UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case No. IPR2023-00462
Patent No. 10,464,992

PETITIONER'S PRE-INSTITUTION REPLY TO PATENT OWNER'S PRELIMINARY RESPONSE[1]

[1] Authorized by the Board via e-mail on May 4, 2023.

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I. INTRODUCTION

Patent Owner ("PO") asks the Board to ignore PO's own voluminous prior art disclosing the claimed formulation of aflibercept on the ground that the term "VEGFTrap$_{R1R2}$," PO's prior-art name for aflibercept, does not refer to aflibercept alone but instead to an ill-defined "genus" of proteins. PO groups "VEGFTrap$_{R1R2}$" with two more general terms, "VEGF Trap" and "R1R2," and then dismisses all three as "generally refer[ring] to *multiple, different* fusion proteins." POPR, 1. This grouping is a factually incorrect shell game. Regardless of how PO used the terms "VEGF Trap" and "R1R2" in the prior art, it consistently used the term "VEGFTrap$_{R1R2}$" to refer to a specific protein, with specific physical properties. PO's *'309 Publication* made crystal clear that this specific protein is VEGFR1R2-FcΔC1(a), which PO later gave the name "aflibercept." PO's later representations to the Office confirm that "VEGFTrap$_{R1R2}$," "VEGFR1R2-FcΔC1(a)," and "aflibercept" all refer to the same protein.

II. ANALYSIS

A. The "VEGFTrap$_{R1R2}$" of *Fraser*, *Wulff*, and *Holash* is a Specific Protein, Not a Genus of Proteins

Fraser (EX1009) describes a clinical study in which PO's scientists administered "VEGFTrap$_{R1R2}$" to macaques. Pet., 23. *Fraser* makes clear that "VEGFTrap$_{R1R2}$" denotes a specific protein molecule, describing it as "*a* recombinant, chimeric *protein*" that is "*a successor molecule*" to PO's earlier

VEGFTrap$_{A40}$. EX1009, 1114-15 (emphasis added). *Fraser* repeatedly refers to this protein in the singular as "*the* VEGF Trap$_{R1R2}$" and notes its specific physical properties, such as its "affinity constant of ~1 pM." *Id*., 1115 (emphasis added). Further, the objective of *Fraser's* study was to report the pharmacokinetics and pharmacodynamics of a specific protein. *Fraser's* report would have been ambiguous had the authors (including PO's scientists) identified the study protein by a name that described a "genus" of proteins rather than a specific one.

Wulff (EX1016), also a clinical study, is also clear that "[t]he VEGF Trap$_{R1R2}$ used in [its] experiments" is a single protein with a specific structure. EX1016, 2798. *Wulff* explains that "VEGFTrap$_{R1R2}$" was a "new compound," "*a* recombinant chimeric protein" that "was expressed" in CHO cells and was "*a* novel antagonist." *Id.*, 2797-98, 2804 (emphasis added). *Wulff* also reported that the "detailed molecular structure" of this protein "and how *it* was created" had been described in the *'319 Publication* (EX1029). EX1016, 2798, n.1 (emphasis added); Pet., 28.

Holash also used "VEGFTrap$_{R1R2}$" to refer to a single protein. *Holash* describes the creation of VEGFTrap$_{R1R2}$ and other VEGF Trap "variants" from a "parental VEGF Trap," and notes various physical properties of this specific protein, including that it "*has* a binding affinity of about 1 pM" and a favorable "pI of 8.82." EX1010, 11395 (emphasis added).

While PO asserts that "VEGFTrap$_{R1R2}$" was used as a general term to refer to more than one protein, it does not cite a single prior- or post-art reference in which that term is used to refer to more than one protein. While PO may have used the terms "VEGF Trap" and "R1R2" when referring to more than one protein, those terms are not the same as "VEGFTrap$_{R1R2}$."

B. PO's Own Prior Art Made Clear That "VEGFTrap$_{R1R2}$" is VEGFR1R2-FcΔC1(a), a.k.a., Aflibercept

The identity of the specific protein named "VEGFTrap$_{R1R2}$" in *Fraser*, *Wulff* and *Holash* is equally clear from PO's prior art. In the *'309 Publication* (EX1027), which expressly incorporates the *'319 Publication* by reference in its entirety, PO explained that VEGFR1R2-FcΔC1(a) "is also termed VEGFTrap$_{R1R2}$" and disclosed its sequence, which is the same as that of aflibercept. Pet., 15, 44.

