BoxInterferences@uspto.gov
Telephone: 571-272-4683

Entered: September 9, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ASHOK **KUMAR**
and
NELLITHANATH THANKACHEN BYJU,

Junior Party,
(Patent 8,541,422)

v.

HONG -BIN **SUNG**, JIAQI SHAN, BOYO ZHANG,
and
FANG YUAN,

Senior Party,
(Application 14/322,939).

Patent Interference 106,039 (JTM)
(Technology Center 1600)

Before: RICHARD E. SCHAFER, SALLY GARDNER LANE, and JAMES T. MOORE, *Administrative Patent Judges*.

MOORE, *Administrative Patent Judge*.

JUDGMENT - PRELIMINARY MOTIONS - Bd. R. 127

The Board has entered a Decision on Motions in this interference. (Paper No. 252). As discussed in the Decision, Kumar's claims are unpatentable over Pereillo under 35 U.S.C. § 103, and Sun has failed to rebut the presumption of Board Rule 207.

Accordingly, both parties claims which correspond to count 1 are unpatentable.

It is:

Ordered that judgment is entered against both parties.

Further Ordered that Kumar is not entitled to claims 1-17 and 28-30 of U.S. Patent 8,541,422, which are hereby canceled;

Further Ordered that Sun is not entitled to claims 11, 18-23, and 25-48 of U.S. Application 14/322,939, which are finally refused;

Further Ordered that a copy of this judgment and the Decision on Motions shall be entered into the files of U.S. Patent 8,541,422 and U.S. Application 14/322,939; and

Further Ordered that should there be a settlement agreement, the parties' attention is directed to 35 U.S.C. §135(c) and Bd. R. 205.

cc (via email):

Attorney for Kumar:

Barry Bretschneider
Peter J. Knudsen
Baker & Hostetler
bbretschneider@bakerlaw.com
pknudsen@bakerlaw.com

Attorney for Sun:

Thomas O. Hoover
Wei Song
McCarter & English, LLP
thoover@mccarter.com
wsong@mccarter.com

BoxInterferences@uspto.gov
Telephone: 571-272-9797

Entered: September 9, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ASHOK **KUMAR**
and
NELLITHANATH THANKACHEN BYJU,

Junior Party,
(Patent 8,541,422)

v.

HONG -BIN **SUNG**, JIAQI SHAN, BOYO ZHANG,
and
FANG YUAN,

Senior Party,
(Application 14/322,939).

Patent Interference 106,039 (JTM)
(Technology Center 1600)

Before: RICHARD E. SCHAFER, SALLY GARDNER LANE, and JAMES T. MOORE, *Administrative Patent Judges*.

MOORE, *Administrative Patent Judge*.

DECISION ON MOTIONS

I. Introduction

This interference was declared June 2, 2015. The reader is referred to the a Declaration (Paper 1) for an identification of (1) the parties, (2) the patent and application involved in the interference, (3) the count and corresponding claims, and (4) earlier constructive reductions to practice (i.e., benefit for the purpose of priority) accorded to the parties.

II. Count

A count defines the interfering subject matter and limits the scope of proofs on the issue of priority.

The count is Count 1.

Count 1 is claim 11 of application 14/322,939, reproduced below:

> 11. A method of treating thrombosis and embolism related diseases comprising administering to a patient in need thereof an effective amount of an optically active 2- hydroxytetrahydrothienopyridine derivative, wherein said derivative is (S)-methyl 2-(2-acetoxy-6,7- dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(2-chlorophenyl)-acetate or a pharmaceutically acceptable salt thereof,
>
> wherein the thrombosis and embolism related disease is atherosclerosis, myocardial infarction, stroke, ischemic cerebral thrombosis, peripheral arterial disease, acute coronary syndrome, or thrombosis after percutaneous coronary intervention (PCI). (Paper 9, 3).

III. Requests for Oral argument

Oral argument was requested by Kumar (Paper 213) and Sun (Paper 228). The panel does not deem oral argument necessary for resolution of the pending motions, which have been adequately briefed. Accordingly, the requests are denied.

IV. Summary of the Motions

A. Kumar Motions

1. Kumar Motion 2

Kumar Motion 2 seeks entry of judgment that Sun's involved claims are unpatentable under 35 U.S.C. § 135(b)(1) on the basis that Sun added material limitations to its involved claims more than one year after Kumar's patent issued. Paper 63. Sun opposed. Paper 90. Kumar replied. Paper 151.

2. Kumar Motion 3

Kumar Motion 3 seeks to deny Sun benefit of its February 2010 Chinese application. Paper 137. Sun opposed. Paper 185. Kumar replied Paper 210.

3. Kumar Motion 4

Kumar Motion 4 seeks to designate Kumar's claims 10-14 as not corresponding to the count. Paper 138. Sun opposed. Paper 179. Kumar replied Paper 211.

4. Kumar Motion 5

Kumar Motion 5 seeks to exclude evidence. Paper 215. Sun opposed. Paper 244. Kumar replied. Paper 247.

B. Sun Motions

1. Sun Motion 2

Sun Motion 2 seeks entry of judgment that Kumar's involved claims are unpatentable under 35 U.S.C. § 103 as obvious over Pereillo. Paper 140. Kumar opposed. Paper 176. Sun replied. Paper 205.

2. Sun Motion 4

Sun Motion 4 seeks to exclude evidence. Paper 229. Kumar opposed. Paper 230. Sun replied. Paper 248.

V. Motions Decisions

Kumar Motion 2

A. Introduction

The Board may take up motions in any order. 37 C.F.R. § 125(a).

We elect to take up Kumar Motion 2 first because it raises a "threshold" issue. If the motion is granted, Kumar prevails. 37 C.F.R. § 411.201 (definition of "Threshold issue" (2)(ii)); 37 C.F.R. § 41.208(a)(1).

Kumar Motion 2 seeks entry of judgment as to all involved Sun claims based on a statutory bar of 35 U.S.C. § 135 (b)(1). Paper 63.

