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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* RUDOLF MOSER, ROGER SCHIBLI,
CRISTINA MAGADELANA MULLER, VIOLA GROEHN,
URS FELIX MICHEL, CHRISTOF SPARR, and
THOMAS LEIGHTON MINDT[1]

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Appeal 2014-008436
Application 12/595,147
Technology Center 1600

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*Before* DEMETRA J. MILLS, ERIC B. GRIMES, and
JOHN G. NEW, *Administrative Patent Judges.*

NEW, *Administrative Patent Judge.*

DECISION ON APPEAL

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[1]Appellants state the real party-in-interest is MERCK & CIE. App. Br. 1.

## SUMMARY

Appellants file this appeal under 35 U.S.C. § 134(a) from the Examiner's Final Rejection of claims 9, 10, 12, 15–18, 20, 21, 23, 24, 26–28, 33, 40, 41, 44, 45, and 47 which stand rejected as unpatentable under 35 U.S.C. § 103(a) as being obvious over the combination of Christopher P. Leamon et al., *Folate-mediated Drug Delivery: Effect of Alternative Conjugation Chemistry*, 7(3) J. DRUG TARGETING 157–69 (1999) ("Leamon"), Green et al. (US 2005/0227985 A9, October 13, 2005) ("Green"), Thomas L. Mindt et al., *Click to Chelate: Synthesis and Installation of Metal Chelates into Biomolecules in a Single Step*, 128 J. AM. CHEM. SOC. 15096–97 (2006) ("Mindt"), and Jae Kyoung Pak et al., *$N^{\varepsilon}$ Functionalization of Metal and Organic Protected L-Histidine for a Highly Efficient, Direct Labeling of Biomolecules with $[Te(OH_2)_3(CO)_3]$*, 9 CHEM. EUR. J. 2053–61 ("Pak").

We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

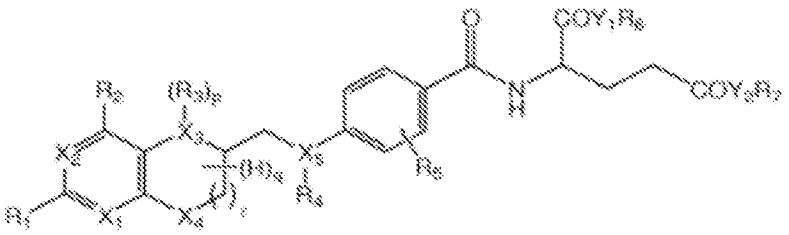
## NATURE OF THE CLAIMED INVENTION

Appellants' invention is directed to novel folate-conjugates and the corresponding metal-chelate complexes as well as pharmaceutical compositions thereof, their method of production and their use in diagnostic and therapeutic medical applications, such as diagnostic imaging and radiotherapy. Spec., 1, ll. 6–10.

REPRESENTATIVE CLAIM

Appellants argue all of the claims on appeal together. Independent claim 9 is representative and recites:

9. A compound according to formula III,



III

wherein

$X_1$, $X_2$, $X_3$, $X_4$ and $X_5$ are independently of each other C or N;

$Y_1$, $Y_2$ are independently of each other C, O or N,

$R_1$ and $R_2$ are independently of each other H, Hal, -OR', -NHR', $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ alkoxy, $C_1$-$C_{12}$ alkanoyl, $C_1$-$C_{12}$ alkenyl, $C_1$-$C_{12}$ alkynyl, ($C_1$-$C_{12}$ alkoxy)carbonyl, and ($C_1$-$C_{12}$ alkylamino) carbonyl,

R' is H or $C_1$-$C_6$ alkyl,

$R_3$ and $R_4$ are independently of each other H, formyl, iminomethyl, nitroso, $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ alkoxy, $C_1$-$C_{12}$ alkanoyl, halosubstituted $C_1$-$C_{12}$ alkanoyl,

