EXHIBIT A

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMGEN INC., Plaintiff, v. F. HOFFMANN-LAROCHE LTD., a Swiss Company, ROCHE DIAGNOSTICS GmbH, a German Company and HOFFMANN LAROCHE INC., a New Jersey Corporation, Defendants.	Civil Action No.: 05-12237 WGY

[PROPOSED] AMGEN INC.'S MEMORANDUM IN OPPOSITION TO ROCHE'S MOTION FOR JUDGMENT AS A MATTER OF LAW REGARDING INVALIDITY AND CROSS-MOTION FOR JUDGMENT AS A MATTER OF LAW THAT ROCHE HAS FAILED TO SATISFY ITS BURDEN OF PROOF REGARDING THE INVALIDITY OF DR. LIN'S ASSERTED PATENT CLAIMS

TABLE OF CONTENTS

Page No.

I. INTRODUCTION AND LEGAL STANDARDS FOR RULE 50 (A) MOTIONS BROUGHT BY THE PARTY WITH THE BURDEN OF PROOF 1

A. Roche's Heightened Burden of Proof on a Motion for Judgment 2

II. ROCHE, NOT AMGEN, BEARS THE BURDEN OF PROVING THAT THE PRODUCT-BY-PROCESS AND SOURCE LIMITATIONS OF LIN'S PRODUCT CLAIMS SHOULD BE DISREGARDED 5

III. ROCHE FAILED TO MEET ITS HEAVY BURDEN OF PROOF THAT THE '933 CLAIMS WERE ANTICIPATED 6

A. Roche Has Failed To Establish By Clear And Convincing Evidence That Goldwasser's Urinary EPO Anticipated '933 Claims 3, 7 or 8 7

1. Roche Failed To Establish That Goldwasser's Urinary EPO Was Identical To Any Product Within '933 Claim 3 7

2. Roche Failed To Establish That Goldwasser's Urinary EPO Was Identical To Any Embodiment Of '933 Claims 7 or 8 17

B. Roche Has Failed To Establish By Clear And Convincing Evidence That '933 Claims 9, 11, 12 or 14 Were Anticipated 18

1. Roche Failed to Present Evidence Sufficient to Show That Any of Its Cited References Anticipated The EPO Glycoprotein Limitation of '933 Claims 9, 11, 12 or 14 19

2. Roche Failed To Prove That Any Cited Reference Anticipated The Remaining Limitations of '933 Claims 9, 11, 12 or 14 21

3. Roche Failed To Prove That The Baron/Goldwasser Three-Patient Experiment Anticipated '933 Claims 9, 11, 12 or 14 22

4. Roche Failed To Prove That Any Of Essers' Publications Regarding Plasma Administration Anticipated '933 Claims 9 or 12 28

5. Roche Failed To Prove That The Eschbach Single-Patient Plasma Experiment Anticipated '933 Claims 9 or 12 31

6. Roche Failed To Prove That Miyake et al. Anticipated '933 Claims 9 or 12 32

7. None of Roche's Allegedly "Anticipatory" References Enabled Dr. Lin's Claimed Inventions 32

IV. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE SUFFICIENT FOR A VERDICT THAT CLAIMS 3, 7, 8, 9, 11, 12 AND 14 OF THE '933 PATENT OR CLAIM 1 OF THE '422 PATENT WERE OBVIOUS 34

A. Roche Failed to Prove That it Would Have Been Obvious to Modify Urinary EPO to Produce The Claimed EPO Products 34

B. The Experiments Using Naturally-Occurring Materials Cited By Roche Do Not Render Obvious '933 Claims 9, 11, 12 And 14 or '422 Claim 1 37

V. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE SUFFICIENT FOR A VERDICT THAT CLONING EPO DNA AND EXPRESSION OF *IN VIVO* BIOLOGICALLY ACTIVE EPO WOULD HAVE BEEN OBVIOUS 40

A. Roche's Attempt To Mischaracterize Its Burden of Proof Regarding Obviousness Should Be Rejected 40

B. Roche Failed To Present Clear And Convincing Evidence That One Of Skill In The Art Had A Reasonable Expectation Of Success In Cloning The Human EPO Gene By October 1983 42

1. Roche Failed To Prove That With Dr. Goldwasser's Urinary EPO, One Skilled In The Art Had By October 1983 a Reasonable Expectation Of Success Of Using Available Methods To Clone The Human EPO Gene 43

C. Roche Failed To Prove By Clear And Convincing Evidence That One Of Skill In The Art Had A Reasonable Expectation Of Success In Producing An *In Vivo* Biologically Active Recombinant EPO Protein By March 1984 50

D. Genetics Institute's Cloning Expression of The Human EPO Gene Does Not Anticipate or Render Obvious Dr. Lin's Asserted Claims-In-Suit 56

E. The Unrebutted Objective Evidence Demonstrates The Non-Obviousness Of Dr. Lin's Claimed Inventions 58

VI. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE SUFFICIENT FOR A VERDICT THAT Dr. Lin's Claims Are Invalid Under 35 U.S.C. § 112 61

A. Roche Has Failed To Prove That a Reasonable Jury Could Only Find "Human Erythropoietin" Indefinite And Inadequately Described 61

1. Because Roche Has Failed To Show That "Human Erythropoietin" Is Not Adequately Described, Its Motion Should Be Denied 62

2. Roche's Motion Regarding The Definiteness Of "Human Erythropoietin" Similarly Ignores The Evidence And Should Be Denied 63

3. Roche's Untimely Assertion That '422 Claim 1 Is Indefinite As Lacking Identifiable Structure Should Be Stricken And Certainly Should Not Serve As Basis For Finding The Claim Indefinite 64

B. Roche Has Failed To Prove That '349 Claim 7 Is Not Enabled 65

C. Roche's Attorney Argument That "Vertebrate Cells" As Set Forth In '349 Claim 7, Is Inadequately Described And Not Enabled Cannot Meet Its Burden of Proving Invalidity 67

VII. CONCLUSION 68

TABLE OF AUTHORITIES

Page No.

Cases

Advanced Display Sys., Inc. v. Kent State Univ.,
212 F.3d 1272 (Fed. Cir. 2000)..... 28

Allen Archery, Inc. v. Browning Mfg. Co.,
819 F.2d 1087 (Fed. Cir. 1987)..... 58

American Hoist & Derrick Co., v. Sowa & Sons,
725 F.2d 1350 (Fed. Cir. 1984)..... 3, 28, 42, 49

Amgen Inc. v. Chugai Pharma. Co.,
13 U.S.P.Q.2d 1737 (D. Mass. 1989) 57

Amgen Inc. v. Hoechst Marion Roussel, Inc.,
126 F.Supp. 2d 69 (D. Mass 2001) 9, 28, 33, 61

Bausch & Lomb, Inc. v. Alcon Laboratories, Inc.,
79 F. Supp. 2d 252 (W.D.N.Y. 2000) 3, 4

Burroughs Wellcome Co. v. Barr Labs., Inc.,
40 F.3d 1223 (Fed. Cir. 1994)..... 56

C.R. Bard v. M3 Sys.,
157 F.3d 1340 (Fed. Cir. 1998)..... 19

CVI/Beta Ventures, Inc. v. Tura LP,
112 F.3d 1146 (Fed. Cir. 1997)..... 62

Demaco Corp. v. F. Von Langsdorff Licensing Ltd.,
851 F.2d 1387 (Fed. Cir. 1988)..... 59, 60

Diversitech Corp. v. Century Steps, Inc.,
850 F.2d 675 (Fed. Cir. 1988)..... 58

EEOC v. Massey Yardley Chrysler Plymouth, Inc.,
117 F.3d 1244 (11th Cir. 1997) 1

Envtl. Designs, Ltd. v. Union Oil Co. of Cal.,
713 F.2d 693 (Fed. Cir. 1983)..... 58

eSpeed Inc. v. BrokerTec USA LLC,
417 F. Supp. 2d. 580 (D. Del. 2006) *aff'd* on other grounds, 480 F.3d 1129 (Fed. Cir. 2007) .. 4

Finnigan Corp. v. Int'l. Trade Comm'n.,
180 F.3d 1354 (Fed. Cir. 1999)..... 9

Fireman's Fund Insurance Co. v. Videfreeze Corp.,
540 F.2d 1171 (3d Cir. 1976)..... 1

Fiskars, Inc. v. Hunt Mfg. Co.,
221 F.3d 1318 (Fed. Cir. 2000)..... 4

Forest Labs., Inc. v. Ivax Pharms., Inc.,
2007 U.S. App. LEXIS 21165 (Fed. Cir. Sep. 5, 2007) 32, 40, 41

Fritsch v. Lin,
21 U.S.P.Q.2d 1739 (B.P.A.I. 1992)..... 10

Froemming v. Gate City Fed. Sav. & Loan Ass'n.,
822 F.2d 723 (8th Cir. 1987) 1

Gay v. Petsock,
917 F.2d 768, 771 (3rd Cir. 1990) 1

General Electric Co. v. Nintendo Co.,
179 F.3d 1350 (Fed. Cir. 1999)..... 21, 32

Graham v. John Deere Co.,
383 U.S. 1, 17 (1966)..... 58

Granite Computer Leasing Corp. v. Travelers Indem. Co.,
894 F.2d 547 (2d Cir. 1990)..... 1

Grey v. First National Bank in Dallas,
393 F.2d 371 (5th Cir. 1968), *cert. den.* 393 U.S. 961 (1968)..... 1

Hewlett-Packard Co. v. Bausch & Lomb Inc.,
909 F.2d 1464 (Fed Cir. 1990)..... 2, 28, 42, 57

Hybritech Inc. v. Monoclonal Antibodies, Inc.,
802 F.2d 1367 (Fed. Cir. 1986)..... 56

In re Deuel,
51 F.3d 1552 (Fed.Cir.1995)..... 35

In re Grabiak,
769 F.2d 729 (Fed. Cir. Sep. 5, 1985)..... 34

In re Hogan,
559 F.2d 595 (C.C.P.A 1977) 17

In re Kratz,
592 F.2d 1169 (C.C.P.A. 1979) 15

In re Marosi,
710 F.2d 799 (Fed. Cir. 1983)..... 6

In re Piasecki,
745 F.2d 1468 (Fed. Cir. 1984)..... 58

In re Wilson,
311 F.2d 266 (C.C.P.A. 1962) 15, 16

In re Wright,
999 F.2d 1557 (Fed. Cir. 1993)..... 17

J. T. Eaton & Co. v. Atlantic Paste & Glue Co.,
106 F.3d 1563 (Fed. Cir. 1997)..... 59

Keisling v. SER-Jobs for Progress, Inc.,
19 F.3d 755 (1st Cir. 1994)..... 42

Kennecott Corp. v. Kyocera Int'l, Inc.,
835 F.2d 1419 (Fed. Cir. 1987)..... 63

KSR International Co. v. Teleflex Inc.,
127 S.Ct. 1727 (2007)..... 40

Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings,
370 F.3d 1354 (Fed. Cir. 2004)..... 58

Micro Motion Inc. v. Exac Corp.,
741 F. Supp. 1426 (N.D. Ca. 1990) 58

Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.,
976 F.2d 1559 (Fed. Cir. 1992)..... 19

Molins PLC v. Textron, Inc.,
48 F.3d 1172 (Fed. Cir. 1995)..... 4

Murray v. Dillard Paper Co.,
1999 U.S. Dist. LEXIS 22630 (E.D. Va. 1999)..... 65

National Research Development Corp. v. Great Lakes Carbon Corp.,
410 F. Supp. 1108 (D. Del. 1975)..... 17

Omegaflex v. Parker Hannifin Corp.,
425 F. Supp.2d 171, 183-84 (D. Mass. 2006)(Ponsor, J.),
rev'd on other grounds, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007) 65

Pfizer, Inc. v. Apotex, Inc.,
480 F.3d 1348 (Fed. Cir. 2007)..... 2

Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.,
315 F.3d 1335 (Fed. Cir. 2003)..... 16

Purdue Pharma L.P. v. Boehringer Ingelheim GMBH,
237 F.3d 1359 (Fed. Cir. 2001) 57

Regents of the Univ. of New Mexico v. Knight,
321 F.3d 1111 (Fed. Cir. 2003)..... 63

Rockwell Int'l Corp. v. United States,
147 F.3d 1358 (Fed. Cir. 1998)..... 6

Rohm & Haas Co. v. Crystal Chemical Co.,
722 F.2d 1556 (Fed. Cir. 1983)..... 4

Rosemount, Inc. v. Beckman Instruments, Inc.,
727 F.2d 1540 (Fed. Cir. 1984)..... 60

Rowe v. Case Equip. Corp.,
1997 U.S. App. LEXIS 227 (6th Cir. 1997) 65

SmithKline Beecham Corp. v. ApotexCorp.,
403 F.3d 1328 (Fed. Cir. 2005)..... 19, 21, 32

Standard Oil Co., v. American Cyanamid Co.,
774 F. 2d 4484 (Fed. Cir. 1985)..... 52

Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd ,
492 F.3d 1350 (Fed. Cir. 2007)..... 34, 35, 40, 41

Texas Digital Systems, Inc. v. Telegenix, Inc.,
308 F.3d 1193 (Fed. Cir. 2002)..... 9

WMS Gaming, Inc. v. Int'l Game Tech.,
184 F.3d 1339 (Fed. Cir. 1999)..... 59

Statutes

35 U.S.C. § 102..... 6

35 U.S.C. § 103(a) 45

35 U.S.C. § 112..... 61, 63, 68

35 U.S.C. § 282..... 2, 4, 5

Other Authorities

Manual of Patent Examining Procedure § 2124
(8th ed. Rev. 5, Aug. 2006)..... 15, 16, 17

I. INTRODUCTION AND LEGAL STANDARDS FOR RULE 50 (a) MOTIONS BROUGHT BY THE PARTY WITH THE BURDEN OF PROOF

Roche moves for judgment as a matter of law present to Fed. R. Civ. P. 50(a), but as discussed in this memorandum, the totality of evidence presented by Roche fails to create a legally sufficient evidentiary basis for a verdict in favor of Roche on any of its invalidity defenses. Rather, because Roche has utterly failed to adduce clear and convincing evidence of invalidity, the Court should grant Amgen's cross-motion for judgment on all of Roche's remaining invalidity defenses.

As the Court is aware, the standard for granting judgment as a matter of law is high. It is particularly remarkable, however, that Roche's current motion asks for such relief when it is ***Roche*** that bears the burden of proof on the invalidity defenses.[1] Where, as here, the party bearing the burden of proof seeks entry of judgment, it has an enormous burden to demonstrate that a directed verdict is warranted. As many courts have said, a verdict should be directed for a party bearing the burden of proof only if the evidence in favor of the movant is so overwhelming that the jury could rationally reach no other result.[2] Or put another way, "A plaintiff's motion for a directed verdict requires the trial court to test the body of evidence not for its insufficiency to support a finding, but rather for its overwhelming effect."[3]

Indeed, courts have characterized the granting of judgment for a party with the burden of proof as an "extreme step,"[4] and one reserved for "extreme circumstances."[5] The court in

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[1] The standard for granting judgment is higher if the movant is the party which bears the burden of proof. *Fireman's Fund Insurance Co. v. Videfreeze Corp.*, 540 F.2d 1171, 1177 (3d Cir. 1976). Here, of course, Roche bears the burden of proving invalidity by clear and convincing evidence.

[2] *E.g., Granite Computer Leasing Corp. v. Travelers Indem. Co.*, 894 F.2d 547, 551 (2d Cir. 1990); *Grey v. First National Bank in Dallas*, 393 F.2d 371, 380 (5th Cir. 1968), *cert. den.* 393 U.S. 961 (1968).

[3] *United Cal. Bank v. THC Finan. Corp.* 557 F. 2d 1351, 1356 (9th Cir. 1977).

[4] *EEOC v. Massey Yardley Chrysler Plymouth, Inc.*, 117 F.3d 1244, 1248 (11th Cir. 1997).

Froemming v. Gate City Fed. Sav. & Loan Ass'n.[6] explained the rationale for such a rigorous rule:

> "A verdict upon an issue of fact should not be directed in favor of the party who has the burden of proof with respect thereto, unless such fact is admitted, or is established by the undisputed testimony of one or more disinterested witnesses and different minds cannot reasonably draw different conclusions from such testimony.' This is so because '[t]he factfinder is not compelled to believe the testimony of a witness even if it is uncontradicted."[7]

Needless to say, none of the validity issues upon which Roche seeks a directed verdict under Rule 50(a) is admitted or established by the undisputed testimony of one or more disinterested witnesses. Roche offers no justification for why this Court should take the "extreme step" of awarding judgment as a matter of law to the party with the burden of proof, a step that would be made even more extreme by the fact Roche's burden of proof on its invalidity defenses is ***clear and convincing*** evidence. For this reason, Roche's Motion for Judgment as a Matter of Law Regarding Invalidity should be denied summarily.

A. ROCHE'S HEIGHTENED BURDEN OF PROOF ON A MOTION FOR JUDGMENT

As the Court has made plain, Amgen's issued patents enjoy a statutory presumption of validity under 35 U.S.C. § 282, and consequently Roche must overcome that presumption and prove its invalidity defenses by clear and convincing evidence.[8] In addition, as discussed in Amgen's Renewed Motion for Judgment as a Matter of Law (D.I. 1270), the fact that the references relied on by Roche in support of its invalidity contentions were before the Patent

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[5] *Gay v. Petsock*, 917 F.2d 768, 771 (3rd Cir. 1990).

[6] 822 F.2d 723, 727 (8th Cir. 1987).

[7] *Id. (internal citations omitted). See also, Anderson v. United States*, 561 F.2d 162, 167 (8th Cir.1977) (the jury 'need not accept as true the testimony of any witness).

[8] As Roche acknowledges, it must adduce "evidence that places in the ultimate fact finder an abiding conviction that the truth of its factual contentions are highly probable." D.I. 1285-2 at 3, *quoting Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 n.5 (Fed. Cir. 2007).

Office means that the burden Roche bears is even higher, an "especially difficult" one.[9] In *American Hoist & Derrick*, the Federal Circuit made clear that "[w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the ***added burden*** of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents."[10]

As discussed in Amgen's Renewed Motion for Judgment as a Matter of Law, Roche has admitted, through its expert Dr. Lowe, that the references he relied on to opine that the patents are invalid were all before the Patent Office.[11] Roche now attempts to take a step back from that admission, claiming that a portion of at least one reference, the Maniatis manual, was not submitted to the PTO. Notwithstanding that partial retreat form its witness' admission, Roche does not deny that virtually all of these references it has relied on were before the PTO during prosecution. As a result, part of Roche's burden is to show that the PTO was wrong in its decision to grant the patent — that is, part of the burden is to overcome the deference due to a governmental agency presumed to have properly done its job.[12] And this Roche has failed to do.

Indeed, Roche's current argument is that Amgen submitted *too many* references to the Patent Office, thus effectively "burying" the more pertinent ones.[13] But other than counting the number of references disclosed to the Patent Office and then speculating about the time frames over which they were considered, Roche fails to point to any particular reference it contends was

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[9] *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed Cir. 1990).

[10] *American Hoist & Derrick Co., v. Sowa & Sons*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (emphasis added).

[11] 9/7/07 Lowe Trial Tr. 379:9 – 380:19.

[12] 725 F.2d. at 1360.

[13] Roche's Memorandum In Support of Its Motion For Judgment as a Matter of Law Regarding Invalidity ("Roche's Memo") (D.I. 1315) at 4.

not properly considered. More importantly, Roche fails to cite a single case for the proposition that allegations that an applicant filed too many references before the Patent Office could affect the deference due to the Patent Office that it properly did its job.

