UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MILTENYI BIOMEDICINE GmbH and MILTENYI BIOTEC INC.,
Petitioner

v.

THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,
Patent Owner

IPR Trial No. IPR2022-00853
U.S. Patent No. 9,464,140
Issue Date: October 11, 2016

Title: Compositions and Methods for Treatment of Cancer

PATENT OWNER'S SURREPLY TO REQUEST FOR REHEARING

(authorized by Order of November 23, 2022, Ex. 3004)

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Miltenyi's Reply confirms that it is not the non-institution decision that is an outlier, but Miltenyi's own Petition, which seeks to relitigate questions the Board neither misapprehended nor overlooked and barely even pays lip service to the high standard for rehearing. The Board's decision was correct and firmly grounded in Miltenyi's failure to demonstrate a reasonable expectation of success and in its reliance on art that the Examiner considered in great detail.

I. Miltenyi Cannot Erase Decades of Failures.

Miltenyi's argument is premised on a suggestion that the Federal Circuit tacitly created a per se rule in *Genzyme* that reasonable expectation of success is satisfied where there is some "successful in-vitro data and a proposed clinical trial." Reply 3. But there is no such rule. As the cases demonstrate, whether there is a reasonable expectation of success depends on the particular facts of the case.

Miltenyi cannot point to any principle the Board overlooked warranting correction on rehearing. Miltenyi made the same argument in its Petition, and the Board correctly rejected it, noting that "the inherent unpredictability of the field and the history of failures of similar technology" meant that Miltenyi had not established a reasonable expectation of success here. Paper 11 at 41.

The Board aptly focused on the unpredictability and history of failures in the field, because the cases repeatedly instruct that those factors critically undermine a reasonable expectation of success. *Boehringer*, 320 F.3d at 1354; *Strathclyde*, 17

F.4th at 164; *Novartis v. West-Ward.*, 923 F.3d 1051, 1060-61, 1053-54 (Fed. Cir. 2019) (noting 70% failure rate for cancer drugs in phase II); *Lilly*, 8 F.4th at 1358; *OSI*, 939 F.3d at 1383. Miltenyi has no answer for that or for the facts here. Miltenyi is silent on Patent Owner's mountain of evidence showing decades of failures, including a more than 84% clinical trial failure rate, and routine expressions of hopelessness in the field. POPR 4-7, 23-28; Paper 11 at 41.

Genzyme does not compel a contrary result. The *Genzyme* invention was a modified enzyme used in enzyme replacement therapy. 825 F.3d at 1363-64. While the *natural* enzyme was not successful because it accumulated in the liver instead of the muscle tissue where it was needed, the art taught that the claimed *modified* enzyme would solve this problem because it "was effectively taken up by muscle cells." *Id.* at 1373. On that record, where there was neither unpredictability nor a reason to expect failure of the modified enzyme, the Board found (and the Federal Circuit affirmed) a reasonable expectation of success. *Id.*

That stands in stark contrast with the history of clinical failures of CAR-T trials here. As in *OSI*, the invention here involves the "highly unpredictable" field of cancer treatment, where *in vitro* data suggesting anti-cancer activity frequently fails to work clinically. Paper 11 at 40 (quoting *OSI*, 939 F.3d at 1377). The Board appreciated that the *in vitro* data here are arguably stronger than those in *OSI*, where data showed enzyme inhibition but not specifically the ability to kill

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