PHIGENIX
EXHIBIT 1037

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Rita STEEVES, et al.

Docket No: A8662

Appln. No.: 10/960,602

Group Art Unit: 1642

Confirmation No.: 8576

Examiner: Brandon J. FETTEROLF

Filed: October 8, 2004

For: METHOD OF TARGETING SPECIFIC CELL POPULATIONS USING CELL-BINDING AGENT MAYTANSINOID CONJUGATES LINKED VIA A NON-CLEAVABLE LINKER, SAID CONJUGATES AND METHODS OF MAKING SAID CONJUGATES

FIRST DECLARATION UNDER 37 C.F.R. § 1.132

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

Sir:

I, Ravi Chari, hereby declare and state:

THAT I am a citizen of the United States;

THAT I have received the degree of Ph.D. in chemistry from the University of Detroit, Detroit, MI, in 1979;

THAT I have been employed by ImmunoGen, Inc. since 1988, where I hold a position as Executive Director, Chemistry & Biochemistry, with responsibility for overseeing the research program on antibody-drug conjugates;

I further declare and state as follows:

I am one of the inventors of the invention described and claimed in the above-identified application.

I am familiar with the above-identified application. In relation thereto I have reviewed the Office action mailed November 25, 2009, in which claims 1-2, 7-11, 14-17, 20, 23, 26, 29, 35-36, 40-41, 43-44, 47-48, 51-55, 56-57, 60-66, 130, 378, 383-387, 390-393, 396, 399, 402, 405, 411-412, 416-417, 419-420, 423-424, 427-433, 436-442, 447, 452-456, 459-462, 465, 468, 471, 474, 481-482, 484-485, 487-488, 505-506, 511-514, 519-522 and 526-527 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chari et al. (US 5,208,020, 1993) in view of Roguska et al. (Protein Engineering 1996; 9: 895-904) and Queen et al. (PNAS 1989; 86: 10029-10033).

In my opinion, one of ordinary skill in the art reading Chari et al. at the time of the present invention would not have considered modifying an antibody-maytansinoid conjugate comprising a non-cleavable linker because the teachings of Chari et al. and the art as of the October 16, 2003 effective filing date of the present application, taught that conjugates of cytotoxic drugs with antibodies required the linker to be cleavable for activity, irrespective of the antibody or the cytotoxic drug used.

My opinion is supported by the following data and teachings of various references as described below.

The art at the time revealed that conjugates of cytotoxic drugs with antibodies required the link to be "cleavable" to be active, irrespective of the antibody or the cytotoxic drug used: See for example: 1) M.C Garnett: *Adv Drug Delivery Rev.*, **53**; 171-216 (2001); 179, right column lines 20-23, "*A linker which specifically releases drug from conjugate is therefore a*

vital component of targeted drug conjugates"; 2) P. Hermentin & F.R Seiler: *Behring Inst Mitt.*, 82; 197-215 (1988); page 211, conclusion 2 "*The anthracycline should be attached to the MoAb via a spacer that would allow liberation of drug*" ; 3) R.Chari, *Adv Drug Delivery Revs*, 31; 89-104 (1998); page 93 line 2 second paragraph, "*the full potency of the drug could not be observed when such non-cleavable linkers were used*".

Thus, the poor potency of non-cleavable murine Antibody-DM1 conjugates reported was consistent with teachings in the art at that time. Antibody-DM1 conjugates linked via disulfide bonds displayed potency in the same range as the free (unconjugated) maytansinoid drugs toward human tumor cells. For example, see Chari et al. US Pat No. 5,208,020, Table 3, disulfide-linked conjugate IC_{50} towards antigen positive cell line range from 2×10^{-10} M (anti-T9-SS-May/KB) to 4×10^{-11} M (A7-SS-May/HT-29), which is in the same range as IC_{50} for the parent unconjugated maytansine drug shown in Table 2 (IC_{50} ranging from 5×10^{-10} M to 3.4×10^{-11} M). In contrast, the non-cleavable conjugate anti-T9-May is much less potent ($IC_{50} = 4 \times 10^{-9}$ M, Table 3) than the free maytansine drug.

This data is consistent with a similar comparison made in the art wherein a vinblastine drug was linked to an antibody either via a cleavable hydrazone link or a non-cleavable amide bond. The authors concluded that the non-cleavable "KS1/4-DAVLB conjugate is *2 orders of magnitude less potent (emphasis added)* than vinblastine sulfate" (the free drug), whereas the cleavable "KS1/4-DAVLB-HY conjugate is *only slightly less potent (emphasis added)* than

vinblastine hydrazide" (the parent free drug) (see I.S. Johnson et al., *Cancer Treatment Revs.*, 1987; **14**, p 194 lines 1-3).

Although the non-cleavable murine antibody conjugates in both studies exhibit a small amount of activity, the potency of non-cleavable murine antibody-DM1 conjugates (IC_{50} of 4 x 10^{-9} M) is in the same range as the non-specific toxicity of non-binding disulfide-linked antibody-maytansinoid conjugates (IC_{50} of 8 x 10^{-9} reported for the non-binding A7-SS-May conjugate towards KB cells, see Table 3, US Pat No. 5,208,020). There are several other examples from experiments done in the inventors' labs showing (Table A) that the potency of *non-binding* murine antibody-SS-DM1 conjugates (IC_{50} = 2-8 x 10^{-9} M) is in the same range as the "specific" potency of a non-cleavable murine antibody antiT9-DM1 conjugate (IC_{50} = 4 x 10^{-9}) reported in the '020 patent. Based on this data, all of the potency of a non-cleavable murine antibody-DM1 conjugate can be attributed to non-specific binding. Thus, because the non-cleavable murine antibody-DM1 conjugate exhibited non-specific levels of potency, and because the art taught that conjugates of cytotoxic drugs with antibodies required cleavable linkers to be active, there was no motivation for one of ordinary skill in the art to study non-cleavable antibody-DM1 conjugates.

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