The single case Roche does cite, *Bausch & Lomb, Inc. v. Alcon Laboratories, Inc.*,[14] hardly supports its position. There, the District Court excluded proposed testimony by an expert about "problems" in the Patent Office, including time constraints and the difficulties in obtaining prior art references, noting that the purpose of such testimony would be to attempt to undermine the presumption of validity under 35 U.S.C. § 282 "by inviting the jury to speculate about possible defects, errors, or omissions in the application process that led to the issuance of the patent-in-suit." The court went on to say that if the attacker "has evidence that there actually were defects in the particular application process at issue in this case, thus suggesting that deference to the PTO's determination may not be appropriate, it may seek to offer such evidence. But generalized testimony about 'problems' in the PTO is not admissible."[15]

The *Bausch & Lomb* decision cited by Roche thus had nothing to do with allegations of burying prior art. Beyond that, of course, Roche's generalized allegations of "burying" are not evidence of "actual defects," but rather, as the court in *Bausch & Lomb* suggested, precisely the type of allegations that invite the jury to speculate about possible errors in the process and are designed to undermine the presumption of validity.[16]

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[14] 79 F. Supp. 2d 252 (W.D.N.Y. 2000).

[15] 79 F.Supp.2d at 255.

[16] Moreover, the Federal Circuit has held that allegations of "burying" prior art references are likewise not sufficient to sustain claims of inequitable conduct. As long as the reference at issue is before the examiner, the duty of disclosure is not violated. *Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1184 (Fed. Cir. 1995); *Fiskars, Inc. v. Hunt Mfg. Co.*, 221 F.3d 1318, 1327 (Fed. Cir. 2000). One exception, not asserted here by Roche, is where the disclosure is made to correct a past misstatement. *See, e.g., Rohm & Haas Co. v. Crystal Chemical Co.*, 722 F.2d 1556, 1571-72 (Fed. Cir. 1983) (describing how to "cure" past misstatements); *eSpeed Inc. v. BrokerTec USA LLC*, 417 F. Supp. 2d. 580, 598 (D. Del. 2006) *aff'd.* on other grounds, 480 F.3d 1129 (Fed. Cir. 2007) (providing unexplained and voluminous submission is insufficient to cure past misstatement).

In short, as detailed below and in Amgen's motions for judgment, nothing Roche cites demonstrates that this Court should take the "extreme step" of granting a directed verdict on defenses for which Roche bears the burden of proof.

II. ROCHE, NOT AMGEN, BEARS THE BURDEN OF PROVING THAT THE PRODUCT-BY-PROCESS AND SOURCE LIMITATIONS OF LIN'S PRODUCT CLAIMS SHOULD BE DISREGARDED

Dr. Lin's EPO product claims each contain one or more elements that are either a product-by-process or a source limitation. Amgen contends that such process/source limitations distinguish Dr. Lin's inventions over the prior art. Roche ignores these limitations entirely. The process source limitations are highlighted below.

Claim 3 of the '933 patent reads:

> A non-naturally occurring glycoprotein ***product of the expression in a mammalian host cell of an exogenous DNA sequence comprising*** a DNA sequence encoding human erythropoietin said product possessing the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells.

Each of the remaining asserted claims of the '933 patent depend from and incorporate the limitations of '933 claim 3 by reference. Claim 1 of the '422 patent reads:

> A pharmaceutical composition comprising a therapeutically effective amount of human erythropoietin and a pharmaceutically acceptable diluent, adjuvant or carrier, wherein said erythropoietin is ***purified from mammalian cells grown in culture***.

As discussed in Amgen's Renewed Motion for Judgment as a Matter of Law,[17] before Roche can disregard the product-by-process and source limitations that distinguish Lin's claimed inventions over the prior art products, it is Roche, not Amgen, that bears the burden to prove that some prior art product was identical in structure and function to the products claimed in Lin's '933 and '422 patents. Rather than meet that burden, Roche instead tries to shift the burden to Amgen. It does so on the pretext that Amgen was required to show a difference over the prior art

[17] Amgen Inc.'s Renewed Motion for Judgment as a Matter of Law Pursuant to Rule 50(a) ("Renewed Motion") (D.I. 1270) at 1-4.

product to establish the patentability of Lin's claimed inventions. But Amgen already satisfied that requirement, and the Patent Office issued the claims because Amgen did so. From that point forward, the burden falls to Roche under 35 U.S.C. § 282 to prove by clear and convincing evidence that Lin's issued claims fail to distinguish the prior art, and that burden cannot be shifted to Amgen. The law is clear that a patentee retains its statutory presumption of validity throughout the obviousness determination, and the party asserting invalidity retains the burden of proof by clear and convincing evidence.[18]

III. ROCHE FAILED TO MEET ITS HEAVY BURDEN OF PROOF THAT THE '933 CLAIMS WERE ANTICIPATED

Roche argues that '933 claims 3, 7 and 8 were anticipated by "Goldwasser's prior art EPO purified from urine," but points to no single reference and no statutory provision under 35 U.S.C. § 102 to establish its anticipation defense. In addition, Roche asserts that '933 claims 9, 11, 12 and 14 were anticipated by any one of four different references (the Baron/Goldwasser three-patient experiment, the Eschbach single-patient plasma experiment, publications describing the Essers plasma experiment, or the 1977 Miyake publication), but once again it points to no statutory provision under 35 U.S.C. § 102 to establish its anticipation defense. Nor does Roche offer any evidence to show that the Goldwasser urinary EPO preparation, or the EPO preparations used in the Baron/Goldwasser study or the plasma preparations described by Essers or Eschbach meet the product-by-process limitations of any of the asserted '933 claims. Specifically, Roche failed to make any showing whatsoever of structural and functional identity between the alleged prior art urinary and plasma preparations and the pharmaceutical

[18] *See Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1364-65 (Fed. Cir. 1998). As discussed in Amgen's Renewed Motion, Roche's reliance on *In re Marosi*, 710 F.2d 799 (Fed. Cir. 1983) and *In re Moeller*, 117 F.2d 565 (C.C.P.A. 1941), two cases involving appeals from decisions of the Board of Appeals of the Patent Office, is misplaced. Both cases addressed the burden that ***applicants*** have in proving that they have a concept of a new product which has characteristics that distinguish it from the prior art product. Neither case held or suggested that ***patentees***, who enjoy the presumption of validity, bear such a burden in defending against

compositions and glycoprotein products of the patented '933 claims.

Because Roche does not even attempt to show that the prior art plasma preparations of Essers and Eschbach were structurally and functionally identical to the products claimed in each of the '933 claims, judgment as a matter of law should be entered in favor of Amgen and against Roche on both of these prior art references.

A. ROCHE HAS FAILED TO ESTABLISH BY CLEAR AND CONVINCING EVIDENCE THAT GOLDWASSER'S URINARY EPO ANTICIPATED '933 CLAIMS 3, 7 OR 8

The only prior art product for which Roche presented evidence of any structural comparison to the glycoprotein product of '933 claim 3 was the urinary EPO described in the 1977 Miyake/Goldwasser publication. But, as demonstrated in Amgen's original and renewed motions for judgment as a matter of law,[19] Roche failed to establish a *prima facie* case that the Miyake/Goldwasser preparation anticipated the invention claimed in '933 claims 3, 7 or 8. Now that Amgen has put forward its rebuttal evidence, Roche's motion for judgment as a matter of law falls even further short of the mark, and it is Amgen's motion, not Roche's, that should be granted.

1. Roche Failed To Establish That Goldwasser's Urinary EPO Was Identical To Any Product Within '933 Claim 3

Two experts testified concerning structural comparisons between Goldwasser's urinary EPO and Dr. Lin's '933 claim 3 product: Roche's Dr. Bertozzi, who was not one of ordinary skill in the art as of 1983/84,[20] and Amgen's Dr. Varki, who was.[21]

Dr. Bertozzi presented no evidence demonstrating what glycoprotein structures were

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attacks on validity.

[19] Amgen Inc.'s Memorandum In Support of Its Motion For Judgment As a Matter of Law Pursuant to Rule 50(a) ("Amgen's Memo") D.I. 1169 at 16-26 and Renewed Motion (D.I. 1270) at 1-8.

[20] 9/14/07 Bertozzi Trial Tr. 1064:12-1065:6.

[21] 10/2/07 Varki Trial Tr. 2171:11-25.

actually present in Dr. Goldwasser's urinary EPO, let alone how those glycoprotein structures compare to the glycoproteins that comprise any recombinant EPO preparation.[22] Significantly, Dr. Bertozzi admitted that only some of the glycoforms from Goldwasser's urinary EPO had in fact been made in mammalian cells.[23] While Dr. Bertozzi speculated that the glycoforms in Dr. Goldwasser's urinary EPO would be the same as the glycoforms in some embodiment of Dr. Lin's claims, she admitted that she had performed no test and could identify no extant recombinant EPO that confirmed her opinion.[24] At most, Dr. Bertozzi asserted without substantiation that there were similarities between Goldwasser's urinary EPO preparation and Lin's claimed products. She also asserted that she "***could***" engineer forms of recombinant EPO within the scope of Lin's claims that "***would be***" identical to the structures in Goldwasser's urinary EPO preparation, but admitted that the she had not performed any experiment to substantiate her assertions.[25] She also admitted the Dr. Lin's recombinant EPO made in CHO cells was different than Goldwasser's urinary EPO,[26] and that, using the CHO cells disclosed in Lin's patent, "it would be difficult to recapitulate Goldwasser's EPO."[27] She was not able to point to any existing product within the scope of Lin's claims that was identical in structure to Goldwasser's prior art urinary EPO, and she failed to identify any references whatsoever to support or corroborate her opinion that she could make forms of recombinant EPO that would be identical to Goldwasser's urinary EPO.[28] Moreover she provided no evidence on how one skilled in the art would do it in the 1983-84 timeframe. Such speculative testimony is

[22] 9/14/07 Bertozzi Trial Tr. 1129:4-9, 1017: 19-21, 1069:20-1072:17; 1128:14-1129:11.

[23] 9/14/07 Bertozzi Trial Tr. 1129:4-9 ("And some of them, in fact, have been made in made in mammalian cells.").

[24] 9/14/07 Bertozzi Trial Tr. 1066:10-19.

[25] 9/14/07 Bertozzi Trial Tr. 1072:19-1074:15.

[26] 9/14/07 Bertozzi Trial Tr. 1116:18-19 ("So in my opinion, these are evidence that there is a difference in the proportions, yes.").

[27] 9/14/07 Bertozzi Trial Tr. 1073:19-21.

insufficient as a matter of law to meet Roche's burden to prove anticipation by clear and convincing evidence. [29]

In support of her opinion that Goldwasser's urinary EPO was the same EPO product as the products claimed in '933 claim 3, Dr. Bertozzi relied primarily on Amgen's early publications documenting SDS-PAGE experiments comparing certain enzymatic digests of urinary EPO to various enzymatic digests of EPO purified from mammalian CHO and COS cells grown in culture.[30] But those Amgen publications did not say that the recombinant EPO was identical structurally to Goldwasser's urinary EPO — only that the SDS-PAGE data indicated "that both molecules are glycosylated to a similar extent" and that the "carbohydrate composition" was "essentially the same."[31] These statements say nothing about the identity of the structures of recombinant EPO as compared to urinary EPO.

Moreover, as Dr. Bertozzi grudgingly admitted, "SDS-PAGE data alone do not provide actual structural information."[32] Indeed, as Dr. Varki explained, SDS-PAGE is the least sensitive technique for analyzing glycoprotein structure.[33] While an SDS-PAGE analysis can, in certain circumstances, reveal a difference in the structure of two EPO products, it cannot, standing alone, provide a sufficient basis to conclude that two products are structurally

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[28] 9/14/07 Bertozzi Trial Tr. 1069:20-1072:18, 1073:14-22.

[29] Such opinions are precisely the kind of speculative, unsupported, and possibly biased oral testimony, offered as clear and convincing evidence to invalidate an issued patent, which is not appropriate absent corroboration. *Finnigan Corp. v. Int'l. Trade Comm'n.*, 180 F.3d 1354, 1369 (Fed. Cir. 1999) (The law requires "corroboration . . . of any witness whose testimony alone is asserted to invalidate a patent, regardless of his or her level of interest"); *see also Texas Digital Systems, Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1217 (Fed. Cir. 2002); *IMX, Inc. v. Lendingtree, LLC*, 405 F. Supp. 2d 479, 488 (D. Del. 2005).

[30] Roche's Memo (D.I. 1315) at 8, citing TX 2059, 2061, and 2062; 9/14/07 Bertozzi Trial Tr. 1037:22-1407:22.

[31] TX 2059 at 6; 9/14/07 Bertozzi Trial Tr. 1042:3-18.

[32] 9/24/07 Bertozzi Trial Tr. 1140:24-ll41:4.

[33] 10/2/07 Varki Trial Tr. 2187:20-2188:25, 2185:14-2186:5.

identical.[34] Because SDS-PAGE differentiates glycoproteins on the basis of their relative size and charge, it cannot establish whether the glycosylated structures of two EPO preparations are identical or not.

As Dr. Varki further explained, the fact that some SDS-PAGE analyses do not show differences does not mean that such differences do not in fact exist.[35] Moreover, as Dr. Varki testified, numerous SDS-PAGE analyses ignored by Dr. Bertozzi demonstrate detectable structural differences between the glycosylated structure of Goldwasser's urinary EPO product and the glycosylated structure of EPO obtained from mammalian CHO and COS cells grown in culture.[36] For example, the SDS-PAGE experiment disclosed in the patent specification showed that the EPO products obtained from CHO and COS cells grown in culture have a higher molecular weight than Goldwasser's urinary EPO.[37] Similarly, SDS-PAGE experiments reported in the laboratory notebooks of Dr. Strickland reveal differences in molecular weight between Dr. Goldwasser's urinary EPO and EPO produced in mammalian cells grown in culture.[38]

The highly selective bases for Dr. Bertozzi's opinions was revealed by her reliance on a single sentence from a 1988 publication by Amgen scientist Dr. Vapnek.[39] Pointing to a statement regarding the physical comparisons made to date between Goldwasser's urinary EPO

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[34] 10/2/07 Varki Trial Tr. 2187:20-2188:25. As this Court previously found, it is "an erroneous notion." *Amgen Inc. v. Hoechst Marion Roussel, Inc*., 126 F.Supp. 2d 69, 143 (D. Mass 2001).

[35] 10/2/07 Varki Trial Tr. 2192:23-2192:8. *See also* TX 2011:312-14 (*Fritsch v. Lin*, 21 U.S.P.Q.2d 1739, 1742 (B.P.A.I. 1992)("The fact that the carbohydrate composition of rEPO and uEPO may be similar in some respects, or that their biological properties are indistinguishable, does not establish that there are no differences in average carbohydrate composition.").

[36] 10/2/07 Varki Trial Tr. 2187:20-2188:10; 2191:13-2192:3.

[37] 10/2/07 Varki Trial Tr. 2189:3-2190:15. This experiment reports different enzymatic digests from the SDS-PAGE experiments reported in the Amgen publications and thus compared different portions of the carbohydrate structures of urinary and recombinant EPO products. Compare TX-1, Col. 28:33-50, with TX-2059, Fig. 4 and 9/14/07 Bertozzi Trial Tr. 1103:5-1112:11.

[38] 10/2/07 Varki Trial Tr. 2191:10-2192:3.

and Lin's recombinant EPO, she told the jury that "I reached the same conclusion, which is that Goldwasser's EPO is not distinguished from the recombinant EPO from CHO cells."[40] But that was not the conclusion reached in the paper, and her testimony conveniently overlooked other passages in the paper where the author and others made clear that they ***did not believe*** that recombinant EPO had the same glycosylation structure as urinary EPO:[41]

> Dr. Vapnek: ***No, I'm not saying they're identical***. By the method that we have used, the only difference we can detect is a difference in the specific activity, and it is higher in the recombinant material. We just have not – we just have not done that much work with the natural material."[42]
>
> * * *
>
> Dr. Liu: . . . that carbohydrate ***will not be identical in any way*** between natural and the rDNA products.[43]

The misleading and unsubstantiated bases for Dr. Bertozzi's opinions became even more apparent when, on ***redirect examination***, she asserted without substantiation that she had performed a "statistical analysis" "to determine the likelihood that the structures from the CHO EPO are the same as those in Goldwasser's EPO."[44] Then on re-cross she admitted that her newly revealed "statistical analysis" was nowhere disclosed in her expert report.[45]

In contrast to Dr. Bertozzi's unsubstantiated opinions, Dr. Varki explained why the different processes and sources from which the claimed EPO glycoproteins are obtained — mammalian, non-human or CHO cells grown in culture — inevitably lead to structural and functional differences between the claimed EPO products and Dr. Goldwasser's prior art urinary

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[39] 9/14/07 Bertozzi Trial Tr. 1046:5-1047:14, citing TX 2062.

[40] 9/14/07 Bertozzi Trial Tr. 1047:7-14.

[41] 9/14/07 Bertozzi Trial Tr. 1097:3-1102:5.

[42] 9/14/07 Bertozzi Trial Tr. 1099:14-1101:4, citing TX 2062 (AM-ITC 00580155)(emphasis added).

[43] 9/14/07 Bertozzi Trial Tr. 1101:13-1102:5, citing TX 2062 (AM-ITC 00580154)(emphasis added).

[44] 9/24/07 Bertozzi Trial Tr. 1149:15-1151:1.

EPO.[46] As Dr. Varki explained, there are many reasons why EPO produced *in vitro* is very different than EPO made in the human body, including differences in cell type, the need for specifically modified cells capable of growth in culture, the environment in which the cells are grown, and the environment in which the resulting EPO products are excreted.[47] And that is why, as Dr. Bertozzi admitted, the glycoyslation of a protein produced by living tissue can differ drastically from the glycosylation of the same protein when produced by cells from the same tissues grown in culture.[48]

As Dr. Varki showed, the differences in EPO glycoprotein structures that result from such differences in process and source are very real. Indeed, all of the various analytical techniques commonly used to compare the structures of glycoprotein products consistently reveal significant differences between Goldwasser's prior art urinary product and the claimed inventions.[49] Based on his extensive analysis of the results available from each of these techniques, Dr. Varki opined that recombinant human EPO differs from urinary EPO in numerous respects such as half-life, specific activity, sulfation and glycosylation, including the identity and structure of the carbohydrates attached to the EPO molecule.[50]

For example, Dr. Varki described — and, unlike Dr. Bertozzi, showed — evidence of a widely used prior art technique for detecting differences in structure between two EPO

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[45] 9/24/07 Bertozzi Trial Tr. 1178:20-23.

[46] 10/2/07 Varki Trial Tr. 2173:24-2174:7 and 2237: 5-2239:19. Roche criticizes Dr. Varki's opinion because there are many different mammalian cell types, but makes no mention of Dr. Varki's testimony noting that the number of mammalian cell types that could produce a glycoprotein like EPO is "far, far, far, far, fewer." 10/2/07 Varki Trial Tr. 2249:17-19.

[47] 10/2/07 Varki Trial Tr. 2173:24-2175:23.

[48] 9/14/07 Bertozzi Trial Tr. 1078:10-16.

[49] 10/2/07 Varki Trial Tr. 2182:24-2183:4, 2185:14-23, 2176:7-15, 2215:22-2218:4, 2196:8-2197:3, 2215:5-2217:6, 2187:20-2188:10, 2191:13-2192:3, 2189:3-2190:15, 10/3/07 Varki Trial Tr. 2264:5-11.

