**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Neil P. DESAI et al.

Application No.: 11/553,339 Confirmation No.: 3605

Filed: October 26, 2006 Art Unit: 1656

For: COMPOSITIONS AND METHODS OF DELIVERY OF PHARMACOLOGICAL AGENTS Examiner: M. Tsay

**DECLARATION OF NEIL P. DESAI PURSUANT TO 37 C.F.R § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Neil P. Desai, declare as follows:

1. I am Senior Vice President of Global Research and Development at Abraxis BioScience, LLC ("Abraxis"), assignee of the above-referenced patent application. A copy of my biography is attached hereto as Exhibit 1.

2. I have more than 17 years of experience in the research and development of drug delivery systems and biocompatible polymers. I was one of the individuals responsible for the development of Abraxis' nanoparticle-albumin bound (nab$^{TM}$) drug delivery platform and its product Abraxane®, one of the leading drugs for treating metastatic breast cancer in the United States.

3. I am one of the named inventors of the above-referenced patent application and am familiar with the technical features of the invention and the amended claims.

4. I have reviewed the Office Action dated December 31, 2009. I understand that previously pending claims in the present patent application are rejected as being obvious over Damascelli et al., Cancer, 2001, 92(10):2592-2602 ("Damascelli"), Ibrahim et al., Proc. Am. Soc. Clin. Oncol., 2000, 19:609F ("Ibrahim"), and one of Abraxis' earlier patents, U.S. Pat. No. 6,537,579 ("the '579 patent"), on which I am also a named inventor. I have read and am familiar with these cited references.

5. The claims as amended in the present patent application are generally directed to a pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, wherein the albumin and the paclitaxel in the composition are formulated as nanoparticles, wherein the nanoparticles have a particle size of less than about 200 nm, and wherein the weight ratio of albumin to paclitaxel in the composition is about 1:1 to about 9:1. In the sections below, I generally refer to a pharmaceutical composition for injection comprising paclitaxel and a pharmaceutically acceptable carrier, wherein the pharmaceutically acceptable carrier comprises albumin, wherein the albumin and the paclitaxel in the composition are formulated as nanoparticles, wherein the nanoparticles have a particle size of less than about 200 nm as an "albumin-based paclitaxel nanoparticle composition."

6. In this declaration, I discuss unexpected results associated with the claimed albumin/paclitaxel ratio, including striking biological and clinical data relating to the ratio.

*An albumin/paclitaxel ratio of about 1:1 to about 9:1 unexpectedly shows increased cellular binding*

7. We have found, unexpectedly, that the ratio of albumin to paclitaxel in an albumin-based paclitaxel nanoparticle composition affects the ability of paclitaxel to bind to endothelial cells. Higher albumin/paclitaxel ratios are associated with poor cellular binding of paclitaxel, while lower albumin/paclitaxel ratios are associated with enhanced cellular binding of paclitaxel. We

have further unexpectedly found that the effect of albumin/paclitaxel ratio on the binding of paclitaxel changes dramatically at an albumin/paclitaxel ratio of about 9:1, as evidenced by an inflection point in the binding curve at an albumin/paclitaxel ratio of about 9:1. These unexpected results are provided in the present application as well as further data that I discuss below.

8. The present application states,

> [T]he ratio of protein, e.g., human serum albumin, to pharmaceutical agent in the pharmaceutical composition affects the ability of the pharmaceutical agent to bind and transport the pharmaceutical agent to a cell. In this regard, higher ratios of protein to pharmaceutical agent generally are associated with poor cell binding and transport of the pharmaceutical agent, which possibly is the result of competition for receptors at the cell surface.
>
> Paragraph [0041] of the present application.

9. Example 45 of the present application provides additional information relating to the finding that increasing amounts of albumin inhibit the binding of paclitaxel to endothelial cells and a hydrophobic surface coated with albumin. Specifically, Example 45 states,

> Albumin was immobilized on a microtiter plate. Fluorescent paclitaxel was added into the wells and the binding of paclitaxel was measured using a scanning fluorometer. Increasing amounts of albumin were added to the wells and the level of inhibition of paclitaxel binding to immobilized albumin was measured. The data showed that as the amount of albumin added was increased, a corresponding decrease in binding was seen. A similar effect was seen with binding to endothelial cells. This indicated that higher albumin concentration inhibited binding of paclitaxel. Thus invention compositions having lower amounts of albumin are preferred.
>
> Paragraph [0149] of the specification.

