PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2010/053600	21.10.2010	22.10.2009

International Patent Classification (IPC) or both national classification and IPC
INV. A61K39/395 C12Q1/37 G01N33/53

Applicant
GENENTECH, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Gonçalves Mauger, M Telephone No. +49 89 2399-8127

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☒ in electronic form

   b. (time)

   ☒ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3, 28, 33, 34
	No:	Claims	4-27, 29-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-34
Industrial applicability (IA)	Yes:	Claims	1-34
	No:	Claims	

2. Citations and explanations

see separate sheet

The Search Report refers to the following documents:

D1 CANCER RESEARCH, vol. 66, no. 7, 1 April 2006 , pages 3611-3619, XP002461477,

D2 TRENDS IN MOLECULAR MEDICINE, vol. 15, no. 7, 1 July 2009 (2009-07-01), pages 303-312, XP026301924,

D3 INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, vol. 40, no. 6-7, 1 June 2008, pages 1297-1316, XP022655973,

D4 FEBS JOURNAL, vol. 277, no. 10, May 2010, pages 2230-2237,

D5 THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 24, 23 March 2001 (2001-03-23), pages 21932-21937,

D6 ADVANCES IN CANCER RESEARCH, vol. 77, 2000, pages 139-167,

D7 CANCER RESEARCH , vol. 69, no. 21, 20 October 2009, pages 8395-8402,

D8 MOLECULAR CANCER THERAPEUTICS, vol. 7, no. 10, October 2008, pages 3343-3351,

D9 WO 2007/149932

D10 WO 2007/149935

D11 WO 2006/014928

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application does not meet the criteria of Article 33(2) PCT, because the subject-matter of claims 4-27 and 29-32 is not new.

D1(pages 3612-3617) discloses antibodies neutralizing hepsin protease activity: the authors expressed an activatable form of hepsin, and have generated a set of monoclonal antibodies that neutralize enzyme activity. The neutralizing antibodies inhibit hepsin enzymatic activity in biochemical and cell-based assays and inhibit the invasion of prostate and ovarian cancer cells in culture.

D7 (pages 8396-8401, figures), a document from the inventors, shows that transmembrane serine protease hepsin is one of the most highly upregulated genes in prostate cancer. Mice bearing LnCaP-34 tumors were treated with a Pegylated kunitz domain inhibitor suppresses hepsin-mediated invasive tumor growth and metastasis. PEGylated form of Kunitz domain-1, a potent hepsin active site inhibitor derived from hepatocyte growth factor activator inhibitor-1 (K(i)(app) 0.30 +/- 0.02 nmol/ L) .Treatment of established tumors with PEGylated Kunitz domain-1 decreased contralateral prostate invasion (46% weight reduction) and lymph node metastasis (50% inhibition). Moreover, serum prostate-specific antigen level remained reduced during the entire treatment period, reaching a maximal reduction of 76% after 5 weeks of dosing. The findings in D7 show that hepsin promotes invasive prostate tumor growth and metastasis and suggest that **active site-directed hepsin inhibition** could be effective in prostate cancer therapy.

D8 (pages 3344-3349, figures) discloses that Hepsin is a type II transmembrane serine protease overexpressed in the majority of human prostate cancers.This document further states that hepsin promotes prostate cancer progression and metastasis and thus represents a potential therapeutic target. D8 reports the identification of novel s**mall-molecule inhibitors of hepsin catalytic activity**. The authors utilized purified human hepsin for high-throughput screening of established drug and chemical diversity libraries and identified sixteen inhibitory compounds with IC50 values against hepsin ranging from 0.23-2.31 mu M and relative selectivity of up to 86-fold or greater. **Two compounds are orally administered drugs established for human use**. Four compounds attenuated hepsin-dependent pericellular serine protease activity in a dose dependent manner with limited or no cytotoxicity to a range of cell types. These compounds may be used as leads to develop even more potent and specific inhibitors of hepsin to prevent prostate cancer progression and metastasis.

D9 (see abstract, examples, figures and claims) relates to anti-hepsin antibodies, and methods of using the antibodies; antibody that binds human HEPSIN, useful in preparing a composition for treating a disease or condition associated with dysregulation of HEPSIN expression, preferably prostate or ovarian cancer. D8 further relates to treating a disease or condition associated with disregulation of HEPSIN expression and comprises administering to the patient the antibody that is linked to a heterologous agent. The heterologous agent is therapeutic. The heterologous agent is a label, cytotoxic agent and/or radioisotope. The patient is a mammalian patient. The patient is human. The disease is cancer, consisting of prostate cancer or ovarian cancer.

