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SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

BOGOTA - COLOMBIA
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Re: P1. -F. HOFFMANN-LA ROCHE AG.-Solicitud de Patente de

Invención en Fase Nacional PCT para "TRATAMIENTO CON OXALIPLATXNO V UN INHIBIDOR DEL EGFR".-Clase A61K

33/24. -Extjediente nümero 06-129.577.-
1

1. Me refiero a mi memorial de 19 de Septiembre de 2007.

2. De conformidad con lo dispuesto en el Articulo 5.2.12 de la Circular

Externa No. 03 de 28 de Abril de 2003, y estando dentro del plazo de seis meses contados desde la fecha de la publicación de la solicitud en la Gaceta de la Propiedad Industrial nümero 597 de 31 de Octubre de 2008, solicito a ese Despacho proceder a realizar el examen de patentabilidad de la presente invención.

3. Anexo me permito acompaæarrecibo nümero 09-25.801, expedido por la

Superintendencia de Industria y Comercio, que acredita el pago de la tasa que dicho examen causa.

4. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

SeæorSuperintendente,

- TCIA LLOREDA RICAURTE
T.P. 53.215

SUPLR1N! LNDLNCiA DL NODS RI/ Y COMLRCO

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No. 06-129577- -00003-0000

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Industria y Comerelo
S PE R I N T E N DEN CIA

DIVISION DE NUEVAS CREACIONES

RADICACION EXPEDIENTE No. 06-129577

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 597 DE

S

FECHA 31 DE OCTUBRE DE 2008 EL TERMINO HABIL SEZALADO POR LA

LEY EXPIRA EL 02 DE FEBRERO DE 2009

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de pubticaciôn en la gaceta de Propiedad industrial, deberÆ soticitar y cancelar et examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con to establecido en el Articulo 44 de la DecisiOn 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS,

SI NO

12) INTERNAIIONA[. APPLICA lION PLBLISHJ-iI) L’Nl)ER THE PATENT COOPERATION TREATY (PCT)

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(43) International Publication Date (10) International Publication Number

11 March 2004 (11-0.2004) PCT WO 2004/019857 A2

(51) International Patent Classification7: A61K (74) Agents: BARNES, Elizabeth, M. et al - c/o Genentech.
Inc.. MS49. I DNA Way. South San Francisco, CA 94080-

(21) International Application Number: 4990 (US
 PCl[IJS 2003/017682

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(25) Filing Language, English

126) Publication Language: English

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601107,087 29 August 2002 (2908 2002) US

(71) Applicant: GE2sEN’lECH, INC. US/US): 1 DNA Way, S,,u:h San Francieo. CA 94080-4990 (1,S).

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(84) Designated States (regional)- ARIP() patent (OH, GM, Ku. 1.5. MW, MZ, SD. ST.. SZ, TZ, 14G. ZM. 7W). Eurasian patent (AM. AZ, BY, KG, KZ, MD, RU, ’iJ TM). Eurupeun patent (AT. BE. 8G. CII, CY, CZ, DL, OK. FE.
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SE. SI, SK, TR. OAPI patent (BF. RI. CF, CU. Cl. CM, GA, UN, GQ. GW, Ml., MR. NT, SN, TI). TG.

Published:

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For rwo.terter codes and other abbreviations, refrr to the "Guid.
once ’Votes on (’odes and.4 hhreviazions" appearing at the begin-
ning of each regular issue ufthe PCT Gazette.

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' )54t Title: ACHAETF.-S(UJIi I.IKF.2 P0I.YPFIPTTDI:S AND ENCODING YUCI.14C ACIDS AND METHODS FOR ’li-Il) DT-
AGNOSIS AND TRLAIMLN t 01 I UMOR

(57) Abstract: the present invention is dirctcd to compositions of matter useful for the diagnosis and treatment of tumor in mam-mals and to methods of using those compositions of matter for the same.

WO 2004/019857 PCT/US2003/017682
bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor
or anticancer agents disclosed below. Other cytotoxic agents are described below. A rumoricidal agent causes

destruction of tumor cells.

Preferred cytotoxic agents herein for the specific tumor types to use in combination with the antagonists

herein are as follows.

