Appeal No. 2018-2362

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

GENZYME CORPORATION, and SANOFI-AVENTIS U.S. LLC,

Plaintiffs-Appellees,

v.

ZYDUS PHARMACEUTICALS (USA) INC.,

Defendant-Appellant.

Appeal from the United States District Court for the District of Delaware
Civil Action No. 1:16-cv-00540-KAJ
Circuit Judge Kent A. Jordan Sitting by Designation

APPELLEES' RESPONSE TO APPELLANT'S COMBINED PETITION FOR REHEARING *EN BANC* AND PANEL REHEARING

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October 31, 2019

CERTIFICATE OF INTEREST

Counsel for Appellees, Genzyme Corporation and sanofi-aventis U.S. LLC, certifies the following:

1. The full names of every party represented by me are:

Genzyme Corporation

sanofi-aventis U.S. LLC

2. The names of the real parties in interest (if the party named in the caption is not the real party in interest) represented by me are:

N/A

3. The parent corporations and publicly held companies that own 10% or more of stock in the parties represented by me are:

Sanofi

4. The names of all law firms and the partners or associates that appeared for the party now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

RatnerPrestia
Karen Riesenburger Poppel

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal are:

Genzyme Corporation, et al. v. Gland Pharma Limited,
1:18-cv-01071-KAJ, U.S. District Court for the District of Delaware

Respectfully submitted,

Dated: October 31, 2019 By: /s/James L. Lovsin

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CITATION FORMS AND ABBREVIATIONS

Explanation of Transcript Citation Form

When transcripts are cited, the Appendix (Appx) page is cited, followed by a parenthetical indicating the witness that provided the testimony unless apparent from the context. The witness testimony referred to herein includes testimony from:

Dr. Mohamad Mohty, Genzyme's expert.

Dr. Michael Andreeff, Zydus's expert.

Abbreviations

'102 Patent	U.S. Patent No. 6,987,102. Appx138-154.
'590 Patent	U.S. Patent No. 7,897,590. Appx155-173.
Aiuti '97	Aiuti et al., *The Chemokine SDF-1 Is a Chemoattractant for Human CD34+ Hematopoietic Progenitor Cells and Provides a New Mechanism to Explain the Mobilization of CD34+ Progenitors to Peripheral Blood*, 185(1) J. EXP. MED. 111 (January 1997). Appx3210-3219.
Asserted Claims	Claim 8 of the '102 Patent and Claims 8 and 19 of the '590 Patent. Appx15 (¶11).
FDA	U.S. Food and Drug Administration
G-CSF	Granulocyte colony stimulating factor
Genzyme	Collectively, Plaintiffs-Appellees Genzyme Corporation and sanofi-aventis U.S. LLC
Genzyme Corp.	Plaintiff-Appellee Genzyme Corporation
GM-CSF	Granulocyte-macrophage colony stimulating factor
Konopleva	Konopleva *et al.*, *G-CSF Induces CXCR4 Expression on CD34+38- Peripheral Blood Progenitor Cells In Vivo*, 94(10) BLOOD 322b, Abstract 4663 (November 1999).

	Appx3475-3478.
Lapidot	Lapidot *et al.*, *A Single Dose of Human G-CSF Inhibited Production of SDF-1 in the Bone Marrow and Upregulated CXCR4 Expression on Immature and Mature Hematopoietic Cells Prior to Mobilization*, 94(10) BLOOD 606a, Abstract 2695 (November 1999). Appx3479-3482.
Peled	Peled *et al.*, *Dependence of Human Stem Cell Engraftment and Repopulation of NOD/SCID Mice on CXCR4*, 283 SCIENCE 845 (February 1999). Appx3492-3496.
Petit	Petit *et al.*, *G-CSF Induces Stem Cell Mobilization by Decreasing Bone Marrow SDF-1 and Up-Regulating CXCR4*, 3(7) NAT. IMMUNOL 687 (July 2002). Appx4021-4029.
Plerixafor	The active ingredient in MOZOBIL® 1,1'-[1,4-phenylene-bis-(methylene)]-bis-1,4,8,11-tetraazacyclotetradecane; a.k.a. AMD3100. Appx9-10 (¶2).
POSA	Person of Ordinary Skill in the Art
Sanofi	Plaintiff-Appellee sanofi-aventis U.S. LLC
SCF	Stem cell factor
SDF-1	Stromal cell-derived factor 1
Whetton	Whetton *et al.*, *Homing and Mobilization in the Stem Cell Niche*, 9 TRENDS IN CELL BIOLOGY 233 (June 1999). Appx3537-3542.
Zydus	Defendant-Appellant Zydus Pharmaceuticals (USA) Inc.