B. Facts[1]

1. Kumar's involved patent issued September 24, 2013. Ex. 2019. Paper 63, 3.
2. The "critical date" for including claims which were the same, or substantially the same, as Kumar's claims, so as not to be time-barred under 35 U.S.C. § 135(b)(1) was September 24, 2014.
3. Claim 11 first appeared *ipse dixit* and in its present form on April 3, 2015. Paper 63, 6.
4. Claim 11 presently reads as follows: 11. A method of treating thrombosis and embolism related diseases comprising administering to a patient in need thereof an effective amount of **an optically active 2-hydroxytetrahydrothienopyridine derivative**, wherein said derivative is (S)-methyl 2-(2-acetoxy-6, 7-dihydrothieno[3,2-c l pyridin-5(4H)-yl)-2-(2-chlorophenyl)-acetate or a pharmaceutically

[1] To the extent that a finding is a conclusion of law, it may be treated as such.

acceptable salt thereof, wherein the thrombosis and embolism related disease is atherosclerosis, myocardial infarction, stroke, ischemic cerebral thrombosis, peripheral arterial disease, acute coronary syndrome, **or** thrombosis after percutaneous coronary intervention (PCI). Paper 9, 3; Ex. 2007, 2–3 (emphasis added).

5. On July 3, 2013, claims 11 and 12 existed in this format in the parent case, albeit withdrawn from consideration as directed to nonelected subject matter: 11. (Withdrawn-Currently Amended) A method of treating thrombosis and embolism related diseases comprising administering to a patient in need thereof an effective amount of (S)-methyl 2-(2- acetoxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)-2-(2-chlorophenyl)-acetate or a pharmaceutically acceptable salt thereof. 12. (Withdrawn) The method of claim 11, wherein the thrombosis and embolism related diseases is **selected from** atherosclerosis, myocardial infarction, stroke, ischemic cerebral thrombosis, peripheral arterial disease, acute coronary syndrome, **and** thrombosis after percutaneous coronary intervention (PCI). Paper 90, 3; Ex. 2016, 5 (emphasis added).

6. Additional facts may be found below.

2. Issue

1. According to Kumar, Sun's amendments in April 2015 were material and the amended claim is barred. Paper 63, 10–11.

2. Sun, on the other hand, takes the position that particular previous claims presented in 2013, but subject to restriction requirement, in the

parent case overcome the potential § 135(b) bar. Paper 90, 1. *Corbett v. Chisholm*, 568 F.2d 759 (C.C.P.A 1977)

3. Burden and Standard of Proof

3. Kumar has the burden of proof. 37 C.F.R. § 41.121(b).

4. The standard of proof is a preponderance of the evidence. *See, e.g.*, *Bilstad v. Wakalopulos*, 386 F.3d 1116, 1120-21 (Fed. Cir. 2004) (in connection with a motion for judgment based on a lack of written description, movant has a burden by a preponderance of the evidence).

5. A party seeking to prevail on the bar must show in its motion that the claim sought to be deemed unpatentable is (1) the same as, or for the same or substantially the same subject matter as, a claim of an issued patent, and (2) that it was made in any application not prior to one year from the date on which the patent was granted. 35 U.S.C. § 135 (b)(1); *Regents of the University of California v. University of Iowa Research Foundation*, 455 F.3d 1371, 1376–1377 (Fed. Cir. 2006)

6. A party refuting and opposing the bar movant, if sufficient evidence has been put forth by the movant, must show that the later filed claim does not differ from an earlier claim in an application in any "material difference." *Id.*

4. Discussion

Both Kumar and Sun raise issues which stray from the central issue in deciding this motion. Although we have carefully considered even the ancillary observations and arguments, we hew to the principal facts and arguments of record and focus our analysis on those pertinent facts.

Kumar bases this motion on the premise that the amendment of a pre-critical date claim to overcome a rejection creates a rebuttable presumption that the change is to a material limitation and the post-critical date claim is therefore barred. Paper 63, 11. *See Adair v. Carter*, 668 F.3d 1334, 1339 (Fed. Cir. 2012).

Kumar's analysis is focused on the amendment of claim 11 on July 3, 2014. That those amendments on that date, from immediately prior claim 11, were material, is beyond question. Kumar then also notes in the "interests of completeness" that Sun had claims in the parent application. Paper 63, 17. Kumar then argues that those claims (11 and 12) were subject to a restriction requirement and therefore are not directed to the same invention as the elected species were. *Id.*

Sun, in opposition, urges that the claim was initially presented as claims 11 and 12 in the parent application 13/576,534. Paper 90, 2. The only difference between those claims is stated to be the phrase "an optically active 2-6 hydroxytetrahydrothienopyridine derivative" Paper 90, 4. Accordingly, Sun urges that no material differences exist. Sun relied upon the declaration of a witness, Dr. Duan. Ex. 1014, in dealing with the comparison of "optically active" and "S" between the two sets of claims.

In reply, Kumar again states that Sun's amendments must have been material. Paper 151, 4–6. Kumar challenges Dr. Duan's statements based on lack of expert qualifications. *Id.* at 3. Kumar also raises numerous other ancillary issues concerning the opposition contents. *Id*. at 4-7.

Where any claim is contained in an application prior to one year from the patent issuance date, then it is not barred. *See, e.g. Bowen v. Bihlmaier*, 231 USPQ 662, 665 (Bd. Pat. App. & Int. 1986); *Pizzuro v. Pfund*, 1 USPQ2d 1056, 1061(Bd. Pat. Int. 1984). It does not matter if the claims were cancelled. *Tezuka v. Wilson*,

224 USPQ 1030, 1036 (Bd. Pat. Int. 1984). It is also logical to us under these facts that it does not matter if the claims were restricted and withdrawn.

We also note that a restriction requirement is simply a matter of administrative convenience, and is not a definitive conclusion that claims are patentably distinct. *See Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568 (Fed. Cir. 1996) (noting restriction requirement is for "administrative convenience"); *Transco Prods. Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 558–59 (Fed. Cir. 1994) (same); *In re Watkinson*, 900 F.2d 230, 233 (Fed. Cir. 1990) (restriction is "a matter within the discretion of the examiner and not tantamount to a rejection of claims"); *In re Hengehold*, 440 F.2d 1395, 1403 (CCPA 1971) (restriction is a "discretionary, procedural or nonsubstantive" matter).