5 1. Prostate cancer: androgens, docetaxel, paclitaxel, escramustirie, doxorubicin, mitoxantrone, antibodies to
FrbB2 domain(s) such as 2C4 (WO 01/00245; hybridoma ATCC HB-12697), which binds to a region in the
extracellular domain of ErbB2 (e.g., any one or more residues in the region from about residue 22 to about
residue 584 of ErbB2, inclusive), AVASTINTM anti-vascular endothelial growth factor (VEGF),
TARCEVATM OSI-774 (erlotinib) (Genenetech and OSI Pharmaceuticals), or other epidermal growth factor
1 C) rcccptor tyrosine kinase inhibitors (EGFR TKI’s).
. 2. Stomach cancer: 5-fluorouracil (5FU), XELODATM capecitabine, inethotrexate, etoposide, cisplatin/carboplatin, pacliitaxel, docetaxel, gemeitabine, doxorubicin, and CPT-1 I (camptothcin-1 I; irinotecan,
USA Brand Name: CAMPTOSARfi),
3. Pancreatic cancer: gemcirabine, 5FU, XELODATM capecitabine, CPT- 11, docetaxel, pacliraxel, cisplatin,
1 5 carboplatin, TARCEVATM erlotinib, and other EGFR TKI’s,
4. Colorectal cancer: 5FU, XELODATM capecitabine, CPT-11, oxaliplatin, AVASTINTM anti-VEGF,
TARCF.VATM erlotinib and other EGFR TKI’s, and ERB[TUXTM (formerly known as IMC-C225) human:murine-chimerized monoclonal antibody that binds to EGFR and blocks the ability of EGF to initiate receptor activation and signaling to the rumor..
20 5. Renal cancer: IL-2, interferon alpha, AVASTINTM anti-VEGF, MEGACETM (Megestrol acetate) progestin
vinhiastine, TARCEVATM erlotinib, and other EGFR TKI’s,
A growth inhibitory agent when used herein refers to a compound or composition which inhibits
growth of a cell, especially a TAT376- or TA1377-expressing cancer cell, either in vitro or in vivo. Thus, the
growth inhibitory agent may be one which significantly reduces the percentage of TAT376- or TAT377-
25 expressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle
progression (at a place other than S phase), such as agents that induce 01 arrest and M -phase arrest. Classical M-phase blockers include the vincas (vincristirie and vinblasrine), taxanes, and topoisomerase II inhibitors such
as doxorubicin, epirubicin, daunorubiciri, etoposide, and bleomycin. Those agents that arrest 01 also spill over
into S-phase arrest, for example, DNA alkylating agents such as tanioxifen, prednisone, dacarbazine,
30 mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The
Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled Cell cycle regulation, oncogenes,
and antineoplastic drugs by Murakami etal. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxaries (laclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTEREfi, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of pactitaxel (TAXOLfi,
35 Bristol-Myers Squibb)- Paclitaxel and docetaxel promote the assembly of microrubules from tubulin dimers and
stabilize microrubules by preventing depolymerization, which results in the inhibition of mitosis in cells. "Doxorubicin’ is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)--lO-[(3-

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The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being
the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species
and isotype of any iminunoglobuiin Fe domain that is present in the antibody. Protein A can be used to purify antibodies that are based on human yl, ’y2 or y4 heavy chains (Lindmark et al, J. Immunol. Meth, 62:1-13
5 (1983)). Protein U is recommended for all mouse isotypes and for human y3 (Guss et al., EMBO J.
5:15671575 (1986)) The matrix to which the affinity ligand is attached is most often agarose, but other
matrices are available. Mechanically stable matrices such as controlled pore glass or poly(snyrenedivinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with
agarose. Where the antibody comprises a C113 domain, the Bakerbond ABXTM resin (J. T. Baker, Phillipsburg,
10 NI) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange
. column, ethanol precipitation, Reverse Phase ILPLC, chromatography on silica, chromatography on heparin
SI3PHAROSETM chromatography on an anion or cation exchange resin (such as a polyaspartic acid column),
chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the
antibody to be recovered.
15 Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at
a pH between about 25-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).
J. Pharmaceutical Formulations
Therapeutic formulations of the anti-TAT376 or anti-TAT377 antibodies, TAT376 or TAT377 binding
20 oligopeptides, TAT376 or TAT377 binding organic molecules and/or TAT376 or TAT377 polypeptides used
in accordance with the present invention are prepared for storage by mixing the antibody, polypeptide, oligopeptide or organic molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington’s Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in
the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are
25 nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris,
phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and metllionine; preservatives
(such as octadecyldimethylbeuzyl ammonium chloride; hexarnethonium chloride; benzalkoniurn chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben: catechol; resorcinol; cyclohexanol; 3-penrartol; and m-cresol); low molecular weight (less than about 10
30 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers
such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating
agents such as EDTA; conicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; metal complexes
35 (e.g., Zn-protein complexes); and/or non-ionic surfacants such as TWEEN, PLURONICSO or polyethylene
glycol (PEG). The antibody preferably comprises the antibody at a concentration of between 5-200 mg/ml, preferably between 10-100 mg/mi.