I. INTRODUCTION

Two panels of this Court and two district courts each conducting independent bench trials have reached the same result: Claim 19 of the '590 Patent is not invalid. Appx4; Judgment, D.I. 62; *Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, 13-cv-1506-GMS, 2016 WL 2757689, at *1 (D. Del. May 11, 2016) ("*Genzyme I*"); *Genzyme Corp. v. Dr. Reddy's Labs., Ltd.*, 716 F. App'x 1006, 1007 (Fed. Cir. 2017) ("*Genzyme II*"). The district court and this Court also found Claim 8 of both the '590 and '102 Patents not invalid. Appx4; Judgment, D.I. 62.

Zydus's petition should be denied. There is nothing about this appeal that requires rehearing, and certainly no issue of "exceptional importance." Fed. Cir. R. 35. Zydus asserts that the district court made *eleven* errors, but tellingly certifies only one issue under Rule 35. *Compare* Pet. 6-10, *with id.* at 1. That issue, however, improperly focuses on only one paragraph of the district court's 119-page Findings of Fact and Conclusions of Law, Appx104-106 (¶41), and ignores the district court's numerous factual findings supporting its finding of no reasonable expectation of success and numerous objective indicia.

Zydus's main argument focuses on the district court's consideration of engraftment in its reasonable expectation of success analysis. Yet Zydus ignores that the district court made independent factual findings of no reasonable expectation of success that never refer to engraftment. Therefore, while the

engraftability issue provided additional evidence supporting the district court's finding of no reasonable expectation of success, it was not essential. And in any event, it was entirely proper for the district court to consider engraftment in its reasonable expectation of success analysis under *Institut Pasteur & Universite Pierre et Marie Curie v. Focarino*, 738 F.3d 1337 (Fed. Cir. 2013). Appellees' Br. 31-34; Oral Arg. 15:17-16:50. Zydus's Petition never addresses *Institut Pasteur*.

Zydus's challenge to the district court's consideration of failure of others in its reasonable success analysis fails as well. The district court considered these failures as evidence of the uncertainty and complexity in the field. Further, the district court made multiple findings of no reasonable expectation of success without reference to these failures. As with engraftment, the failures of others were not essential to the district court's finding of no reasonable expectation of success.

The district court's detailed factual findings and conclusion of nonobviousness are well supported by the record. This Court typically does not grant rehearing to consider whether four federal judges misunderstood the facts. Here, moreover, seven federal judges have concluded that Claim 19 of the '590 Patent is not obvious. Zydus's Petition should be denied.[1]

[1] The panel's resolution of the appeal pursuant to Federal Circuit Rule 36 supports denial of Zydus's Petition. Practice Note to Fed. Cir. R. 35. Zydus, however,

II. BACKGROUND

The claimed invention is for a method of mobilizing and harvesting stem cells, which can be used in stem cell transplantation. Appx172; Appx10 (¶3). As the district court noted, stem cell transplantation requires mobilization, homing, and engraftment. Appx12 (¶6). During mobilization, stem cells move out of the bone marrow into the peripheral blood; whereas during homing, stem cells move from the peripheral blood back into the bone marrow where they engraft. Appx780 (Mohty); Appx346 (Andreeff); Appx11-12 (¶¶5-6).

Granulocyte colony stimulating factor ("G-CSF") was the "gold standard" stem cell mobilization agent at the time of invention. Appx37-38 (¶61); Appellees' Br. 4. However, G-CSF did not work for a significant number of patients, required multiple days of injections to cause mobilization, and often required patients to endure multiple days of apheresis in order to collect the necessary number of stem cells for a transplant. Appx37-38 (¶61), Appx39 (¶63 & n.17).