[50] 10/2/07 Varki Trial Tr. 2182:24-2183:4, 2185:3-11, 2194: 3-17, 2215:22-2218:4, 2174:4-2175:23, 2196:8-2197:3, 2215:5-2217:6, 2239:13-19; 2264:5-11.

glycoprotein preparations: isoelectric focusing (IEF).[51] As Dr. Varki explained, IEF analyses published in the scientific literature and in Amgen's own laboratory notebooks reveal marked differences in glycosylation patterns between urinary and recombinant EPO.[52] For example, one IEF analysis performed by Dr. Strickland and submitted to the Patent Office revealed a dramatic structural difference between Goldwasser's urinary EPO and recombinant EPO based on the residual negative charge in urinary EPO after the enzymatic removal of sialic acids.[53] That difference in charge demonstrates that Goldwasser's urinary EPO contains negatively charged chemical structures other than sialic acid, and that such structures are missing in recombinant EPO.[54] As Dr. Varki explained, the most likely explanation for that structural difference is the presence of additional sulfation in the glycans of urinary EPO as compared to recombinant EPO.[55]

Similarly, IEF analysis of urinary and recombinant EPO products, reported in the learned treatise *Nature*, showed that human EPO in urine does not contain many of the glycoforms contained in recombinant EPO.[56] While the IEF analysis reported in *Nature* did not analyze Goldwasser's urinary EPO, the test results are nonetheless relevant because the test examined all of the forms of EPO that are present in human urine. Since it is not possible to purify an isoform that is not present in the starting material, the EPO glycoforms observed in whole urine necessarily define the set of EPO glycoforms that could have been present in Goldwasser's prior art urinary EPO.[57] Consequently, the IEF differences observed in the test between human EPO

[51] 10/2/07 Varki Trial Tr. 2194:18-2195:5, 2230:5-2231:1, 2204:24-2209:6. The IEF technique was available in 1983-84. 10/2/07 Varki Trial Tr. 2225:23-25.

[52] 10/2/07 Varki Trial Tr. 2196:21-2197:3, 2207:24-2209:3, 10/3/07 Varki Trial Tr. 2264:5-11.

[53] TX 2011A; 10/2/07 Varki Trial Tr. 2207:24-2208:24.

[54] 10/2/07 Varki Trial Tr. 2208:25-2209:3.

[55] 10/3/07 Varki Trial Tr. 2284:7-2285:17.

[56] 10/2/07 Varki Trial Tr. 2231:8-13, 2230:14-2231:1.

[57] 10/2/07 Varki Trial Tr. 2226:22-2227:14.

in urine and recombinant EPO necessarily reflect differences that must exist between any EPO purified from urine and recombinant EPO.[58] From the gel it is very easy to distinguish each recombinant EPO from total urinary EPO, which necessarily encompasses everything that was in Goldwasser's EPO.[59]

In addition to SDS-PAGE and IEF, Dr. Varki also relied on the analytical results obtained using another highly sensitive test: Dionex HPLC anion exchange chromatography. As Dr. Varki explained, the Dionex test reveals dramatic differences in the structures of the sugar chains present in Goldwasser's urinary EPO as compared to EPO produced in mammalian cells grown in culture.[60] The Dionex analysis shows that the types of sugar chains present on Goldwasser's urinary EPO were "quite, quite different" from those on recombinant EPO.[61] Each peak in the Dionex analysis represents a separate kind of sugar chain with different structures, different sialic acids, and different amounts of sulfate residues.[62] It is "very clear that essentially none of the peaks observed in the urinary EPO can be precisely aligned with the peaks observed in the recombinant EPO."[63] In addition, because all of the recombinant EPO peaks come off the HPLC column early, whereas the majority of urinary EPO peaks come off the column much later the preparations must include different sugar chains. Even the urinary peaks that come off the column early do not overlap with the peaks found in recombinant EPO. This difference is consistent with the difference between urinary and recombinant EPO detected in IEF analyses, and further demonstrates that urinary EPO is structurally different than recombinant EPO.[64]

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[58] 10/2/07 Varki Trial Tr. 2226:22-227:14, 2195:16-2196:12.
[59] 10/2/07 Varki Trial Tr. 2230:14-2231:13.
[60] 10/2/07 Varki Trial Tr. 2213:14-2218:4.
[61] 10/2/07 Varki Trial Tr. 2215:22-2216:20.
[62] 10/2/07 Varki Trial Tr. 2216:21-2218:4.
[63] 10/2/07 Varki Trial Tr. 2215:20-2216:15.
[64] 10/2/07 Varki Trial Tr. 2217:7-2218:4.

Notably, Dr. Bertozzi did not even address the IEF gels or Dionex experiments in her testimony.[65] While Dr. Bertozzi stated that "one needs a collection of data" to conclude that the structures of EPO included within the claims are the same as the structures in Goldwasser's urinary EPO, she ignored the most salient data available and chose not to present any data to the jury other than a few irrelevant SDS-PAGE analyses.[66]

Finally, Roche mistakenly suggests that the Dionex test cannot be relied on to show differences between the prior art and Dr. Lin's inventions because it was not available at the time the patent application was filed.[67] Roche's cited cases are irrelevant to the issue here: whether evidence that became available after 1984 can be used to show what characteristics and properties prior art molecules inherently possessed for purposes of comparing between prior art preparations and products claimed in the patents.

It is a well-established principle that post-filing evidence is admissible to establish such inherent facts that were true before the filing date and are equally true after the filing date:

> In certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. *In re Wilson*, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism.[68]

This widely-cited principle stated in the current Manual of Patent Examining Procedure was set out in *In re Wilson*,[69] where the Court of Customs and Patent Appeals affirmed the use of a post-filing publication as evidence "to show a state of fact" — the characteristics of properties of polyurethane foam made by the processes of the prior art of record — characteristics that were

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[65] 9/24/07 Bertozzi Trial Tr. 1151:27.

[66] 9/24/07 Bertozzi Trial Tr. 1139: 12-16.

[67] Roche's Memo (D.I. 1315) at 10.

[68] Manual of Patent Examining Procedure ("MPEP") § 2124 (8th ed. Rev. 5, Aug. 2006).

[69] 311 F.2d 266, 268-69 (C.C.P.A. 1962) ("The board considered that the publication was properly cited to show a state of fact. After reading the entire publication, so do we. It clearly is a discussion of the properties of polyurethane foam products generally, products made by the processes of the prior art of record in this case . . . As evidence of the characteristics of prior art

equally true before the 1954 filing date and on the 1956 date of the post-filing evidence relied upon by the examiner. Similarly, in *In re Kratz*,[70] the Court of Customs and Patent Appeals upheld reliance on post-filing evidence that the claimed chemical compound occurred naturally in strawberries.

As this Court correctly noted, "if the existential fact is that the source limitation imparts a difference, when the source limitation is called out we are entitled to use all the data we have to understand what that difference in fact is."[71] The Court's ruling is consistent with the principle set out in *In re Wilson* and relied upon by the Manual of Patent Examining Procedure that evidence to show existential facts is admissible regardless of whether the evidence became available before or after the date of the patent application.[72]

Because the structures and functions of Goldwasser's urinary EPO and EPO produced from mammalian cells grown in culture are the same today as they were in 1983, admission of evidence that first became available in 1992 to demonstrate those inherent and existential facts is entirely proper. Because such inherent, universal properties do not change over time, evidence of their existence is equally probative regardless of when that evidence becomes available. For example, the fact that the Earth is not exactly round was as true in 1983 as it is in 2007. If that fact were at issue in a trial, it would be unfair to admit a crude measurement made in 1983 that suggested the earth ***is*** perfectly round but refuse to admit an experiment conducted by a more sophisticated technique that only became available in 2007 to prove the actual truth as it existed in 1983. Were the later experiment precluded, then the wrong party would prevail, despite

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foam products, however, we know of no reason in law why it is not acceptable.")

[70] 592 F.2d 1169, 1174 (C.C.P.A. 1979) ("the Kratz and Mussinan et al. publications establish the 'inherent scientific fact' . . . that 2M2PA is a naturally occurring constituent of strawberries and is not 'per se' novel . . . Mussinan et al. was published after the filing date . . . .")

[71] 10/2/07 Varki Trial Tr. 2179:6-18.

[72] *In re Wilson*, 311 F.2d 266, 268-69 (C.C.P.A. 1962); *Plant Genetic Systems, N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1343-44 (Fed. Cir. 2003); MPEP § 2124 (8th ed. Rev. 5, Aug.

contradictory facts that had always been true.

Roche's cases say nothing about the issue; instead, the cases concern the use of tests developed after the filing date as proof for purposes of whether the claims satisfy Section 112 requirements.[73] As the Court in *In re Hogan* made clear, post-filing evidence is not permissible for purposes of determining whether the specification complies with Section 112, but post-filing evidence is permissible for a number of other purposes including understanding the characteristics of prior art products:

> This court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application. That approval does not extend, however, to the use of a later . . . publication disclosing a later . . . existing state of the art in testing an earlier (1953) application for compliance with § 112, first paragraph. The difference may be described as that between the permissible application of later knowledge about art-related facts existing on the filing date and the impermissible application of later knowledge about later art-related facts . . . which did not exist on the filing date.[74]

Roche has therefore presented no case law that actually supports its argument that the Dionex test, presented as evidence of the pre-existing characteristics and properties of Goldwasser's urinary EPO as compared to the claimed inventions should be excluded.

2. Roche Failed To Establish That Goldwasser's Urinary EPO Was Identical To Any Embodiment Of '933 Claims 7 or 8

With respect to claims 7 and 8 of the '933 patent, which are dependent on '933 claim 3 and further require that the EPO be produced in non-human mammalian cells and CHO cells, respectively, Dr. Varki identified additional structural differences between the claimed EPO

2006).

[73] *In re Wright*, 999 F.2d 1557, *1563 (Fed. Cir. 1993) (no discussion of obviousness and anticipation); *National Research Development Corp. v. Great Lakes Carbon Corp*., 410 F. Supp. 1108, 1123 (D. Del. 1975) ("Neither this finding nor any other remark in connection with the distinction over the prior art for definiteness purposes should be interpreted as prejudging or otherwise relating to any issues within the purview of 35 USC 102 and 103. In particular, the Court is making no judgment on novelty or obviousness, neither of which were issues tried to the Court.").

[74] *In re Hogan*, 559 F.2d 595, 604 (C.C.P.A 1977); *see also* MPEP § 2124 (8th ed. Rev. 5, Aug. 2006).

preparations and Goldwasser's urinary EPO.[75] EPO produced in the non-human mammalian cells of '933 claim 7 will contain a different type of sugar known as Neu5Gc that is not produced by human cells and therefore cannot be present in Goldwasser's urinary EPO.[76] EPO produced in CHO cells, as required in '933 claim 8, will contain different sialic acid linkages than urinary EPO. In particular, Dr. Varki testified that sialic acid linkages called alpha 2-6 linkages are found in human urinary EPO but not in EPO produced from CHO cells.[77] Dr. Varki's observations were echoed in the testimony of Dr. Strickland (by deposition) in Roche's case that not all the structures in Goldwasser's urinary EPO are found in recombinant EPO; for example, there are different sialic acid linkages in each.[78] While these differences in sialic acid linkages were explicitly reported in Amgen's PLA, [79] Dr. Bertozzi failed to address these or the Neu5Gc differences in her testimony.

In short, it is Roche, not Amgen, that has failed to present a legally sufficient evidentiary basis for a verdict in its favor on its defense of anticipation to '933 claims 3, 7 or 8, and Amgen respectfully requests that judgment be entered for Amgen on Roche's anticipation defense to these claims.

B. ROCHE HAS FAILED TO ESTABLISH BY CLEAR AND CONVINCING EVIDENCE THAT '933 CLAIMS 9, 11, 12 OR 14 WERE ANTICIPATED

Claims 9, 11, 12 and 14 of the '933 patent all incorporate by reference the limitations of '933 claim 3 to "a non-naturally occurring EPO glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence encoding human erythropoietin said

[75] 10/2/07 Varki Trial Tr. 2237:21-2239:19.

[76] 10/2/07 Varki Trial Tr. 2237:21-2239:4.

[77] 10/2/07 Varki Trial Tr. 2239:5-19.

[78] 9/25/07 Strickland Trial Tr. 1376:17-25.

[79] 10/2/07 Varki Trial Tr. 2193:17-2194:17; TX 2057 at AM-ITC 00092890 ("Although the structures of the carbohydrate moieties of r-HuEPO and u-HuEPO are the same (the only qualitative difference is the apparent presence of a sialic acid linkage other than a2-3 in uEPO), the relative amounts of each population are different.").

product possessing the *in vivo* biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells."[80] Claims 9, 11, 12 and 14 of the '933 patent also add various additional limitations, including the requirement of a "pharmaceutical composition," an amount of the claimed EPO glycoprotein product "effective for erythropoietin therapy," an "amount effective to increase the hematocrit level of a patient," and a "pharmaceutically acceptable diluent, adjuvant or carrier." Because '933 Claims 12 and 14 further depend from '933 claim 7, they are further limited by the restriction to glycoprotein products of the expression in a non-human mammalian cell.

1. Roche Failed to Present Evidence Sufficient to Show That Any of Its Cited References Anticipated The EPO Glycoprotein Limitation of '933 Claims 9, 11, 12 or 14

An invention is anticipated only if it is not novel; that is, only if the *identical* invention was already known to others.[81] As explained at length above, it was incumbent upon Roche to come forward with clear and convincing evidence that the naturally occurring EPO preparations purportedly contained in its asserted prior art references were in fact structurally identical to the non-naturally occurring EPO product of '933 claim 3. Roche failed to present clear and convincing evidence sufficient to show that any of the four references asserted against '933 claims 9, 11, 12 and 14 (the Baron/Goldwasser three-patient experiment, the Eschbach single-patient plasma experiment, publications describing the Essers plasma experiment, or the 1977 Miyake publication) described a non-naturally occurring EPO glycoprotein product that was structurally and functionally *identical* to the non-naturally occurring EPO glycoprotein product

[80] TX 1 ('933 claim 3).

[81] *See C.R. Bard v. M3 Sys.*, 157 F.3d 1340, 1360 (Fed. Cir. 1998)("'Anticipation' requires that the ***identical invention*** was already known to others, that is that the claimed invention is not new")(emphasis added)(citing *Minnesota Mining & Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559 (Fed. Cir. 1992); *SmithKline Beecham Corp. v. ApotexCorp.*, 403 F.3d 1328, 1329 (Fed. Cir. 2005)(Newman, J., dissenting)("Invalidity based on 'anticipation,' 35 U.S.C. § 102, requires that the ***identical invention*** was known or its existence would reasonably have been known to a person of ordinary skill in the field of the invention")(emphasis added).

claimed in '933 claim 3.[82]

Roche did not offer *any* evidence that any product contained in the human plasma preparations described by Drs. Essers and Eschbach was identical to the EPO products claimed in '933 claim 3. Roche presented absolutely no evidence establishing that the EPO purportedly present in either Essers' plasma or Eschbach's plasma was identical to the claimed EPO product. It is indisputable that whatever EPO may have been present in these human plasma preparations would have been naturally occurring and not man-made.

The only EPO preparation for which Roche offered any comparative evidence was the urinary EPO described in the 1977 Miyake/Goldwasser paper. But, as detailed above, that showing falls woefully short of clear and convincing proof that Goldwasser's urinary EPO was identical to the non-naturally occurring glycoprotein product of '933 claim 3. Moreover, as Dr. Brugnara's uncontroverted testimony established, Goldwasser's urinary preparation also increased the white blood cell count of test hamsters.[83] Because recombinant human EPO does not increase white blood cell counts, this dramatic difference in function necessarily demonstrates a significant difference in structure as well.[84] The only reasonable inference that can be drawn from this dramatic difference is that Goldwasser's urinary EPO differs in structure

[82] Dr. Spinowitz admitted that none of the references he reviewed involved an exogenous DNA sequence encoding human EPO (9/12/07 Spinowitz Trial Tr. 875:2-12), and that none of the references he reviewed contained EPO recovered from cell culture. (9/12/07 Spinowitz Trial Tr. 873:19-874:19. This Court defined "expression" to mean that "the glycoprotein was produced in a cell and recovered from the cell culture." *See* 7/3/07 Memorandum and Order as to Claim Construction ("Claim Construction Order") (D.I. 613) at 32 n.2 (7/3/07 Memorandum and Order as to Claim Construction). Regarding *Miyake*, Roche proffered Dr. Bertozzi but she conceded that *Miyake* described a process for purifying EPO ***from urine***. 9/14/07 Bertozzi Trial Tr. 1012:16-1013:6. Dr. Spinowitz offered no opinions as to whether *Miyake* anticipates any of the '933 claims.

[83] 10/1/07 Brugnara Trial Tr. 2036:25-2039:8. *See also* TX 2050 at BARON 00078 (The test hamsters (labeled E, F, G, H) had an average white blood cell count ("WBC") of 15.1, 100% higher than the average white blood cell count of the control hamsters (labeled A, B, C, and D), 7.5.

[84] 10/1/07 Brugnara Trial Tr. 2038:2-2039:8.

from the claimed EPO products.[85] Additionally, the Baron/Goldwasser investigators noted shortly after injecting Goldwasser's urinary EPO that the product fell apart into "subunits or breakdown products" or "fragments" and demonstrated an "unexpectedly rapid" half-life — occurrences again not found with recombinant human EPO,[86] further evidencing that Goldwasser's urinary EPO was fundamentally different than Lin's claimed glycoprotein products.

Because Roche failed to present a legally sufficient evidentiary basis for a verdict of anticipation of '933 claims 9, 11, 12 or 14 based on any of its asserted references, judgment should be entered for Amgen on Roche's anticipation defense to each of these claims.

2. Roche Failed To Prove That Any Cited Reference Anticipated The Remaining Limitations of '933 Claims 9, 11, 12 or 14

Roche also failed to present clear and convincing evidence sufficient for a verdict that any one of the prior art references also satisfied each of the remaining limitations of '933 claims 9, 11, 12 or 14. The law of anticipation requires that ***each and every*** claim limitation must be found in the allegedly anticipating reference.[87] None of the specific references Roche asserts describes the "pharmaceutical composition," "increase production of reticulocytes and red blood cells," and "effective amount of a glycoprotein product effective for erythropoietin therapy" limitations of '933 claims 9 and 12.[88] And, none possesses the "administering a pharmaceutical

[85] 10/1/07 Brugnara Trial Tr. 2038:2-2039:8.

[86] 10/1/07 Brugnara Trial Tr. 2036:25-2039:8; 2040:12-2042:15. *See also* TX 2004 at AM-ITC01006623-25; TX 2045 at AM-ITC 00991063.

[87] *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1324 (Fed. Cir. 2006)("The term 'anticipation' in patent usage means that the invention was previously known to the public; that is, that it previously existed in the precise form in which it is claimed, including all of the limitations in the claim.")(citing *General Electric Co. v. Nintendo Co.*, 179 F.3d 1350, 1356-57 (Fed. Cir. 1999)).

[88] In its entirety, '933 claim 3 reads "A non-naturally occurring glycoprotein product of the expression in a mammalian host cell of an exogenous DNA sequence comprising a DNA sequence encoding human erythropoietin said product possessing the in vivo biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells." '933 claim 9 recites "a pharmaceutical composition comprising an effective amount [of] a glycoprotein product

composition of [claims 9 or 12] in an amount effective to increase the hematocrit" of a kidney dialysis patient limitation of '933 claims 11 and 14.[89] Because Roche failed to present clear and convincing evidence sufficient for a verdict that any specific reference possesses all of the limitations of any given claim, Roche's motion to direct a verdict of anticipation must be denied.

3. Roche Failed To Prove That The Baron/Goldwasser Three-Patient Experiment Anticipated '933 Claims 9, 11, 12 or 14

Roche failed to prove that the Baron/Goldwasser three-patient experiment involved a "pharmaceutical composition." A "pharmaceutical composition," as defined by this Court, is a composition suitable for administration to humans.[90] As Dr. Brugnara testified, the ordinarily skilled person as of 1983-84 would not have considered the urinary EPO preparation used in the Baron/Goldwasser experiment to be suitable for administration to humans because it was associated with a significant increase in white blood cell count in test hamsters (indicative of a toxin or contaminant), fell apart shortly after injection into "subunits and breakdown products" or "fragments," showed an "unexpectedly rapid" half-life, and lacked any significant erythropoietic effect.[91] These worrisome attributes of the urinary preparation, as Dr. Brugnara testified, would have convinced the ordinarily skilled physician and his or her Institutional Review Board as of 1983-84 not to permit any more of this urinary material to be given to any human.[92] Thus, the urinary material was not a "pharmaceutical composition."[93] Not only did

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effective for erythropoietin therapy according to claim 1, 2, 3, 4, 5, or 6 and a pharmaceutically acceptable diluent, adjuvant, or carrier." '933 claim 12 is similar to claim 9, and is dependent on claim 7 rather than claims 1, 2, 3, 4, 5, or 6. TX 1.