While PO's explanation was concise and clear, PO now seeks to muddy it by suggesting that a POSA would have understood it to mean that VEGFR1R2-FcΔC1(a) is merely one protein in the class of proteins referred to as "VEGFTrap$_{R1R2}$." POPR, 35. Nothing in PO's simple statement supports this strained reading. While PO latches on to the fact that the *'319 Publication* refers to both VEGFR1R2-FcΔC1(a) and Flt1.D2.Flk1D3.FcΔC1(a) as "R1R2" proteins, since they both contain R1 and R2 domains from the VEGF receptor (POPR, 14, 20), "R1R2" is not the same term as "VEGFTrap$_{R1R2}$."

Amgen v. Alexion, IPR2019-00741, Paper 15, cited by PO, presented different facts. There, the claim was directed to eculizumab with a hybrid IgG2/G4 structure. *Hillmen* was alleged to anticipate because it disclosed the use of "eculizumab" in a clinical study. But the claimed IgG2/G4 sequence had not been yet published, and the term "eculizumab" had been used to refer to two different isotypes, an earlier one with an IgG4 structure and a later one with the hybrid G2/G4 structure. *Id*., 22. Thus, at the institution stage, the Board found that the petitioner had not shown a reasonable likelihood of anticipation based on *Hillmen*'s disclosure of the term "eculizumab" alone. *Id.*, 23. Here there was no such dual usage and PO had in fact published the sequence of VEGFTrap$_{R1R2}$.

C. PO Represented to the Office that "VEGFTrap$_{R1R2}$" and "VEGFR1R2-FcΔC1(a)" Both Refer to Aflibercept

PO's "genus" argument also lacks candor. As explained in the Petition, when PO sought a PTE for its '758 patent based on the approval of EYLEA®, PO represented to the Office that aflibercept is "also known as … VEGF Trap$_{R1R2}$" and that "aflibercept is described in [*Holash*] as VEGF Trap$_{R1R2}$." Pet., 14 n.1. Having obtained the benefit of a PTE via this representation, PO's argument here that VEGFTrap$_{R1R2}$ is not aflibercept should be rejected out of hand.

Indeed, PO's shell game here is surprising given that the Board has previously rejected a similar attempt by PO to walk away its representation to the Office. In IPR2021-00880 and -00881, PO argued that the term "VEGF Trap-Eye,"

another term that it used before the PTO to refer to aflibercept, encompassed a genus of proteins. IPR2021-00880, Paper 89 ('880 FWD), 45-46; IPR2021-00881, Paper 94, 31-32. The Board rejected PO's argument, relying on PO's "repeated statements to the Patent Office during prosecution that the sequence of … 'aflibercept, also known as … VEGF Trap-Eye and VEGF-Trap$_{R1R2}$' is set forth in Patent Owner's prior art '758 and '959 patents." *See e.g.,* '880 FWD, 52-53; *see also* EX1020, 2. The Board should reject PO's similar attempt here.

D. Dr. Klibanov's Opinion Should Be Given No Weight

At this institution stage, the Board should give no weight to Dr. Klibanov's opinion that a POSA would understand "VEGFTrap$_{R1R2}$" to refer to a genus of proteins. Petitioner has not yet had an opportunity to cross examine Dr. Klibanov and his views are contradicted by the record evidence. For example, Dr. Klibanov opines that *Holash* refers to a genus of proteins known as "VEGF Traps", (EX2001 ¶32) despite PO's reliance on *Holash*'s disclosure of VEGFTrap$_{R1R2}$ as a disclosure of aflibercept (EX1020, 5) and *Holash's* usage of "VEGFTrap$_{R1R2}$" to refer to a specific protein. While Dr. Klibanov relies on *Daly*, that reference refers only to the term "R1R2" and never to VEGFTrap$_{R1R2}$. EX2001 ¶¶51-52 (citing EX2013). It is immaterial whether "R1R2" or "VEGF Traps" are terms that were used to describe more than one protein. As explained, PO consistently used "VEGFTrap$_{R1R2}$"—a different term—to refer to a *single* protein, aflibercept.

Respectfully submitted,

Date: May 10, 2023

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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Petitioner's Pre-Institution Reply was served on May 10, 2023, on the Patent Owner at the following electronic correspondence addresses:

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