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US 60/460,348 (CIP)
Filed on 3 Aptil 2003 (03.04.2003)

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Sb, 51. SK. ’FR), OAPI patent (BE, BJ, CF. CG. CI, CM.
GA, GN, GQ, (3W, \fl., MR. NT., SN, TI), TG.

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(71) Applicant (r all l’ ina’,J Stwes except (S): COM- For iwo-letter -ode., and other abbrpi-iation.v, refer ui the Guid-
HlN.-.’J’ORX, INCORPOR_.TED [[S/US!: 650 Albany ance Votes on Codes and.-tbbrec-iations’appearing at the bcin-
Street. Boston. SI/I (C 118 (L’S), rung c’J each regular issue ofthe PCT Gazette-

(54) 111k: \’[FTI-TODS FOR TIFF 1RiIAT\IFXT OF NI’OPI.ASMS

(57) Abstract: The invention Retures a method or treating a patient having a cancer Or other neoplasm by administering to the pattent a niclusarrudc, or a structural or functional analog thereof, and, optionally, one or more antiprolifcrative agents in an amount effective to inhibit the growth (it’ he neoplasm.

NA 0 2004/006906 PCT/US2003/022026

Other include brain cancer, breast cancer, cervical cancer, colon
cancer, gastric cancer, kidney cancer, leukemia, liiier cancer, lymphoma, ovarian cancer,, pancreatic cancer, prostate cancer, rectal cancer, sarcoma, skin cancer, testicular cancer, and uterine cancer. These cancers, like lung cancer, are
sometimes treated with chemotherapy.
Antiproliferative agents currently in use or in clinical trials include
paclitaxel, docetaxel, tamoxifen, vinorelbine, gemcitabine, cisplatin, etoposide, topotecan, irinotecan, anastrozole, rituximab, trastuzumab, fludarabine, cyclophosphamide, gentuzumab, carboplatin, interferon, and doxorubicin. The
10 most commonly used antiproliferative agent is paclitaxel, which is used alone or in combination with other antiproliferative agents such as: 5 -FU, doxorubicin, vinorelbine, cytoxan, and cisplatin.

Summary of the Invention
15 We have discovered that niclosamide, a salicylanilide compound, acts as an antiproliferative agent against cancer cells, and enhances the activity of antiproliferative agents when used in combination therewith. Structural and functional analogs of niclosamide are known and can also be used alone or in combination with antiproliferative agents in the methods ofthe invention.
20 Accordingly, the invention features a method for treating a patient who has a neoplasm or is at risk for developing a neoplasm by administering to the patient
a compound having formula I:

R7

R

R2 P

#’

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25 or a salt thereof. In formula I D is N or CR9; E is N or CR’°; F is N or CR"; and R’ is 1-I, halide, OR’2, SR", NR’4R’5, or described by one of the formulas:

w:J 204/006906 PCT/1JS2003/022026

Table 1.