[89] '933 claim 11 reads, "[a] method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient." '933 claim 14 reads "[a] method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product." TX 1.

[90] Claim Construction Order (D.I. 613) at 21.

[91] 10/1/07 Brugnara Trial Tr. 2036:25-2039:8; 2040:12-2042:15.

[92] 10/1/07 Brugnara Trial Tr. 2041:2-2042:15.

[93] 10/1/07 Brugnara Trial Tr. 2037:2-12.

Roche completely fail to rebut Dr. Brugnara's testimony but elsewhere it relies upon the very documents — TX 2004 and TX 2045 — which report to the FDA and NIH the worrisome subunits and breakdown products and unexpectedly short half life of the urinary material.[94]

Similarly, Roche has not presented clear and convincing evidence sufficient to show that "an effective amount of a glycoprotein product effective for erythropoietin therapy"[95] was used in the Baron/Goldwasser three-patient experiment. The Court's construction requires that the preparation at issue must be one "***that elicits***" one or all of the recited effects. Roche, therefore, must prove that (1) there was in fact such an effect, and (2) it was actually caused by the urinary EPO preparation used in the experiment. Merely pointing to a purported effect in one or two patients while ignoring the absence of any effect in the other patient as well as other alternative explanations does not constitute clear and convincing proof that the urinary preparation caused the observed effect. Rather it was incumbent upon Roche to prove by clear and convincing evidence that there was in fact an effect and that nothing other than the urinary EPO — in particular as opposed to natural variation or range of error — plausibly accounts for its cause. But Roche failed to do so. Nor could it since as Dr. Goldwasser testified, "the experiment did not show anything conclusive; that one could not draw any conclusions from it, from the data," and that "there weren't enough measurements made, there weren't enough patients studied, there wasn't a long enough time of administration."[96] Dr. Brugnara, after reviewing all of the data

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[94] TX 2004 at AM-ITC 01006623-24; TX 2045 at AM-ITC 00991063. *See* Roche's Memo (D.I. 1315) at 11.

[95] This Court has defined "effective amount of a glycoprotein product effective for erythropoietin therapy" to have the same meaning as "therapeutically effective amount." "A therapeutically effective amount is one that elicits any or all of the effects often associated with in vivo biological activity of natural EPO, such as those listed in the specification, column 33, lines 16 through 22, stimulation of reticulocyte response, development of ferrokinetic effects (such as plasma iron turnover effects and marrow transit time effects), erythrocyte mass changes, stimulation of hemoglobin C synthesis, and as indicated in Example 10, increasing hematocrit in mammals" Claims Construction Order (D.I. 613) at 23-25.

[96] 10/1/07 Goldwasser Trial Tr. 1998:24-1999:5; 1998:24-1999:23.

produced by Dr. Baron, independently found the data to be contradictory and inconclusive.[97]

Regarding reticulocytes, Roche failed to prove that the urinary preparation caused any purported increase. As Drs. Baron and Brugnara testified, establishing the state of the patient before he or she received any test agent — the "baseline" — was essential to any comparison to determine if the urinary material had caused any erythropoietic effect.[98] They also testified that the investigators failed to conduct the full baseline measurements the investigators represented to the FDA would be taken.[99] Drs. Baron and Brugnara confirmed that the three patients exhibited natural variation in their normal levels of reticulocytes, and Dr. Baron testified specifically that Patient 1 exhibited a three-fold variation in reticulocyte measurements in the pre-test phase.[100] Additionally, Dr. Brugnara testified that the ordinarily skilled person at the time would have understood that the manual reticulocyte counting method used in the experiment was subject to a wide range of error due to its subjective nature.[101] Given these facts, it was Roche's burden to prove by clear and convincing evidence that (1) there was, in fact, an increase in reticulocytes, ***and*** (2) it was caused by the urinary material ***and not*** the patients' natural biological variation or the technician's range of error. But once again Roche failed to do so.

The third page of TX 2049A is representative of the contradictory and inconclusive nature of the reticulocyte data for all three patients. As Dr. Spinowitz was forced to concede, that exhibit shows the widely divergent reticulocyte values taken on the same days from the

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[97] 10/1/07 Brugnara Trial Tr. 2029:2-2030:19. As Dr. Brugnara testified, he reviewed the entirety of the clinical data from the experiment, TX 2049, "at least twice, page by page . . . " *See* 10/1/07 Brugnara Trial Tr. 2076:9-21; 2045:2-9. Roche's attacks as to the completeness of Dr. Brugnara's review are simply untrue.

[98] 9/11/07 Baron Trial Tr. 676:18-23; 10/1/07 Brugnara Trial Tr. 2024:24-2025:19.

[99] 9/11/07 Baron Trial Tr. 676:24-678:3; 10/1/07 Brugnara Trial Tr. 2033:12-22.

[100] 10/1/07 Brugnara Trial Tr. 2029:2-2030:12; 2033:12-2034:13; 9/11/07 Baron Trial Tr. 678:11-21.

[101] 10/1/07 Brugnara Trial Tr. 2032:15-2033:7. Notably, Drs. Baron, Spinowitz, and Brugnara all agree that the reticulocytes counts were done manually. *See* 9/11/07 Baron Trial Tr. 675:7-676:12; 9/12/07 Spinowitz Trial Tr. 897:6-19; 10/1/07 Brugnara Trial Tr. 2030:21-2031:6.

same sample for the same patient (#3) as measured by two different laboratories.[102] Virtually all of the reticulocyte data points for this patient fell within both the range of natural variation and range of error.[103] As to the single reticulocyte measurement just outside those ranges, Dr. Baron testified that he wrote a question mark next to it because he could not make any sense of it in light of the other data points.[104] Further demonstrating the imprecision of the manual and subjective reticulocyte assay, on the same day that one laboratory measured this reticulocyte count so high that it was questioned, a second laboratory measured the same sample on the same day and returned a value that was ***well below*** the ranges of natural variation and error.[105] As Dr. Brugnara explained, the range of error, or noise, and natural variation associated with the assay prevent one from drawing any conclusion that reticulocytes increased as a result of the urinary preparation.[106] The same was true for Patient 1, who again had conflicting data from two different laboratories[107] and Patient 2, whose values did not meaningfully change.[108]

Regarding ferrokinetics, Roche failed to prove the urinary preparation caused an increase in any of the patients. This is because of the investigator's failure to measure plasma iron turnover and to measure marrow transit time.[109] Notably, these are the very two measures identified in the Court's construction to exemplify ferrokinetic effects. What ferrokinetic data

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[102] TX 2049A BARON 211A; 10/1/07 Brugnara Trial Tr. 2031:20-2035:3; 9/12/07 Spinowitz Trial Tr. 896:10-22; 922:8-923:19; 926:8-10.

[103] 10/1/07 Brugnara Trial Tr. 2033:12-2034:13.

[104] 9/11/07 Baron Trial Tr. 679:3-22.

[105] 9/11/07 Baron Trial Tr. 679:3-22; 9/12/07 Spinowitz Trial Tr. 906:17-910:22; 10/1/07 Brugnara Trial Tr. 2033:8-2034:7.

[106] 10/1/07 Brugnara Trial Tr. 2033:12-2035:3.

[107] 10/1/07 Brugnara Trial Tr. 2034:14-2035:3. *Compare* reticulocyte values recorded in TX 2049 at BARON 00801 with BARON 00717. For each day there are divergent values: 7/12/79 (1.5 vs. 1.0), 7/14/79 (2.2. vs. 0.9), 7/16/79 (2.5 vs. 1.4), 7/18/79 (3.1 vs. 1.8), and 7/20/79 (4.1 vs. 0.3 "probably incorrect").

[108] 10/1/07 Brugnara Trial Tr. 2034:14-2035:3. *See also* TX 2049A at BARON 00210A (graph of reticulocytes for patient 2 that Dr. Brugnara characterized as "flat").

[109] 10/1/07 Brugnara Trial Tr. 2035:22-2036:19.

there were regarding iron incorporation were incomplete and contradictory as this parameter was measured in only two of the three patients, with one showing an increase and the other a decrease[110] — hardly clear and convincing evidence of anything.

Regarding erythrocytes (red blood cells),[111] Roche failed to prove that the urinary EPO preparation caused a real increase. Significantly, this is relevant not only to the Court's construction of "effective amount" but also as to the limitation of '933 claim 3 and the claims dependent upon it ('933 claims 7, 8, 9, 11, 12, and 14) which require an "increase in production of reticulocytes ***and red blood cells***."[112] As Dr. Brugnara testified, the red cell mass data are "all over the place," with one patient showing an increase, one showing a decrease, and one showing inconsistent results[113] — once again, not clear and convincing evidence.

Regarding hematocrit, Drs. Baron, Goldwasser, and Brugnara ***all*** concluded that there was no increase.[114] Indeed, as Dr. Brugnara testified this is the only consistent, coordinated, and uniform result in all 3 patients.[115] It should be noted that while the lack of an increase in hematocrit shows that one of the alternative parameters of the Court's construction of "effective amount" was not fulfilled,[116] it by itself is ***fully dispositive*** of no anticipation of '933 claims 11

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[110] *Id*. See also TX 2049 at BARON 00877 (showing a substantial decrease in iron incorporation from 63% to 43%.

[111] 9/12/07 Spinowitz Trial Tr. 929:24-25.

[112] TX 1 ('933 claim 3)(emphasis added).

[113] 10/1/07 Brugnara Trial Tr. 2035:8-21. *See*, *e.g.*, TX 2049 at BARON 00876 (Patient 2: with "? error" written next to red blood cell mass value of 1856); TX 2049 at BARON00892 (Patient 3: evidencing a decrease in red blood cell mass from 1002ml to 869ml).

[114] TX 19. Dr. Spinowitz admitted that Dr. Baron wrote, on a summary document, "no change" in hematocrit for each of the three patients enrolled in the experiment. 9/12/07 Spinowitz Trial Tr. 888:1-889:22. 10/1/07 Goldwasser Trial Tr. 2001:10-15 (as Dr. Goldwasser testified: "Because that was the observation made, that there was no data showing any change in hematocrit in the patients.") 10/1/07 Brugnara Trial Tr. 2028:3-17.

[115] 10/1/07 Brugnara Trial Tr. 2028:3-17.

[116] Since, as Dr. Brugnara testified, if the material had actually caused an effect, one would have expected to see a consistent, coordinated, and uniform pattern of response in all three patients, 10/1/07 Brugnara Trial Tr. 2025:20-2026:19, the failure to increase hematocrit in all three

and 14 since those claims separately require proof that the preparation actually caused an increase in hematocrit.[117]

Finally, Roche tries to rely on a putative increase in nucleated red blood cells ("NRBCs") as evidence of an erythropoietic response. But such reliance is misplaced since an increase in NRBCs is not an effect "***often associated*** with *in vivo* biological activity of natural EPO," as defined by the Court.[118] Roche failed to introduce any evidence that the art as of 1983-84 viewed NRBCs as an effect "***often associated*** with *in vivo* biological activity of natural EPO."[119] This is hardly surprising given that, as Dr. Brugnara testified, the procedure to extract bone marrow and count NRBCs is painful and not routinely employed.[120] That means it could not be repeated sufficient times to insure the accuracy of any such measurements. In any event, the NRBC measurements from the three patients were not properly done and the results were inconsistent and contradictory,[121] again not clear and convincing evidence.

For all of these reasons, Roche cannot meet its heavy burden of proof that the urinary preparation demonstrated an effective amount of a glycoprotein product effective for erythropoietin therapy.[122]

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patients provides additional corroboration that the urinary material failed to achieve an effect in any of the other parameters encompassed by the Court's construction.

[117] *See* TX 1. '933 claim 11 reads, "[a] method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 9 in an amount effective to increase the hematocrit level of said patient." '933 claim 14 reads "[a] method for treating a kidney dialysis patient which comprises administering a pharmaceutical composition of claim 12 in an amount effective to increase the hematocrit level of said product."

[118] Claim Construction Order (D.I. 613) at 23-25.

[119] Indeed, Dr. Baron did not include NRBCs as indicative of the "best ways of monitoring bone marrow function." 9/11/07 Baron Trial Tr. 668:13-20.

[120] 10/1/07 Brugnara Trial Tr. 2057:8-12. It is significant that for as much reliance as Roche places upon TX 2032 — the Eschbach 1984 article — which appears in the very section of the specification upon which the Court's construction is based, *see* TX 1 Col. 33: 29-30, that reference nowhere even mentions NRBCs, much less establishes a change in NRBCs as an effect ***often associated*** with the in vivo biological activity of natural EPO.

[121] 10/1/07 Brugnara Trial Tr. 2077:13-25.

[122] Roche's request for a directed verdict that the Baron/Goldwasser reference anticipates '933

4. Roche Failed To Prove That Any Of Essers' Publications Regarding Plasma Administration Anticipated '933 Claims 9 or 12

Roche asks this Court to enter judgment in its favor that '933 claims 9 and 12 are invalid as anticipated by the "Essers studies."[123] In its list of Anticipatory Prior Art,[124] Roche asserts Essers' TX 2051, TX 2052, and TX 2053 are printed publications under §§102(a) or (b) and ***no*** other basis. As such, all of the limitations of '933 claims 9 or 12 must be found within the four corners of each single publication.[125] But Roche failed to demonstrate that *any* specific limitation of claims 9 or 12 is found in any of the Essers publications, much less all of the limitations.[126] It should be noted that since Dr. Essers' 1973 (TX 2051) and Essers 1975 (TX2053 —which is a re-hash of Essers' 1973 and 1974 results) were specifically examined by the Patent Office, it was incumbent upon Roche to discharge a heightened burden of proof that any of Dr. Essers' publications anticipate '933 claims 9 or 12.[127] As shown, it failed to do so.

Dr. Essers' experiment infused a blood product — plasma — collected from one set of sick patients (suffering from aplastic anemia) into another set of sick patients (suffering from

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claims 9, 11, 12, and 14 should be denied and Amgen respectfully requests that judgment be entered that Baron/Goldwasser does not anticipate these claims.

[123] Roche's Memo (D.I. 1315) at 14-15.

[124] Roche's List of Prior Art and Chart Identified by Category Requested by the Court at the October 4, 2007 Afternoon Hearing ("Roche's List of Prior Art" (D.I. 1340) at 3.

[125] *Advanced Display Sys., Inc. v. Kent State Univ*., 212 F.3d 1272, 1282 (Fed. Cir. 2000).

[126] *See* Roche's Memo (D.I. 1315) at 14-15. Roche makes the blanket statement that "three articles by Dr. Essers . . . show that use of EPO-rich human plasma . . . in humans caused a measurable reticulocyte response, evidencing the stimulation of erythropoiesis by human EPO . . . " Nowhere in its Memorandum does Roche attempt to demonstrate where a single limitation is found in any of the three Essers' publications.

[127] The Essers publications are expressly identified and discussed in the Sytkowski declaration which was disclosed to the PTO and is in evidence at TX 2012 at 1069-70. *See Hewlett-Packard Co. v. Bausch & Lomb Inc*., 909 F.2d 1464, 1467 (Fed. Cir. 1990) (discussing heightened standard where evidence was previously considered by the PTO examiner during prosecution); s*ee also American Hoist & Derrick Co. v. Sowa & Sons, Inc*., 725 F.2d 1350, 1359 (Fed. Cir. 1984) (same); *Amgen, Inc. v. Hoechst Marion Roussel, Inc*., 126 F. Supp. 2d 69, 105 (D. Mass. 2001) (same).

kidney failure).[128] Notably, Dr. Essers did not use EPO. Indeed, she explained why: "Erythropoietin [was] not currently available commercially in the quantity and purity required for therapeutic use."[129] As discussed above, because Roche failed to prove that the structure of the EPO purportedly present in Essers' plasma renders the claimed EPO product not new, none of the Essers references anticipates '933 claims 9 or 12.

Furthermore, Roche failed to prove that the plasma administered by Dr. Essers is a "pharmaceutical composition," as defined by the Court. The ordinarily skilled person in 1983/84 would not have considered plasma taken from ***sick*** patients to be a pharmaceutical composition.[130] Plasma is not a "pharmaceutical composition" for the simple reason that it is a blood product. Indeed, the real world recognizes this distinction, as plasma is kept in the blood bank, not the pharmacy.[131] The reason for this practical distinction is clear: in contrast to a pharmaceutical product whose exact formulation is precisely defined and controlled, not all of the components of plasma are known. [132] As both Dr. Spinowitz and Dr. Brugnara testified, plasma contains a variety of substances that can vary by individual over time.[133] Unlike plasma, whose major components cannot be traced after the plasma is administered,[134] the components of a pharmaceutical composition are traceable. This uncharacterized and variable nature of blood products gives rise to a very real and dangerous risk of infection. Notably, here, Dr. Essers' experimental plasma was taken from ***sick*** patients.[135] Moreover, as Drs. Spinowitz, Friedman and Brugnara confirmed, the risks of viral transmission are similarly inherent in plasma

[128] 10/1/07 Brugnara Trial Tr. 2042:16-19.
[129] TX 2051 at AM-ITC 01005329.
[130] 10/1/07 Brugnara Trial Tr. 2042:16-19-2043:4.
[131] 10/1/07 Brugnara Trial Tr. 2042:16-2043:22.
[132] 10/1/07 Brugnara Trial Tr. 2043:6-22.
[133] 9/12/07 Spinowtiz Trial Tr. 935:11-14; 10/1/07 Brugnara Trial Tr. 2043:6-22.
[134] 10/1/07 Brugnara Trial Tr. 2043:6-23.
[135] 10/1/07 Brugnara Trial Tr. 2042:16-19.

infusions.[136] Indeed, for this reason, Dr. Lin's specification describes the claimed inventions in express contradistinction to the transfusion of blood products.[137] As the specification makes plain, two critical purposes of the claimed invention were to reduce transfusion dependence and avoid its attendant risks, including the transmission of viral infections. Given the specification, it makes no sense to deem Essers' plasma as an anticipatory "pharmaceutical composition."

In any event, Roche failed to prove that any of the Essers publications demonstrated an effective amount of a glycoprotein product effective for erythropoietin therapy. Dr. Spinowitz agreed that there was: (1) no increase in reticulocytes in four out of the five patients in Essers' 1973 study;[138] (2) no increase in hematocrit in any patient studied for any of the references;[139] and (3) no increase in erythrocytes (i.e., red blood cells) in any patient in any of the references.[140] Furthermore, it is uncontested that Dr. Essers did not measure ferrokinetic effects of any sort.

Dr. Essers' work does not anticipate '933 claims 9 or 12 for the further reason that Roche presented no evidence, other than Dr. Spinowitz's unsupported opinion that the plasma administered by Dr. Essers contained a diluent, adjuvant, or carrier.[141] In truth, the plasma was merely a blood product and there is no evidence that Dr. Essers added any diluent, adjuvant, or carrier to it.

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[136] 10/1/07 Brugnara Trial Tr. 2042:16-2043:22 9/25/07 Friedman Trial Tr. 1433:5-20; 9/12/07 Spinowitz Trial Tr. 936:8-15.

[137] TX 1, '933 patent, Col. 33:31-44.

[138] TX 2051 at AM-ITC 01005330-31. The fifth patient was not included in any statistical analysis. 9/12/07 Brugnara Trial Tr. 929:4-9.