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misunderstands Rule 36 judgments in arguing that the panel erred. Pet. 2, 11 (heading), 16 (heading). *Rates Tech., Inc. v. Mediatrix Telecom, Inc*., 688 F.3d 742, 750 (Fed. Cir. 2012) ("Since there is no opinion, a Rule 36 judgment simply confirms that the trial court entered the correct judgment. It does not endorse or reject any specific part of the trial court's reasoning.").

As both experts agreed, G-CSF's shortcomings created a need for a regimen that could, with minimal toxicity, mobilize greater numbers of stem cells in fewer apheresis sessions than G-CSF. *Id.*, Appx108-109 (¶46).

Genzyme's product at issue, MOZOBIL®, contains plerixafor, a known CXCR4 blocker. The district court found that it was unexpected that plerixafor could mobilize stem cells at all because other CXCR4 blockers inhibit stem cell mobilization. Appx76 (¶112); Appx3494, Appx3496; Appx3484-3485, Appx3487; Appx4021, Appx4024-26 ("Anti-CXCR4 …prevent[s] G-CSF-induced mobilization."). The clinical use of plerixafor revealed other significant, unexpected benefits, including the ability to mobilize higher quality of stem cells than G-CSF alone, to mobilize stem cells more rapidly and predictably than G-CSF, and to mobilize stem cells in patients who had failed prior mobilization attempts. Appx112-113 (¶51) (*citing, inter alia,* Appx3873; Appx4353-4355; Appx4375; Appx4315-4316; Appx3864; Appx3923, Appx3925), Appx79-80 (¶118).

In 2008, the FDA approved MOZOBIL® to be used in combination with G-CSF, which finally fulfilled the unmet need for a regimen better than G-CSF alone that had existed since at least 1994. Appx24 (¶24), Appx77 (¶113), Appx78-79 (¶116), Appx108-109 (¶46). As noted by the district court, MOZOBIL® "was the first and only CXCR4 blocker approved by the FDA for such purposes, and the

FDA has not approved any other stem cell mobilizing agents to join it and G-CSF." Appx77 (¶113). As a result, plerixafor has become part of the standard of care for stem cell mobilization and has been praised by experts. Appx78-79 (¶116); Appx858 (Mohty); Appx4030; Appx4421; Appx4394; Appx861-863 (Mohty); *see also* Appx4287 ("major advance").

III. REASONS FOR DENYING THE PETITION

A. The District Court's Factual Findings Regarding No Reasonable Expectation of Success Support Nonobviousness

The district court's factual finding of no reasonable expectation of success is supported by numerous underlying factual findings, most of which do not relate to engraftment or failure of others. Appx62-63 (¶93), Appx76-77 (¶112), Appx104-106 (¶41), Appx106-107 (¶43). The district court found, for example, that uncertainty and complexity in the art and the fact that known stem cell mobilizers had the opposite effect on CXCR4 from plerixafor supported the lack of a reasonable expectation of success. Appx62-63 (¶93); Appx76-77 (¶112); Appx104-106 (¶41); Appx106-107 (¶43). These district court findings involve fact-bound, case-specific application of settled law, and Zydus's Petition does little to dispute them. Pet. 7-8, 16-19. None is mentioned in Zydus's Rule 35 statement. Pet. 1. They do not warrant rehearing.

1. Uncertainty and Complexity in the Art

As the district court found, "everyone … viewed the mechanisms of stem cell mobilization to be uncertain and complex." Appx104 (¶41); *see also* Appx106-107 (¶43), Appx62-63 (¶93), Appx76-77 (¶112). Zydus's expert admitted that the complexity of the systems and mechanisms involved in stem cell mobilization is "enormous." Appx376-378 (Andreeff). The district court found that it would have been "difficult to predict with any degree of certainty how blocking CXCR4 expression would impact other interactions that may have been necessary for mobilizing stem cells" and "particularly difficult to predict how manipulation of one variable[,]" such as CXCR4, "would affect the overall mobilization process…." Appx104 (¶41); *see also* Appx106-107 (¶43), Appx62-63 (¶93), Appx76-77 (¶112). The district court also found that the POSA was faced with an uncertain and unpredictable area and had a large number of possible research pathways to consider, only one of which had any connection to CXCR4. Appx104-106 (¶41), Appx49-50 (¶78). Uncertainty surrounding stem cell mobilization continued well after 2000. *See, e.g.,* Appx4021 (in Petit 2002: mobilization mechanism is "poorly understood" and "unclear"). Even as of the time of trial in 2018, both experts agreed that much about stem cell mobilization was uncertain and unknown. Appx376-377 (Andreeff); Appx748-749 (Mohty).