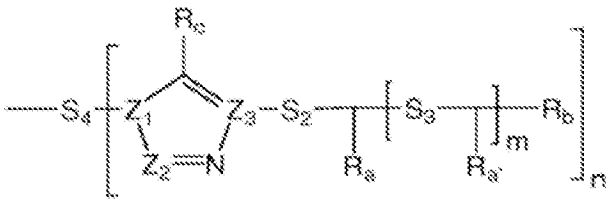
$R_5$ is H, CN, Hal, $NO_2$, $C_1$-$C_{12}$ alkyl, $C_1$-$C_{12}$ alkoxy, $C_1$-$C_{12}$ alkanoyl, $C_{12}$ alkenyl, $C_1$-$C_{12}$ alkynyl, ($C_1$-$C_{12}$ alkoxy) carbonyl, and ($C_1$-$C_{12}$ alkylamino) carbonyl,

p has a value of 0, 1 or 2,

q has a value of 1 to 7,

r is 0 or 1,

$R_6$ and $R_7$ are independently of each other H, straight chain or branched $C_1$-$C_{12}$ alkyl, which is unsubstituted or substituted by at least one CN, Hal or $NO_2$, or a group of formula IV,



IV

wherein

$Z_1$, $Z_2$, are, independently of each other, CH or N,

$Z_3$ is C or N,

$S_2$, $S_3$, $S_4$ are independently of each other a single bond or a spacer group,

$R_a$, $R_{a'}$, $R_b$ are independently of each other H, -OR′, -COOR′, -NHR′, -CONHR′, -SR′, a phosphine or a heterocyclic group, or a folate or derivative thereof, and

wherein of groups $R_a$, $R_{a'}$ and $R_b$ at least two adjacent groups are a donor group -OH, -COOH, -NHR′, $-CONH_2$, -SH, a phosphine or a heterocyclic group,

$R_c$ is H, $CO_2R'$, COR′, $-SO_3R'$, -NHR′, or straight-chain or branched $C_1$-$C_{12}$ alkyl, which is unsubstituted or substituted by at least one CN, Hal, or $NO_2$, or a folate or derivative thereof,

m is 0, 1, 2, 3, or 4, and

n is 1 or 2,

> with the proviso that at least one of $R_6$ and $R_7$ is a group of formula IV.

App. Br. 12–13.

## ISSUES AND ANALYSES

We agree with, and adopt, the Examiner's findings and conclusion that the appealed claims are *prima facie* obvious over the cited prior art references. We address the arguments raised by Appellants below.

*Issue*

Appellants argue the Examiner erred in finding that the compounds of claim 9 are obvious over the prior art. App. Br. 4.

*Analysis*

Appellants dispute the Examiner's conclusion that the claims on appeal are *prima facie* obvious over the combined cited prior art. App. Br. 4. Specifically, Appellants argue that the references relied upon by the Examiner do not support a finding that combining pteroates, pteroate dipeptides, or "non-peptide" folic acid analogs with the histidine-like portion of a histidine/bombesin conjugate would have been obvious to one of ordinary skill in the art at the time the claimed invention was made. *Id.* Appellants also contend that none of the references provide any suggestion of a linker structure in accordance with Formula III of claim 9. *Id.*

Appellants also dispute the Examiner's finding that Leamon teaches the parent structure Pte-Glu (i.e., folic acid), and that this structure is "a compound of instant formula III." App. Br. 5 (citing Leamon 159, Fig. 1).

Appellants contend Pte-Glu is not a compound of claim 9's formula III since it does not meet claim 9's requirement that at least one of $R_6$ and $R_7$ is a group of formula IV.

Appellants assert that Green teaches the use of linkers that do not contain peptide bonds, i.e., "non-peptide" folic acid analogs. App. Br. 6. Appellants contend that, rather than proposing an alternative to a Pte-Glu linkage, Green is specifically teaching a replacement of the Pte-Glu linkage and therefore teaches away from Leamon.

Moreover, Appellants argue, Green teaches a very broad genus of "non-peptide" folic acid analogs and, as defined by Green's formula I, teaches a further very large number of possible linkers. *Id.* at 7 (citing Green, Formula I ¶¶ 37–48). Appellants point to the two exemplary embodiments explicitly taught by Green, CYK4-013 and CY 4-036, and to their intermediates, and argue that these do not suggest the linker of formula III. *Id.* at 7–8 (citing Green, Figs. 2, 3).

Appellants argue Pak teaches compounds (*viz.*, Pak's compounds 7a and 7b), which can be coupled to a free amino group of a biomolecule via the acetyl group to form an amide bond (e.g., the acetyl group can be reacted with an $NH_2$ group of a peptide as shown in scheme 1). App. Br. 9. Appellants contend Pak teaches that the $N^{\alpha}$ can be deprotected and the ester subjected to hydrolysis, thereby freeing all three of the coordination sites for chelation (i.e., $N^{\alpha}$, $N^{\delta}$, and $COO^{-}$). *Id.* (citing Pak schemes 1, 2; 2055).