[139] 9/12/07 Spinowitz Trial Tr. 929:10-12. It should be noted that Roche's election not to seek directed verdict as to '933 claims 11 and 14 on the basis of Essers' publications is a clear concession that none of such publications shows any increase in hematocrit.

[140] 9/12/07 Spinowitz Trial Tr. 930:17-931:10.

[141] 10/1/07 Brugnara Trial Tr. 2043:23-2044:2.

5. Roche Failed To Prove That The Eschbach Single-Patient Plasma Experiment Anticipated '933 Claims 9 or 12

Roche also asks that the Court award it a directed verdict that the single-patient experiment conducted by Dr. Eschbach invalidates '933 claims 9 or 12 by anticipation. In its list of Anticipatory Prior Art, Roche asserts that the Eschbach single-patient plasma experiment is a prior invention under §102(g), and prior public knowledge or use under §§ 102(a) or (b).[142] As discussed below, Roche has failed to prove as a matter of law that the Eschbach plasma experiment constitutes prior art to Dr. Lin's claimed inventions. Moreover, the plasma used by Dr. Eschbach does not anticipate '933 claims 3, 7, 8, 9, and 12 for the same reasons the plasma used by Dr. Essers does not anticipate those claims.[143]

Roche utterly failed to prove that Dr. Eschbach's experiment, including its plasma, occurred ***before*** Dr. Lin's claimed invention. Roche relies on Dr. Spinowtiz's unsubstantiated opinion testimony, but even he admitted that the experiment itself (the two infusions) occurred in November 1984,[144] months after Dr. Lin's March 1984 invention date.[145] Dr. Spinowitz's wholly derivative testimony was not based on a single public document dated before 1984. Instead, Roche points to Dr. Eschbach's 1987 publication (TX 20) as its sole bit of documentary evidence.[146] But this publication ***nowhere*** mentions the single patient plasma experiment. Roche also failed to prove that Dr. Eschbach's plasma experiment was ***public*** before Dr. Lin's

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[142] Roche's List of Prior Art (D.I. 1340) at 3.

[143] Notably, Roche again did not move for a directed verdict as to '933 claims 11 and 14 because it is indisputable that that the Eschbach single-patient experiment did not increase hematocrit in the single patient studied.

[144] 9/11/07 Spinowitz Trial Tr. 748:19-22; 9/12/07 Spinowitz Trial Tr. 931:23-932:18. Dr Spinowitz also admitted that he had no knowledge as to the date when Dr. Eschbach actually obtained the plasma.

[145] *See* Amgen's Response to Various Filings By Roche Regarding Date of Invention (D.I. 1367). It would be a miscarriage of justice to deny Amgen's clear showing as to Dr. Lin's March 1984 accomplishment while affording Roche's utterly deficient showing award Eschbach's activities the status of "prior" art.

[146] Roche's List of Prior Art (D.I. 1340) at 3.

claimed inventions and, likewise, that it was not abandoned, suppressed, or concealed. Roche, therefore, has failed as a matter of law to prove that under §§ 102(g), 102(a), or § 102(b), Dr. Eschbach's plasma experiment was a ***prior*** invention, or ***prior public*** use, or ***prior public*** knowledge to Dr. Lin's claimed inventions.

6. Roche Failed To Prove That Miyake et al. Anticipated '933 Claims 9 or 12

Roche asks for a directed verdict that the Miyake 1977 publication (TX 2002) invalidates '933 claims 9 or 12.[147] Roche argues that Miyake anticipates both claims 9 and 12 because it discloses a purification method for urinary EPO.[148] As discussed above, for the Miyake publication to anticipate, it must describe each and every claim limitation of '933 claims 9 and 12.[149] Roche fails to identify the presence of even a single limitation of claims 9 or 12 present within the publication. On this ground alone, Roche's argument fails.

Additionally, Miyake cannot anticipate '933 claims 9 or 12 because once again Roche failed to prove that the urinary EPO of Miyake was identical in structure to the claimed product. Indeed, all concede the urinary material was not a non-naturally occurring product of the expression of an exogenous DNA sequence and recovered from cell culture. Furthermore, as shown in connection with the 3-patient experiment, Miyake does not demonstrate that the urinary material was either a pharmaceutical composition or effective for EPO therapy.

7. None of Roche's Allegedly "Anticipatory" References Enabled Dr. Lin's Claimed Inventions

In addition to the failure to meet all of the limitations of the claims, none of the four

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[147] Roche's Memo (D.I. 1315) at 15.

[148] *Id*.

[149] *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1324 (Fed. Cir. 2006) ("The term 'anticipation' in patent usage means that the invention was previously known to the public; that is, that it previously existed in the precise form in which it is claimed, including all of the limitations in the claim.") (citing *General Electric Co. v. Nintendo Co.*, 179 F.3d 1350, 1356-57 (Fed. Cir. 1999)).

references cited by Roche are enabling. "A reference that is not enabling is not anticipating."[150] In other words, "[a] claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled."[151] Notably, Roche failed to show how any of the references teaches an ordinary skilled physician how to make or carry out Dr. Lin's claimed inventions.

As discussed above, the preparation used in the Baron/Goldwasser 3-patient experiment caused an increase in white blood cells in test hamsters, broke down, and had an unexpectedly short half-life when administered to humans. These worrisome effects made it unlikely that urinary EPO preparation would be given to additional patients. And Dr. Baron testified that there was not enough urinary material to give to additional patients.[152] The data from the experiment were never published,[153] and Roche has offered no evidence that anyone could or would be able to reproduce the experiment. Indeed, the skepticism in the field that EPO would have been therapeutically effective,[154] combined with the inconclusive and contradictory results of the experiment, would have taught away from making and using Dr. Lin's claimed inventions.

The Miyake publication, which Roche contends describes a purification process for producing the same urinary preparation used in the Baron/Goldwasser experiment,[155] is non-enabling of any embodiment of '933 claims 9, 11, 12 or 14 for the same reasons that the Baron/Goldwasser experiment is non-enabling. Additionally, the Miyake paper plainly does not teach an ordinary skilled physician about a "pharmaceutical composition," or "an effective

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[150] *Forest Labs., Inc. v. Ivax Pharms., Inc*., 2007 U.S. App. LEXIS 21165 at * 12 (Fed. Cir. Sep. 5, 2007)(citing *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003))

[151] *Amgen Inc. v. Hoeschst Marion Roussel*, 314 F.3d 1313, 1354 (Fed. Cir. 2003).

[152] 9/11/07 Baron Trial Tr. 669:10-11.

[153] 9/11/07 Baron Trial Tr. 669:14-18.

[154] 9/25/07 Friedman Trial Tr. 1438:21-1442:7.

[155] 9/12/07 Spinowitz Trial Tr. 975:5-976:3.

amount of a glycoprotein product effective for erythropoietin therapy."

Dr. Essers used naturally occurring plasma, a blood product, not recombinant human erythropoietin. For all of the reasons discussed above, none of the three Essers publications teaches an ordinary skilled physician about a "pharmaceutical composition," "an effective amount of a glycoprotein product effective for erythropoietin therapy," or the use of a "pharmacologically acceptable diluent, adjuvant, or carrier."

Finally, the plasma used by Dr. Eschbach is non-enabling for all the same reasons that the plasma used by Dr. Essers is non-enabling. Additionally, because the Eschbach experiment did not occur until after Dr. Lin's invention, it could not teach *anything* to an ordinary skilled physician at the time just before Dr. Lin's inventions.

Roche's request for a directed verdict that Baron/Goldwasser, Eschbach, Essers, and/or Miyake anticipate '933 Patent, Claims 9, 11, 12 and 14 should be denied and Amgen respectfully requests that judgment be entered in its favor that Roche has failed to prove by clear and convincing evidence that any of these references anticipate any of Claims 9, 11, 12 and 14 of the '933 Patent.

IV. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE SUFFICIENT FOR A VERDICT THAT CLAIMS 3, 7, 8, 9, 11, 12 AND 14 OF THE '933 PATENT OR CLAIM 1 OF THE '422 PATENT WERE OBVIOUS

A. ROCHE FAILED TO PROVE THAT IT WOULD HAVE BEEN OBVIOUS TO MODIFY URINARY EPO TO PRODUCE THE CLAIMED EPO PRODUCTS

To the extent that Roche asserts that Goldwasser's urinary EPO rendered obvious the EPO products of Lin's '933 claims 3, 7, 8, 9, 11, 12 or 14, and '422 claim 1, Roche failed to present any evidence — let alone clear and convincing evidence — of prior art support for an approach to make the structural modifications needed to obtain Lin's claimed products from urinary EPO. A *prima facie* case of obviousness requires that, in addition to proving the structural similarity between the claimed compound and a prior art compound, a patent

challenger must prove "adequate support in the prior art" for effecting that change in structure.[156]

The Federal Circuit recently addressed obviousness of new compounds which are structurally related to prior art compounds in *Takeda Chemical Indus., Ltd. v. Alphapharm Pty., Ltd.*,[157] a post-KSR case decided earlier this year. In *Takeda Chemical*, the patent challenger, Alphapharm, alleged that the claimed compound, pioglitazone, an antidiabetic agent, was obvious in light of a prior art chemical structure referred to as "compound b."[158] The Federal Circuit clarified its prior decisions, explaining that there must be some teaching in the prior art to make the ***specific molecular modifications*** required to produce the claimed compound from prior art compounds:

> We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound…. We clarified, however, that ***in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention***" was also required.[159]

Moreover, the CAFC expressly recognized that this test for *prima facie* obviousness of similar chemical compounds is consistent with the principles set forth in KSR,[160] and that even in the wake of KSR, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound."[161]

Dr. Bertozzi was Roche's ***only*** witness who addressed the relationship between

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[156] *See Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd* , 492 F.3d 1350, 1356 (Fed. Cir. 2007) (*citing In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. Sep. 5, 1985).

[157] *Id.*

[158] *Id.* at 1356.

[159] *Id.*

[160] *Id.*

[161] *Id.*at 1356-1357.

Goldwasser's urinary EPO and the claimed EPO products. All of Dr. Bertozzi's obviousness opinions are premised on the incorrect notion that Goldwasser's urinary EPO and the claimed EPO products are identical.[162] As described above, this is an incorrect premise. Dr. Bertozzi ***never*** testified that the prior art taught or suggested that Goldwasser urinary EPO product could be modified to create the structures found in recombinant EPO. Indeed, she did not identify a single reference that could be used to modify the Miyake/Goldwasser product to produce the structures found in recombinant EPO or that identified any reason or motivation to make such a modification. This is not surprising since the structures of EPO produced by mammalian cells grown in culture were unknown before Dr. Lin's invention.

Dr. Bertozzi did testify that Dr. Lin's inventions "could" be used to modify the products claimed in his '933 and '422 patents (using unspecified techniques) to produce a product that "would" have the structures found in Goldwasser's urinary EPO.[163] But that opinion is simply irrelevant to any analysis of obviousness as set forth in *Takeda Chemical*. The test is whether it would have been obvious to modify a prior art product to make the claimed invention, not whether it would have been obvious to modify the claimed invention to make the prior art product. Nor did Bertozzi provide any evidence to show how or why one skilled in the art as of the date of Lin's inventions would have been motivated to modify Lin's inventions to make and use the prior art products, or known how to do so with any reasonable expectation of successfully obtaining a product possessing the structures of Goldwasser's prior art product.

Moreover, as Dr. Varki explained, the structures of urinary EPO are inevitably different from Dr. Lin's claimed EPO products due to the difference in source from which both products are obtained.[164] Not only did Goldwasser's urinary EPO disappear from the body very rapidly

[162] 10/2/07 Varki Trial Tr. 2240:19-24.

[163] 9/14/07 Bertozzi Trial Tr. 1074:8-15, 1066:10-19.

[164] 10/2/07 Varki Trial Tr. 2173:24-2174:7, 2237:5-2239:19.

by comparison to Lin's claimed products,[165] but it also contained negatively charged sulfate structures not present on Lin's claimed products.[166] In addition, recombinant EPO contains glycoforms that are absent from urinary EPO, thus making it impossible to purify the claimed EPO from Goldwasser's product.[167] Thus, until Dr. Lin's inventions, there was simply no road map to his claimed EPO products.

Because Roche failed to adduce ***any*** evidence — much less clear and convincing evidence — of the prior art motivation and teaching how to modify Goldwasser's urinary EPO to produce the structures of Dr. Lin's claimed recombinant EPO, Roche has failed to present a *prima facie* case of obviousness of Claims 3, 7-9, 11, 12, 14 of Dr. Lin's '933 patent or Claim 1 of Dr. Lin's '422 patent.

B. THE EXPERIMENTS USING NATURALLY-OCCURRING MATERIALS CITED BY ROCHE DO NOT RENDER OBVIOUS '933 CLAIMS 9, 11, 12 AND 14 OR '422 CLAIM 1

Roche contends that '933 claims 9, 11, 12, and 14 and '422 claim 1 were obvious because three sets of activities — the Essers plasma work, the Eschbach single patient experiment, and the Baron/Goldwasser 3-patient experiment — purportedly taught the use of EPO compositions to treat dialysis patients. But recasting Roche's flawed argument as an obviousness position does nothing to bridge the gulf between the three preparations and Lin's patent claims. Indeed, Roche utterly failed to show how one skilled in the art in 1983-4 would be able to alter any of the three cited preparations to achieve Dr. Lin's structurally distinct and functionally different claimed products and compositions.[168]

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[165] 10/2/07 Varki Trial Tr. 2185.

[166] 10/2/07 Varki Trial Tr. 2136:4-7 and Strickland Trial Tr. 2139:1-8; 10/2/07 Varki Trial Tr. 2217:23-2218:4.

[167] 10/2/07 Varki Trial Tr. 2231:10-11, 2224:3-10.

[168] As Roche's experts Dr. Spinowitz admitted, none of the references at issue disclose man-made human EPO purified from mammalian cells grown in culture as specified by '422 claim 1 or a non-naturally occurring glycoprotein product of the expression of an exogenous DNA sequence encoding human EPO. 9/12/07 Spinowitz Trial Tr. 855:19-856:21, 861:7-23, 863:21-

Viewed from the perspective of the ordinarily skilled person as of 1983-84, the references Roche asserts under §103, at most, afford information regarding a few specific preparations of material from ***naturally occurring*** sources. But there was no knowledge before Dr. Lin's inventions of how to make a non-naturally occurring human EPO expressed by a mammalian host cell. Moreover, even if such an EPO product was achievable, there was no way of knowing that such an EPO product would in fact have sufficient structural identity with natural human EPO to have the recited in vivo biological activity. Roche's cited references cannot possibly be deemed to render obvious Dr. Lin's claimed human EPO products. Indeed, before Dr. Lin's inventions, no one in the entire history of the world had demonstrated that non-naturally occurring human EPO expressed by mammalian host cells would in fact be *in vivo* biologically active: not Essers, not Eschbach, not Baron/Goldwasser. Moreover, the long-felt and unmet need for such a product is compelling evidence that it was not obvious. Until Dr. Lin's demonstration of *in vivo* biological activity, there was an insurmountable gap in knowledge that precluded the ordinarily skilled person in 1983-84 from reasonably expecting that whatever was known about naturally occurring EPO would in fact be the case for non-naturally occurring EPO. That is why Roche's cited art cannot possibly render obvious '422 claim 1 and '933 claims 9, 10, 11, 12, and 14.

In fact, so poor was the state of knowledge before Dr. Lin's inventions, that not a single EPO preparation had ever been proven to increase hematocrit in humans.[169] Thus, at trial Roche did not prove a single instance before Dr. Lin's inventions in which hematocrit in humans was raised by an EPO preparation: not Essers, not Eschbach, not Baron/Goldwasser. In fact, Roche failed to prove that any of the preparations of these references actually caused an increase in red

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864:1, 864:18-865:18, 875:2-18, 873:19-24, 874:15-19, 876:18-877:1.

[169] 9/25/07 Friedman Trial Tr. 1442:18-22.

blood cells or hematocrit.[170] These failures are why Roche's cited references cannot possibly render obvious '933 claims 11 and 14 which require an increase in hematocrit.

Given the lack of teaching as to humans, it is hardly surprising that Roche points to tests in animals. It argues that Dr. Eschbach's experiments on sheep with sheep plasma "when combined with other prior art references" renders the claims obvious. But there is host of reasons why Roche's position is completely unfounded.

First, Roche never identifies this "other prior art." Second, Dr. Eschbach's work involved ***naturally occurring sheep EPO-containing plasma*** and therefore affords no reasonable expectation as to whether ***non-naturally occurring human EPO*** would be *in vivo* biologically active. Third, because his experiment made use of plasma rather than a composition containing purified EPO, Dr. Eschbach expressly stated that it was not certain that the effects observed were caused by EPO.[171] Fourth, the contradictory results in humans versus sheep with different preparations of EPO led to doubts that any EPO preparation, could correct the anemia of dialysis patients.[172] As Dr. Eschbach wrote in the New England Journal of Medicine immediately after summarizing the results of his prior sheep experiments:

> Thus, it has been necessary to await clinical trials with recombinant human erythropoietin to determine whether, and to what degree anemia could be corrected in patients with end-stage renal disease.[173]

Fifth, as Dr. Goldwasser testified, the one experiment using sheep EPO in humans only

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[170] 9/12/07 Spinowitz Trial Tr. 888:23-890:22, 930:17-931:10; 9/25/07 Friedman Trial Tr. 1442:18-22, 9/26/07 Friedman Trial Tr. 1492:21-1493:2, 1496:6-24; 10/01/07 Brugnara Trial Tr. 2028:3-17.

[171] TX 2032 at 440 ("Nevertheless, until purified Ep is available, we cannot conclude unequivocally that it was only Ep that produced the erythropoietic changes noted in our uremic sheep.").

[172] TX 20 at AM-ITC 0076144 ("It is uncertain whether there are important inhibitors of erythropoiesis in the circulation of patients with end-stage renal disease.") As Dr. Friedman testified, until a preparation of EPO was shown to correct the anemia in a clinical trial, the question of whether or not anemia could be corrected in spite of uremic inhibitors remained to be proven. 9/25/07 Trial Tr. 1440:13-1442:7.

[173] TX 20 at AM-ITC 0076148.

succeeded in making the subject immediately sick.[174]

Roche next points to a purported increase in hematocrit in hamsters that it seeks to associate with Goldwasser's urinary EPO material. But this same material failed to increase hematocrit in humans so Roche's reliance on the hamster data while ignoring the failed human results is puzzling. Moreover, as proven at trial, this urinary material did not behave like Dr. Lin's claimed human EPO at all in that it caused a significant increase in white blood cells which along with the appearance of breakdown products, unexpected rapid half-life, and lack of erythropoietic effect in humans would have strongly discouraged any further use in humans.[175]

Roche's position on obviousness only highlights the extraordinary gap in knowledge between the world before and after Dr. Lin's inventions. When viewed in the context of the overwhelming objective evidence of non-obviousness discussed below, there is simply no basis for concluding that the work of Essers, Eschbach, or Baron/Goldwasser renders any of the claims in suit obvious. Roche's motion in this regard should be denied.

V. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE SUFFICIENT FOR A VERDICT THAT CLONING EPO DNA AND EXPRESSION OF *IN VIVO* BIOLOGICALLY ACTIVE EPO WOULD HAVE BEEN OBVIOUS

A. ROCHE'S ATTEMPT TO MISCHARACTERIZE ITS BURDEN OF PROOF REGARDING OBVIOUSNESS SHOULD BE REJECTED

Roche's obviousness discussion ignores a fundamental aspect of the obviousness analysis: whether a skilled artisan had a reasonable expectation of success in making the invention from what was known in the prior art at the time. Recent Federal Circuit case law makes clear that the Supreme Court's decision in *KSR International Co. v. Teleflex Inc.*[176] regarding teaching, suggestion, or motivation to combine prior art references did not eliminate or

[174] 10/01/07 Goldwasser Trial Tr. 2010:24-2012:21.

