

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FORTE BIOSCIENCES, INC.,
Petitioner,

v.

UNIVERSITY OF MASSACHUSETTS,
Patent Owner.

Case No. PGR2023-00014
Patent No. 11,278,505

RESPONSE TO INTERROGATORY

Forte Biosciences, Inc. Exhibit - 1036
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I. INTRODUCTION

During a conference call on Friday, September 15, 2023, the Board considered and rejected Patent Owner's discovery request "related to Petitioner's public statements in a press release regarding the use of and reliance on animal models for development of its IL-15 receptor antibody (FB-102) for the treatment of vitiligo and other autoimmune diseases." Paper 17, 2-4. The Board authorized Patent Owner to promulgate an interrogatory limited specifically to: "identify and describe the particular models referred to in the press release." Paper 17, 3-4. The Board required Petitioner to respond to the authorized interrogatory no later than 6:00 p.m. Eastern time on Wednesday, September 20, 2023. *Id.* As of 5:59 p.m. Eastern time on Wednesday, September 20, 2023, Patent Owner has not promulgated the authorized interrogatory to Petitioner. Out of an abundance of caution, this response is timely served. However, Patent Owner's failure to comply with the Board's order renders their discovery request moot. Accordingly, Petitioner objects to any use of this interrogatory response by Patent Owner for any purpose.

II. RESPONSE TO INTERROGATORY

None of Petitioner's objections or responses is an admission as to the relevance or admissibility of any information, or to the truth or accuracy of any statement or characterization contained in any interrogatory. Petitioner objects to

Patent Owner's Interrogatory and any definitions or instructions purporting to depart from the limited scope authorized by the Board. Petitioner objects to any interrogatory, definition, or instruction to the extent it seeks information that is not in Petitioner's possession, custody, or control. Petitioner objects to any interrogatory, definition, or instruction to the extent it seeks information that is not directly related to factual assertions advanced by Petitioner in this proceeding and to the extent Patent Owner has not shown good cause supports Patent Owner's request. Petitioner objects to any interrogatory, definition, or instruction to the extent it purports to seek information that is unduly broad, unduly burdensome, cumulative, cannot be found through a reasonable search, or is already available to Patent Owner by other means. Petitioner objects to any interrogatory, definition, or instruction to the extent it is vague, ambiguous, indefinite, cumulative, unintelligible, or otherwise unclear as to the information sought.

Petitioner objects to any interrogatory, definition, or instruction to the extent it seeks information that is protected from production by the attorney-client privilege, work-product immunity, or any other applicable statutory or common law privilege, prohibition, limitation, or immunity from disclosure. Petitioner will not disclose such privileged information. Any inadvertent disclosure thereof shall not be deemed a waiver of any privilege, immunity, prohibition, or limitation with respect to such information. Nothing contained in these responses is intended as a

waiver of the attorney-client privilege, the work product doctrine, or any other applicable privilege, immunity, prohibition, or limitation. Petitioner reserves the right to assert objections on the basis of such privileges, immunities, prohibitions, and limitations to the greatest extent permitted by law.

Petitioner objects to any interrogatory, definition, or instruction to the extent it seeks confidential or proprietary information of a non-party, or information that is covered by a confidentiality agreement or subject to a confidentiality obligation between Petitioner and a non-party, or is protected from discovery by any right to privacy or any other applicable privilege.

Subject to Petitioner's objections, Petitioner responds as follows:

On August 1, 2023, Forte Biosciences, Inc. issued a press release announcing that "FB-102 had demonstrated potentially best in class activity including in graft versus host disease (GvHD), an indication for which there is a very high unmet medical need and potentially abbreviated clinical development pathway." The press release continued to state: "We plan to advance FB-102 into the clinic in 2024." The models Forte referenced in the press release that Forte used and relied upon for the development of FB-102 for treatment of autoimmune disease (specifically GvHD) consist of post-critical date, head-to-head studies of FB-102 and FDA-approved ruxolitinib in acute and chronic GvHD mice as validated by post-critical date ruxolitinib clinical studies in GvHD in humans.