Appellants argue that a person of ordinary skill in the art would not have been motivated to modify the pteroate dipeptide Pte-Gly-Cys of Leamon by replacing the cysteine moiety with a histidine moiety. App. Br. 9. According to Appellants, even though Mindt teaches histidine-like

structures, i.e., 1, 2, 3-triazole-4-yl alanines, a person of ordinary skill would find no reason to look to the disclosures of Mindt or Pak to modify the dipeptide folate ligands taught by Leamon, i.e., Pte-γGlu-Cys, Pte-αGlu-Cys, and Pte-Gly-Cys. *Id.* Appellants further argue a person of ordinary skill would modify the resultant compound to "optionally include a linker as taught by Green," because Green teaches linkers that represent many thousands of possible compounds. *Id.* (citing, e.g., Green ¶¶ 84–89). Moreover, argue Appellants, the linkers of Green do not contain peptide bonds, i.e., they form "non-peptide" folic acid analogs. Appellants contend the compound proposed in the rejection is explicitly a dipeptide compound (Pte-Gly-His). Consequently, Appellants argue, Green either teaches away from the proposed modification, by suggesting linkers that contain no amino acids, or provides no suggestion to modify the ligands taught by Leamon in such a manner that the resultant compound retains a dipeptide structure, let alone has the proposed structure of Pte-Gly-His. *Id.* at 9–10.

The Examiner responds that Leamon teaches Pte-Glu, a compound that reads in part on Appellants' claimed formula III. Ans. 9. The Examiner finds Leamon also teaches dipeptide conjugate $^{125}$I-BSA-Cys-Glu-Pte exhibits substantially increased binding to HeLa cells relative to controls and $^{125}$I-BSA-Glu-Pte; consequently Leamon would have motivated a person of ordinary skill to attach an additional spacer moiety, such as an amino acid, to the distal end of the glutamyl moiety. *Id.* The Examiner finds Leamon expressly teaches that carbodiimide-activated Pte-Glu or any of the pteroate-dipeptide derivatives afforded equipotent delivery of functionally active cytotoxic enzyme into treated cells. *Id.* at 9–10 (citing Leamon 168).

The Examiner relies upon Green as teaching diagnostic imaging of folate receptor-positive cells using Pte-linker-diagnostic agent conjugates. The Examiner finds Green teaches that folate-binding proteins involved in endocytosis are less sensitive to modification of the folate molecule than the membrane transport proteins, and often recognize folate conjugates. Ans. 10. The Examiner finds that both targeting and uptake of the Pte-linker-conjugated diagnostic and therapeutic agents are enhanced and that Green suggests a wide range of chelators and metals may be attached to folate derivatives. *Id.*

The Examiner next finds Pak teaches derivatizing biologically active molecules for radiopharmaceutical purposes. Ans. 10. Specifically, the Examiner finds Pak teaches that the targeting vector has to be (1) derivatized with appropriate chelator for $^{99m}Tc$; (2) should be labeled with high specific activity; and (3) retain its physiochemical properties and its affinity for the corresponding receptor. *Id.* The Examiner finds Pak teaches histidine derivatized at the ε-nitrogen as an efficient chelator of $[^{99m}Tc(OH_2)_3(CO)_3]^+$. The Examiner finds that histidine derivatized at the ε-nitrogen reads on formula IV of claim 9. *Id.* at 10–11.

In summary, the Examiner concludes that a person of ordinary skill in the art would have combined the prior art teachings with a reasonable expectation of success because Leamon and Green teach the Pte-Glu (folate) compound confers binding to high affinity folate recognition sites, such as sites on tumor cells. *See* Final Act. 9. Green suggests incorporation of a linker and diagnostic moiety, such as a chelating agent suitable for binding $^{99m}Tc$, into folate derivatives to enable visualization with SPECT. *Id.* Pak teaches that the introduction of tripodal $N^{\varepsilon}$-derivatized histidine into a

biomolecule enables labeling with $^{99m}$Tc to yield a single radiopharmaceutical compound of very high specific activity without further purification. *Id.*

