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(54) Title: INDUCTION OF THYROID IODIDE-HANDLING GENE EXPRESSION IN HUMAN CANCERS

(57) Abstract: Dual suppression of the MAP kinase and PI3K/Akt pathways showed synergistic or greatly enhanced anti-melanoma cell effects, compared to suppression of a single pathway, including the inhibition of cell proliferation, transformation and invasion, induction of G0/G1 cell cycle arrest and, importantly, cell apoptosis. Remarkably, suppression of either pathway induces the expression of thyroid iodide-handling genes and dual suppression of the two pathways synergistically and robustly induces expression of these genes, accompanied by uptake of radioiodine in the cells. These genes include sodium/iodide symporter, thyroid-stimulating hormone receptor, thyroglobulin, thyroperoxidase, pendrin gene, thyroid transcription factors (e.g., TTF-1, TTF-2, PAX8) and other thyroid genes. Targeting major signaling pathways, such as the MAP kinase and PI3K/Akt pathways, for potent cell death, optionally coupled with induction of thyroid gene expression for adjunct radioiodine ablation therapy may be used for many human cancers, both thyroid and non-thyroid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/33214

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40; C07H 21/04; A61M 36/14 (2009.01)
USPC - 514/320; 514/350; 536/24.5; 424/1.85
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)
IPC(8)-A01N 43/40; C07H 21/04; A61M 36/14 (2009.01)
USPC-514/320; 514/350; 536/24.5; 424/1.85

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)
PubWEST(PGPB,USPT,USOC,EPAB,JPAB); Google Patents; Google Scholar
melanoma, radioiodine, PI3 kinase, AKT, map kinase, radiotherapy, iodine, kinase inhibitor, siRNA, induction, radiation, thyroid stimulating hormone, perifosine, triciribine, temsirolimus, everolimus, motesanib, axitinib, sunitinib, Wortmanin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	(RIESCO-EIZAGUIRRE et al.) New insights in thyroid follicular cell biology and its impact in thyroid cancer therapy Endocrine-Related Cancer (2007) 14 957?977. (pg 958 para 6, pg 970 para 1)(pg 959 para 3) (pg 962 para 3) (pg 963 para 2) (pg 964 para 2) (pg 964 para 2-5) (pg 968 para 1-4) (pg 969 para 1-3, Table 2) (pg 970 para 1) (pg 970 para 4)	1-17, 20-22, 24-27 --- 18, 19, 23
Y	US 2005/0026232 A1 (YAMAMOTO et al.) 03 February 2005 (03.02.2005) (para [0068])	18
Y	US 2003/0186867 A1 (FACCI et al.) 02 October 2003 (02.10.2003) (para [0118])	19
Y	US 6,238,644 B1 (RILLEMA) 29 May 2001 (29.05.2001) (col 1 ln 45-62)	23

☐ Further documents are listed in the continuation of Box C. ☐

* 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 but published on or after the international filing date
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA/US	Authorized officer:
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