GvHD is a serious complication of allogeneic stem cell transplantation. It is caused when donor immune cells attack host tissues. On information and belief, acute GvHD has a 70% mortality rate in 2 years in grade 3 and 4 disease. Forte's press release states that ruxolitinib is "the only FDA-approved treatment for acute GvHD." On information and belief, FDA approved ruxolitinib in 2019 for acute GvHD based on the results of an open-label, single-arm study showing a modest 57% response rate and only a 30% complete response rate. On information and belief, ruxolitinib shows moderate activity against acute GvHD but potentially significant toxicity.

Forte's August 1, 2023 press release describes results of "a validated preclinical model of aggressive acute GvHD using transplanted human donor PBMCs." Specifically, the press release states that "FB-102 reported 90% survival versus 0% survival on vehicle control and compared to 60% survival on ruxolitinib." The press release further states that FB-102 "[i]n combination with ruxolitinib" reported 90% survival compared to 0% survival in vehicle control and 30% survival for ruxolitinib alone with extended duration of dosing compared to the single agent study.

FB-102 demonstrated significant preclinical activity in validated GvHD studies using a humanized mouse model of acute GvHD. The mice were irradiated and human peripheral blood mononuclear cells were transplanted into the mice.

The human donor immune cells then attacked the host tissues. Once daily i.p. injection of FB-102 at one of three doses (75, 125 or 175 mpk) or control vehicle, or twice-daily oral administration of ruxolitinib (60 mpk) or control vehicle was administered to cohorts of N=10 beginning at day 5 through day 14. The survival rate of mice receiving control was 0% at 14 days. The survival rate for ruxolitinib after 14 days was 60%. The survival rate for FB-102 ranged from 80-90% depending on the dosage used. When 60 mpk ruxolitinib (2x-daily oral) was administered in combination with 75 mpk FB-102 (1x-daily i.p. injection), ruxolitinib had only a 30% survival rate at 18 days whereas the FB-102 combination had a 90% survival rate at 18 days ($p=0.02$).

Forte asserts that the magnitude of FB-102's preclinical efficacy in the humanized acute GvHD mouse provides promising results that correlate based on a post-critical date publication with desired patient response. When the maker of ruxolitinib obtained preclinical data for ruxolitinib by measuring survival in a humanized GvHD mouse model, on information and belief, they reported 90% survival (vs. 0% for control). When they reported their clinical data, on information and belief, they observed a 62% overall response rate at day 28. In contrast, on information and belief, another inhibitor reported 20% (vs. 0% for control) survival in the humanized GvHD model and reported the results were not significant as compared to placebo. Accordingly, based on clinical data translating

humanized acute GvHD mouse findings into patient response post-critical date, Forte believes that FB-102 provides promising results for treating acute GvHD.

Forte's August 1, 2023 press release further states that, "in a mouse model of chronic GvHD conducted by Forte, anti-CD-122 treatment has shown superior activity compared to placebo or ruxolitinib." In this study, allogeneic stem cell transplantation is performed from a mouse with an intact immune system into a mouse whose immune system has been significantly eliminated via irradiation. Treatment is begun 30 days after transplantation and followed for 30 days to observe a statistically significant separation in GvHD score as compared to ruxolitinib treatment or placebo.

Forte's August 1, 2023 press release refers to a body of preclinical work, including its own developmental work discussed above and post-critical date publications discussing proof of concept mechanistic studies. For example, the press release states that "published preclinical PoC data also support the therapeutic potential of anti-CD122 in multiple autoimmune diseases anti-CD122 including in vitiligo, celiac disease, alopecia areata, Type 1 diabetes, and solid organ transplant."

For example, in 2009, Seiji Yokoyama et al. published "Antibody-mediated blockade of IL-15 reverses the autoimmune intestinal damage in transgenic mice

that overexpress IL-15 in enterocytes” in Volume 106 of the Proceedings of the National Academy of Sciences. Yokoyama et al. explained in the Abstract:

Transgenic mice that express human IL-15 specifically in enterocytes (T3^b-hIL-15 Tg mice) develop villous atrophy and severe duodeno-jejunal inflammation with massive accumulation of NK-like CD8⁺ lymphocytes in the affected mucosa. We used these mice to demonstrate that blockade of IL-15 signaling with an antibody (TM-β1) that binds to murine IL-2/IL-15Rbeta (CD122) leads to a reversal of the autoimmune intestinal damage. The present study, along with work of others, provides the rationale to explore IL-15 blockade as a test of the hypothesis that uncontrolled expression of IL-15 is critical in the pathogenesis and maintenance of refractory CD [celiac disease].