Zydus argues that "[a]t least six prior art references indicated that CXCR4 and SDF-1 played a role in stem cells' movement between the bone marrow and blood stream." Pet. 5 (citing Appellant's Op. Br. 14-23). However, none of those prior art references would have provided a POSA with a reasonable expectation of success. Indeed, several of these references emphasized the uncertainty surrounding the mechanisms of stem cell mobilization.

Aiuti '97 noted that "[t]he mechanisms and specific molecules" involved in mobilization, homing, and trafficking of stem cells "are still unclear." Appx3210. Whetton repeatedly noted the uncertainty and lack of understanding regarding the homing and mobilization mechanisms. Appx3541 ("This process [mobilization], which is currently understood poorly…"; "little is known of the mechanisms regulating stem cell mobilization…"); *see also* Appx751-752 (Mohty).

Lapidot emphasized that mobilization of stem cells involves "a complex interplay between cytokines, chemokines and adhesion molecules, though details of this regulatory system are poorly understood." Appx3482. And Konopleva did not "predict[] the claimed invention." Pet. 5. As the district court found, "Konopleva does not expressly teach a method for, or any agents capable of, blocking CXCR4." Appx54 (¶83).

2. Known Stem Mobilizers Had The Opposite Effect

The district court also found that the prior art taught that known stem cell mobilizers increased CXCR4 expression, the opposite effect of a CXCR4 blocking agent such as plerixafor:

> Known stem cell mobilizers had been shown to increase CXCR4 expression, which put into serious question whether an agent that blocks the CXCR4 receptor would prompt mobilization in a successful way. Because G-CSF, SCF, and IL-6 were all known stem cell mobilizers that were reported to increase CXCR4 expression, a person having ordinary skill in the art would not have reasonably expected something that blocks CXCR4, and thus counteracts CXCR4 expression, to succeed.

Appx105 (¶41) (exhibit cites omitted); *see also* Appx62-63 (¶93).

The district court's reliance on known stem cell mobilizers having the opposite effect on CXCR4 than plerixafor was proper. *Arctic Cat Inc. v. Bombardier Recreational Prod. Inc*., 876 F.3d 1350, 1360 (Fed. Cir. 2017), *cert denied*, 139 S. Ct. 143 (2018) ("[P]rior art need not explicitly 'teach away' to be relevant to the obviousness determination.").

B. The District Court's Consideration of Engraftment In Its Reasonable Expectation of Success Analysis Does Not Justify Rehearing

The district court made two independent factual findings of no reasonable expectation of success that do not refer to engraftment. Appx62-63 (¶93); Appx76-77 (¶112). First, the district court found that there was no reasonable expectation that a CXCR4 blocker would succeed:

> [B]ased on the uncertainties regarding the mechanisms of stem cell mobilization, the known complexity in the art, and the fact that G-CSF, SCF, and IL-6 were known stem cell mobilizers that increased CXCR4 expression, a person of ordinary skill in the art would not have had a reasonable expectation of success in September 2000.

Appx62-63 (¶93). Second, the district court reiterated this finding:

> [I]t should not be lost on those of us looking back to September 2000 that a person of ordinary skill in the art would not have had a reasonable expectation that using plerixafor as a stem cell mobilizer would succeed. Again, based on the uncertainties regarding the mechanisms of stem cell mobilization, the known complexity in the art, and the fact that G-CSF, SCF, and IL-6 were known stem cell mobilizers that increased CXCR4 expression, even if a person of ordinary skill in the art may have given plerixafor a try, that does not mean that such a person could, at that time, have reasonably expected it would succeed in mobilizing stem cells.

Appx76 (¶112). Therefore, the district court's opinion makes it clear that the uncertainty and complexity in the art and the opposite effect of known mobilizers were sufficient, standing by themselves, to support its finding of no reasonable expectation of success. Appellees' Br. 34 n.10; *see also* Oral Arg. 13:54-14:47, 17:13-19:25.