Thus, the central question to be decided presently is whether the difference between claims 11-12 pre-bar in the parent application and claim 11 post-bar is "material." Kumar's reply relies on its position that the restriction requirement *de facto* means that the claims are separate inventions.

We take notice that the term "S" in the structure in the claim is a well-known term for a particular type of chiral enantiomeric stereoisomers. Using the Cahn-Ingold-Prelog (CIP) priority rules, R- and S- assign the absolute configuration around a stereocenter. S stands for counterclockwise rotation about the center.[2] Thus, we find that there is no material difference between "optically active" and the designation (S) for the particular enantiomer, which is itself optically active.

[2] *See, e.g.*, Carey and Sundberg, *Advanced Organic Chemistry*, Third Edition, 1990, Plenum Press, New York, pp. 67–75, *see esp*. p. 71 (Board Ex. 3001). *See* also Ex. 2034, pp. 285-288.

In reply, Kumar points out that Sun also amended the claim to limit the claim to a single species, and to certain specific disease. Paper 151, 4. Those elements, however, are present in the 2013 claims reproduced above. We therefore do not find the existence of a material difference.

Accordingly, we Deny Kumar Motion 2.

Kumar Motion 4

A. Background

Kumar Motion 4 seeks to designate Kumar's claims 10-14 and 16 as not corresponding to the count. Paper 138.

Sun opposed. Paper 179.

Kumar replied Paper 211.

B. Facts

1. Kumar claim 10 reads as follows:

> 10. The method of claim 1, wherein the amount of the S oxo-clopidogrel or the compound of formula IIA is about 20 to about 100 mg as a loading dose. Paper 5, A-2.

2. Kumar claim 11 reads as follows:

> 11. The method of claim 1, wherein the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 35 to about 70 mg as a loading dose. *Id.*

3. Kumar claim 12 reads as follows:

> 12. The method of claim 1, wherein the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 20 to about 100 mg as a loading dose. *Id.* This claim appears to be a duplicate of claim 10.

4. Kumar claim 13 reads as follows:

13. The method of claim 1, wherein the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 5 to about 30 mg as a maintenance dose. *Id.*

5. Kumar claim 14 reads as follows:

14. The method of claim 1, wherein the amount of S oxo-clopidogrel or the compound of Formula IIA is about 6 to about 20 mg as a maintenance dose. *Id.*

6. Kumar claim 16 reads as follows:

16. The method of claim 1, wherein the administration step comprises administering an initial loading dose of about 20-100 mg of the (S)-oxo-clopidogrel or the compound of Formula IIA to the person in need thereof, followed by administering a maintenance dose of about 5-30 mg. *Id.* at A-3.

7. Additional facts are found below.

C. Analysis

A motion to have a claim designated as not corresponding to a count must show why the subject matter of the count, if treated as prior art, would not have anticipated or rendered obvious the subject matter of the claim. 37 C.F.R. § 207(b)(2). The gravamen of Kumar Motion 4 is that "[a]bsent undue experimentation, one of ordinary skill in the art would have not known what an effective dosage range was or how to determine one for the derivative set forth in the count from the count and the other prior art." Paper 138, 3.

While admitting that an effective amount of clopidogrel was known by pharmacologists, Kumar contends that it would not have been possible to predict the relative potency of the optically active (S)-2-oxoclopidogrel acetyl compound

of the count from that prior knowledge. *Id.* at 4, *citing* Ex. 2019 cols. 16-18; Ex. 2040 at ¶ 20.

Kumar asserts that its results with optically active 2-oxo-clopidogrel are surprising and unexpected over the teachings of Pereillo. *Id.* at 7, *citing* FF 52; Ex. 2045 *passim*; Ex. 2019 at cols. 17-18; Ex. 2040 at ¶ 29.

Kumar Motion 4 is flawed in its approach. Whether it would have been possible to predict the relative potency is not the correct issue to be decided in a motion to undesignate claims. The question to be addressed is whether it would have been obvious to one of ordinary skill in the art to optimize the dose of (S)-2-oxoclopidogrel acetyl compound of the count as a loading dose, a maintenance dose, or a combination of doses at the levels recited in the claims, knowing to use "an effective amount" as recited in the count.[3]

Where general conditions of the appealed claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation. *See, e.g. In re Boesch*, 617 F.2d 272, 276 (CCPA 1980); *In re Aller*, 220 F.2d 454, 456 (CCPA 1955).

Neither Kumar Motion 4 nor the Declaration of Dr. Jafari discusses conventional methods of dosage determination and why any experimentation required would have been undue. Moreover, we are unpersuaded by Kumar's assertion that the results are unexpected in view of the count and known prior art. That determination is made by Dr. Jafari, who simply and conclusorily refers a reader to Pierello as a whole "Exhibit 2045, *passim."* and a selection of the Sun patent in rendering that judgment. To the extent Dr. Jafari has testified

[3] Maintenance doses and loading doses are conventional approaches to initiating maintaining levels of medicaments in the patient. *See, e.g*. Ex. 2050, p. 1483 and Ex. 2049, pp. 225–228.

conclusorily and her background has not been adequately established, we give her testimony diminished weight.

We are not provided with sufficient credible evidence as to why conventional, even if laborious, optimal dosage determination methods would not have resulted in a determination of the optimal ranges as claimed. Dr. Jafari also fails to address the known higher activity of the 2-oxo-clopidogrel acetyl compound observed by Pereillo, who notes the S enantiomer is the active chiral molecule. Ex. 2045, 1294. This is despite Dr. Jafari's testimony that she has studied Pereillo (Ex. 2040 ¶ 27).

We need not consider either the opposition or reply, as the Motion fails to carry the initial burden of persuasion. Accordingly, Kumar Motion 4 is denied.

Sun Motion 2

A. Background

Sun Motion 2 seeks entry of judgment that Kumar's involved claims are unpatentable under 35 U.S.C. § 103 as obvious over Pereillo. Paper 140.

Kumar opposed. Paper 176.

Sun replied. Paper 205.

