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(54) Valproic acid and derivatives for the sensitisation of human cancer cells to increase efficacy in a combination therapy

(57) The present invention relates to the use of the drug valporic acid and derivatives thereof as inhibitors of enzymes having histone deacetylase activity for the manufacture of a medicament to sensitize human cancer cells for treatment efficacy in combination with clinically established anti-cancer therapeutic drugs. The invention also relates to the treatment of tumor metastasis and minimal residual disease.

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EUROPEAN SEARCH REPORT

Application Number
EP 05 01 9659

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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Y	FERRARA F F ET AL: "Histone deacetylase-targeted treatment restores retinoic acid signaling and differentiation in acute myeloid leukemia." CANCER RESEARCH. 1 JAN 2001, vol. 61, no. 1, 1 January 2001 (2001-01-01), pages 2-7, XP002386586 ISSN: 0008-5472 * abstract * ----- -/--	1-6, 13-28	

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
The Hague	6 October 2006	Langer, Oliver

CATEGORY OF CITED DOCUMENTS

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A : technological background
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Y	MILLER WILSON H JR: "The emerging role of retinoids and retinoic acid metabolism blocking agents in the treatment of cancer" CANCER, AMERICAN CANCER SOCIETY, PHILADELPHIA, PA, US, vol. 83, no. 8, 15 October 1998 (1998-10-15), pages 1471-1482, XP002213936 ISSN: 0008-543X * abstract * * page 1474, right-hand column, paragraph 3 - page 1475, right-hand column, paragraph 1 *	1-6, 13-28	
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Y	DRIEVER PH, KNÜPFER MM, CINATL J, WOLFF JEA: "Valproic acid for the treatment of pediatric malignant glioma" KLINISCHE PAEDIATRIE, vol. 211, July 1999 (1999-07), pages 323-328, XP000997401 * abstract * * page 324 * * page 325, column 2, paragraph 4 * * page 326, column 1, paragraph 2 * * page 327, paragraph 2 * * page 327, paragraph 3 *	1-6, 13-28	

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TECHNICAL FIELDS SEARCHED (IPC)

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
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Y	EP 0 632 008 A (ONO PHARMACEUTICAL CO) 4 January 1995 (1995-01-04) * page 6, line 34 - page 7, line 11 * * page 30, line 6 - line 13 * * page 35, line 36 - line 38 * * claims 12,14 * -----	1-6, 13-28	TECHNICAL FIELDS SEARCHED (IPC)
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~~The present search report has been drawn up for all claims~~

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Y	US 5 672 746 A (NAU HEINZ ET AL) 30 September 1997 (1997-09-30) * abstract * * column 4, line 62 - column 5, line 6 * * column 7, line 23 - line 42 * ----- -/--	1-6, 13-28	

~~The present search report has been drawn up for all claims~~

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A	YAO C-P, MATHER GG, STEPHENS JR, LEVY RH: "Cytotoxicity Induced by the Combination of Valproic Acid and Tumor Necrosis Factor-alpha" BIOCHEMICAL PHARMACOLOGY, vol. 58, 1999, pages 455-459, XP002203825 * abstract * * page 456, column 2, paragraph 4 *	1-6, 13-28	
A	VAMECQ J ET AL: "PRELIMINARY STUDIES ABOUT NOVEL STRATEGIES TO REVERSE CHEMORESISTANCE TO ADRIAMYCIN REGARDING GLUTATHIONE METABOLISM, PEROXISOMAL AND EXTRAPEROXISOMAL HYDROPEROXIDE AND VALPROIC ACID METABOLIC PATHWAYS" BIOLOGY OF THE CELL, ELSEVIER, PARIS, FR, vol. 77, 1993, pages 17-26, XP008004943 ISSN: 0248-4900 * abstract * * page 25, left-hand column, paragraph 2 *	1-6, 13-28	TECHNICAL FIELDS SEARCHED (IPC)

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~~The present search report has been drawn up for all claims~~