D10 discloses a method for identifying a candidate inhibitor substance that inhibits hepsin activation of pro-urokinase type plasminogen activator (pro-uPA) by comparing amount of pro-uPA substrate activation in the sample with that in a reference sample. Further claims are: (1) an antagonist molecule that inhibits interaction of hepsin and pro-uPA; (2) a method of inhibiting a biological activity associated with pro-uPA activation by contacting a cell or tissue with the antagonist molecule; and (3) a method of treating a pathological condition associated with pro-uPA activation in a subject. In D10 the preferred antagonist comprises an antibody or a polypeptide comprising a Kunitz domain 1 sequence. The antagonist molecule comprises a small organic molecule (see abstract, examples, figures and claims).

Also D11 provides methods and compositions for modulating hepsin activity and the HGF/c-met signaling pathway, in particular by regulating pro-HGF activation by hepsin.An antagonist molecule, antibody or its fragment, or polypeptide comprising kunitz domain 1 sequence that inhibits interaction of hepsin and hepatocyte growth factor, is useful in treatment of cancer or autoimmune disorders.Preferred Antagonist: (I) comprises an antibody or its fragment, or polypeptide comprising kunitz domain 1 sequence. The following are disclosed:(1) a molecule capable of enhancing pro-HGF cleavage by hepsin;(2) use of the enhancer molecule in the preparation of a medicament for the therapeutic and/or prophylactic treatment of wound healing;(3) nucleic acids encoding (I) or the enhancer;(4) vectors comprising the nucleic acids encoding (I) or the enhancer;(5) host cells comprising the nucleic acids encoding (I) or the enhancer, or the vectors comprising the nucleic acids encoding (I) or the enhancer;(6) method of producing (I) or the enhancer; and(7) an article of manufacture or a kit comprising (I) or the enhancer (see abstract, examples and claims).

From the above analysis of the prior art, the subject-matter of the claims 4-19 (antagonist molecules), 20-27 (nucleic acids, vectors, host cells, methods of making, compositions, and uses of the antagonist molecules), 29-31(methods of treatment of various cancers with the antagonist molecules) are anticipated by the disclosures in D1, D7, D8-D11 and are thus not novel.

The present application does not meet the criteria of Article 33(3) PCT, because the subject-matter of claims 1-3, 28 and 33-34 does not involve an inventive step.

Either D10 or D11 are regarded as being the prior art closest to the subject-matter of claim 1, and disclose methods for: D10, identifying a candidate inhibitor substance that inhibits hepsin activation of pro-urokinase type plasminogen activator (pro-uPA) by comparing amount of pro-uPA substrate activation in the sample with that in a reference sample; D11 , identifying a candidate inhibitor substance that inhibits hepsin activation of pro-HGF by comparing amount of pro-HGF substrate activation in the

sample with that in a reference sample. D10 and D11 provide methods and compositions for inhibiting a biological activity associated with pro-uPA activation/ modulating hepsin activity and the HGF/c-met signaling pathway, in particular by regulating pro-uPA/pro-HGF activation by hepsin. An antagonist molecule, antibody or its fragment, or polypeptide comprising kunitz domain 1 sequence that inhibits interaction of hepsin and hepatocyte growth factor/pro-uPA, is useful in treatment of cancer or autoimmune disorders.

The subject-matter of claim 1 therefore differs from this known D10/D11 in that hepsin activation of pro-MSP (instead pro-uPA or por-HGF) is taken for identifying a candidate inhibitor and is therefore new.

The problem to be solved by the present invention may therefore be regarded as the provision of an alternative hepsin substrate for inhibitor screening.

The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons:

D6 discloses that pro-MSP can be converted by trypsin like serine proteases to active MSP. It further states that MSP is a functional factor mediating its biological activities via the RON receptor tyrosine kinase and that MSP is expressed in tumours and carcinomas Finally, D6 discloses that on the basis of the structure similarity to HGF (80% identity), mMSP is also called HGF-like protein.

The person skilled in the art, in the search for alternative substrates for hepsin, would consider the (very similar to HGF) MSP, arriving at the claim subject-matter. Further more, the methods presently claimed do not appear to have any unexpected results or advantages over the prior art ones. In fact, the antagonist molecule, antibody or its fragment, or polypeptide comprising kunitz domain 1 sequence that inhibits interaction of hepsin and MSP is the same that was known from the prior art to inhibit interaction of hepsin and pro-hepatocyte growth factor/pro-uPA, useful in treatment of cancer or autoimmune disorders. The subject-matter of claim 1 (and claims 2-3 dependent thereon) is thus not based on an inventive concept.

The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 28 and 33-34 , which therefore are also considered not inventive.