10. Exhibit 2 provides further evidence that the amount of albumin affects the ability of paclitaxel to bind to endothelial cells in a cell binding assay. In this experiment, the binding of fluorescent-labeled paclitaxel to human umbilical vein endothelial cells (HUVEC) was analyzed in the presence of various concentrations of albumin. As shown in Exhibit 2, as the albumin concentration increased, the binding of paclitaxel to the endothelial cells decreased, suggesting that an increase in the amount of albumin inhibits the binding of paclitaxel to the endothelial cells.

11. Exhibits 3 and 4 provide further evidence that the amount of albumin affects the ability of paclitaxel to bind to cells in an artificial system simulating a cell membrane in the milieu of albumin. In this experiment, binding of paclitaxel onto a hydrophobic surface coated with albumin in the presence of varying amounts of albumin added to the albumin-coated hydrophobic surface was analyzed. The albumin-coated hydrophobic surface was an artificial system used to simulate a cellular membrane in a milieu of albumin, such as endothelial cells exposed to albumin in the blood. Fluorescent-labeled paclitaxel and various concentrations of albumin were added to the albumin-coated hydrophobic surface. Binding of the paclitaxel to the albumin-coated hydrophobic surface was determined using a scanning fluorometer.

12. Exhibit 3 shows the correlation between the binding of paclitaxel to the simulated cellular membrane with the concentration of albumin added to the simulated cellular membrane. As shown in Exhibit 3, as the concentration of the added albumin increased, the binding of paclitaxel decreased, suggesting that an increase in the amount of albumin added to the simulated cellular membrane inhibits the binding of paclitaxel to the simulated cellular membrane.

13. The binding results discussed above were further analyzed by examining the correlation between the binding of paclitaxel with the weight ratio of albumin/paclitaxel added to the simulated cellular membrane. *See* Exhibit 4. As shown in Exhibit 4, as the albumin/paclitaxel ratio increased, the binding of paclitaxel to the simulated cellular membrane decreased, suggesting that an increase in the ratio of albumin/paclitaxel added to the simulated cellular membrane inhibits the binding of paclitaxel to the simulated cellular membrane.

14. Surprisingly, we found that the effect of the albumin/paclitaxel ratio on the binding of paclitaxel changes dramatically at an albumin/paclitaxel weight ratio of about 9:1. Exhibit 4. Specifically, when the albumin/paclitaxel ratios were above about 9:1, the paclitaxel binding decreased linearly as the log of the albumin/paclitaxel ratio increased with a slope of -14. When the albumin/paclitaxel ratios were about 9:1 or less, the paclitaxel binding decreased linearly as the log of the albumin/paclitaxel ratio increased with a slope of -95, a nearly seven fold increase in the slope. The two lines intersect creating an unexpected inflection point in the binding curve at an

albumin/paclitaxel ratio of about 9:1. This suggests a dramatic change in the binding of paclitaxel that occurs at an albumin/paclitaxel ratio of about 9:1.

15. Albumin-based paclitaxel nanoparticle compositions utilize the natural receptor-mediated albumin transportation process to facilitate the delivery of paclitaxel to tumor sites. *See* paragraphs [0045] and [0048] of the present application. Albumin mediates endothelial transcytosis of plasma constituents via albumin receptor gp60. It is believed that when an albumin-based paclitaxel nanoparticle composition is injected into the blood vessel, the albumin-bound paclitaxel binds to gp60 on endothelial cells and is transported to the endothelial cells. *See* paragraph [0045] and [0048] of the present application. We have unexpectedly found that 1) the albumin/paclitaxel ratio affects the binding of paclitaxel to endothelial cells and simulated cellular membrane, and 2) there is a dramatic change in the binding of paclitaxel that occurs at an albumin/paclitaxel ratio of about 9:1. These findings suggest a biological significance of albumin/paclitaxel ratio in an albumin-based paclitaxel nanoparticle formulation.

*The biological significance of albumin/paclitaxel ratio in the claimed composition could not be predicted based on the cited references*

16. The three references cited in the Office Action report earlier clinical studies either conducted or supported by Abraxis.[1] These references provide no indication of any biological significance of a albumin/paclitaxel ratio in a pharmaceutical composition. The biological significance of albumin/paclitaxel ratio could not be predicted based on these references.

17. The albumin-based paclitaxel nanoparticle compositions used for the clinical studies reported in the cited references were provided by Abraxis and represent an old formulation developed by Abraxis prior to the filing of the present application (hereinafter referred to as "the old formulation"). The albumin/paclitaxel weight ratio in the old formulation was about 19:1.

18. The old formulation allowed paclitaxel to be administered without using toxic organic solvents, thus avoiding allergic reactions and side effects caused by the organic solvents

[1] ABI-007 is a code name used by Abraxis to refer to an albumin-based paclitaxel nanoparticle composition, and is not tied to any particular formulation.

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