[175] 10/01/07 Brugnara Trial Tr. 2038:12-2039:8.

[176] *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

supplant the reasonable expectation of success required for a determination of obviousness.[177]

For example, in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*,[178] a post-*KSR* decision, the Federal Circuit affirmed the district court's finding that a claimed compound pioglitazone, an antidiabetic agent, was non-obvious due to the lack of a reasonable expectation of success. The district court concluded that even if Alphapharm had succeeded in showing that there was a motivation to select a prior art compound as the lead compound, Takeda the patentee would still prevail because obviousness was rebutted by the fact that one of ordinary skill in the art would not have had a reasonable expectation of success that the claimed compound would possess the unexpected property of non-toxicity.[179]

Similarly, in *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc*.,[180] the Federal Circuit affirmed the district court's finding of non-obviousness of a pharmaceutical compound (+)-citalopram for treating depression based on the lack of reasonable expectation of success in purifying the claimed compound.[181] The Federal Circuit took note of evidence of the failure of other researchers, the unpredictability of the art, and the unexpected properties of the compound.[182]

Under *KSR* and subsequent case law, regardless of whether the challenger has presented evidence of motivation to combine prior art references to demonstrate the obviousness of a claimed invention, a challenger must additionally demonstrate that one of ordinary skill in the art had a reasonable expectation of success in making and using the claimed invention. As

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[177] *See Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd* , 492 F.3d 1350 (Fed. Cir. 2007); *see also Forest Labs., Inc. v. Ivax Pharmaceuticals, Inc*., 2007 WL 2482122, *3 (Fed. Cir. 2007).

[178] 492 F.3d 1350.

[179] 492 F.3d at 1354, 1362.

[180] 2007 WL 2482122 at *3.

[181] *Id*. at *4-6.

[182] *Id*..

discussed below, Roche has not and cannot make this showing based on the evidence adduced at trial.

B. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE THAT ONE OF SKILL IN THE ART HAD A REASONABLE EXPECTATION OF SUCCESS IN CLONING THE HUMAN EPO GENE BY OCTOBER 1983

Because all of Roche's obviousness arguments depend on the cloning of the human EPO gene, to succeed on its instant Rule 50(a) motion,[183] Roche must first establish by clear and convincing evidence that one of ordinary skill in 1983 had a reasonable expectation of success in obtaining the DNA encoding human EPO. The evidence Roche cites in its motion fails to satisfy Roche's heavy burden,[184] and the evidence of record confirms that Dr. Lin's claimed inventions were not obvious at the time of the invention.

As discussed in Amgen's Renewed Motion for Judgment as a Matter of Law, Roche has failed to present *prima facie* evidence of obviousness with respect to DNA encoding human EPO and Roche has failed to identify any prior art compound structurally similar to the recited DNA.[185] Because Federal Circuit case law is clear that cloning methods in the prior art cannot, as a matter of law, render claims to a DNA sequence obvious, Roche has failed to meet its burden of proving that cloning the human EPO gene was obvious — a necessary predicate to its obviousness challenge against each of Dr. Lin's claims in suit.[186]

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[183] *Keisling v. SER-Jobs for Progress, Inc.*, 19 F.3d 755, 760 (1st Cir. 1994) (to withdraw any claim from the jury, the court must find that the record would permit a reasonable jury to reach only one conclusion on that issue).

[184] Roche's burden of proving obviousness is particularly heavy because the prior art "cloning" references on which it relies were considered by the Examiner and overcome during prosecution of the patents-in-suit. *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990)(A challenger's burden is "especially difficult when the prior art was before the PTO examiner during prosecution of the application."); s*ee also American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984). Dr. Lowe admitted this on cross-examination. 9/7/07 Lowe Trial Tr. 379:9-380:21.

[185] 10/3/07 Renewed Motion (D.I. 1270) at 8-10.

[186] Amgen believes that, for the reasons discussed in its motion *in Limine* No. 17 to Exclude Roche from Presenting Evidence to Challenge the Non-obviousness of the DNA Sequence Encoding for Human Erythropoietin in 1983, judgment as a matter of law on the collateral

In its current motion, Roche argues that cloning the human EPO gene would have been obvious to a skilled artisan had they been in possession of Goldwasser's urinary EPO.[187] In particular, Roche argues that with Goldwasser's urinary EPO protein, one of ordinary skill could have either synthesized the EPO gene or used other available cloning methods to obtain the human EPO gene. [188]

Roche's argument fails for several reasons. First, Roche's "but-for Dr. Goldwasser's urinary EPO" argument ignores the overwhelming evidence in the record that demonstrates that even with Dr. Goldwasser's urinary EPO in hand, there were substantial difficulties and uncertainties that would have precluded an ordinarily skilled artisan as of October 1983 from having a reasonable expectation of success in cloning the human EPO gene. Dr. Goldwasser published the partial N-terminal amino acid sequence information for his urinary EPO and although many tried to use that as a basis for cloning the EPO gene all efforts resulted in failure. Without any supporting evidence, Roche assumes that more amino acid sequence information from urinary EPO would have been useful for cloning the gene. That position, however, is improperly based on pure hindsight. Second, Goldwasser was not the only source of urinary EPO. If workers in the field had thought that getting more urinary EPO was the key to success to cloning the human EPO gene, they could have purified their own urinary EPO.

1. Roche Failed To Prove That With Dr. Goldwasser's Urinary EPO, One Skilled In The Art Had By October 1983 a Reasonable Expectation Of Success Of Using Available Methods To Clone The Human EPO Gene

Roche relies on Dr. Lowe's opinion testimony for its argument that with Dr. Goldwasser's purified urinary EPO, an ordinarily skilled artisan could have used available

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estoppel issue is appropriate. *See* Amgen's Motion *in Limine* No. 17 and Reply Memorandum in Support of Motion *in Limine* No. 1 for a More Complete Discussion on Collateral Estoppel. (D.I. 876-78; 1003, attachment 1.)

[187] Roche's Memo (D.I. 1315) at 17.

[188] Roche's Memo (D.I. 1315) at 19-24.

techniques to clone the human EPO gene with a reasonable expectation of success.[189] Notably, Dr. Lowe admitted that by 1984, he had no personal experience with EPO nor had he ever constructed a genomic DNA library.[190] By contrast, Amgen offered the rebuttal testimony of Dr. Stuart Orkin, Dr. Fu-Kuen Lin, and Dr. Leroy Hood, each of whom was actually working on cloning human genes, including the human EPO gene, in the early 1980's, and each of whom testified that one of ordinary skill would not have had a reasonable expectation of cloning the EPO gene by 1984, even with Dr. Goldwasser's urinary EPO protein.[191]

Dr. Orkin testified that there were "a whole multitude of problems" associated with cloning the EPO DNA in the early 1980's, any one of which could have resulted in failure,[192] even if one had Dr. Goldwasser's urinary EPO.[193] In particular, Dr. Orkin identified the following difficulties in pursuing cDNA cloning: (1) the absence of a known source of EPO mRNA from which one could create an EPO-enriched cDNA library;[194] (2) the difficulty in creating a cDNA library containing full-length cDNA clones;[195] and (3) the difficulty in finding

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[189] Roche' Memo (D.I. 1315) at 20, 23-24.

[190] 9/7/07 Lowe Trial Tr. 436:5-19, 397:7-9.

[191] 9/26/07 Orkin Trial Tr. 1585:10-24, 1600:10-24; 9/28/07 Lin Trial Tr. 1811:14-20, 1815:5-10; 10/1/07 Hood Trial Tr. 1989:7-15, 1991:6-1992:2.

[192] 9/26/07 Orkin Trial Tr. 1584:2-17.

[193] 9/26/07 Orkin Trial Tr. 1600:10-24.

[194] 9/26/07 Orkin Trial Tr. 1557:21-1558-8; 1562:14-17; 1563:1-3; 1565:8-14; 1566:5-8. Dr. Lowe's only evidence on the availability of a source of EPO mRNA was a single statement in the "Background" section of Dr. Lin's patents, referencing a Farber abstract and suggesting that the human kidney was a site of EPO production, and that it may allow for the construction of an enriched human kidney cDNA library. Dr. Orkin explained that the Farber abstract would not have provided a skilled artisan with a reasonable expectation that one could clone a cDNA because given the very low level reported for EPO production in the kidney, one could not have been confident that that human kidney could serve as an enriched source of EPO mRNA to make a useful cDNA library. 9/26/07 Orkin Trial Tr. 1564:4-17.

[195] 9/26/07 Orkin Trial Tr. 1566:22-1567:5; 1567:18-20. Roche offered no affirmative evidence that producing full length cDNA clones for a low-abundance protein, like EPO. Notably, Roche's only rebuttal is to mischaracterize Dr. Orkin's 1980 grant application to support that obtaining full-length cDNA clones would not be an obstacle to obtaining an EPO cDNA clone (Roche's Memo (D.I. 1315) at p. 22.), ignoring Dr. Orkin's statement in the same document

or selecting appropriate hybridization conditions[196] as obstacles that would have precluded one skilled in the art from having a reasonable expectation of being able to use cDNA cloning to isolate the human EPO gene.

Dr. Lowe relied heavily on a 1982 Maniatis cloning manual (TX 10), which he characterized as a "cookbook" that "taught one of skill in the art recipes for isolating and cloning DNA sequences."[197] But the Maniatis manual did not teach ordinarily skilled workers how to overcome these obstacles identified by Dr. Orkin. In fact, from 1981-1983, Dr. Orkin and his colleagues — who were clearly above ordinarily skilled artisans[198] — with the benefit of the Maniatis manual attempted a variety of techniques, including cDNA cloning, to clone the human EPO gene, but they were unable to do so.[199]

Roche also argued that cloning the human EPO gene using a genomic cloning approach — Dr. Lin's approach — would have been obvious.[200] At bottom, Roche argues that Dr. Lin's cloning approach was obvious because some of the steps in Dr. Lin's cloning approach were routine and others took only a few hours of time to complete.[201] But Roche ignores the fact that Dr. Lin was the ***first person ever*** to clone ***any*** gene using short oligonucleotide probes to screen a genomic library.[202] More fundamentally, Roche's obviousness argument is legally flawed because 35 U.S.C. § 103(a) provideS that, "patentability shall not be negatived by the manner in which the invention was made," which is precisely what Roche is arguing here.

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where he recognized that one may not be able to obtain a full-length EPO cDNA clone. 9/27/07 Orkin Trial Tr. 1659:7-1660:4; TX 2100 at 678.

[196] 9/26/07 Orkin Trial Tr. 1531:10-13; 1531: 18-25; 1576:5-15; 1578:12-23.

[197] Roche's Memo (D.I. 1315) at 21.

[198] 9/26/07 Orkin Trial Tr. 1545:8-15; 1545:19-1546:3; 1585:25-1586:10.

[199] 9/26/07 Orkin Trial Tr. 1546:22-1547:2; 1547:4; 1547:6-9.

[200] Roche's Memo (D.I. 1315) at pp. 23-24.

[201] Roche's Memo (D.I, 1315) at p. 24.

[202] 9/28/07 Lin Trial Tr. 1866:8-11; 9/27/07 Orkin Trial Tr. 1580:14-15; 1580:21-24.

Roche suggests that because Dr. Lin had Dr. Goldwasser's urinary EPO, Dr. Lin's contribution was ordinary.[203] Dr. Lin aptly analogized Roche's argument to putting a man on the moon — everyone knew the steps involved, some of which were routine, but it was far from simple or obvious to accomplish the feat:

> It's the combination of all these things put together to make it work in the complex human genomic background, that's what is make it to work. It's not that each one – just like if we go to the moon, for the shuttle to go to the moon take only a few hours, but it take years of preparation to get the thing to work."[204]

Dr. Lin appreciated the difficulty attendant in genomic cloning at the time of his patent filing and that appreciation is reflected in his patent application.[205]

Both Drs. Orkin and Hood — who each had considerable experience with gene cloning in the early 1980s — concluded that Dr. Lin's approach was remarkable and an approach that no one was considering at that time.[206] Dr. Hood recognized that Dr. Lin's approach to cloning the EPO gene was wholly novel: "To my knowledge, this was the first, if — one of the first, if not the very first, rare message gene that was cloned, and it required, it required a different strategy than people like myself talked about for the abundant messenger RNAs."[207]

By contrast, Roche offered no evidence that anyone had successfully cloned a gene using Dr. Lin's approach (or that anyone even attempted to do so) prior to Dr. Lin's success. Instead, Roche's obviousness of cloning argument rests on Dr. Lowe's conclusory opinion testimony — admittedly not based on personal knowledge or experience — based entirely, as he acknowledged on cross-examination, on references that Amgen provided to the Patent Office

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[203] *Id.*

[204] 9/28/07 Lin Trial Tr. 1893:19-1894:4.

[205] TX 1, Col. 4:40-46.

[206] 9/26/07 Orkin Trial Tr. 1554:14-21; 1580:25-1581:5; 1581:13-19.

[207] 10/1/07 Hood Trial Tr. 1991:23-1992:2.

during the prosecution of Dr. Lin's patents.[208]

Regarding other methods for cloning the gene, both Drs. Lin and Orkin testified about other techniques for cloning available to one skilled in the art that did not require protein sequence information.[209] For example, Dr. Lin testified that one of the techniques he attempted was a cloning technique called "expression cloning," which was an approach that used messenger RNA and did not require the amino acid sequence of the protein of interest.[210] Dr. Orkin likewise testified that he tried using an antibody (as opposed to a sequence-based probe) to clone the EPO gene.[211] Because there were known cloning methods available that did not require protein sequence information and, in fact, Dr. Lin even attempted to use such methods, Roche's contention that Dr. Goldwasser's urinary EPO was the *sine qua non* of cloning the human EPO gene is baseless.

In addition, even if one of skill wanted to pursue a probe-based strategy such as cDNA or gDNA cloning, the evidence at trial demonstrated that Dr. Goldwasser was not the only source of urinary EPO or EPO protein sequence information in the pertinent time frame. Roche's expert, Dr. Lowe, admitted that Miyake was also a separate source of purified urinary EPO in the relevant time frame.[212] And beyond that, Roche does not dispute that the publication of Dr. Goldwasser's method of urinary EPO purification in 1977 in the *Journal of Biological Chemistry*[213] allowed any person of ordinary skill to purify urinary EPO from the urine of anemic patients.[214] The laboratory equipment and reagents that Dr. Goldwasser used were

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[208] 9/7/07 Lowe Trial Tr. 379:9-380:19; 385:23-386:10.

[209] 9/26/07 Orkin Trial Tr. 1589:10-1590:10; 9/27/07 Lin Trial Tr. 1691:11-18, 1692:14-21.

[210] 9/27/07 Lin Trial Tr. 1691:11-18, 1692:14-21. *See also* 10/1/07 Hood Trial Tr. 1993:21-1994:9.

[211] 9/26/07 Orkin Trial Tr. 1589:10-1590:10.

[212] 9/7/07 Lowe Trial Tr. 453:7-11.

[213] TX 2002.

[214] 9/10/07 Goldwasser Trial Tr. 585:17-21; 611:13-20.

available to persons of ordinary skill in the art,[215] and when scientists asked Dr. Goldwasser about the methods reported in the Miyake *et al*. paper, he answered those questions.[216]

In addition to telling anyone who was interested how to purify urinary EPO, Dr. Goldwasser also made his own urinary EPO available to others in the field. Of the eight milligrams of urinary EPO that he purified from human urine, Dr. Goldwasser gave only a small portion of that (about 10-15%) to Amgen.[217] The bulk of his urinary EPO was used for his own research, or he donated it to the NIH for use by persons of ordinary skill at both universities and other companies.[218] In addition to the urinary EPO that he purified in 1976, Dr. Goldwasser was willing to purify EPO from human urine and send milligram quantities (sufficient for amino acid sequencing) to persons of ordinary skill in the art in 1983 (*e.g*., Dr. Gisela Clemons of the Lawrence Berkeley National Laboratory), regardless of whether that person had any connection to Amgen.[219] And, as Dr. Goldwasser testified, no one other than Amgen ever asked him for quantities of urinary EPO sufficient for amino acid sequencing (including Biogen).[220]

Lastly, in its Memo, Roche contends that with Dr. Goldwasser's urinary EPO in hand, one of skill in the art could have synthesized a human EPO gene.[221] While Roche contends that a skilled artisan could have used the Alton patent (TX 2034) to create a synthetic human EPO gene, Roche failed to present ***any*** evidence that anyone in the early 1980's tried this approach,[222] or that any scientist thought such an approach was even remotely likely to succeed. Instead,

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[215] 9/10/07 Goldwasser Trial Tr. 587:11-21.

[216] 9/10/07 Goldwasser Trial Tr. 587:22-588:3.

[217] 9/10/07 Goldwasser Trial Tr. 594:23-595:6.

[218] 9/10/07 Goldwasser Trial Tr. 595:7-15; 597:13-16; 598:3-11; 600:11-601:25; 602:6-605-12.

[219] TX 18; 9/10/07 Goldwasser Trial Tr. 608:9-610:22.

[220] 9/10/07 Goldwasser Trial Tr. 527:4-11; 535:22-24.

[221] Roche's Memo (D.I. 1315) at 19.

[222] Other than Dr. Lin, who synthesized and expressed DNA encoding EPO only *after* he cloned the human EPO gene, and only in yeast and bacterial cells (not in vertebrate or mammalian cells, as Dr. Lin's asserted patent claims require). *See* TX 1 Col. 29:10 – 32:60 (Examples 11 & 12).

Roche relies on Dr. Lowe's conclusory testimony to support its synthetic DNA argument. But Dr. Lowe failed to address the steps that would have been critical for this approach, such as how a person of ordinary skill would have actually selected, assembled and incorporated a DNA encoding the "signal peptide" or "leader sequence" required for the EPO protein to be expressed in vertebrate or mammalian cells.

As Roche acknowledges, Dr. Lin's patent discusses the utility of the synthetic gene approach (and TX 2034 in particular) "when the entire sequence of amino acid residues of the desired polypeptide produce is known."[223] But, even with access to Dr. Goldwasser's urinary EPO, the complete amino acid protein sequence of human EPO was not known until long after Dr. Lin cloned the EPO gene and deduced the amino acid sequence.[224] In fact, a few sentences later, Dr. Lin's patent teaches that "when the entire sequence of amino acid residues of the desired polypeptide is not known, direct manufacture of DNA sequences is not possible."[225] By assuming that one skilled in the art could have used a synthetic DNA approach, both Dr. Lowe and Roche improperly rely on hindsight information that was not available but-for Dr. Lin's inventions.

The weight of the evidence in the record demonstrates that Roche has not satisfied its clear-and-convincing-evidence burden to show that cloning the human EPO gene was obvious, particularly where, as here, Roche bears the added burden of overcoming the deference due to the PTO where each reference it relies on for its obviousness challenge has been placed before the Patent Examiner and overcome during prosecution of Dr. Lin's patents-in-suit.[226]

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[223] TX 1 Col. 3: 14-37.

[224] The tryptic fragments of Goldwasser's urinary EPO did not comprise the complete amino acid sequence of EPO and one of skill would not have known the orientation, duplication, or completeness of the amino acid sequence of EPO from the urinary EPO tryptic fragments supplied by Dr. Goldwasser. *See* TX 1, Table 1.

[225] TX 1 Col. 3: 38-45.

[226] *American Hoist & Derrick Co.*, 725 F.2d at 1359-60.