Ali:ylating agents cyclophosphamide lomuttine
busulfari procarbazine
ifost’amide altretamine
meiphalan estTaniustine phosphate
hexamethylmelamine mechlorethamine
thotcpa streptozocin
chlorarnhucil ternozolomide
dacarbazine semustine
carmustine

Platinum agents cisplatin carboplatinum
oxaliplatin ZD-0473 (AnorMED)
spiroplatinum, lobaplatm (Actcrna)
carboxyphthaatoplatinum, satraplatin (Johnson Matthey)
tetraplatiu BBR-3464 (Hoffmann-La Roche)
ormiplatin SM-I 1355 (Sumitomo)
ipropiatin AP-5280 (Access)

Antimetabohtes azacvticiine tomudex
gemc itabine trimetrexate
capecirabine deoxycoformycin
5-fluorouracil fludarabine
floxuridine pentostatin
2-chlorodeoxyadenosine raltitrexed
6-mercaptopunne hydroxyurea
6-thi oguanine decitabine (SuperOen)
cytarabin clofarabine (Bioenvision)
2-tluorodeoxy cyudine irofulven (MGI Pharrna)
methotrexate DMDC (Hoffmann-La Roche)
idatrexate ethynylcytidine (Taiho)

Topoisorncrasc amsacrine rubitecan (SuperOen)
inhibitors epirubicin exatecan mesylate (Daiichi)
etoposide quinamed (ChemOenex)
teniposi de or mitoxantrone gimatecan (Sigma-Tau)
irinotecan (CPT-1 1) diflomotecan (Beaufour-Ipsen)
7-ethyl-10-hydraxy-camptothecin TAS-103 (Taiho)
topotecan elsamitrucin (Spectrum)
dexrazoxanct (TopoTarget) J-107088 (Merck Co)
pixantrone (ovuspharrna) BNP-1350 (BioNumerik)
rebeccamycin analogue (Exelixis) CKD-602 (Chong Kun Dang)
BBR-3 576 (Novuspharma) KW-2170 (Kyowa Hakko)

Antitumor dactinomycn (actinomycin D) amonafide
antibiotics doxorubiciri (adriamycin) azonafide
deoxyrubicin anthrapyrazole
valrubjcjn oxantrazole
daunorubicin (daurtomycin) losoxantrone
epirubicin bleomycin sulfate (blenoxane)
therarubicirt bleomycinic acid
idarubicin bleomycin A
rubidazone bleomycin B
plicarnyc:np mitomycin C
porfromycin MEN-10755 (Menarini)
cyanomorpholiriodoxorubicin GPX- 100 (Gem Pharmaceuticals)
mitoxantrone (riovaritrone)

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Eudothlin A atraseruiri (Abbott) YM-598 (Yamanouchi)
receptor antagonist ZD-4054 (AtraZeneca)

Rctinoic acid fenretinide (Johnson & Johnson) ahtretinoiri (Ligand)
receptor agonists LGD-1550 (Ligand)

lmmuno- interferon dexosome therapy (Anosys)
modulators oncophage (Antigenics) pentrix (Australian Cancer Technology)
GMK (Progenies) 1SF- 154 (Tragert)
adenocarcinorna vaccine (Biomira) cancer vaccine (Intercell)
CTP-37 (AVI BioPharma) norelin (Biostar)
IRX-2 (Immuno-Rx) BLP-25 (Biomira)
PFP-005 (Peplin Biotech) MGV (Progenies)
synchrovax vaccines (CTL Immune) 13-alethirie (Dovetail)
melanoma vaccine (CTL. Immuno) CLL therapy (Vasogen)
p21 RAS vaccine (QemVax)

Hormonal and estrogens prednisone
antihormonal conjugated estrogens methylprednisolone
agents ethinyl etradiol prednisolone
chlortrianisen aminoglutethisnide
idenestrol leuprolide
hydroxyprogesterone caproate goserelin
medroxyprogesterone leuporelin
testosterone bicalutamide
testosterone propionate; flutamide
uluoxymesterone octreotide
mcthyltestosteronc nilutamide
di ethylstilbestrol mitotane
megestrol P-04 (Novogen)
tamoxitŁn 2-methoxyestradiol (EntreMed)
toremofine at-zoxifene (Eli Lilly)
dexamethasone

Photodynamic talaporfin (Light Sciences) Pd-bacteriopheophorbide (Yeda)
agents Theralux (Theratechnologies) lutetium texaphyrin (Pharmacyclics)
ntotexafin gadolinium (Pharmacyclics) hypericin