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A	US 5 939 455 A (REPHAELI ADA) 17 August 1999 (1999-08-17) * column 1 * * claims 1,9-12,56 *	1-6, 13-28	
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Y	WO 98/39965 A (BEACON LABORATORIES L.L.C) 17 September 1998 (1998-09-17) * abstract * * claims 9,10,24,26 *	1-4, 7-11, 13-28	TECHNICAL FIELDS SEARCHED (IPC)
Y	WO 98/39966 A (BEACON LABORATORIES, L.L.C) 17 September 1998 (1998-09-17) * claims 1,10,27 *	1-4, 7-11, 13-28	
Y	WO 98/40065 A (BEACON LABORATORIES, L.L.C) 17 September 1998 (1998-09-17) * claims 14,17,34 *	1-4, 7-11, 13-28	

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~~The present search report has been drawn up for all claims~~

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	WO 98/40066 A (BEACON LABORATORIES L.L.C) 17 September 1998 (1998-09-17) * claims 6,12,78 * -----	1-4, 7-11, 13-28	
Y	WO 98/40078 A (BEACON LABORATORIES, L.L.C) 17 September 1998 (1998-09-17) * claims 10,11,19,85,96 * -----	1-4, 7-11, 13-28	
			TECHNICAL FIELDS SEARCHED (IPC)

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Place of search	Date of completion of the search	Examiner
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Application Number
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CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☒ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

7-11, and partially 1-6
13-28 (as far as part of inventions 1 and/or 6)

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

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LACK OF UNITY OF INVENTION SHEET B

Application Number
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The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-6, 13-28 (all partially)

   The use of compounds according to formula (I) to sensitise human cancer cells for the treatment with differentiation-inducing vitamin A-based drugs.

   ---

2. claims: 1-6, 13-28 (all partially)

   The use of compounds according to formula (I) to sensitise human cancer cells to enhance treatment efficacy in combination with differentiation-inducing vitamin D3-based drugs, as far as not comprised by invention 1.

   ---

3. claims: 1-6, 13-28 (all partially)

   The use of compounds according to formula (I) to sensitise human cancer cells to enhance treatment efficacy in combination with differentiation-inducing cytokines, as far as not comprised by inventions 1-2.

   ---

4. claims: 1-6, 13-28 (all partially)

   The use of compounds according to formula (I) to sensitise human cancer cells to enhance treatment efficacy in combination with chemotherapeutic and/or cytotoxic drugs, as far as not comprised within inventions 1-3.

   ---

5. claims: 12, and partially 1-4, 13-28

   The use of compounds according to formula (I) to sensitise human cancer cells to enhance treatment efficacy in combination with hormone therapy, in particular 'antagonistic acting hormonal reagents', as far as not comprised within inventions 1-4.

   ---

6. claims: 7-11 and partially 1-4, 13-28

   The use of compounds according to formula (I) to sensitise human cancer cells to enhance treatment efficacy in combination with immunotherapy, as far as not comprised within invention 1-5.

   ---

7. claims: 1-4, 13-28 (all partially)

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LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 05 01 9659

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

The use of compounds according to formula (I) to sensitise human cancer cells to enhance treatment efficacy in combination with antiangiogenic therapy, as far as not comprised within invention 1-6.

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8. claims: 29-32

A method for the identification of sensitising agents being useful for combinatorial cancer therapy.

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9. claims: 33-37

A method for the identification of genes regulated by combinatorial treatment with compounds according to formula (I) with one or several other methods of anti-tumor therapy.

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10. claims: 38-40

A diagnostic method for the in vitro identification of tumors or tumor cells.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 05 01 9659