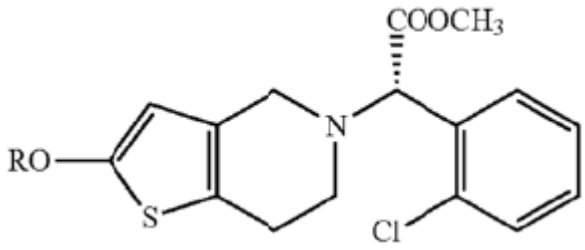
B. Facts

1. Pereillo[4] was published in 2002.
2. Periello describes the structure and stereochemistry of the active metabolite of clopidogrel. Ex. 1018, title.
3. Clopidogrel is also known as Plavix®. *Id.*

[4] Jean-Marie Pereillo et al. "Structure and Stereochemistry of the Active Metabolite of Clopidogrel," Drug Metabolism and Disposition, Vol 30. No. 11, pp. 1288–1295(2002) (Ex. 1018) (also present in the record as Ex. 2045).

4. Plavix is a known antiplatelet agent used to inhibit blood clots in the treatment of various vascular diseases. *Id.*

5. The claims of the Kumar patent are directed to a method comprising administering S-oxo-clopidogrel, or a compound of the formula:



or its pharmaceutically acceptable salts thereof, wherein R is hydrogen or an acyl group or alkyl substituted silyl group. Paper 5, 3.

6. Pereillo describes that clopidogrel has an absolute S configuration at carbon 7, and that the corresponding R enantiomer is totally devoid of antiaggregating activity. Ex. 1018 at 1288.

7. Pereillo describes that clopidogrel is not itself an active compound, it is a precursor to an active compound formed by metabolism in the liver. *Id.*

8. Pereillo describes that S-oxo-clopidogrel is formed by metabolism of clopidogrel in the liver. *Id.*

9. Pereillo describes that S-oxo-clopidogrel is not itself an active compound, and the active antiaggregating compound is formed in downstream metabolism. *Id.*

10. Pereillo describes that clopidogrel is known for preventive treatment of patients at risk for vascular thrombotic events. *Id.*

11. Pereillo describes that its compounds can be acquired by methods described in US Patents 4,740,510 and 5,190,938. *Id.*

12. Pereillo describes that 2-oxo-clopidogrel has been shown to be generated from clopidogrel by the liver and to show a higher antiaggregating activity *ex vivo*. *Id.* at 1294.

13. A person of ordinary skill in the art at the time the invention was made would have person having experience in stereochemistry, pharmacology, receptor physiology, clinical cardiovascular therapy involving the use of P2Y12 receptor blockers and human metabolic processes. Such a person of ordinary skill could be a pharmacologist, cardiologist, or researcher having a Ph.D. or M.D. degree and at least three years of experience in the field. Ex. 1025, ¶ 11.

C. Analysis

A party seeking to show the unpatentability of a claim has the burden of establishing unpatentability. 37 C.F.R. § 41.121(b). When a motion for judgment of unpatentability against an opponent's claim on the basis of prior art is granted, each of the movant's claims corresponding to the same count as the opponent's claim will be presumed to be unpatentable in view of the same prior art unless the movant in its motion rebuts this presumption. 37 C.F.R. § 41.207(c).

Sun asserts that the metabolic pathway of clopidogrel was known, and ultra-rapid metabolism of clopidogrel was a known problem. Paper 140, 5. Further, Sun asserts that S-oxo-clopidogrel was "known for 20 years" (Paper 140, 6). Finally, Sun is of the belief that "it is readily apparent that administering the metabolite immediately after the problematic metabolic step would avoid the problem of that problematic metabolic step." Paper 140, 8.

Kumar, in opposition, notes that Sun has failed to address the presumption of cross-applicability of prior art under 37 C.F.R. § 41.207. Paper 176, 3. We

note that Kumar is correct in that observation. Accordingly, the decision on this motion will equally impact the corresponding Sun claims.

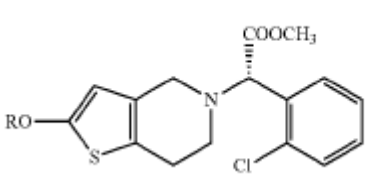
Kumar's substantive opposition is that Pereillo does not suggest or describe a method of treatment or prophylaxis of thrombosis or embolism with an effective amount of S-oxo-clopidogrel or a compound of Formula IIA. Paper 176, 6. According to Kumar, Pereillo 's objective was "to identify the chemical structure of the active metabolite of clopidogrel." *Id.* at 6. Because Pereillo only uses *in vitro* compositions that are mixtures of S-oxo-clopidogrel and liver enzymes, it is urged that no therapeutically effective treatment is disclosed. *Id.* at 7., *citing* FF17; Ex. 1018 at 1289, left column; and Ex. 2058 at ¶ 5.

1. Kumar Claim 1

Kumar claim 1 recites the following:

1. A method for reducing or alleviating inter individual platelet response variability and metabolic loading in humans in the treatment or prophylaxis of thrombosis or embolisms observed following administration of clopidogrel comprising administering to a person in need thereof, a composition containing an effective amount of S-oxo-clopidogrel or a compound of Formula IIA

Formula IIA



Formula IIA

or pharmaceutically acceptable salts thereof, wherein R is hydrogen or an acyl or alkyl substituted silyl group. Ex. 2019, at 18:49-67.

Initially, we observe that the preamble can be construed broadly as essentially a statement of intended use. The intended use is in that patient population who have not responded well (the so-called "inter individual platelet response variability and metabolic loading"[5]) to an initial dose of clopidogrel. As is well settled, an intended use generally does not make a claimed invention new and patentable. *See, e.g., In re Thuau*, 135 F.2d 344, 347 (CCPA 1943). *See also Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp*., 320 F.3d 1339, 1345 (Fed. Cir. 2003) ("An intended use or purpose usually will not limit the scope of the claim because such statements usually do no more than define a context in which the invention operates.")