Tyrosine Kinase imatinib (ovartis)
Inhibitors leflunomide (Sugen/Pharmacia)
ZD 1839 (AstraZeneca)
erlotinib (Oncogene Science)
canertinib (Pfizer)
squalamine (Genacra)
SU5416 (Pharmacia)
SU6668 (Pharmacia)
ZD4190 (AstraZeneca)
ZD6474 (AstraZereca)
vata]anjb (Novartis
PKI66 (Novar’s)
GW2016 (GaxoSrnithKline)
E,10-509 (Wyeth)
EKB-569 (Wyeth)

kahalide F (Pharmaar)
CEP-701 (Cephalon)
CEP-751 (Cephalon)
MLN5 18 (Millenium)
PKC412 (ovartis)
phenoxodiol (Novogen)
trastuzumab (Genentech)
C225 (ImClorte)
rhuMab (Genentech)
MDX-H210 (Medarex)
2C4 (Genentech)
MDX-442 (Medarex)
ABX-EOF (Abgenix)
IMC-lCl I (ImClone)

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WO 2004/006906

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E
Miscellaneous agents

SR-27897 (CCK A inhibitor, Sanofi-Synthelabo) tocladesine (cyclic AMP agonist, Ribaphann)
aliocidib (CUK inhibitor, Avmis)
CV-247 (COX- inhibitor, Ivy Mdica)
P54 (COX-2 inhibitor, Phytopharm)
CapCellM (CYP45O stimulant, Bavarian Nordic) GCS-100 (gal3 antagonist, GlycoCenesys)
CI7DT immunogen (gastrin inhibitor, Aphton) efaproxiral (oxygenator, Alias Therapeutics) P1-88 (heparanase inhibitor, Progen)
tesrniiifene (histamine antagonist, YM
BioSciences)
histamine (histamine H2 receptor agonist, Maxim) tiazofurin (IMPDH inhibitor, Ribapharm)
cilengitide (integrin antagonist, Merck KGaA) SR-31747 (IL-i antagonist, Sanofi-Synthelabo) CC!-779 (mTOR kinase inhibitor, Wyeth)
exisulind (PDF. V inhibitor, Cell Pathways)
CP-461 (PDE V inhibitor, Cell Pathways)
AG-2037 (CART inhibitor, Pfizer)
WX-UKJ (plasminogen activator inhibitor, Wilex) PBI-1 402 PMN stimulant, ProMetic LifeSciences) bortezomib (proteasome inhibitor. Millennium) SRL-172 (T cell stimulant, SR Phanna)
TLK-286 (glutathione S transferase inhibitor, Tehk)
PT-100 (growth factor agonist, Point Therapeutics) midostaurin (PKC inhibitor, Novartis)
bryostatin-1 (PKC stimulant, GPC Biotech) CDA-I1 (apoptosis pronlotor, Everlife)
SDX-I01 (apoptosis promotor, Salmedix)
celiatonin (apoptosis promotor, ChemOenex)

PCT/1fS2003/022026

BCX-1777 (PNP inhibitor, BioCryst)
ranpirnase (ribonucleasc stimulant, Althceli) galarubicm RNA synthesis inhibitor, Dong-A) tirapazarninc (reducing agent. SRI International) N-acetylcysteine (reducing agent, Zainbon)
R-flurbiprofen (NF-kappaB inhibitor, Encore) 3CPA (NF-kappaB inhibitor, Active Biotech) seocaicitol (vitamin D receptor agonist, Leo)
131 -1-TM-601 (DNA antagonist, TransMolecular) eflornithirie (ODC inhibitor, ILEX Oncology) minodronic acid (osteoclat inhibitor, Yamanouchi) indisuiam (p53 stimulant, Eisai)
aplidine (PPT inhibitor, PharmaMar)
rituximab (CD20 antibody, Genentech)
gemtuzumab (CD33 antibody. Wyeth Ayerst)