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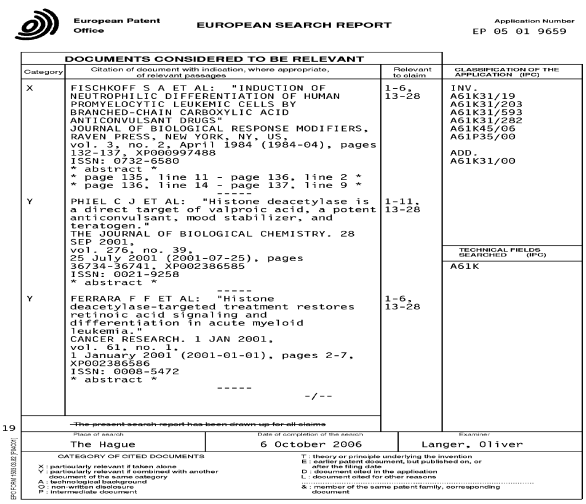
专利名称(译)	丙戊酸和衍生物用于增强人类癌细胞的敏感性，以增加联合疗法的疗效		
公开(公告)号	EP1602371A3	公开(公告)日	2006-11-15
申请号	EP2005019659	申请日	2002-09-17
[标]申请(专利权)人(译)	G2M癌症DRUSG		
申请(专利权)人(译)	G2M抗癌药物AG		
当前申请(专利权)人(译)	TOPOTARGET德国AG		
[标]发明人	GRONER BERND HEINZEL THORSTEN HENTSCH BERND WELS WINFRIED STEPHAN HERRLICH PETER A MINUCCI SAVERIO PELICCI PIER GIUSEPPE GOTTLICHER MARTIN		
发明人	GRONER, BERND HEINZEL, THORSTEN HENTSCH, BERND WELS, WINFRIED STEPHAN HERRLICH, PETER A. MINUCCI, SAVERIO PELICCI, PIER GIUSEPPE GÖTTLICHER, MARTIN		
IPC分类号	A61K31/19 A61K31/203 A61K31/593 A61K31/282 A61K45/06 A61P35/00 A61K31/00 G01N33/50 A61K31/20 A61K31/28 A61K31/59 A61K39/00 A61K39/395 A61K45/00 A61P43/00 G01N33/15 G01N33/53 G01N33/566 G01N33/574		
CPC分类号	A61K31/19 A61K31/20 A61K31/28 A61K31/59 A61K45/06 A61P35/00 A61P43/00 A61K2300/00		
优先权	2001121722 2001-09-18 EP		
其他公开文献	EP1602371A2		
外部链接	Espacenet		

摘要(译)

本发明涉及药物valporic acid及其衍生物作为具有组蛋白脱乙酰酶活性的酶的抑制剂在制备药物中的用途，所述药物与临床上建立的抗癌治疗药物组合使人癌细胞对治疗功效敏感。本发明还涉及肿瘤转移和微小残留病的治疗。



European Patent Office — EUROPEAN SEARCH REPORT — Application Number EP 05 01 9659

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	FISCHKOFF S A ET AL: "INDUCTION OF NEUTROPHILIC DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIC CELLS BY BRANCHED-CHAIN CARBOXYLIC ACID ANTICONVULSANT DRUGS" JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS. RAVEN PRESS, NEW YORK, NY, US, vol. 3, no. 2, April 1984 (1984-04), pages 132-137, XP000997488 ISSN: 0732-6580 * abstract * * page 135, line 11 - page 136, line 2 * * page 136, line 14 - page 137, line 9 *	1-6, 13-28	INV. A61K31/19 A61K31/203 A61K31/593 A61K31/282 A61K45/06 A61P35/00 ADD. A61K31/00
Y	PHIEL C J ET AL: "Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen." THE JOURNAL OF BIOLOGICAL CHEMISTRY. 28 SEP 2001, vol. 276, no. 39, 25 July 2001 (2001-07-25), pages 36734-36741, XP002386585 ISSN: 0021-9258 * abstract *	1-11, 13-28	TECHNICAL FIELDS SEARCHED (IPC) A61K
Y	FERRARA F F ET AL: "Histone deacetylase-targeted treatment restores retinoic acid signaling and differentiation in acute myeloid leukemia." CANCER RESEARCH. 1 JAN 2001, vol. 61, no. 1, 1 January 2001 (2001-01-01), pages 2-7, XP002386586 ISSN: 0008-5472 * abstract *	1-6, 13-28	

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~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
The Hague	6 October 2006	Langer, Oliver

CATEGORY OF CITED DOCUMENTS
X : particularly relevant if taken alone
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