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(71) Applicants *(for all designated States except US)*: **MASSACHUSETTS INSTITUTE OF TECHNOLOGY** [US/US]; Five Cambridge Center, Cambridge, MA 02142-1493 (US). **THE BRIGHAM AND WOMEN'S HOSPITAL, INC.** [US/US]; 75 Francis Street, Boston, MA 02115 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ORAY, Serkan** [US/US]; 19 York Place, Cambridge, MA 02141 (US). **SUR, Mriganka** [IN/US]; 131 Antrim Street, Cambridge, MA 02139 (US). **MAJEWSKA, Ania, K.** [PL/US]; 380 Quaker Meetinghouse Road, Honeoye Falls, New York 14472 (US). **TENG, Yang** [US/US]; 24 Dunedin Road, Wellesley, MA 02481 (US).

(74) Agent: **GERBER, Monica R.**; Choate, Hall & Stewart LLP, Two International Place, Boston, MA 02110 (US).

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(54) Title: COMPOSITIONS AND METHODS FOR ENHANCING STRUCTURAL AND FUNCTIONAL NERVOUS SYSTEM REORGANIZATION AND RECOVERY

(57) **Abstract:** The present invention provides methods and compositions for enhancing recovery in a subject suffering from damage to the nervous system. In particular, the invention includes a method for promoting recovery and/or reorganization in the nervous system of a subject in need of enhancement of recovery and/or reorganization of the nervous system as a result of ischemic, hemorrhagic, neoplastic, degenerative, or traumatic damage by focally administering a composition comprising a proteolysis-enhancing agent such as tissue plasminogen activator (tPA), plasmin, or a PAI inhibitor to the nervous system of the subject. In some embodiments an additional active agent is also administered. The composition can be delivered using a variety of techniques including injection, via infusion pump, from an implantable microchip, or using a polymeric delivery vehicle. The composition can be administered, for example, to one or more subdivisions or areas of the brain, the spinal cord, or to one or more nerves or nerve tracts innervating diverse regions of the body. The invention also includes a drug delivery device for implantation into the nervous system to promote nervous system reorganization and/or recovery following ischemic, hemorrhagic, neoplastic, traumatic or degenerative damage, the drug delivery device comprising a biocompatible polymer and a proteolysis-enhancing agent such as tissue plasminogen activator (tPA), plasmin, or a PAI inhibitor, wherein the proteolysis-enhancing agent is released from the polymer in an amount effective to promote structural reorganization of the nervous system. In some embodiments the biocompatible polymer is a hydrogel.

WO 2006/023530 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/29214

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8): **A61K 38/16**(2006.01)

USPC: 514/12
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)
U.S. : 514/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EAST, Pubmed, Dialog

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Kumar K. Recombinant Tissue Plasminogen Activator in the Treatment of Intraventricular Hemorrhage Secondary to Periventricular Arteriovenous Malformation Before Surgery: Case Report. 2003. Neurosurgery 52:964-969	1-4, 6-9, 11-13, 23-29, 31, 33-34, 38-39, 42, 50 --- 5, 40
Y	US 4,783,330 (Furie) 8 November 1988	14-15, 35
Y	US 2002/0197233 (Relton) 26 December 2002	36-37
Y	US 5,265,604 (Vince) 30 November 1993	19-21, 41
Y	US 6,465,425 (Tracy) 15 October 2002	18
Y	US 4,889,722 (Sheffield) 26 December 1989	

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
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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
DANIEL KOLKER
Telephone No. (571) 272-1600

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/29214

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,593,974 (Rosenberg) 14 January 1997	22
Y	US 6,440,455 (Benowitz) 27 August 2002	30
Y	WO 01/12236 (Finkelstein) 22 February 2001	43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/29214

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:
Please See Continuation 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 any 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.: 1-43 and 50

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.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1 - 43 and 50, drawn to methods of administering compositions to patients, and to a composition.

Group 2, claim(s) 44 - 49, drawn to drug delivery devices.

The inventions listed as Groups 1-2 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: Group 1 is directed to methods comprising "focally administering a composition comprising a proteolysis-enhancing agent to the central or peripheral nervous system of a subject in need of recovery ... as a result of ischemic ... damage to the nervous system." However, because Kumar et al. (2003. Neurosurgery 52:964-969) teaches administration of tissue plasminogen activator, which is a proteolysis-enhancing agent, to the ventricles of a subject who has had ischemia, no special technical feature exists for Group 1 as defined by PCT Rule 13.2, because it does not define a contribution over the prior art. Group 2 is drawn to a drug delivery device which does not share the same technical feature as Group 1. The technical feature of Group 2 is a device which is not required for the practice of the method of Group 1. Note PCT Rule 13 does not provide for multiple products within a single application. Because the technical feature of Group 1 is not a special technical feature and because the technical features of Groups 1 and 2 are different, unity of invention is lacking.