significant value. This combination has not been shown to improve overall survival compared to pembrolizumab alone and is not approved for any clinical indication.

6. These considerations teach away from combining an anti-EGFR antibody with pembrolizumab and would certainly not guide (leave alone provide any obvious reason) to conceptualize or predict the present invention of anti-EGFR-TGFbRII with pembrolizumab. Indeed, our own conceptualization of this invention was only rendered possible in light of surprising results from our own experiments (as described below).

7. In our investigation of the molecular determinants of resistance to pembrolizumab, we observed that treatment with anti-PD1 results in increased TGFb signaling in the tumor (measured by phospho-Smad2 western blot) (Appendix A Figure 2A). To investigate whether this tumor-intrinsic TGFb signaling was causing resistance to pembrolizumab, we conducted the following experiments.

8. In the same MDA-MB-231 model, we investigated whether the addition of a TGFb inhibitor (IgG-TGFbRII) can improve the antitumor activity of PD1/PDL1 inhibition (Appendix A Figure 2B). NSG mice were humanized with $1e5$ CD34+ hematopoietic stem cells (HSCs). Mice were injected with MDA-MB-231 TNBC cells (1.5×10^6 cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 7 days following tumor cell inoculation, mice were randomized and treated i.p. with 5mg/kg/week with the following (either alone or in combination, as indicated): (i) vehicle control; (ii) PD1/PDL1 inhibitor; (iii) PD1/PDL1 inhibitor + TGFb inhibitor (IgG-TGFbRII). Tumor size was evaluated weekly and tumor volume calculated [length $\times$ width $\times$ height]. Neither of the treatment groups exhibited a significant reduction in tumor volume compared to vehicle control. Therefore, addition of IgG-TGFbRII alone was insufficient to render tumor cells responsive to PD1/PDL1 inhibition.

9. In contrast to the above result, we surprisingly found that the addition of anti-EGFR-TGFbRII to pembrolizumab (i.e., the instant invention) demonstrated striking antitumor activity in tumors that failed to respond to pembrolizumab alone, in the same tumor model (Appendix A Figure 3A). NSG mice were humanized with $1e5$ CD34+ hematopoietic stem cells (HSCs). Mice were injected with MDA-MB-231 TNBC cells (1.5×10^6 cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 7 days following tumor cell inoculation, mice were randomized and treated i.p. with 5mg/kg/week with the following (either alone or in combination, as indicated): (i) vehicle control; (ii) pembrolizumab + cetuximab (anti-PD1 + anti-EGFR); or (iii) pembrolizumab + anti-EGFR-TGFbRII (anti-PD1 + anti-EGFR-TGFbRII). Tumor size was evaluated weekly and tumor volume calculated [length $\times$ width $\times$ height]. While the combination of pembrolizumab + cetuximab was ineffective (as in Appendix A Figure 1), pembrolizumab + anti-EGFR-TGFbRII resulted in a significant inhibition of tumor growth compared to vehicle control ($p < 0.002$) and pembrolizumab + cetuximab ($p < 0.002$). We confirmed that addition of anti-EGFR-TGFbRII to anti-PD1 counteracts the tumor TGFb signaling induced by treatment with anti-PD1 (measured by phospho-Smad2 western blot) (Appendix A Figure 3B).

10. Finally, we show that anti-EGFR-TGFbRII + pembrolizumab is more effective than pembrolizumab alone or anti-EGFR-TGFbRII alone (Appendix A Figure 4). NSG mice were humanized with 1×10^5 CD34+ hematopoietic stem cells (HSCs). Mice were injected with MDA-MB-231 TNBC cells (1.5×10^6 cells in 50% PBS/50% matrigel; mammary fat pad implantation). At 7 days following tumor cell inoculation, mice were randomized and treated with MEK inhibitor (0.4 mg/kg) and the following (either alone or in combination, as indicated, 5 mg/kg/week, i.p.): (i) pembrolizumab (anti-PD1); (ii) anti-EGFR-TGFbRII; or (iii) pembrolizumab + anti-EGFR-TGFbRII (anti-PD1 + anti-EGFR-TGFbRII). Tumor size was evaluated weekly and tumor volume calculated [length $\times$ width $\times$ height]. Addition of anti-EGFR-TGFbRII to pembrolizumab resulted in significant inhibition of tumor growth compared to pembrolizumab or anti-EGFR-TGFbRII alone ($p < 0.02$).

11. The results described above in Appendix A Figure 3A and Figure 4 are surprising since one would not have expected anti-EGFR-TGFbRII + pembrolizumab to exhibit striking antitumor efficacy in a setting where neither anti-EGFR (cetuximab) nor anti-TGFb (IgG-TGFbRII) alone enhance the antitumor response to PD1 inhibition. Therefore, the unexpected efficacy of anti-EGFR-TGFbRII with pembrolizumab in controlling tumor growth renders the instant invention non-obvious.

12. Despite the existence of anti-EGFR-TGFbRII and pembrolizumab at the time of the instant invention, in my opinion, it would not be obvious to one of skill in the art to combine these two specific agents. In particular, there was no motivation for one to select anti-EGFR-TGFbRII as the combination agent for pembrolizumab in a setting where anti-EGFR does not add value to pembrolizumab. The cited UChicago art itself writes extensively about anti-EGFR and pembrolizumab, while making no suggestion of combining the two. The only setting where anti-EGFR showed value when added to pembrolizumab is in the combination of anti-EGFR-TGFbRII and pembrolizumab: the subject of this invention. Similarly, IgG-TGFbRII only added value to pembrolizumab when fused to anti-EGFR antibody. Until our unexpected results and the

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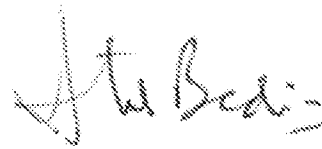
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instant invention, the surprising efficacy of this specific combination of pembrolizumab + anti-EGFR-TGFbRII was unforeseen in the art.

13. I declare that all statements made herein are of my own knowledge and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

4/17/2025

Date



Dr. Atul Bedi