As another example, Luzhou Xing et al., published “Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition” (EX1007) in Nature Medicine on August 17, 2014. Xing describes experiments performed in a mouse strain that spontaneously develops alopecia areata. EX1007, 1. Alopecic lesions in the skin of mice are characterized by the accumulation of autoreactive CD8⁺ T cells. EX1007, 1. Xing explains that these CD8⁺ T cells are necessary and sufficient to induce disease. EX1007, Abstract (“[W]e show that cytotoxic CD8⁺NKG2D⁺ T cells are both necessary and sufficient for the induction of AA in mouse models of disease.”), 2, Figure 1. Xing discloses that a specific CD122

antibody (named TM-β1) “blocked the accumulation of CD8+NKG2D+ T cells in the skin” and prevented AA lesions. EX1007, 3-4, Figure 2.

Dr. Abbas explained during his deposition that it was entirely predictable before 2017 that the TM-β1 CD122 antibody would durably reverse vitiligo lesions induced in the Harris mouse model (EX1006) because the Harris lesions were known to be caused by CD8+ T cells placed in the skin, whereas Xing had demonstrated that TM-β1 eliminates CD8+ T cells in the skin. For example, Dr. Abbas explained that in the Harris mouse model, unlike in natural or spontaneous vitiligo, the mice have been irradiated so that the only immune cells in the mouse are the CD8+ T cells: “So if you get rid of them, you’ll cure the disease. To me, this is a—this is a completely predictable result.” Abbas Deposition Tr., Pg. 92:25-93:14; *see also id.*, 90:22-25 (in Harris model mice “the endogenous immune cells have been significantly eliminated”), 98:2-99:17 (the activated CD8+ T cells transplanted into the Harris mouse model “have to be the cause of the disease” in that model because the endogenous immune system has been eliminated), 100:23-101:5 (similar), 101:25-102:16 (similar), 102:17-103:23 (durable reversal of lesions expected in Harris mouse model using TM-β1 to eliminate CD8+ T cells from the skin because the transplanted CD8+ T cells in the skin are the only possible cause of the lesions in the Harris mouse model). Richmond et al., reported in 2018 that the Fc-diminished chimeric rat/mouse CD122 antibody ChMBC7

depleted CD8⁺ PMEL in the dermis of the Harris transgenic mice and, by substantially eliminating the only remaining immune cells in the mice, reversed the vitiligo lesions induced by the transplanted CD8⁺ PMELs. 10 Sci. Transl. Med. 1-20.

Dr. Abbas explained during his deposition that the ability of the TM- β 1 anti-CD122 antibody to eliminate CD8⁺ T cells (whether NKG2D⁺, CD49a⁺, PMEL or not) in the skin of mice would have been reasonably expected by a person of ordinary skill in the art before the critical date, but that the Harris model in EX1006 and in the challenged patent is not representative of natural or spontaneous vitiligo because the Harris model causes depigmentation lesions exclusively by activating CD8⁺ T cells to target melanocytes. Abbas Deposition Tr., Pg. 85:21-91:8, 92:3-94:14. Dr. Abbas testified that his own lab “used mouse models like this for decades...very similar to what is being done here” in the challenged patent, that these models are valuable “for asking fundamental mechanistic questions: How does a T cell respond to an antigen? How does it respond to an antigen in a tissue in circulation? But we never claimed...that these models were representative of human disease. They’re representative of a transgenic mouse.” Abbas Deposition Tr., Pg. 91:9-92:1.