The preamble does, on the other hand, provide some basis for interpreting what an "effective amount" is in the context of use. The claimed method is a single step, the administration of an "effective amount" of S-oxo-clopidogrel or a compound of Formula IIA to a patient in need thereof.[6] We interpret the term "effective amount" to be an amount of S-oxo-clopidogrel effective "in the treatment or prophylaxis of thrombosis or embolisms."[7]

---

[5] Serious adverse drug reactions associated with clopidogrel therapy include bleeding (hemorrhage), particularly at higher dosages. Ex. 2042, at 121. Ex. 2043, at 13-19. Ex. 2051, at 445. Ex. 2040, at ¶ 5.

[6] We observe that Kumar did not draft Claim 1 to recite multiple steps, e.g. those of administering clopidogrel, observing the response, and administering S-oxo-clopidogrel as an alternative. Consequently, we do not read those steps into the body of the claim.

[7] Because the language of the claim preamble is somewhat vaguely drafted, it is also possible to read the effective amount as that amount required for "reducing or alleviating inter individual platelet response variability and metabolic loading in humans," which would not make sense chemically. However, the evidence of

We next turn to the most objective evidence of record. The documentary evidence of record supports a finding that S-oxo-clopidogrel was known. Ex. 1018, 1288-1289 (also denominated 2-oxo-clopidogrel [(7S) SR121683] – as opposed to the inactive enantiomer [(7R) SR121682]). A racemic mixture of both enantiomers was also known. [(7R,S) SR25552]. Ex. 1018, 1289, first column. *See also Id.* at 1291, where it is noted "SR121683 is the 2-oxo-SR25990C and therefore should have an S configuration at carbon 7."

Clopidogrel generally was known to be an anti-aggregant and anti-thrombotic drug in human patients at risk. Ex. 1018, 1288. Having no *in vitro* activity of its own, it was known that it must be metabolized by the liver first before activity is observed. Clopidogrel is a precursor of an active component. *Id.* Similar to Clopidogrel, 2-oxo-clopidogrel is also inactive *in vitro*. When SR121683 (the active enantiomer) is incubated with liver enzymes *in vitro,* a further metabolite fraction called H4 was known to have activity. *Id.* at 1292. *See also* Paper 140, 11–12.

It had further been known that 2-oxo-clopidogrel has a higher anti-aggregating activity than clopidogrel *ex vitro*. *Id.* at 1294.

To further support the objective evidence, Sun supplied the testimony of Dr. Paul Gurbel, a medical doctor (Ex. 1025). We find him to be qualified to testify to the subject matter of this proceeding. Ex. 1025, ¶¶ 2–6.

---

record supports the finding that S-oxo-clopidogrel's purpose in the method is in the treatment or prophylaxis of thrombosis or embolisms. Ex. 2019, Abstract. This interpretation also corresponds with Kumar's own interpretation. Paper 176, 6, lines 11–12.

Dr. Gurbel testifies that the two-step metabolic pathway of clopidogrel by CYP450 enzymes to S-oxo-clopidogrel and then to the active metabolite was described in Pereillo. *Id.* at ¶ 13.

Dr. Gurbel also testifies that Pereillo 1294, left column, last four lines describes that "2-oxo-clopidogrel was used instead of clopidogrel because it has been shown to be generated from clopidogrel by the liver and to show a higher antiaggregating activity ex vivo." This testimony and reference cite Savi et al., 1992 (Ex. 1031) and Savi et al., 1994 (Ex 1030). Ex. 1025, ¶ 15.

Dr. Gurbel testifies that "[g]iven the known metabolic scheme of clopidogrel, the known poor responsiveness and resistance to clopidogrel, and the prior evidence of a superior anti-aggregating effect of 2-oxo-clopidogrel as compared to clopidogrel, a person with ordinary skill in the art would conclude that 2-oxo-clopidogrel would be associated with less resistance and improved responsiveness in comparison with clopidogrel." *Id.* He also testifies that Pereillo suggests that 2-oxo-clopidogrel (i.e., S-oxo-clopidogrel) could be used as an active agent in the treatment or prophylaxis of thrombosis or embolisms with a better effect than clopidogrel since it is an intermediate as compared with clopidogrel. *Id.* at ¶17. We find this testimony credible, insofar as it relates to the known superior anti-aggregating ability of 2-oxoclopidogrel.

Kumar's principal substantive opposition[8] is that Pereillo does not disclose or suggest either the relative potency of S-clopidogrel or the common elements of Kumar's claims directed to administering to a person in need thereof a composition

[8] Kumar makes numerous procedural arguments, including reliance on additional prior art (Paper 176, 3), sufficiency of statement of material facts (*Id*. at 4), and weight to be given Dr. Gurbel's declaration (*Id.* at 5). We have considered these arguments, but they are not persuasive.

containing an effective amount of S-oxo-clopidogrel or a compound of Formula IIA. Paper 176, 6. This is said to be so because Pereillo's "objective" was to identify the chemical structure of the active metabolite of clopidogrel. *Id.* In furtherance of that goal, it is argued that the only description of biological activity lo is "inhibition of binding of radiolabeled 3 2-methyl-S-ADP to rat platelets." *Id.* at 7, *citing* FF 19; Ex. 1018 at 1288, left column, and Table 1 at page 4.

According to Kumar, this in vitro bioactivity is exclusively limited to the binding of an active metabolite to a receptor on the surface of platelet cells, and S-oxo-clopidogrel is inactive when measured in vitro by this assay. FF 19; Ex.1018 at 1288, left column.

The problem with this analysis is that it omits the entire context of Pereillo's description, which is as a study of the metabolic pathway of Plavix® (clopidogrel), a known antithrombotic drug. One with ordinary skill in the art is presumed to have skills apart from what the prior art references explicitly say. *See In re Sovish*, 769 F.2d 738, 743 (Fed. Cir. 1985). "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1742 (2007).