PG2 (hematopolesis enhancer, Pharmagenesis) lmmunolTM (thclosan oral rinse, Endo)
triacetyluridine (uridine prodrug, Wellstat) SN-407 1 (sarcoma agent, Signature BioScience) TransMlD- 107TM (immunotoxin, KS Biomedix) PCK-3 145 (apoptosis promotor, Procyon)
doranidazole (apoptosis promotor, Pola)
CHS-828 (cytotoxic agent, Leo)
transretinoic acid (differentiator, MIT)
MX6 (apoptosis promotor, MAXIA)
apomine (apoptosis promoter, ILEX Oncology)
urocidin (apoptosis promotor, Bioniche)
Ro-31-7453 (apoptosis promotor, LaRoche)
brostailicin (apoptosis promotor, Pharniacia)

Furthermore, the invention also features a composition that includes (i) a compound described above (e.g., of formula (I), an antthelminthic agent, or otherwise listed above) and (ii) an antiproliferative agent.

The invention also features a method for identifying combinations of compounds useful for treating a patient having a neoplasm. The method includes the steps of (a) contacting cancer cells in vitro with (i) niclosamide or an antiproliferative agent and (ii) a candidate compound, and (b) determining whether the combination of niclosamide or an antiproliferative and the candidate compound reduces growth of the cancer cells relative to cancer cells contacted with niclosamide or an antiproliferative agent but not contacted with the candidate compound, or cancer cells contacted with the candidate compound but

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chioronicotinic acid coupled with 2-ehloro-4-nitroaniline (Aldrich Cat No.
45,685-3), as in reaction 6, using standard amide coupling tecbniques.

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II ,.- NO 0,NO2

N OH

H21\1C1 N
Cl

CI N OH

reaction 6

The resulting product is a compound of formula I and can be used in the methods
of the invention

Antipróliferative Agents
10 Antiproliferative agents that can be administered in the combinations of the invention are alkylating agents, platinum agents, antimetabolites,
topoisomerase inhibitors, antitumor antibiotics, aritimitotic agents, aromatase inhibitors, thymidylate synthase inhibitors, DNA antagonists, farnesyltransferase inhibitors, pump inhibitors, histone acetyltransferase inhibitors, metalloproteinase
15 inhibitors, ribonucicoside reduetase inhibitors, TNF alpha agonists and
antagonists, endothelin A receptor antagonists, retinoic acid receptor agonists, immunomodulators, hormonal and antihormonal agents, photodynamic agents,
and tyrosine kinase inhibitors. Any one or more ofthe agents listed in Table 1
can be ised. Exemplary antiproliferative agents include, without limitation,
20 paclitaxel, gemcitabine, doxorubicin, vinbiastine, etoposide, 5-fluorouracjl,
carbopatin, altretarnthe, aniirioglutethimide, arnsacrine, anastrozole, azacitidine, bleomycin, busulfan, carmustine, chiorambucil. 2chlorodeoxyadenosine,
cisplatin, coichicine, cyclophosphamide, cytarabine, cytoxan, dacarbazirie, dactinomvcin, daunorubicin, docetaxel, estramustine phosphate, floxuridine,
25 fludarabine, gentuzumab, hexamethylmelamine, hydroxyurea, ifosfamide,
irnatinib, interferon, irinotecan, lornustine, mcchlorethamine, melphalen, 6-mercaptopurine, methotrexate, rnitomycin, mitotane, mitoxa.ntrone, pentostatin,

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iThy of a number of strategies can be, pvr.ued in ordi to -obtain conITolled
release in ovhich the rate of release outweighs the rate ofmetabolism ofthe compound in question. In one example, controlled release is obtained by appropriate selection of various formulation parameters and ingredients,
5 including, e.g., various types of controlled release compositions and coatings.
Thus, the drug is formulated with appropriate excipients into a pharmaceutical composition that, upon administration, releases the drug in a controlled manner. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, niicrocapsules, microspheres, nanoparticles,
10 patches, and liposomes.