Among the district court's numerous factual findings in Appx104-106 (¶41), Zydus's Petition focuses on one of them: the district court's finding that the prior art "would have put a damper on a [POSA's] reasonable expectation of mobilizing useful stem cells because stem cell transplantation requires successful mobilization, homing, and engraftment." Appx105-106 (¶41); *see* Pet. 11. As noted by the district court, "the [data in the] Peled article cited in Konopleva …

demonstrated that two different CXCR4 antibody blocking agents reduced engraftment of stem cells." Appx80 (¶118, footnote 42). The POSA would have viewed this as a highly undesirable result. Appx286, Appx330 (Andreeff).

In light of the factual findings of (1) the uncertainty and complexity in the art and (2) the opposite effect of known mobilizers which do not mention engraftment at all, the district court's references to engraftment were at most additional support for its finding. Furthermore, the district court's consideration of engraftment in this context was proper under *Institut Pasteur*. 738 F.3d at 1337. The reasonable expectation of success analysis must match the POSA's motivating need or goal. *Id.* at 1346 ("Importantly, without a sound explanation for doing otherwise, which is not present here, the expectation-of-success analysis must match the highly desired goal, not switch to a different goal that may be a less challenging but also less worthwhile pursuit.").

Here, the district court found that "a person of ordinary skill in the art in September 2000 would have pursued a panoply of potential stem cell mobilizing agents in an effort to improve upon G-CSF." Appx49 (¶78). Therefore, it was entirely appropriate to view the need to find a better mobilizing agent than G-CCF as the measure of the reasonable expectation of success.

Furthermore, mobilizing and harvesting viable stem cells is the relevant measure of success. Zydus does not dispute that Peled and Möhle both

demonstrate that CXCR4 blocking antibodies decreased stem cell engraftment. Appx59-60 (¶89), Appx104-106 (¶41); Appx3484-3485; Appx3494, Appx3496; Appx424-425 (Andreeff). As found by the district court, "[m]obilizing regimens … are used to increase the number of stem cells in the blood to an amount sufficient to conduct a stem cell transplantation procedure." Appx11 (¶5). The POSA would understand that the purpose of mobilizing and harvesting stem cells as recited in the claims is to use the harvested stem cells in transplantation. This requires mobilizing and harvesting viable stem cells capable of engraftment. As found by the district court, "[e]ngraftment is essential." Appx12 (¶6), Appx76-77 (¶112). A POSA would have recognized that mobilizing stem cells that fail to engraft would be of no help to patients. Appx286, Appx330 (Andreeff) ("The patient would die [from a failure to engraft]."). Thus, it was proper for the district court to have considered engraftment as an implicit claim feature.

Institut Pasteur is directly on point. 738 F.3d at 1346. Although cell viability was not expressly required by the claims, the Court concluded that "continuing viability was implicit in the claims." *Id*. The Court reached this conclusion because the research goal facing the POSA, as stated in the prior art, required a living cell. Similarly, the research goal facing the POSA in this case is to mobilize and harvest viable stem cells capable of engraftment. As the Court explained in *Institut Pasteur*:

> In any event, the Board identified no reason at all that a skilled artisan would have pursued a method toxic to cells [here, a method to mobilize stem cells that won't engraft]. [The Board] relied, rather, on the interest stated by the prior art reference Old: [i]t would be a great advance if such alterations could be engineered into copies of a chosen gene in situ within the chromosomes of a living animal cell.

Id. (emphasis omitted). Because "[t]oxicity would bear heavily on whether a [POSA] would have had a reasonable expectation of success in achieving that objective [from the prior art], [t]he Board thus erred by disregarding evidence of toxicity of the method at issue." *Id.*

Zydus's Petition does not address *Institut Pasteur*.[2] Instead, Zydus points to *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, but this case is inapposite. 821 F.3d 1359 (Fed. Cir. 2016); Pet. 2, 6, 7, 11. Unlike viability in *Institut Pasteur* and engraftment in this case, removal of the claimed protecting group in *Intelligent Bio-Sys.* was not implicit in the claims. 821 F.3d at 1367; Appellees' Br. 33-34. Zydus did not include *Intelligent Bio-Sys.* in its Rule 35 statement. Pet. 1.

