

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

MetiMedi Pharmaceuticals Co., Ltd.

Application No.: 15/629,445

Filing Date: June 21, 2017

Title: **PHARMACEUTICAL
COMPOSITION FOR TREATING
CANCER, CONTAINING LACTATE
METAL SALT**

Confirmation No.: 1760

Art Unit: 1629

Examiner: Finn, Meghan R.

Atty. Docket No.: 19097-0030003/JUK

Declaration of Dr. Hwan Mook Kim under 37 C.F.R. § 1.132

I, Hwan Mook Kim, state as follows.

1. I am a co-inventor of the claims of the captioned application. A copy of my curriculum vitae is attached (Exhibit 1).
2. It is my understanding that claim 21 has been amended and recites: "A method of inhibiting metastasis of cancer in a subject in need thereof, comprising administering an effective amount of calcium lactate to the subject, wherein the calcium lactate is administered subcutaneously, intravenously, or intratumorally." It is also my understanding that claims 40 and 45 relate to a method of treating cancer in a subject in need thereof, by administering calcium lactate to the subject, wherein the calcium lactate is administered subcutaneously, intravenously, or intratumorally.
3. It is my understanding that the claims of the captioned application have been rejected over the combination of Vinas-Salas *et al.*, *Euro. J. Cancer* 34:1941-1945 (1998), and Baron, U.S. Patent No. 6,251,439.
4. I was informed that I should review the 2 documents, Vinas-Salas and Baron, from the viewpoint of "one of ordinary skill in the art" before the priority date of the captioned application, December 29, 2014.
5. I have reviewed the 2 documents, Vinas-Salas and Baron, and it is my opinion that the Vinas-Salas and Baron, individually or combined, do not disclose, suggest, or provide a

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reasonable expectation of success of the claimed invention to one of ordinary skill in the art.

6. Vinas-Salas discloses the effect of calcium supplement on experimental colon carcinogenesis induced by parenteral administration of DMH. 3.2 g/l calcium lactate was added to the drinking water from the start to the end of the experiment. See p. 1942, Materials and Methods section, lt. col.
7. According to Vinas-Salas,

There were a higher number of tumour-free rats in group E, (DMH + calcium) compared with group B (DMH treated; $P = 0.006$; Table 4). Furthermore, the number of rats which developed two or more colon tumours was lower in group E than in group B, 11 in the DMH + calcium treated group compared with 20 in the DMH treated group ($P < 0.01$; Table 4). *There was no difference in tumour size (68% tumours < 0.8 mm in the DMH + calcium group compared with 71% in the DMH group), in the appearance of metastasis (55% in the DMH + calcium group compared with 49% in the DMH group)*

P. 1943, rt. col. (emphasis added).

8. Thus, the Vinas-Salas study shows that while giving calcium lactate in the drinking water may *prevent* colon tumors, it does not reduce the tumor size, i.e., kill tumor cells, or inhibit metastasis of cancer.
9. Baron describes throughout the patent a method for *reducing the risk* of carcinogenesis. For example, some of the issued claims state:

1. A method for reducing a risk of carcinogenesis in a human subject comprising administering a dose of elemental calcium to the subject that is effective to reduce carcinogenesis, *wherein the subject is at risk of adenoma recurrence and the elemental calcium is administered as a liquid or solid dosage form, wherein the solid dosage form comprises a tablet, capsule, lozenge, chewable tablet or bulk powder.*

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15. A method for reducing a risk of recurrence of colorectal adenomas in a human subject, comprising administering a dose of calcium carbonate to the subject effective to reduce the risk of colorectal adenomas, *wherein the calcium carbonate is in a solid dosage form and includes a film coating of cellulose, hydroxy-propylmethylcellulose, cellulose phthalate, methacrylic copolymer or shellac.*

See US 6,251,439 C1 (amended by reexamination).

10. Baron also states:

In its broadest aspect, the present invention provides a *method for reducing a risk of carcinogenesis* in a subject comprising administering a dose of calcium to the subject that is effective to reduce carcinogenesis. Preferably, the carcinogenesis is development of a colorectal adenoma, e.g., a recurrence of an adenoma. Thus, in a specific embodiment, the method provides for reducing the risk of recurrence of colorectal adenomas, comprising administering a dose of calcium carbonate effective to reduce the risk of colorectal adenomas.

Col. 1, line 61, to col. 2, line 3 (emphasis added).

11. Baron further states:

More particularly, the present invention is able to *reduce the risk ratio of adenoma recurrence*, resulting in a risk ratio of 0.74 to 0.98, e.g., about 0.85, with a 95% confidence interval. Indeed, as demonstrated in the Example, *infra*, the risk ratio of at least one adenoma was by 0.67 to 0.99, e.g., about 0.81, with a 95% confidence interval.

Col. 2, lines 4-9 (emphasis added). Thus, Baron discloses throughout the patent that the invention is for *reducing the risk* of occurrence or recurrence of cancer, i.e., preventing cancer. Baron does not disclose, suggest, or provide a reasonable expectation of successfully treating cancer or inhibiting metastasis of cancer to one of ordinary skill in the art.

