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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, **BB**, BG, **BH**, **BR**, **BW**, **BY**, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, **DK**, **DM**, **DO**, DZ, EC, EE, EG, ES, FT, GB, GD, GE, GH, GM, GT, HN, **HR**, HU, **ID**, **IL**, IN, **IS**, **JP**, KE, KG, KM, KN, **KP**, **KR**, KZ, LA, LC, LK, **LR**, LS, LT, LU, LY, MA, **MD**, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, **PH**, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, **TJ**, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
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[Continued on next page]

(54) **Title:** METHODS, COMPOSITIONS AND DEVICE FOR DIRECTED AND CONTROLLED HEATING AND RELEASE OF AGENTS

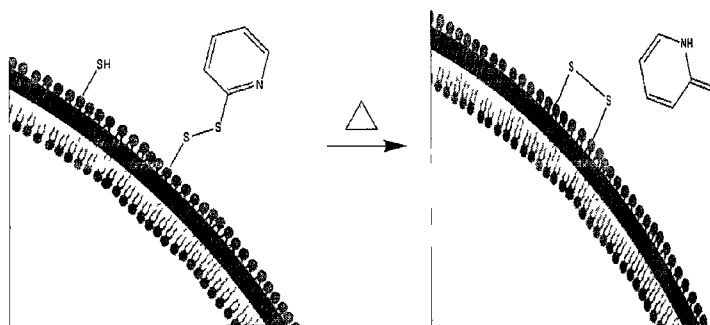


FIG. 2

(57) **Abstract:** A composition coupled to an agent with a cleavable linker is provided. Specifically, the composition is used for releasing the agent through a temperature-sensitive mechanism at a targeted location in a subject with heat. The composition allows release of toxic or rare agents in a targeted manner in the subject, e.g., for treatment of a disease. It is advantageous to applications where there is a need to accurately deploy an agent in a targeted location to reduce adverse side effects or increase efficacy of the agent. A device and method for providing heat at the targeted location in the subject is also provided. The device and method allows release of the agents in a targeted manner and prevents overheating of the targeted location or the tissue surrounding the targeted location. It is advantageous to applications where there is a need to accurately control the temperature in a targeted location in a biological body, for instance, to deploy an agent in the targeted location.

WO 2008/091655 A3



European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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PCT/US 08/00915

A CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61 K 9/127 (2008.04) USPC - 424/450 According to International Patent Classification (IPC) or to both national classification and IPC													
B FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) USPC 424/450 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC 424/1 11,283 1 450. 457. 468 606/27 (text search-see search terms below) Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PUBWEST(PGPB ,USPT ,USOCEPAB ,JPAB), Google, PubMed Search terms liposome, micelle, phospholipid, cleavable, linker, heat, transition temperature													
C DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No</th> </tr> </thead> <tbody> <tr> <td>X --- Y</td> <td>US 6,548,048 B1 (CUTHBERTSON et al) 15 April 2003 (15 04 2003) abstract, col 2, ln 45-50, col 3, ln 19-30, col 5, ln 21-24, col 7, ln 49-67, col 8, ln 1-22, col 20, ln 7-19</td> <td>1, 3, 6-10, 14, 17-18, 20, 25 ----- 2, 4-5, 11-13, 15-16, 19</td> </tr> <tr> <td>Y</td> <td>HOSOKAWA et al Alteration in the temperature-dependent content release property of thermosensitive liposomes in plasma Chem Pharm Bull (Tokyo) , November 2003, Vol 51, No 11, pp 1227-1232, abstract, pg 1227, para 5</td> <td>2, 4-5, 11-13, 15-16, 19</td> </tr> <tr> <td>A</td> <td>US 6,984,396 B2 (ZALIPSKY et al) 10 January 2006 (10 01 2006)</td> <td>1-20 and 25</td> </tr> </tbody> </table>		Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No	X --- Y	US 6,548,048 B1 (CUTHBERTSON et al) 15 April 2003 (15 04 2003) abstract, col 2, ln 45-50, col 3, ln 19-30, col 5, ln 21-24, col 7, ln 49-67, col 8, ln 1-22, col 20, ln 7-19	1, 3, 6-10, 14, 17-18, 20, 25 ----- 2, 4-5, 11-13, 15-16, 19	Y	HOSOKAWA et al Alteration in the temperature-dependent content release property of thermosensitive liposomes in plasma Chem Pharm Bull (Tokyo) , November 2003, Vol 51, No 11, pp 1227-1232, abstract, pg 1227, para 5	2, 4-5, 11-13, 15-16, 19	A	US 6,984,396 B2 (ZALIPSKY et al) 10 January 2006 (10 01 2006)	1-20 and 25
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<input type="checkbox"/> Further documents are listed in the continuation of Box C <input type="checkbox"/>													
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"P" document published prior to the international filing date but later than the priority date claimed													
Date of the actual completion of the international search 9 July 2008 (09 07 2008)	Date of mailing of the international search report 06 AUB 2008												
Name and mailing address of the ISA/US Mail Stop PCT, Attn ISA/US, Commissioner for Patents P O Box 1450, Alexandria, Virginia 22313-1450 Facsimile No 571-273-3201	Authorized officer Lee W Young PCT Helpdesk 571-272-4300 PCTOSP 571-272-7774												

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

- 1 Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely
- 2 Claims Nos
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically
- 3 Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6 4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows

see extra sheet

- 1 As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
- 2 As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees
- 3 As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos
- 4 No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos 1-20 and 25

Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation
- No protest accompanied the payment of additional search fees

Continuation of Box III (Lack of Unity)

Group I claims 1-20 and 25, drawn to compositions and method of treating a subject by administering a composition, etc
Group II claims 21-24, drawn to an ultrasound heating device, etc

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons

It will be readily understood that an ultrasound heating device of the claims of group II is distinct from and does not share any special technical feature with the compositions of claims 1-20 and the method of claim 25 of group I. While the heating device of the claims of group II may be used in conjunction with the same or similar compositions for releasing an agent to a subject, there is no requirement that such application be limited thereto.

Thus, the inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because under PCT Rule 13.2 they lack the same or corresponding special technical feature. According to PCT Rule 13.2, unity of invention exists only when the same or corresponding technical feature is shared by all claimed inventions.