One of ordinary skill would immediately recognize that the entire thrust of the Pereillo article is in the context of determining which metabolite makes clopidogrel function as a preventer of thrombosis in humans by its antiaggregating ability. Ex. 1018, Abstract. One of ordinary skill would also immediately recognize that Plavix® must have a dosing regimen for patients. *See, e.g.*, Ex. 2050, p. 1483 (75 mg/day maintenance and 300 mg initial loading dose). *See also* Ex. 2049, pp. 225–228 (discussing 300 and 600 mg loading dose and 150 and 75 mg maintenance doses for efficacy). Thus, the identification of S-oxo-

clopidogrel as being the more efficacious fraction, even *ex vivo*, is a powerful motivation to one of ordinary skill in the art, regardless of the particular problem being solved by the present inventors. Finding the correct dosage is a technical challenge only, which – as Kumar's witness notes, requires only a commonly done dosing study.[9]

Kumar also urges that the lack of actual comparative biological results are fatal to the case of obviousness. Paper 176, 8. We are not persuaded that this is the case. Pereillo indicates the choice to use 2-oxo-clopidogrel for its work was because of its known status as a metabolite of clopidogrel and it had already shown a higher anti-aggregating ability *ex vivo*. Ex. 1018 1294, left column.

Kumar also urges that Pereillo fails to describe clopidogrel resistance, poor responsiveness, inter individual platelet response variability, metabolic loading, and other side effects in its independent claims 1, 28, 29, and 30. Paper 176, 8. As noted above, each of those elements are a statement of intended use of the method, which is a single step of administering the composition to a patient. For example,

---

[9] Dr. Jafari, Kumar's witness testified as follows:

14 BY MR. HOOVER:
15 Q. So, if you were to do a clinical trial for
16 S-oxo-clopidogrel, would that involve incrementally
17 increasing the dose given to patients in the study to
18 determine its safety and effectiveness?
19 MR. KNUDSEN: Objection, relevance.
20 THE WITNESS: I would not say incrementally
21 increasing.
22 I would call it a dose-finding study, which is
23 commonly done. But you are not talking about a big
24 range of dosing because this is a drug that can cause
25 bleeding, so ...

Ex. 1054, page 22.

each of claims 28, 29, and 30 contain the same administering step of the same compound, but the preambles each read differently for a different patient population for the method to be used on –

> 28. A method of treatment or prophylaxis of thrombosis or embolisms in a patient in need thereof comprising administering a composition containing an effective amount of S-oxo-clopidogrel … **wherein said administration avoids the side effects associated with the clopidogrel acid metabolite**…"
>
> 29. A method of treatment or prophylaxis of thrombosis or embolisms **in a clopidogrel non-responder- or poor-responder-patient** in need thereof comprising administering a composition containing an effective amount of S-oxo-clopidogrel …"
>
> 30. A method of treating **clopidogrel resistance** in a patient in need of treatment or prophylaxis of thrombosis or embolisms, comprising administering a composition containing an effective amount of S-oxo-clopidogrel …" (emphasis added).

Accordingly, this argument is unpersuasive.

Kumar next urges that Pereillo identifies not a single problem associated with clopidogrel's use and accordingly there was no motivation to use S-oxo-clopidogrel. Paper 176, 8–9. This argument fails to consider that Pereillo itself notes higher anti-aggregating ability for the oxo-clopidogrel racemic mixture. Ex. 1018, 1294, left column. A claim may be nonetheless obviousness even if the problem being addressed by the reference solved is not the same one faced by the inventors. *In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990).

Kumar next urges that this higher anti-aggregating ability noted in Pereillo is not the specific S isomer, but is due to the racemic mixture of 2-oxo-clopidogrel. Paper 179, 9. Kumar urges that Dr. Gurbel's testimony substantially "mischaracterizes" Pereillo. *Id.* We disagree. Kumar's position itself ignores a later discussion in Pereillo of anti-aggregating superiority, which expressly notes that "[i]ncubation of (7S) 2-oxo-clopidogrel with human microsomes led to a pool of metabolites (fraction H), which exhibited a potent in-vitro activity as assessed by measuring P-2-methyl-*S*-ADP binding to human platelets." Ex. 1018, 1294, right column. Pereillo thus expressly highlights the S-enantiomer of 2-oxo-clopidogrel as generating the potent fractions.

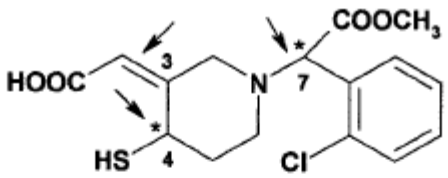
Kumar next urges that Dr. Gurbel is generally unreliable and inaccurate. Paper 176, 5 and 10–16. First, Kumar asserts the opinions are mere attorney arguments unsupported by facts and should be disregarded. *Id*. at5. We disagree that the testimony should be disregarded in its entirety; instead, we will assign the testimony appropriate weight if it is adequately and factually supported.

Second, Kumar urges that Dr. Gurbel is inaccurate. *Id*. at 10. With this, we agree in part. Dr. Gurbel occasionally mis-cites the references, in part because the references mis-cite other references.

Given the importance of this issue, we reproduce text of the actual Pereillo reference below:

Discussion

Clopidogrel has to be administered in vivo to selectively and irreversibly inhibits the binding of 2MeS-ADP to its platelet receptors (Savi et al., 1994a, 2001; Herbert et al., 1999). Clopidogrel is inactive in vitro and has to undergo metabolic activation by hepatic cytochrome P450–1A to exhibit its antiaggregating activity (Savi et al., 1992, 1994b). From these studies, a possible metabolic pathway leading to the formation of active metabolite of clopidogrel was tentatively deduced (Savi et al., 2000). In the liver, clopidogrel is metabolized into 2-oxo-clopidogrel through a cytochrome P450-dependent pathway. This intermediate metabolite is then hydrolyzed and generates the highly labile active metabolite, which reacts as a thiol reagent with the ADP receptors on platelets when they pass through the liver. This in situ biological effect could account for the absence of an antiaggregating activity in the plasma. In this study, we isolated in sufficient amounts the metabolites of Clopidogrel by incubating the synthetic 2-oxo-clopidogrel with human liver microsomes to determine the chemical structure and biological activity of the active metabolite. The 2-oxo-clopidogrel was used instead of clopidogrel because it has been shown to be generated from clopidogrel by the liver and to show a higher antiaggregating activity ex vivo (Savi et al., 1992, 1994b).