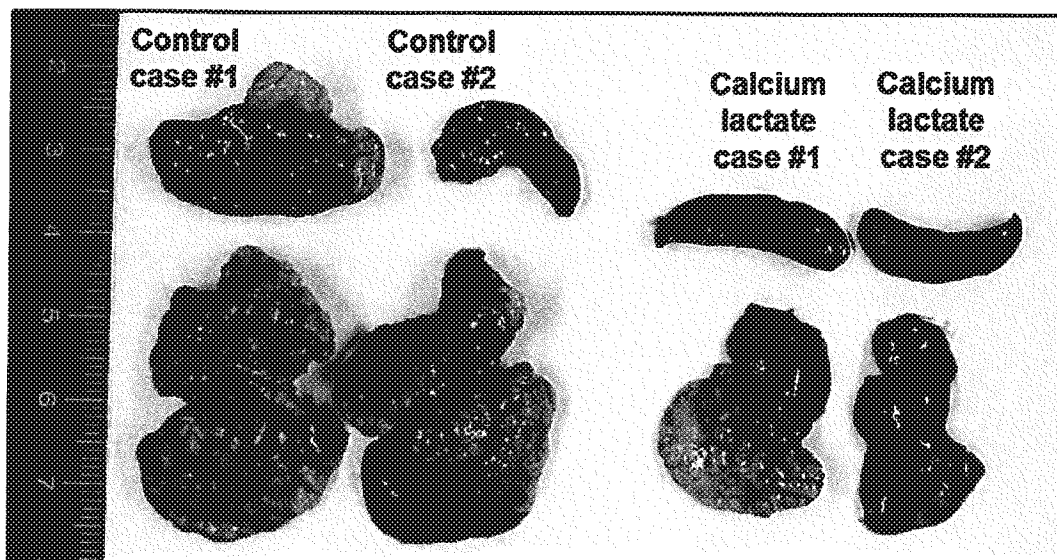
12. In sum, each of Vinas-Salas and Baron or the combination of the two documents does not disclose, suggest, or provide a reasonable expectation of successfully treating cancer or

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inhibiting metastasis of cancer to one of ordinary skill in the art. Moreover, Vinas-Salas explicitly teaches that calcium lactate did not decrease tumor volume or inhibit metastasis of cancer.

13. In contrast, our data in the captioned application show that calcium lactate can treat cancer or inhibit metastasis of cancer. For example, Example 10-6 of the captioned application demonstrates the decrease in colorectal tumor volume in an animal model injected intratumorally with calcium lactate compared to the control. See also Fig. 32. Example 10-8 of the captioned application demonstrates the decrease in colorectal tumor volume in an animal model injected subcutaneously with calcium lactate compared to the control. See also Fig. 34.
14. Examples 8-1 to 8-3 of the captioned application show that calcium lactate can inhibit metastasis of cancer such as colorectal cancer, breast cancer, and melanoma cells. See also Figs. 18-20.
15. Examples 11-2, and 12-1 to 12-15 of the captioned application also provide data showing the effect of treating various cancer cell lines with calcium lactate, irradiation, known anti-cancer drugs, or combinations of calcium lactate and irradiation or known anti-cancer drugs. See also Figs. 37a to 55b.
16. We have also shown that that injection of colorectal cancer cells into the spleen and administration of calcium lactate inhibits metastasis of colorectal cancer cells into the liver. Mice were anesthetized with a 2% isoflurane. HCT116 cells (5×10^6) were suspended in 100 μ L phosphate buffered saline. A small left abdominal flank incision was made and the spleen was exteriorized for the intra-splenic injection. The prepared cells were injected into the spleen with a 30-gauge needle. To prevent tumor cell leakage and bleeding, a cotton swab was held over the site of injection for 1 min. The injected spleen was returned to the abdomen and the wound was sutured with 6-0 black silk. Three weeks after *subcutaneous injection* of calcium lactate, liver metastasis was suppressed compared to the control. See figure below.

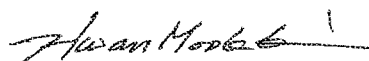


17. My co-inventors and I have determined that calcium lactate is dissociated into calcium ion and lactate in the stomach due to the gastric acid and the calcium ion is absorbed by the duodenum. However, bypassing the stomach, such as by subcutaneous, intravenous, or intratumoral administration, protects calcium lactate in its bound salt form with a neutral charge for diffusion into cancer cells.
18. It is believed that intake of calcium lactate by cancer cells produces pyruvate by activating lactate dehydrogenase B (LDHB), and the pyruvate is converted to Acetyl CoA via pyruvate dehydrogenase (PDH) in the mitochondria. This phenomenon activates the deactivated TCA-cycle of cancer cells. When the production of alpha-ketoglutarate (α -KG) is increased by the activated TCA-cycle, prolyl-hydroxylase (PHD) is activated to induce degradation of HIF-1a, which is a transcriptional regulator for oncogene expression. Thus, expression of vascular endothelial growth factor (VEGR), hexokinase 2 (HK2), and glucose transporter (GLUT) 1 is inhibited by degradation of HIF-1a, and these effects lead to cancer treatment and inhibition of metastasis.

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19. All statements made herein based on my own knowledge are true and all statements made herein on information and belief are believed to be true. I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of the application or any patent issuing thereon.

Signature: _____



Hwan Mook Kim, Ph.D.

Date: April 17, 2018