When Patent Owner’s counsel inquired of Dr. Abbas during deposition, Dr. Abbas testified that the Harris mouse model described in EX1006 and in the

challenged patent does not recapitulate the human condition of vitiligo because it “does not recapitulate how it [depigmentation] is achieved” in human vitiligo (where “very few T cells can recognize the melanocyte antigen and they never see a virus expressing that antigen”), because the Harris model is “completely different from what you would expect to see in the human,” and because the Harris model merely recapitulates the end result, the “loss of pigmentation,” by “taking a single population of T cells, all of which or almost all of which express the receptor for the melanocyte antigen, parking those T cells in a mouse, and then hitting them with a melanocyte antigen in the form of a virus.” Abbas Deposition Tr., Pg. 33:9-36:9. When Patent Owner’s counsel asked Dr. Abbas whether it is “improper” to “try to extrapolate from a mouse model to human,” Dr. Abbas corrected him: “It’s improper to extrapolate from this [Harris] mouse model to the human situation—to the human disease.” Abbas Deposition Tr., Pg. 38:2-8.

Dr. Abbas also testified during his deposition that the ChMBC7 antibody used in the Harris model in the challenged patent is not representative of IL-15 inhibition, IL-15R inhibition, small molecule inhibition of IL-15 signaling, peptide inhibition of IL-15 signaling, RNA inhibition of IL-15 signaling, the genus of IL-15 or IL-15R antibodies, IL-15R α inhibition, IL-15R β inhibition, or IL-15R γ inhibition. Abbas Deposition Tr., Pg. 93:16-97:25. Dr. Abbas explained during his deposition why success in using different antibodies to treat GvHD or rheumatoid

arthritis does not validate Patent Owner's counsel's hypothesis that the patent's use of ChMBC7 in the Harris mouse model would be expected to successfully treat spontaneous or natural vitiligo in humans. Abbas Deposition Tr., Pg. 99:19-101:23.

After the critical date of the '505 patent, additional publications employed animal models to perform preclinical proof of concept mechanistic investigations. For example, non-obese diabetic (NOD) mice have been used as an animal model for type 1 diabetes. On information and belief, diabetes develops in NOD mice as a result of insulinitis, a leukocytic infiltrate of the pancreatic islets. On information and belief the incidence of spontaneous diabetes in the NOD mouse is 60-80% in females and 20-30% in males. On information and belief, diabetes in these mice can be prevented by a single injection of mycobacterial adjuvants. On information and belief, NOD mice were developed at Shionogi Research Laboratories in Aburahi, Japan by an outbreeding of a cataract-prone strain from Jcl:ICR mice and were first reported in 1980.

Regarding solid organ transplant, on information and belief, researchers after the critical date transplanted dermal or renal tissue into mice or nonhuman primates. C57BL/6 mice, BALB/c mice, OT-I transgenic mice, and mOVA mice were used. Acute infection was induced by inoculating mice with 2×10^5 PFU LCMV acute Armstrong strain (i.p. injection). OVA-specific memory T cells were generated by resuspending splenocytes from Thy1.1+ OT-1 mice in PBS and

1.0x10⁴ Thy1.1+ and injecting OT-I T cells i.v. 24-48 hours prior to inoculation with 10⁴ CFU Lm.OVA by i.p. injection. Peripheral frequencies of Thy1.1 OT-I T cells were assessed and mice were given recall challenge with OVA-expressing skin graft from mOVA donors. For skin transplantation model, full-thickness tail or ear skin was transplanted onto the dorsal thorax of recipient mice and secured with adhesive bandages. For acute graft versus host disease model, C57BL/6 splenocytes were labeled with Cell Trace Violet and transferred i.v. into sublethally irradiated (800 rads) BALB/c recipients. For kidney transplantation, outbred rhesus monkeys (*Macaca mulatta*) ranging between 3 and 5 years old were obtained, donor-recipient pairs were chosen to maximize genetic disparity at both MHC class I and class II alleles based on 454 deep-sequencing analysis, animals were heparinized (100 U/kg) during organ procurement and implantation, left native nephrectomy was performed at least 3 weeks prior to transplantation, and a completion right native nephrectomy was performed at the time of transplantation. Rhesus macaques underwent bilateral nephrectomy and life-sustaining renal allograft transplantation. All donor-recipient pairs were MHC defined and maximally mismatched.

Respectfully submitted,

Dated: September 20, 2023

/Michael T. Rosato /
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CERTIFICATE OF SERVICE

This is to certify that I caused the foregoing document to be served on this
20th day of September, 2023, on the Patent Owner, as follows:

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Dated: September 20, 2023

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