Solid Dosage Forms For Oral Use
Formulations for oral use include tablets containing the active ingredient(s)
in a mixture with non-toxic pharmaceutically acceptable excipients. These
15 excipients may be, for example, inert diluents or fillers (e.g., sucrose, sorbitol,
sugar, mannitol, microcrystalline cellulose, starches including potato starch,
calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate,
or sodium phosphate); granulating and disintegrating agents (e.g., cellulose
derivatives including microcrystalline cellulose, starches including potato starch,
20 croscarmellose sodium, alginates, or alginic acid); binding agents (e.g., sucrose,
. glucose, sorbitol, acacia, alginic acid, sodium alginate, gelatin, starch,
pregelatinized starch, microcrystalline cellulose, magnesium aluminum silicate, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl niethylcellulos e, ethylcellulose, polyvinylpyrrolidone, or polyethylene glycol); and lubricating
25 agents, glidants, and antiadhesives (e.g., magnesium stearate, zinc stearate, stearic
acid, silicas, hydrogenated vegetable oils, or talc). Other pharmaceutically
acceptable excipients can be colorants, flavoring agents, plasticizers, humectants, buffering agents, and the like.
The tablets may be uncoated or they may be coated by known techniques,
30 optionally to delay disintegration and absorption in the gastrointestinal tract and
thereby providing a sustained action over a longer period. The coating may be

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SUPERINTENDENCIA DE INDUSTRIA V COMERCIO DIRECCION DE NUEVAS CREACIONES

2020
Bogota, D.C.

Abogado
ALICIA LLOREDA RICAURTE

ASUNTO Radicaciôn 06129577
Tramite 011
Everito 379
Actuaciôri 411
Oficio
Folios 014

Patente de Invenciôn

Via Nacionat El

Via PCT (fase nacional)

No. Sot. Internacional

Fecha de Presentación Internal

Patente de Modelo de Utilidad

Cap.I Cap. II

PCT/EP2005/005638

25/05/05

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Como resultado del examen de fondo, realizado con fundamento en el artIculo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le comunica:

40 1. Documentos estudiados
1, 1. DescripciOn: Folios: 48 a 118 como se radicO inicialmente.

1.2. Reivindicaciones: Folios: 23 a 27 como se radicó inicialmente
Folios: 156 a 159 (modificado).

1.3. Prioridad:

2. Objeto de la invención

03/06/2004; US; 60/576,435

Tituto de la invenciôn: TRATAMIENTO CON OXALIPLATINO Y UN INHIBIDOR DEL EGFR.

Problema TØcnico Planteado: Necesidad de mejorar los tratamientos para el cancer colorrectal y otros cÆnceres.

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Solución: Una composciOn de acuerdo a la reivindicaciOn 1 y mØtodo de eIa bora dOri.

IPC: A61k33/24,31/517,31/5377,31/519,31/4706, A61p35100.

3. De la solicitud de Patente

3.1 Reivindicaciones (artIculo 30 0 486)

Reivindicación 1, no esta susteritada con un ejemplo de una composición que contenga los dos principios activos (Erlotinib y Oxaliplatino) y concentraciones especIficas, que muestren claramente un efecto tØcnico logrado, coma Una posible sinergia.

La reivindicación 4, reclama una composiciOn que ademâs contiene uno u otros agentes anticancerosos; esta reivindicaciOn no es concisa ademÆs no existe sustento con un ejemplo de una composiciÆnde este tipo con la cual se evidencie un efecto tØcnico inesperado.

La reivindicactOn 19, reclama una composición que ademÆs contiene uno u otros agentes anticancerosos; esta reivindicaciOn no es concisa ademªs no existe sustento con un ejemplo de una composidión de este tipo con la cual se evidencie un efecto tØcnico inesperado.

4. Determinación del Estado de la TØcnica

La fecha que se ha tenido en cuenta para determinar el Estado de Ia TØcnica es:

Fecha de presentación de la solicitud prioritaria: 03/06/2004.

Teniendo en cuenta la fecha indicada se realizO la büsqueda en el estado de la tØcnica de documentos relacionados con la solicitud encontrÆndose los siguierites documentos mÆs relevantes:

NO DocumentoF To Fecha de
publicacion*
Achaete-scutelike-2polypeptides

and encoding nucleic acids and Marzo 11 de D1 W02004019857 methods for the diagnosis and 2004

treatment of tumor

D2 W02004006906 Methods for the treatment of Enero 22 de
neoplasms 2004
Dl (folios, 164-166), D2 (folios 167-173)

5. AnÆlisis de patentabilidad (articulo 14 D486)

5.2 Nivel inventivo (articulol8 0486)

La reivindicaciÆri 1, reclama unacomposiciOn farmacØutica, que comprende: Un

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inhibidor de la quinasa del EGFR y Oxaliplatino, en un vehculo farmacØuticamente aceptable.