C. ROCHE FAILED TO PROVE BY CLEAR AND CONVINCING EVIDENCE THAT ONE OF SKILL IN THE ART HAD A REASONABLE EXPECTATION OF SUCCESS IN PRODUCING AN *IN VIVO* BIOLOGICALLY ACTIVE RECOMBINANT EPO PROTEIN BY MARCH 1984

To meet its burden of showing obviousness of the asserted claims, in addition to showing that the cloning of the EPO gene was obvious, Roche must also show that there was a reasonable expectation of producing isolatable quantities of *in vivo* biologically active EPO products. While Dr. Lowe said those words, the evidence he relied upon was woefully inadequate to support such a conclusion especially given that the PTO considered precisely the very same references that Dr. Lowe relied upon for his obviousness opinion.[227]

Roche's experts, Drs. Lowe and Harlow, acknowledged that Dr. Lin's claims-in-suit require that the recombinant EPO produced possess *in vivo* biological activity.[228] Yet, even with the EPO DNA sequence in hand, an ordinarily skilled artisan as of March of 1984 would have understood that the isolated DNA sequence was necessary but not sufficient to produce a recombinant EPO protein.[229] Dr. Harlow admitted that even with the correct DNA sequence, a number of steps must occur before one obtains a functional, secreted glycoprotein, like EPO. [230] Dr. Harlow's testimony was confirmed by Dr. Lin obtaining the EPO gene was only the first step and that much additional work was needed to be done to produce an *in vivo* biologically active EPO product. [231]

Roche's Dr. Harlow acknowledged that by December of 1983, one of skill in the art would have understood that particular sugars must be added to the EPO protein in order for the EPO glycoprotein to have *in vivo* biological activity.[232] Dr. Harlow acknowledged that EPO

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[227] 9/7/07 Lowe Trial Tr. 379:9-380:19, 385:23-386:10.

[228] 9/5/07 Lowe Trial Tr. 148:13-21, 181:11-19; 9/27/07 Harlow Trial Tr. 1787:16-18.

[229] 9/27/07 Harlow Trial Tr. 1788:24-1789:8.

[230] 9/27/07 Harlow Trial Tr. 1787:23-1788:1.

[231] 9/27/07 Lin Trial Tr. 1750:3-23.

[232] 9/28/07 Harlow Trial Tr. 1797:20-24.

must persist in the bloodstream and travel to the bone marrow in order to have *in vivo* biological activity.[233] In fact, by December of 1983, Goldwasser had published that the removal of a particular kind of sugar — sialic acid — eliminated *in vivo* biological activity for EPO.[234] While it was known that certain post-translational modifications (*i.e.* glycosylation), were necessary for EPO *in vivo* biological activity, it was unknown which particular structures (other than sialic acid) or modifications would be required. As Dr. Lin (clearly above one skilled in the art) testified, he did not know which glycosylation structures were required for *in vivo* biological activity.[235]

At the same time, it was widely recognized by 1984 that different cell types from different species effectuate post-translational modifications differently. Roche's experts Drs. Harlow and Bertozzi each admitted that different cell types from different species or even different tissues perform post-translational modifications differently.[236] In particular, Dr. Bertozzi admitted that different cell types from different species were known to glycosylate proteins differently.[237]

One skilled in the art by 1984 would have understood that these differences in glycosylation or other post-translational modifications could affect or even eliminate a protein's *in vivo* function. For example, Dr. Harlow testified that it was known to one skilled in the art that post-translational modifications can affect the conformation of a protein and it would be reasonable to expect that these post-translational modifications would affect the protein's ability to bind to a receptor.[238] Importantly, Dr. Harlow admitted that one skilled in the art would have

[233] 9/28/07 Harlow Trial Tr. 1796:22-1797:4.
[234] TX 41 at AM-ITC 00213261.
[235] 9/28/07 Lin Trial Tr. 1905:8-18.
[236] 9/28/07 Harlow Trial Tr. 1794:20-1795:8; 9/14/07 Bertozzi Trial Tr. 1076:21-1077:11.
[237] 9/14/07 Bertozzi Trial Tr. 1077:9-14.
[238] 9/28/07 Harlow Trial Tr. 1795:9-21

understood that differences in post translational modifications could affect and even eliminate the *in vivo* biological activity of a given protein:

> Q. Can differences in post-translational modification of a protein eliminate the *in vivo* biological activity of a given protein?
> A. Yes.[239]

In fact, Dr. Hood testified that no one would have known whether foreign host cells — including CHO cells — would produce *in vivo* biologically active human EPO before Dr. Lin cloned and expressed human EPO:

> Q. And as of 1983 before Amgen cloned and expressed the EPO protein in a functional way, did you have an understanding whether or not that any recombinantly-produced EPO would be biologically active *in vivo*?
> A. No one would know the answer to that.
> Q. And before Lin cloned and expressed EPO in the Chinese hamster ovary cell, did anyone know whether or not Chinese hamster ovary cells would be an appropriate host for expressing EPO?
> A. To the best of my knowledge they did not.[240]

Because it wasn't known which foreign host cells could impart the necessary structures, as Drs. Varki and Hood testified, it would have been very difficult to predict by 1984 whether one could produce a biologically active glycoprotein in a transformed mammalian host cell before actually carrying out the experiment.[241]

Dr. Lowe improperly relies on Dr. Lin's expectations for *in vivo* biological activity as a proxy for what one skilled in the art would have expected before Dr. Lin's inventions. Plainly, as an inventor, Dr. Lin's expectations are not relevant to assessing what one of ordinary skill would have expected by March of 1984.[242] Beyond that, though, Dr. Lowe takes out of context

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[239] 9/28/07 Harlow Trial Tr. 1795:5-8

[240] 10/1/07 Hood Trial Tr. 1993:11-20.

[241] 10/2/07 Varki Trial Tr. 2243:8-22.

[242] It has long been held that the inventor's skill and his subjective beliefs that make up the act of conception are irrelevant to obviousness. Thus it is improper to determine "obviousness under § 103 by inquiring into what the patentees (i.e. inventors) would have known or what would likely

Dr. Lin's statements in his patent. Dr. Lin's statement in his original patent application regarding producing an *in vivo* active EPO was with respect to producing biologically active monkey EPO in monkey kidney host cells — not producing human EPO in a foreign host cell from a different species and a different tissue type.[243] Moreover, as Dr. Lin testified, he did not mean that monkey EPO would work *in vivo*, but only that he hoped it would work, and that he wouldn't know it would work until the recombinant product was actually tested for *in vivo* activity.[244]

Amgen's experience in producing an *in vivo* biologically active EPO protein confirms the uncertainty that existed by March of 1984. Dr. Lin testified that he pursued three different expression strategies (*E. coli*, yeast, and mammalian cell expression) because he did not know which system would work the best.[245] In fact, Dr. Lin testified that he did not know which cell type would produce *in vivo* biologically active EPO before actually performing the experiment.[246]

Dr. Lowe testified that by 1983-1984, CHO cells had been used to make human proteins that were both glycosylated and biologically active — citing in particular to tPA and human beta interferon.[247] In point of fact, none of the references Dr. Lowe relied on for his testimony either disclosed or demonstrated *in vivo* biological activity for a recombinantly-produced human glycoprotein before March of 1984.[248] Instead, the very references that he relied upon

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have done . . ." at the time of invention. This is because "[i]nventors, as a class, according to the concepts underlying the constitution and the statutes that have created the patent system, possess something call it what you will — which sets them apart from the workers of ordinary skill. . . ." *Standard Oil Co., v. American Cyanamid Co.,* 774 F. 2d 448, 454 (Fed. Cir. 1985).

[243] 9/27/07 Lin Trial Tr. 1761:19-1762:3.

[244] 9/27/07 Lin Trial Tr. 1760:24-1761:15.

[245] 9/27/07 Lin Trial Tr. 1753:9-1754:2; 9/28/07 Lin Trial Tr. 1904:4-12.

[246] 9/27/07 Lin Trial Tr. 1750:24-1751:4.

[247] 9/5/07 Lowe Trial Tr. 181:4-182:4.

[248] TX 2001, 2026-2030.

demonstrate the uncertainty then-extant in the art of producing an *in vivo* biologically active human glycoprotein in a foreign host cell.

For example, Dr. Lowe relies on a publication by Haynes and Weissman (TX 2001) regarding the production of human beta interferon for his obviousness opinion. Not only does TX 2001 fail to disclose or even test for *in vivo* activity, but it notes that use of a foreign host cell may not produce the glycosylation structures required for *in vivo* activity of a human glycoprotein:

> As it is not known whether glycosylation in hamster and human cells leads to identical structures, it may be more appropriate to generate and use a human dhfr- cell line for the production of human glycoproteins."[249]

In addition, Dr. Lowe relied on Dr. Goeddel's work at Genentech for the production of recombinant tPA. But as Dr. Lowe admitted on cross-examination, neither the Goeddel EP '619 patent (TX 2029) nor the '075 U.S. Patent (TX 2030) demonstrates or discloses the *in vivo* biological activity of the recombinant tPA product produced from mammalian cells.[250]

In fact, Dr. Goeddel's own statements to the U.S. PTO during the prosecution of his patents on recombinant human tPA confirms that the state of the art for producing an *in vivo* biologically active human glycoprotein by 1983 was entirely unpredictable:[251]

> At the time this invention was made, it was unknown (a) what effect glycosylation differences would have on the biological activity of a protein, and (b) whether the cell type used for expression of the protein would effect the glycosylation pattern. [252]
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> ***
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> It would not have been predictable whether glycosylation differences would, in fact, produce intact, functionally and

[249] TX 2001 at 703.

[250] 9/5/07 Lowe Trial Tr. 388:6-20; 389:9-19; 389:2-390:9; TX 2029 and TX 2030.

[251] TX 51. *See also*, TX 45 at 24-26.

[252] TX 51 at 5.

> biologically active glycoprotein. On this point, even later published papers reiterate this uncertainty.[253]
>
> ***
>
> These authors thus emphasize the unpredictability as to what effects, if any, changes in glycosylation may have on the biological profile of a given glycoprotein.[254]

When confronted by Dr. Goeddel's contemporaneous statements of uncertainty, Dr. Lowe's meager response was to state "That's his opinion, not mine."[255] It is worth noting that by 1984, Dr. Lowe had never expressed any recombinant protein — let alone a human glycoprotein — in a mammalian cell.[256] Moreover, Dr. Lowe had no experience working with EPO, has never produced an EPO glycoprotein, and, as he acknowledged on cross-examination, all of the information he relies upon regarding the cloning and expression of EPO is based on publications he reviewed after the fact and with which he was not personally involved.[257]

None of the references cited or relied upon by Dr. Lowe disclosed *in vivo* biological activity. Based on the reports in the literature regarding desialated and deglycosylated EPO, one of skill in the art would have understood that prior art reports of *in vitro* activity were not predictive of *in vivo* biological activity.[258] In particular, TX 41 reported:

> Erythropoietin, a glycoprotein that induces normal erythrocyte development, has 16 to 18 sialic acid residues per mole. ***Desialation results in complete loss of biological activity when it is assayed in vivo. When the assay is done in vitro, asialoerythropoietin has full activity***….[259]

For this reason, both Drs. Varki and Hood testified, there was simply insufficient knowledge and insufficient examples of any prior success to guide an ordinarily skilled artisan with any

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[253] TX 51 at 6.

[254] TX 51 at 7.

[255] 9/7/07 Lowe Trial Tr. 393:14-22.

[256] 9/7/07 Lowe Trial Tr. 396:23-397:6.

[257] 9/7/07 Lowe Trial Tr. 435:24-436:19.

[258] *See* TX 41 at AM-ITC 00213261.

[259] TX 41 at AM-ITC 00213261.

reasonable expectation of successfully obtaining an *in vivo* biologically active EPO.[260]

D. GENETICS INSTITUTE'S CLONING EXPRESSION OF THE HUMAN EPO GENE DOES NOT ANTICIPATE OR RENDER OBVIOUS DR. LIN'S ASSERTED CLAIMS-IN-SUIT

Roche contends that Dr. Fritsch's cloning and expression of the human EPO gene is § 102(g) prior art that either anticipates or renders obvious each of Dr. Lin's asserted claims-in-suit.[261] Roche erroneously asserts that Amgen has not introduced evidence to establish a date of invention before the effective filing date of the patents-in-suit.[262] But Roche cannot satisfy the key component of § 102(g) — that Dr. Fritsch conceived and reduced to practice his invention before Dr. Lin. Roche ignores the incontrovertible evidentiary record establishing Dr. Lin's invention dates of October 1983 for cloning the EPO gene[263] and March 1984 for producing an *in vivo* biologically active EPO product in a mammalian host cell.[264] These earlier invention dates for Dr. Lin's claims-in-suit demonstrate that Dr. Fritsch's work cannot serve as prior art under § 102(g)(2).

The uncontroverted testimony of Drs. Lin and Browne, corroborated by documentary evidence, establishes that the product and process claims were conceived when Dr. Lin demonstrated *in vivo* biological activity of man-made EPO in March of 1984. Only at that time did Dr. Lin have a "definite and permanent idea of the complete and operative invention."[265] Dr. Browne testified that Dr. Lin's team achieved expression of *in vivo* biologically active EPO

[260] 10/1/07 Varki Trial Tr. 2243:8-22; 10/1/07 Hood Trial Tr. 1993:11-20.

[261] Roche's Memo (D.I. 1315) at 34.

[262] Roche's Memo (D.I. 1315) at 41.

[263] 9/27/07 Lin Trial Tr. 1688:24-1692:2; TX 2014.

[264] 9/28/07 Browne Trial Tr. 1924:20-1925:11, 1937:7-1939:20; 9/27/07 Lin Trial Tr. 1755:18-1756:11; TX 30 at 2.

[265] *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994)(citing *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1376 (Fed. Cir. 1986).

using COS cells in March 1984.[266] Dr. Browne's testimony is corroborated by March 27, 1984 EPO Project Team Meeting Minutes (TX 30), which reflect the demonstration of *in vivo* biologically active recombinant EPO.[267] Dr. Lin testified that he obtained further confirmatory evidence, expression of *in vivo* biologically active EPO using CHO cells, in May 1984.[268]

By contrast, Dr. Fristch did not clone the EPO gene until July 1984 and did not express EPO using CHO cells until September 1984[269] — a full six months after Dr. Lin first demonstrated the *in vivo* biological activity of recombinant EPO. In fact, Dr. Fritsch did not even have EPO DNA in hand by the time Dr. Lin demonstrated the *in vivo* biological activity of COS and CHO produced EPO.[270] The evidence Roche uses to support its § 102(g)(2) defense, the laboratory notebook of Dr. Fritsch,[271] makes no mention of *in vivo* biological activity. Even if Roche could establish that Dr. Fritsch detected EPO using an *in vivo* bioassay, Dr. Lin's inventions would still pre-date the work of Dr. Fritsch by many months.

Because Amgen has met its burden of production regarding the respective dates of Dr. Lin's inventions, Roche must now present clear and convincing evidence of invalidity.[272] Roche's burden is especially heavy here, as this issue has been adjudicated by multiple courts and was considered by the Patent Office during prosecution.[273]

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[266] 9/28/07 Browne Trial Tr. 1924:20-1925:11.

[267] TX 30 at 2.

[268] 9/27/07 Lin Trial Tr. 1755:18-17:56:11.

[269] 9/7/07 Fritsch Trial Tr. 360:5-21.

[270] Dr. Fritsch's testimony established that he cloned the EPO gene on August 20, 1984. 9/7/07 Fritsch Trial Tr. 355:19-356:17.

[271] Roche's List of Prior Art (D.I. 1340) at 4 (referencing TX 2084).

[272] *See Purdue Pharma L.P. v. Boehringer Ingelheim GMBH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001) (The defendant "bears the ultimate burden of proof at trial of proving invalidity by clear and convincing evidence.").

[273] *See Hewlett-Packard Co.*, 909 F.2d at 1467 (discussing heightened standard where evidence was previously considered by the PTO examiner during prosecution); s*ee also American Hoist*, 725 F.2d at 1359 (same). In *Amgen Inc. v. Chugai Pharma. Co.*, 13 U.S.P.Q.2d 1737, 1746-50

Roche bears the ultimate burden of proving invalidity, yet it has presented no evidence that controverts the facts illustrated by the trial record — that the claims-in-suit were invented in March 1984. Those claims were invented months before Dr. Fritsch cloned or expressed EPO. Therefore, Dr. Fritsch's work cannot stand as "***prior***" art under § 102(g) for any purpose.

E. THE UNREBUTTED OBJECTIVE EVIDENCE DEMONSTRATES THE NON-OBVIOUSNESS OF DR. LIN'S CLAIMED INVENTIONS

The United States Supreme Court has made plain that in assessing whether a patent claim is obvious, it is necessary to consider, among other things, objective evidence of non-obviousness.[274] At trial, the objective evidence showed that before Dr Lin's inventions there was a long-felt and increasing need for a treatment of the anemia associated with kidney failure,[275] an absence of any effective treatment,[276] failures of others attempting to address the need,[277] and in fact, doubts that EPO could solve the problem.[278] Dr Lin's claimed inventions

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(D. Mass. 1989), Magistrate Judge Saris detailed each step carried out by Dr. Lin and his team in developing the inventions of the claims-in-suit, including the expression of an *in vivo* biologically active EPO product in COS cells in March 1984 and in CHO cells in May 1984. *Id.* at 1748-49. Those dates were upheld by the Federal Circuit, 927 F.2d 1200, 1203 (Fed. Cir. 1991) and later were considered and referenced by the Patent Office on multiple occasions.

[274] *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)(listing commercial success, long-felt need, and failure of others as objective evidence of non-obviousness). Evidence of skepticism or disbelief before the invention, public praise, unexpected results, industry acceptance also has been considered by courts assessing the non-obviousness of inventions. *See*, *e.g.*, *Envtl. Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 697-98 (Fed. Cir. 1983)(considering skepticism or disbelief before the invention as highly probative evidence of nonobviousness); *Allen Archery, Inc. v. Browning Mfg. Co.*, 819 F.2d 1087, 1092 (Fed. Cir. 1987)(copying by others, public praise, unexpected results, and industry acceptance); *Micro Motion Inc. v. Exac Corp.*, 741 F. Supp. 1426, 1434 (N.D. Ca. 1990)(praise); *In re Piasecki*, 745 F.2d 1468, 1474 (Fed. Cir. 1984)(praise); *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 679 (Fed. Cir. 1988)(copying); *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1368 (Fed. Cir. 2004)(skepticism and licensing).

[275] 9/25/07 Friedman Trial Tr. 1431:8-1432:5.

[276] 9/25/07 Friedman Trial Tr. 1433:5-25, 1434:19-1435:9; 9/26/07 Spaeth Trial Tr. 1526:3-1529:13; 1530:13-1532:12.

[277] Roche contends that the only evidence of failures of others is Dr. Orkin's failure to clone the EPO gene, however, there are numerous other examples of failures of others in the record, in particular the failure to treat the anemia associated with chronic kidney disease. As Dr. Friedman and even Roche's own witness, Dr. Spinowitz, testified, the attempts by Dr Essers, Dr Goldwasser, and others all failed to increase hematocrit or solve the major problem of the anemia

not only satisfied the long-felt need, but were met with "shock and awe" by the medical community as recombinant human EPO revolutionized the lives of dialysis patients and changed the way medicine was practiced. As both Dr. Friedman and Ms. Spaeth, a kidney dialysis patient who suffered from chronic anemia for 29 years, testified, before recombinant human EPO, there were no effective treatments: transfusions were given to the more severely anemic patients but these only lasted a few days and carried with them the risk of hepatitis and viral infections, a risk of death from receiving the wrong type of blood, androgens and heavy metals were ineffective, carried risks, and had undesirable side effects.[279]

Where the prior art was ineffective and often harmful, EPOGEN® remarkably and to an extraordinary extent corrected the anemia of patient, it was "miraculous."[280] Even Roche's witness Bruce Spinowitz agreed that by 1990 recombinant human EPO replaced transfusions — the previous standard of care — and made a marked improvement in the quality of life of patients on dialysis.[281] This evidence is not in dispute.