Zydus asserts that the claims are broad enough to cover basic research and other methods involving stem cell mobilization and harvesting. Pet. 4. But this argument is unsupported by any record cites and contrary to the testimony of

[2] Genzyme discussed *Institut Pasteur* in its brief and during oral argument. Appellees' Br. 32-34; Oral Arg. 15:17-16:50. In its Petition, Zydus omitted the reference to *Institut Pasteur* at oral argument with ellipses. Pet. 14.

Zydus's own expert who testified that "[f]ailure of engraftment results in death." Appx286 (Andreeff).

C. The District Court's Consideration of Failures In Its Reasonable Expectation of Success Analysis Does Not Justify Rehearing

There was no dispute that many researchers failed to fulfill the long-felt need for a mobilizing agent better than G-CSF. More than a dozen unsuccessful candidates either failed to mobilize sufficient numbers of stem cells, exhibited undesirable side effects, or both. Appx41 (¶67), Appx109-110 (¶48). These failures would have been well known to the POSA. Appx41 (¶67); Appx379 (Andreeff). In light of the overarching uncertainty and unpredictability and in light of the failures by top research groups to fulfill that need, a POSA could not have had a reasonable expectation of success that any new proposed stem cell agent would fulfill that need.

Zydus asserts that the district court erroneously considered failure of others in its reasonable expectation analysis. Pet. 11-12. Similar to engraftment, however, the district court made multiple factual findings of no reasonable expectation of success without referring to the failures, demonstrating that these failures were not essential to its finding. Appx62-63 (¶93), Appx76-77(¶112), Appx106-107 (¶43). Instead, the district court considered these failures as additional evidence consistent with the uncertainty and complexity of stem cell mobilization that would have prevented a POSA from having a reasonable

expectation of success of arriving at the claimed invention. *See* Appx104-106 (¶41).

D. The District Court Did Not Require Reasonable Expectation of Success As to Large Quantities of Stem Cells

Zydus argues district court imposed a quantity requirement. Pet. 5 n.1 (citing Appx115-116), 9 (citing Appx115), 12. But Zydus's citation of the district court's nexus analysis at Appx114-116 is inapposite to the district court's reasonable expectation of success analysis. Nexus for purposes of objective indicia and reasonable expectation of success are different issues with different tests. *Compare In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011), *with Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994-96 (Fed. Cir. 2009). Zydus improperly argues that the district court mixed the *prima facie* case with objective indicia. Pet. 13. However, that is exactly what Zydus is doing by conflating reasonable expectation of success and nexus.[3]

[3] Another example of Zydus's conflation is Zydus's complaint that the district court relied on Petit in its reasonable expectation of success analysis. Pet. 7 (citing Appx112-113 (¶ 51)). To the contrary, the district court cited Petit for unexpected results. Appx111-113 ("Unexpected Results" subsection, ¶51 *citing, inter alia,* Appx4021, Appx4024-4026); Appellees' Br. 41-42.

E. Zydus's Other Arguments Do Not Justify Rehearing

1. Motivation to Combine

Zydus notes the district court's finding of no motivation to combine and quotes a question from the Court at oral argument about motivation. Pet. 5-6 (quoting Oral Arg. 19:26). Of course, such questions do not reflect the Court's Rule 36 judgment. *See Rates Tech*, 688 F.3d at 750.

Motivation to combine does not equal a reasonable expectation of success. Appellees' Br. 38-41; Oral Arg. 19:51-21:12. They are "two different legal concepts" that should not be "conflated." *Intelligent Bio-Sys.*, 821 F.3d at 1367; *see also Arctic Cat*, 876 F.3d at 1359; *Regents of Univ. Cal. v. Broad Inst., Inc.*, 903 F.3d 1286, 1291-1296 (Fed. Cir. 2018).

This is especially the case here where the district court found that "[t]he complexity and uncertainty in the art, … may have encouraged a person of ordinary skill in the art to at least try CXCR4 blockers, despite potential misgivings." Appx102 (¶35). The district court's finding of motivation to combine does not warrant rehearing.