El Estado de la TØcnica mªs cercano es Dl (W02004019857) que da a conocer composiciones anticancerIgenas, que contienen: agentes citotôxicos, entre otros

mÆs, como un inhibidor de la quinasa del EGFR el erlotinib, el cisplatin (agente de platino) (folios 164-165, abstract y pg 45) y vehIculos farmacØuticamente aceptables (folio 166, pg 96).

La composición reclamada en esta reivindicación, se diferencia de las composiciones de Dl, en que esta, contiene otro agente de platino como el oxaliplatino.

El hecho de que las composiciones reclamadas contengan el compuesto oxaliplatino a cambio del ciasplatin, no da evidencia de un efecto tØcnico inesperado.

El Problema TŁcnico Objetivo era "cómo obtener composiciones coma alternativa, a las ya existentes en Dl".

D2 (W02004006906), describe una manera de solucionar el problema tØcnico, mediante composiciones farmacØuticas, que sirven para el cancer (folio 168, pg2 lIneas 1-4; folio 171, pg 10; folio 173, pg 32 Uneas 13-15) y ademÆs logran disminuir la toxicidad de los antiproliferativos ( reivindicación 25), que incluyen: un compuesto de formula (I), que actüan como agente antiproliferativo
- agentes antiproliferativos: como agentes de platino (Oxaliplatino, folio 166), un inhibidor de tirosina quinasa (inhibidor de EGFR, erlotinib, folio 170).
- un vehiculo (folio 173).

AdemÆs, en ausencia de un ejemplo de una composiciOn que contenga los dos
principios activos (Erlotinib y Oxaliplatino) y concentraciones especIficas, que
mediante un ensayos muestren claramente un efecto tØcnico inesperado, como
una posible sinergia; se concluye por lo tanto que, la presente reivindicación, es
obvia, porque el Experto en la Materia enfrentado al problema de ’cOmo obtener
$ composiciones como alternativa, a las ya existentes en Dl", incluiria el Oxaliplatino, que se revela en D2, dentro de las composiciones que se enseæan
en Dl, log rando de esta forma la composición objeto de esta solicitud.

Par lo tanto las reivindicaciones 1 y sus dependientes 2-4, 1920, 22-24.

La reivindicaciOn 5, reclama un mØtodo de elaboración de un medicamento
caracterIzado porque se utilizan un inhibidor de la quinasa de EGFR y
Oxaliplatino. Dicha reivindicaciOn no esta caracterizada por las etapas y condiciones y solo menciona los componentes que se utilizan en dicho mØtodo.

Los documentos Dl y D2 que se refieren a composiciones anticancergenas, muestran los principios activos mediante los cuales estâ caracterizado el mØtodo de elaboraciôn, por lo tanto la presente reivindicaciôn, no tiene nivel inventivo, asI como las reivindicaciones 6-18 y 21, que reclaman un mØtodo de elaboraciÆnde un medicamento, de acuerdo con la reivindicaciôn 5, que no agregan ninguna caracteristica esencial de un mOtodo de elaboración de un medicamento.

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6. Conclusion:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados asi:

No Documento NO
Reivindicaciones Requisito que afecta afectadas
Dl W02004019857
D2 W02004006906

1-24 - j_ Nivel inventivo
1-24 Nivel inventivo

En cumplimiento del artIculo 45 de la Decision 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del tØrmino de sesenta dias contados a partir de la fecha de notificaciOn de la presente comunicaciOn. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la coricesiôn, se denegarÆla patente.

Notifiquese el presente oficio conforme a 10 dispuesto en el numeral 5.2, literal e), del capitulo quinto detuIo ppde la Circular Cjnica NO 10 de 2001.

ALIX CARMENZA’CE PEDES DE VERGEL
Directora de Nuevas Creaciones (C)

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El anterior requerimiento fue notificado por fijaciôn en lista, de fecha

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