SCHEME 5. *2-{1-[2-(chlorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanyl-3-piperidinylidene}acetic acid.*

Incubation of (7S) 2-oxo-clopidogrel with human microsomes led to a pool of metabolites (fraction H), which exhibited a potent in vitro activity as assessed by measuring ^{33}P-2-methyl-*S*-ADP binding to human platelets. This result confirmed the key role played by bio-oxidation of clopidogrel at carbon 2 as an important first step toward the formation of an active metabolite. The active fraction H was shown to be composed of four diastereoisomers only one of which (named H4) with antiplatelet activity. Moreover, parallel microsomal incubations conducted with the inactive (7R) 2-oxo-isomer gave the same HPLC and MS data patterns, whereas no biologically active metabolite could be detected in that case. Altogether, these results underlined the critical importance of a specific absolute stereochemistry and in particular the 7S configuration associated to the active metabolite. We conducted parallel experiments with either the active (7S) or (7R) 2-oxo precursors with a systematic analytical and biological measurement at each step of the purification process. The results indicated that S configuration is preserved in the active fraction since only metabolites issued from the 7S precursor retained biological activity. This strongly suggests that no, even partial, racemization reaction occurs during the incubation with microsomes and/or purification conditions.

Ex. 1018, 1294.

As to the substance of the reference itself, Pereillo states that the 2-oxo-clopidogrel has higher anti-aggregating abilities. But Kumar is correct that the two cited references do not stand for the specific proposition cited. We have carefully reviewed the Savi references (Ex. 1030 and Ex. 1031), and are surprised that Dr. Gurbel failed to note this problem. However, despite Pereillo's mis-citation, the statement stands as a prior art acknowledgement that the 2-oxo-clopidogrel has higher anti-aggregating ability. Indeed, it appears that the citation in Pereillo is in error and should have been to Savi 2000 (Ex. 1024), cited on page 1295 of Pereillo, reproduced below:

Results

Purification and structural identification of the active metabolite of clopidogrel. In preliminary experiments, incubation of clopidogrel with rat hepatic microsomes was found to generate 2-oxo-clopidogrel, through a CYP450-dependent pathway (20). Similar results have been found with human hepatic microsomes (not shown). It is noteworthy that, like clopidogrel, 2-oxo-clopidogrel is not active *in vitro* but shows a higher antiaggregant activity *ex vivo*, when administered intravenously or orally to rats (not shown). In order to generate sufficient amounts of the active metabolite of clopidogrel and determine its chemical structure and biological activity, we have incubated 2-oxo-clopidogrel with human hepatic microsomes and purified the active metabolite by preparative reverse phase FPLC and RP-HPLC. The chemical structure of the metabolite was then determined by mass spectrometry and ^{1}H and ^{13}C NMR (see Pereillo et al. for details, 16). The active metabolite of clopidogrel was identified as: 2-{1-[(1S)-1-(2-chlorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanyl-3-piperidinyli-diene} acetic acid (Fig. 1). Four different isomers were identified but only one of them showed an antiaggregating activity which was shown to be related to a 7(S) carbon and a Z isomerv of the C_{3}-C_{14} double bond.

Ex. 1024.

Accordingly, despite the compounded error in citation, we are not persuaded by this argument.

Kumar next urges that Dr. Gurbel's publications all fail to observe S-oxo-clopidogrel would be a solution to the clopidogrel resistance facing certain patients. Paper 176, 11–13. More specifically, Kumar observes that even armed

with the same facts as are presented in Pereillo, "Dr. Gurbel's publications betray no appreciation whatever of the solution of Kumar's involved claims to the problem he wrote about in dozens of his publications and which he now testifies would have plainly been obvious to a person of ordinary skill in the art. This is evidence of Dr. Gurbel's use of hindsight in arriving at his opinions on unpatentability." *Id.*at 12. According to Kumar, all of Dr. Gurbel's solutions involved the use of different approaches using different inhibitors. *Id.* at 13.

We are not persuaded by this argument. That Dr. Gurbel did not pursue the path in Kumar's claims, noted issues, and instead was looking to other solutions does not in our view negate the express disclosure in Pereillo that 2-oxo-clopidogrel has a higher anti-aggregating ability and the active fraction is the S enantiomer. We are therefore persuaded that the single step method claims are rendered obvious by the description in Pereillo. We need not reach whether the intended use of overcoming clopidogrel resistance would have been obvious, as the intended use does not confer patentability.

Turning now to the dependent claims, claim 2 depends from claim 1 and also recites administering one or more anti-platelet agents selected from the group consisting of aspirin, cilostazol, and dipyridamole. Paper 5, A-1.

Sun asserts that these additional therapeutic agents are commonly known agents used for the treatment of thrombosis or embolism. Moreover, Sun contends that in the absence of unexpected synergistic effects from the combination administration, it would be obvious for one skilled person in the art to combine these agents in order to achieve the desired therapeutic effects. Paper 140, 17–18.

Kumar does not appear to have a contrary argument in Opposition 2 (Paper 176).

The use of a known product for its known use to achieve an expected result is obvious, i.e., a pharmaceutical composition with a known use. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991). While Sun has not pointed us to specific evidence in the record, we observe that the therapeutic effect of at least aspirin in platelet anti-aggregation is well-known. Ex. 1018, 1288, left column. Accordingly, we agree that claim 2 is obvious.

Claim 3 recites that the response variability of claim 1 is due to a CYP450 polymorphism or a failure to efficiently metabolize clopidogrel. Claim 4 depends from claim 3 and recites that the polymorphism is CYP2C19*2 or CYP2C19*17. Claim 5 depends from claim 1 and recites that the platelet response variability is due to P-glycoprotein efflux transports. Paper 5, A-1.

Sun urges that it does not matter which genotype of polymorphism causes the patient issues. Paper 140, 16. Kumar does not appear to have any contrary argument for these specific claims. Paper 176. We agree that these claims further define the intended use of the method, and accordingly do not impart patentability.

Claim 6 depends from claim 1 and recites that the method avoids or alleviates the side effects associated with the clopidogrel acid metabolite of Formula IV. Paper 5, A-2. We fail to see how this claim differentiates in any meaningful way from claim 1, which inherently would accomplish the same effect of avoiding the side effects of a metabolite which does not now form.