2. Written Description

Zydus asserts that if engraftment capability is a requirement of the Asserted Claims, they would lack adequate written description. Pet. 15. This, however, is a new argument that was never argued at trial or in Zydus's Opening Brief, and is

waived. *United States v. Ford Motor Co.*, 463 F.3d 1267, 1276 (Fed. Cir. 2006). Zydus's waived written description argument does not warrant rehearing.

3. Claim Construction

Each Asserted Claim requires (1) the administration of plerixafor in an amount effective to mobilize stem cells into the peripheral blood, and (2) harvesting the stem cells mobilized by the effective amount of plerixafor (*i.e.*, "said" stem cells). Appx15-16 (¶11); Appellees' Br. 3-4. Neither side sought claim construction in this case. Appx28 (¶33). Having lost at the district court and the panel, Zydus now wants claim construction. Pet. 15; *see also id.* 3, 12.

Zydus's assertion of "secret hurdles to proving obviousness" particularly rings hollow here because the district court in *Genzyme I* found no reasonable expectation of success, and this Court affirmed. Pet. 15; *Genzyme I*, 2016 WL 2757689 at *12; *Genzyme II*, 716 F. App'x at 1009-1010. Zydus thus knew Genzyme's position on reasonable expectation of success and could have sought claim construction for the issue. It did not. Zydus's waived claim construction arguments do not warrant rehearing.

F. The District Court Found Numerous Objective Indicia Support Nonobviousness

The district court found that fulfillment of a long-felt need, failure of others, unexpected results, and praise support nonobviousness. Appx107-116. These objective indicia provide independent support for nonobviousness. *Transocean*

Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc., 699 F.3d 1340, 1349-55 (Fed. Cir. 2012). Zydus's petition does little to dispute objective indicia. Pet. 9, 19. None is included in Zydus's Rule 35 statement. Pet. 1.

The objective indicia in this appeal involve fact-bound, case-specific application of settled law. They do not warrant rehearing.

Fulfillment of a Long-Felt Need. As found by the District Court, the invention fulfilled the long-felt need for an improved mobilization regimen Appx108-109 (¶46), Appx79 (¶117).

Failure of Others. Many researchers failed to fulfill the long-felt need for a mobilizing agent better than G-CSF. More than a dozen unsuccessful candidates either failed to mobilize sufficient numbers of cells, exhibited undesirable side effects, or both. Appx41 (¶67), Appx109-110 (¶48).

Unexpected Benefits. Among other findings, the district court found that plerixafor unexpectedly mobilizes higher quality stem cells than G-CSF alone. Appx79-80 (¶118), Appx112-113 (¶51, *citing, inter alia,* Appx3873; Appx4353-4355; Appx4375). Further, as found by the district court, plerixafor unexpectedly mobilized stem cells more rapidly and predictably than G-CSF—mobilizing in just a few hours as compared to G-CSF's multiple days. Appx79-80 (¶118); Appx112-113 (¶51, *citing, inter alia,* Appx4315-4316).

***Praise*.** The patented method has been praised by experts as a "new and important agent" and "significant advance" that has "strongly impacted" the field of stem cell transplantation. Appx4030; Appx4421; Appx4394; Appx861-863 (Mohty)); *see also* Appx4287 ("major advance"); Appx113 (¶53).

Genzyme fully addressed Zydus's arguments about closest prior art, nexus, and blocking patents in its brief. Appellees' Br. 47-48, 50-54; *see also* Oral Arg. 22:11-26:54.

IV. CONCLUSION

For the foregoing reasons, rehearing and rehearing *en banc* should be denied.

Respectfully submitted,

Dated: October 31, 2019

By: /s/Paul H. Berghoff

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PROOF OF SERVICE

I hereby certify that I filed the foregoing Appellees' Response to Appellant's Combine Petition for Rehearing *En Banc* And Panel Rehearing with the Clerk of the United States Court of Appeals for the Federal Circuit via the CM/ECF system this 31st day of October, 2019, and served a copy on counsel of record by the CM/ECF system.

Dated: October 31, 2019

By: /s/James L. Lovsin

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CERTIFICATE OF COMPLIANCE

1. This response complies with the type-volume limitation of Federal Circuit Rules 35(e)(4) and 40(d). This response contains 3,845 words, excluding the parts of the response exempted by Federal Circuit Rules 35(c)(2) and 40(c)(1).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point Times New Roman font.

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