Roche's only defense is to contend that Amgen has failed to prove a nexus between the success of Amgen's commercial product — EPOGEN® — and Dr. Lin's specification. This argument is wrong as a matter of law. A nexus is *prima facie* established by comparing the successful commercial product to the *claims* in suit, not the specification, and showing that the commercial product falls within the scope of the asserted claims.[282] Here, Amgen established

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of chronic renal failure. 9/11/07 Baron Trial Tr. 668:23-669:4; 9/12/07 Spinowitz Trial Tr. 889:12-890:22, 930:17-931:10, 945:23-946:2, 10/1/07 Goldwasser Trial Tr. 2011:6-12; 9/25/07 Friedman Trial Tr. 1442:18-22, 9/26/07 Friedman Trial Tr. 1492:21-1493:2, 1496:6-24. *See also* TX 20 at AM-ITC 00076148, noting that until clinical trials with recombinant human EPO, it was not known whether EPO preparations could correct the anemia of CRF patients.

[278] 9/25/07 Friedman Trial Tr. 1438:21-1440:8.

[279] 9/25/07 Friedman Trial Tr. 1448:4-13, 1435:10-18.

[280] 9/25/07 Friedman Trial Tr. 1435:10-18, 1426:23-1428:11.

[281] 9/12/07 Spinowitz Trial Tr. 941:17- 942:7, 943:4-9.

[282] *Demaco Corp. v. F. Von Langsdorff Licensing Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988)("A *prima facie* case of nexus is generally made out when the patentee shows both that there is

that EPOGEN® and its use meet every limitation of at least '422 claim 1 and '933 claims 3, 7, 8, 9, 11, 12, and 14.[283] Moreover, Dr. Browne testified that he used the very cells reported in Example 10 of the Lin patents to produce the Master Working Cell Bank that was used for the commercial production of EPOGEN®.[284] As the case law clearly shows, the burden is on Roche to rebut the presumption of nexus using clear and convincing *evidence* — not just argument or conjecture — that something other than the features of the claimed inventions accounts for the success of Amgen's commercial product.[285] Roche cites to no proof that EPOGEN®'s success is caused by a factor other than the inventions' features as claimed, instead arguing irrelevantly that manufacture of EPOGEN® involves steps other than those set forth in the specification.[286]

That EPOGEN®, the commercial embodiment of Dr Lin's recombinant human EPO inventions, miraculously improved the lives of dialysis patients and awed the medical community, where so many had failed to solve the long-felt need despite significant incentive,[287]

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commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent."); *J. T. Eaton & Co. v. Atlantic Paste & Glue Co*., 106 F.3d 1563, 1571-72 (Fed. Cir. 1997)("When a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent, it is presumed that the commercial success is due to the patented invention."). Furthermore, any showing is made relative to the claims at issue: as stated in *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999), the nexus must be drawn to "the claimed features of the invention" and the objective evidence.

[283] *See* Amgen's Bench Brief on Documents Already in Evidence that Demonstrate a Nexus Between EPOGEN® and at Least One Claim of a Patent-in-Suit (D.I. 1126), and Nexus Between EPOGEN® and Claims-in-Suite (D.I. 1351-2).

[284] 10/1/07 Browne Trial Tr. 1062:14-1963:21.

[285] *Demaco*, 851 F.2d at 1393 ("When the patentee has presented a *prima facie* case of nexus, the burden of coming forward with evidence in rebuttal shifts to the challenger, as in any civil litigation."); *J.T. Eaton & Co.*, 106 F.3d at 1571-72. *See also Demaco*, 851 F.2d at 1393 (noting that "argument" and "conjecture" are insufficient to overcome objective evidence of non-obviousness). *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984)(argument and conjecture are inadequate to overcome objective evidence).

[286] As explained in detail in Amgen's Opposition to Roche's Memorandum Regarding Amgen's Demonstration of the Requisite Nexus (D.I. 1351), Roche's position fails because there is no evidence, much less clear and convincing evidence, that such additional steps exclusively account for EPOGEN®'s success.

[287] Roche's own witness, Dr Lowe, testified that there was an acknowledged desire in the scientific community to develop an EPO product and yet, before Dr Lin, no one succeeded.

is powerful evidence of the non-obviousness of Dr. Lin's inventions.

VI. ROCHE FAILED TO PRESENT CLEAR AND CONVINCING EVIDENCE SUFFICIENT FOR A VERDICT THAT DR. LIN'S CLAIMS ARE INVALID UNDER 35 U.S.C. § 112

In its Memo, Roche asserts that the Court should find Dr. Lin's asserted claims invalid under 35 U.S.C. § 112 on four grounds: (1) that the claims are inadequately described and indefinite based on the claim limitation "human erythropoietin"; (2) that '422 claim 1 is indefinite as lacking an identifiable structure; (3) that the "radioimmunoassay" limitation of '349 claim 7 is not enabled; and (4) the "vertebrate cells" limitation of the same claim is neither adequately described nor enabled. Roche has failed to show by clear and convincing evidence, let alone by the overwhelming evidence necessary to support its JMOL, that Dr. Lin's claims are invalid for any of these reasons.

A. ROCHE HAS FAILED TO PROVE THAT A REASONABLE JURY COULD ONLY FIND "HUMAN ERYTHROPOIETIN" INDEFINITE AND INADEQUATELY DESCRIBED

The Court has construed "human erythropoietin" to mean "a protein having the amino acid sequence of human EPO, such as the amino acid sequence of EPO isolated from human urine."[288] Unsatisfied with this construction, Roche has offered a number of strawman constructions through its expert, Richard Flavell, in an attempt to render the asserted claims invalid for lack of written description or for indefiniteness.

Roche argues that its invalidity attacks based on the term "human erythropoietin" reach to all of the asserted claims.[289] But, in fact, Dr. Flavell's testimony did not address the asserted claims of the '698 or '868 patent, or '933 claim 14.[290] The reason for this is clear: in each of these claims, indeed in all of the asserted claims except for '422 claim 1, the complete limitation

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9/05/07 Lowe Trial Tr. 186: 18-25; 9/06/07 Lowe Trial Tr. 264:15-21.

[288] Claim Construction Order (D.I. 613) at 15.

[289] Roche's Memo (D.I. 1315) at 36.

[290] *See* 9/24/07 Flavell Tr. at 1206:19-23; 1238:9-1244:6.

is "DNA sequence encoding human erythropoietin."[291] Because Roche's expert did not offer any opinion as to the asserted '698 and '868 claims, or '933 claim 14, Roche cannot meet its burden under Fed. R. Civ. P. 50(a) at least with respect to any such claims.

Regarding the claims at issue for which Dr. Flavell actually provided an opinion ('422 claim 1 and '349 claim 7), Roche's motion must again fail. As discussed below and as more fully set forth in Amgen's Renewed Motion for Judgment As a Matter of Law,[292] the ***evidence offered by Roche*** is simply insufficient to meet its burden of proving by clear and convincing evidence that the limitation "human erythropoietin" is neither adequately described nor definite. In the context of Roche's motion for judgment as a matter of law, Roche's failure to even consider the import or weight of ***evidence presented by Amgen*** dooms it. The standard under Fed. R. Civ. P. 50(a) — that there is not sufficient evidence to raise a genuine factual controversy[293] — cannot be met simply by ignoring the evidence presented by Amgen or the Court's claim construction.

1. Because Roche Has Failed To Show That "Human Erythropoietin" Is Not Adequately Described, Its Motion Should Be Denied

As the Court made abundantly clear during Dr. Flavell's examination, the term "human erythropoietin," as construed, does not expressly specify an amino acid length.[294] Dr. Flavell's written description argument is based on his assumption that "human erythropoietin" must mean a 165 amino acid molecule only and that because Dr. Lin does not expressly recite a 165 amino acid human EPO molecule, "human erythropoietin" is not described.[295]

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[291] *See Amgen Inc. v. Hoescht Marion Roussel, Inc.*, 339 F. Supp. 2d 202, 251 (D. Mass. 2004)(ruling that "DNA encoding the mature erythropoietin amino acid sequence of FIG. 6" and "mature erythropoietin amino acid sequence of FIG. 6" are distinct limitations).

[292] Renewed Motion (D.I. 1270) at 16-18.

[293] *See CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1152 (Fed. Cir. 1997).

[294] 9/24/07 Flavell Trial Tr. at 1242:19-1243:8.

[295] *See* Roche's Memo (D.I. 1315) at 36-37.

Roche's failure to reference at all the evidence presented by Amgen is fatal to its motion, and in particular the evidence showing that:

(1) "human erythropoietin" includes the material made in Example 10;[296]

(2) the cells in Example 10 were used to create the master working cell bank Amgen used to make it commercial EPO product, EPOGEN®;[297] and

(3) As conceded by Roche's counsel at the outset of trial EPOGEN® has 165 amino acids.[298]

Because the written description requirement of 35 U.S.C. § 112 is satisfied by showing that a claimed product is made using the process described in a patent,[299] Roche cannot show that Dr. Lin did not describe a 165 amino acid human erythropoietin product based on all of the evidence before the jury.

Finally, to say that Dr. Lin did not provide any amino acid sequence information for "human erythropoietin" is entirely unsupported. The deduced amino acid sequence of human erythropoietin is set forth at Figures 6 and 9 of Dr. Lin's patents.[300]

2. Roche's Motion Regarding The Definiteness Of "Human Erythropoietin" Similarly Ignores The Evidence And Should Be Denied

In support of its assertion that the term "human erythropoietin" is indefinite, Roche does

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[296] *See e.g.*, TX 1 at Col. 25:31-33; Col. 26:11-18; 28:1-12.

[297] 10/1/07 Browne Trial Tr. 1959-1963.

[298] 9/5/07 Trial Tr. 126:22-23 (Roche's counsel acknowledging that EPOGEN® is a 165 amino acid product).

[299] *Regents of the Univ. of New Mexico v. Knight*, 321 F.3d 1111 (Fed. Cir. 2003); *Kennecott Corp. v. Kyocera Int'l, Inc.*, 835 F.2d 1419 (Fed. Cir. 1987).

[300] TX 1, Figs. 6 and 9, Col. 21:20-27 (describing the amino acid sequence of human erythropoietin set forth in Figure 9 as the "deduced" sequence); Col. 10:65-11:2 (providing that the amino acid sequence for human erythropoietin provided in the specification is human erythropoietin's deduced sequence); and Col. 35:10-17 (describing the amino acid sequence in Figure 6 as a deduced sequence). Roche's reference to other sequences set forth in Dr. Lin's patents, Roche's Memo (D.I. 1315) at 35-36 is simply a red-herring since it ignores the description of the 165 amino acid product of Example 10 and the amino acid information set forth in the patent.

not cite to any testimony or evidence.[301] Rather, Roche makes attorney argument that is not tethered to any offer of proof made by Roche, and takes out of context (and again without citation) incomplete pieces of Dr. Lin's patent.

Indeed, the evidence is to the contrary. As Dr. Lodish testified to during trial, one of ordinary skill in the art would understand the metes and bounds of the claim limitation "human erythropoietin" because Dr. Lin defined its as precisely as the subject matter would have allowed in 1983-84.[302] As explained by Dr. Lodish, a skilled artisan would know that he had obtained a "human erythropoietin" so long as he had used human EPO DNA, as described by Dr. Lin, to make such EPO.[303] Furthermore, one of skill could verify that he or she had obtained human EPO by comparing the identity of the amino acids made by following Dr. Lin's teaching to the identity of amino acids identified in the correctly deduced amino acid sequence for human EPO in Dr. Lin's patent.[304] Roche's unsubstantiated argument does not meet the requirements of Fed. R. Civ. P. 50 (a).

3. Roche's Untimely Assertion That '422 Claim 1 Is Indefinite As Lacking Identifiable Structure Should Be Stricken And Certainly Should Not Serve As Basis For Finding The Claim Indefinite

None of Roche's five interrogatory responses to Amgen's request for Roche's invalidity contentions, Roche's expert reports, or Roche's Pre-Trial Brief included the assertion that '422 claim 1 is indefinite for lacking identifiable structure. As such, Roche's 11th hour (indeed thirteenth hour) attempt to invalidate '422 claim 1 — the one claim Roche knows it must invalidate in light of the Court's ruling that it is literally infringed — by offering a defense that it

[301] Roche's Memo (D.I. 1315) at 39. Although Roche asserts in the single paragraph it devotes to arguing that "human erythropoietin" is indefinite and Dr. Flavell offered testimony on the matter, Roche does not offer a single citation to such testimony (citing only to a single sentence in Dr. Lin's patents).

[302] 10/3/07 Lodish Trial Tr. 2323:22-2324:16.

[303] *Id.* at 2322:22-2323:17

[304] 10/3/07 Lodish Trial Tr. 2322:22-2323:27.

never previously disclosed to Amgen should be stricken.[305]

Even if not stricken, the defense is insufficient to support a judgment as a matter of law under Fed. R. Civ. P. 50(a) for at least two reasons. First, as explained above and in Amgen's Renewed Motion under Fed. R. Civ. P. 50(a),[306] the term "human erythropoietin" is definite.

Second, the issue of whether "human erythropoietin" encompasses multiple glycosylation structures assumes that the Court's construction of "human erythropoietin" includes a glycosylation requirement. That simply is not the case. The Court's claim construction refers only to an amino acid sequence and the Court expressly rejected including or excluding additional structure in its claim construction "the patent itself is silent as to the presence or absence of any structural characteristics beyond the required amino acid sequence."[307] Thus, the Court's previous decision in the *TKT* litigation regarding '933 claim 1[308] is inapposite.

Roche's last-ditch attempt to invalidate '422 claim 1 by asserting a previously undisclosed argument should be stricken, and should not serve as a basis for judgment under Fed. R. Civ. P. 50(a).

B. ROCHE HAS FAILED TO PROVE THAT '349 CLAIM 7 IS NOT ENABLED

The entirety of Roche's motion on the issue of whether it is entitled to judgment as a matter of law based on its assertion that '349 claim 7 is not enabled is based on the premises that "absolutely none of this evidence [set forth in Roche's motion] was contradicted by Amgen" and that "Amgen presented no evidence whatsoever, let alone credible evidence, to defeat Roche's

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[305] *See Omegaflex v. Parker Hannifin Corp.*, 425 F. Supp.2d 171, 183-84 (D. Mass. 2006)(Ponsor, J.), *rev'd on other grounds*, 2007 U.S. App. LEXIS 14308 (Fed. Cir. 2007); *Rowe v. Case Equip. Corp.*, 1997 U.S. App. LEXIS 227, at *6-7 (6th Cir. 1997)(not recommended for publication)(holding expert opinion was untimely and properly excluded where supplemental interrogatory failed to reveal expert opinion); *Murray v. Dillard Paper Co.*, 1999 U.S. Dist. LEXIS 22630, at *8-9 (E.D. Va. 1999) (same).

[306] Renewed Motion (D.I. 1270) at 16-18.

[307] Claims Construction Order (D.I. 613) at 14.

[308] *See* Roche's Memo (D.I. 1315) at 41.

clear and convincing evidence."[309] Both premises are false.

As Roche's expert Dr. Edward Harlow testified at trial, one of skill in the art would have known how to perform a radioimmunoassay to detect the amount of EPO being produced by vertebrate cells:

> Q. So, it is your opinion that one of ordinary skill in the art could have followed the RIA referred to in the patent in the suit in order to quantify the levels of EPO protein being produced by vertebrate cells?
> A. Yes.[310]

Dr. Lowe similarly testified, opining that a radioimmunoassay was "a standard laboratory technique."[311] For Roche to assert that the testimony of its own experts lack credibility stretches all bounds of credulity.

Likewise, the superficial testimony offered by Dr. Flavell is insufficient. First, Dr. Flavell's testimony is the subject of a motion to strike. If granted, Roche's entire non-enablement defense vanishes.

Second, Dr. Flavell's reliance on TX 2073 is not reasonable. The reference to EPO fragments was made in the context of proteins found in the sera of chronic renal disease patients, ***not*** whether EPO fragments are found in the culture media of vertebrate cells that have been recombinantly engineered to produce human EPO. More importantly, Dr. Flavell ignored: (1) that the reference also states that the presence of any fragments can be accounted for by separating out such fragments using known techniques;[312] (2) the deposition testimony of Dr.

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[309] Roche's Memo (D.I. 1315) at 43.

[310] 9/28/07 Harlow Trial Tr. 1800:9-13. *See also* 9/28/07 Harlow Trial Tr. 1800:9-13; 1798:16-1799:2 (providing that Dr. Harlow's expertise extends to radioimmunoassay techniques).

[311] 9/6/07 Lowe Trial Tr. 304:20-23. Similarly, Roche's expert Dr. Kadesch testified before the Court during arguments on the ODP issue that RIA was a standard assay used in 1983 or 1984 to measure the amount of protein, and that one of skill in the art would have certainly known about the RIA assay. 10/1/07 Kadesch Trial Tr. 12:4-13:3 (afternoon session).

[312] TX 2073 at AM-ITC 01006802 ("These small fragments can be separated by gel permeation chromatography").

Joan Egrie offered by Roche at trial of that provides evidence that Amgen used Western analysis to account for fragments;[313] and (3) that based on all of this information, Roche's own expert, Dr. Harlow, acknowledging that "fragments" must be considered when performing a radioimmunoassay, nonetheless still opined that an ordinarily skilled artisan could have used the RIA set forth in Dr. Lin's patent to quantify the amount of EPO in cell culture media.[314] Dr. Flavell also ignored the fact that the publication itself characterized the development of an RIA for EPO as "easy" with the advent of human EPO's "purification" six years before the earliest filing date of Dr. Lin's applications.[315]

Dr. Flavell's cursory opinion, unsupported by any credible evidence, in combination with the admissions contained in the other Roche witness testimony offered at trial, does not meet Roche's burden to prove non-enablement by clear and convincing evidence and certainly does not meet the standard of Rule 50(a).

C. ROCHE'S ATTORNEY ARGUMENT THAT "VERTEBRATE CELLS" AS SET FORTH IN '349 CLAIM 7, IS INADEQUATELY DESCRIBED AND NOT ENABLED CANNOT MEET ITS BURDEN OF PROVING INVALIDITY

At trial, Roche presented no witness, expert or otherwise, to support its contention that "vertebrate cells" is not adequately described or enabled. In light of this failure, Roche seeks to cobble together an argument based on snippets from the testimony of Drs. Lin, Lowe, Harlow, and Varki.[316] But each of these snippets is directed to only two facts: (1) that there are many types of vertebrate cells; and (2) not all vertebrate cells would be able to make EPO. These two facts, taken as true, are insufficient by themselves to establish either inadequate written description or non-enablement.

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[313] 9/24/07 Egrie Trial Tr. 1184:6-16.

[314] 9/28/07 Harlow Trial Tr. at 1800:14-24

[315] TX 2073 at AM-ITC 01006801 ("Once the purification of human erythropoietin was complete (Miyake *et al*, 1977) ***it was relatively easy to develop an RIA*** . . .")(emphasis added).

[316] D.I. 1315 at 44-45.

These two facts fail to address whether or not Dr. Lin's disclosure and examples can describe the genus of vertebrate cells claimed or whether undue experimentation would be required to determine which cells would work and which would not. Roche's attorney argument cannot rectify these deficiencies.

As such, as more fully set forth in Amgen's renewed motion for judgment as a matter of law, Amgen, and not Roche, is entitled to judgment that claim 7 of the '349 patent is adequately described and enabled with regard to the "vertebrate cells" claim limitation and Roche's motion should be denied.

VII. CONCLUSION

For all of the foregoing reasons, the Court should deny Roche's Rule 50(a) Motion for Judgment as a Matter of Law. In addition, given the evidence adduced at trial, Amgen respectfully requests that the Court enter judgment as a matter of law that Roche has failed to meet its burden of proving by clear and convincing evidence that Dr. Lin's asserted claims are invalid as anticipated, obvious, or failing to satisfy 35 U.S.C. § 112.

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Respectfully Submitted,

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