Compositions are not rendered patentable merely by including a recitation of the assertedly different properties in the claims. *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990). Moreover, "the mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *In re Geisler*, 116 F.3d 1465, 1468 (Fed. Cir. 1997). The same holds true for the present method.

Claim 7 depends from claim 1, and further recites that the method achieves a therapeutic effect greater than or equivalent to that observed following the administration of a substantially higher dose of clopidogrel. Paper 5, A-2.

Claim 8 depends from claim 1, and further recites that the method results in the *in vivo* formation of the active metabolite of clopidogrel at a concentration greater than or equivalent to that observed following administration of a substantially higher dose of clopidogrel. Paper 5, A-2.

Claim 9 depends from claim 1, and further recites that the onset of therapeutic action is at least 50% more rapid than that observed following administration of a substantially higher dose of clopidogrel. Paper 5, A-2.

Sun asserts that one of ordinary skill in the art would expect these results as a result of administering a dose of S-oxo-clopidogrel due to the description of its higher anti-aggregating ability. Paper 140, 16. We agree that Pereillo does describe a higher anti aggregating ability *ex vivo*, which provides motivation to substitute S-oxo-clopidogrel for clopidogrel. Ex. 1018, 1294. Dr. Gurbel testifies that these results would be expected by utilizing a later more efficacious metabolite in the metabolic pathway. Ex. 1025, 14–15. We find this testimony credible, despite Kumar's insistence that it is hindsight-based and ignores the unpredictability in clinical research. Paper 176, 15.

Claim 10 depends from claim 1, and recites that the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 20 to about 100 mg as a loading dose. Paper 5, A-2.

Claim 11 depends from claim 1, and recites the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 35 to about 70 mg as a loading dose. *Id.*

Claim 12 depends from claim 1, and recites that the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 45 to about 100 mg as a loading dose. *Id.*

Claim 13 depends from claim 1, and recites that the amount of the S oxo-clopidogrel or the compound of Formula IIA is about 5 to about 30 mg as a maintenance dose. *Id.*

Claim 14 depends from claim 1, and recites that the amount of S oxo-clopidogrel or the compound of Formula IIA is about 6 to about 20 mg as a maintenance dose. *Id.*

Claim 15 depends from claim 1, and recites the additional step of administering a proton inhibitor. *Id.*

Claim 16 depends from claim 1, and recites that the administration step comprises administering an initial loading dose of about 20-100 mg of the (S)-oxo-clopidogrel or the compound of Formula IIA to the person in need thereof, followed by administering a maintenance dose of about 5-30 mg. *Id.*

Sun, relying on the testimony of Dr. Gurbel, asserts that it would be routine to try different dosage levels to achieve a desired therapeutic effect. Paper 140, 16, *citing* Ex. 1025, ¶ 22. Kumar in response asserts that only its patent describes the relative potency of S-oxo-clopidogrel. Paper 176, 19. Therefore, according to Kumar, it is impossible to predict the dosage levels. *Id.*

Kumar's argument ignores the known routine methods of dosage determination. Kumar's own witness admitted that such determinations were standard procedure. Ex. 1054, page 22. Accordingly, we agree with Sun that claims 10-16 are obvious.

Claim 17 depends from claim 1, and recites that R is an acyl group having the formula R^1---CO- wherein R^1 is selected from the group consisting of aryl, alkyl, alkenyl and alkynyl. Paper 5, A-3.

Claim 18 depends from claim 17, and further recites that R^1 is acetyl. Paper 5, A-3.

Sun asserts that this narrowing does not exclude S-oxo-clopidogrel. Paper 140, 17. Kumar does not appear to challenge this assertion. Paper 176. As it is evident that these claims do not further limit the S-oxo-clopidogrel of claim 1, we agree that they, likewise, are obvious.

Sun Motion 2 is therefore GRANTED.

As Sun has failed to indicate why the cited prior art is not applicable to its claims in a timely fashion, Sun's corresponding claims are likewise found to be obvious.

As the claims of both parties have been determined to be obvious over the description in Pereillo, Ex. 1018, we need not address any additional substantive motions.

Kumar Motion 5

Kumar Motion 5 seeks to exclude evidence.

The first objected to piece of evidence is Exhibit 1014 – the declaration of Dr. Duan. As we have not relied upon this exhibit, the motion is dismissed as to this exhibit.

The second objected to piece of evidence is Exhibit 1025, Dr. Gurbel's first declaration. The objection is to the fact that Dr. Gurbel utilized additional references in his declaration. To the extent that those references (the Savi References) were utilized in the present decision, we find that they were expressly

cited and discussed in Pereillo, and as such under the specific facts of this case, it is proper that Dr. Gurbel's declaration relied upon them and discussed them. We therefore deny the motion as it relates to Exhibit 1025. We also deny the motion as to Exhibits 1030 and 1031 for the same reasons.

The remaining objected to pieces of evidence are Exhibits 1027, 1029, 1040, 1041, 1043, 1045, 1046, 1055, 1058, and 1059. As we have not relied upon these pieces of evidence, the motion is dismissed as to these exhibits.

Sun Motion 4

Sun Motion 4 seeks to exclude Exhibits 2040, 2058, and portions of 1054 and 1070. Exhibit 2040 and 2058 is Dr. Jafari's declaration testimony while Exhibits 1054 and 1070 is her deposition testimony. We have already determined an appropriate weight to ascribe to her testimony, and deny the motion.

Judgment will be entered against both parties.

ORDER

Kumar Motion 2 is denied.

Kumar Motion 3 is dismissed as moot.

Kumar Motion 4 is denied.

Kumar Motion 5 is denied in part and dismissed in part.

Sun Motion 2 is granted, but under the rule of cross-applicability applies also to Sun's claims.

Sun Motion 4 is denied.

cc (via email):

Attorney for Kumar:

Barry Bretschneider
Peter J. Knudsen
Baker & Hostetler
bbretschneider@bakerlaw.com
pknudsen@bakerlaw.com

Attorney for Sun:

Thomas O. Hoover
Wei Song
McCarter & English, LLP
thoover@mccarter.com
wsong@mccarter.com