We are not persuaded by Appellants' arguments. We agree with the Examiner that Leamon teaches folic acid derivatives comprising pteroic acid and dipeptides that can bind macromolecules and still be capable of binding to folic acid receptor species linked to endocytosis. *See* Leamon 167. Furthermore, we agree with the Examiner that Green teaches a folic acid mimetic conjugated to a diagnostic or therapeutic agent to enable selective delivery of the agent to the targeted cell population. *See* Green Abstr. Green also teaches chelation of metals to these linkers, including $^{99m}$Tc. *See, e.g.*, Green ¶ 106. We also agree with the Examiner that Pak teaches histidine (an amino acid) linker complexes that can chelate $^{99m}$Tc and are capable of being bound to biomolecules with pendant amines. *See* Pak Abstr.

We conclude that a person of ordinary skill would be motivated to combine the teachings of the cited prior art references. All of the references are analogous art from the same highly-specialized field of endeavor and would be within the scope of the knowledge of a person of ordinary skill. We agree with the Examiner that such an artisan would realize that combining the references would provide a desirable means by which a radioactive marker such as $^{99m}$Tc can be targeted specifically at cells expressing the appropriate folic acid receptors.

Appellants contend that Leamon does not teach the entire claimed molecule because it does not teach that a moiety of formula IV must be attached to either $R_6$ or $R_7$. However, Leamon does teach (and Appellants

do not dispute) formula III of claim 9, and it is not necessary that a single reference teach the entire composition when the rejection is based on obviousness over a combination of references. *See In re Keller*, 642 F.2d 413, 426 (C.C.P.A. 1981). Moreover, Pak explicitly teaches histidine, which corresponds to formula IV and is an amino acid capable of forming a peptide linkage to the glutamate moiety of folate. Indeed, the Pte-Glu-His dipeptide folate derivative is explicitly depicted as a specific embodiment in Figure 1 of Appellants' Specification.

Appellants also argue that their claimed folate-conjugate compounds of the present application show an unexpected high tumor-to-blood value, which proves the high potency of the compounds for applications in diagnostic imaging and treatment of tumors. App. Br. 4 (citing Spec. Tables 1a and 2a). Although it may well be true that the claimed compounds do show excellent results, Appellants do not demonstrate that the results are unexpectedly different when compared with the closest prior art. *See In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art"). Indeed, the prior art cited by the Examiner directly suggests that a number of different folate-dipeptide compounds are capable of being internalized into the cytosol via endocytosis. *See, e.g.*, Leamon 167; Green ¶ 21.

Nor are we persuaded by Appellants' argument that Green teaches away from the teachings of Leamon and their claimed invention because Green specifically teaches a replacement of the Pte-Glu linkage. *See* App. Br. 6. Green explicitly acknowledges the Pte-Glu linkage, as well as other Pte-amino acid linkages, and teaches non-peptide linkages as an alternative.

*See* Green ¶ 22 ("A folic acid analog capable of expanding the number or diversity of agents, via the conjugates of such agents and these folic acid analogs, presentable to target cells would be advantageous"). However, a reference teaches away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Appellants point to no teachings of Green that would necessarily discourage or divert a person of ordinary skill from either the teachings of Leamon or their claimed invention. Furthermore, merely teaching an alternative or equivalent method does not teach away from the use of a claimed method. *See, e.g., In re Dunn*, 349 F.2d 433, 438 (C.C.P.A. 1965).

Finally, we are not convinced by Appellants' implicit allegation that the Examiner impermissibly employed hindsight reasoning in combining the references. *See* App. Br. 10. We have related *supra* our reasoning as to why a person of ordinary skill in this sophisticated art would be motivated to combine the analogous art references cited by the Examiner. Moreover, Appellant point to no finding of the Examiner's that could have been gleaned only from Appellants' Specification or was not within the scope of knowledge of a person of ordinary skill in the art at the time Appellants' application was filed. *See In re McLaughlin*, 443 F.2d 1392, 1395 (C.C.P.A. 1971).

Consequently, and for the reasons we have set forth, we affirm the Examiner's rejection of the claims on appeal.

## DECISION

The Examiner's rejection of claims 9, 10, 12, 15–18, 20, 21, 23, 24, 26–28, 33, 40, 41, 44, 45, and 47 as unpatentable under 35 U.S.C. § 103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED