(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 July 2010 (22.07.2010)

PCT

(10) International Publication Number
WO 2010/081778 A1

(51) International Patent Classification:
A61K 31/00 (2006.01) *A61K 31/502* (2006.01)
A61K 31/166 (2006.01) *A61K 31/55* (2006.01)
A61K 31/366 (2006.01) *G01N 33/50* (2006.01)
A61K 31/4184 (2006.01) *A61P 35/00* (2006.01)
A61K 31/473 (2006.01)

(21) International Application Number:
PCT/EP2010/050194

(22) International Filing Date:
11 January 2010 (11.01.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09000636.2 17 January 2009 (17.01.2009) EP

(71) Applicant *(for all designated States except US)*: **UNIVERSITÄT ZÜRICH** [CH/CH]; Prorektorat MNW, Rämistrasse 71, CH-8006 Zürich (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **HOTTIGER, Michael O.** [CH/CH]; Storeneichweg 2, CH-8606 Nänikon (CH). **MÜLLER, Anne** [DE/CH]; Bürglistrasse 16, CH-8600 Dübendorf (CH). **ALTMEYER, Matthias** [DE/CH]; Bucheggstrasse 169, CH-8057 Zürich (CH). **TOLLER, Isabella** [CH/CH]; Thurwiesenstrasse 15, CH-8037 Zürich (CH).

(74) Agent: **SCHMAUDER & PARTNER AG**; Zwängiweg 7, CH-8038 Zürich (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2010/081778 A1

(54) Title: BLOCKERS OF PARP FOR THE PREVENTION AND TREATMENT OF HELICOBACTER PYLORI INDUCED GASTRIC CANCER

(57) Abstract: This invention relates to the prevention and treatment of Helicobacter pylori induced gastric cancer comprising administering a blocker of Poly (ADP-ribose) Polymerase (PARP), and the use of such blockers in said prevention and treatment and in the manufacture of medicaments for preventing and treating Helicobacter pylori induced gastric cancer.

Blockers of PARP for the prevention and treatment of Helicobacter pylori induced gastric cancer

Field of the invention

This invention relates to the prevention and treatment of Helicobacter pylori induced gastric cancer using blockers of Poly (ADP-ribose) Polymerase (PARP).

Background of the invention

Poly(ADP-ribose) polymerases (PARPs) synthesize poly(ADP-ribose) (PAR) using nicotinamide adenine dinucleotide (NAD) as a substrate. PARP1 was the first protein described to catalyze PAR formation. During the last 10 years, more than 17 novel PARP-like genes were cloned or described based on thorough searches of non-redundant databases, with overlapping functional consequences.

Since the early benzamide inhibitors of the 1980s PARP inhibitors, novel compounds have been developed through structure-activity relationships and crystal structure-based drug design, that are 1,000 x more potent. These novel PARP inhibitors have been shown to enhance the antitumour activity of temozolomide (a DNA-methylating agent), topoisomerase poisons and ionising radiation in advanced pre-clinical studies. There are currently at least five PARP inhibitors in clinical trial development. Recent in vitro and in vivo evidence suggests that PARP inhibitors could be used not only as chemo/radiotherapy sensitizers, but as single agents to selectively kill cancers defective in DNA repair, specifically cancers with mutations in the breast cancer associated (BRCA) 1 and 2 genes.

The specific use of PARP blockers in the prevention and treatment of Helicobacter pylori induced gastric cancer has not been investigated yet.

Summary of the invention

The present invention relates to a method of preventing and treating Helicobacter pylori induced gastric cancer comprising administering a PARP blocker, and the use of such blockers in said prevention and treatment and in the manufacture of medicaments for preventing and treating Helicobacter pylori induced gastric cancer.

The invention further relates to a method of screening for a compound effective in the prevention and treatment of Helicobacter pylori induced gastric cancer comprising contacting a candidate compound with a PARP, and choosing candidate compounds which selectively reduce the activity of PARP. The invention further relates to compounds selected by these methods of screening.

Brief description of the Figures

Fig. 1: Inhibition of Helicobacter*-induced gastric preneoplastic changes by oral administration of the PARP inhibitor PJ34.*
Interleukin-10-deficient mice were infected for 4 weeks with *Helicobacter felis*, and treated with the PARP inhibitor PJ34 (30mg/kg per day, administered in the drinking water) for either the last 2 or all 4 weeks of the experiment (5 mice in each group) or left untreated (5 mice). Gastric paraffin sections were Giemsa-stained (representative fields are shown in A) and scored with respect to the degree of chronic inflammation as well as the development of atrophy, intestinal metaplasia and compensatory pit cell hyperplasia (B). The quantitative assessment of these four parameters is shown on a scale of 0-6 for all 15 animals included in the study. The median of every group is indicated by a bar. The significance analysis was done using the Mann-Whitney test.

Fig. 2: Reversal of Helicobacter*-induced gastric preneoplastic changes by oral administration of the PARP inhibitor PJ34.*
CD4$^{-/-}$ mice were infected for 4 months with *Helicobacter felis*, and treated with the PARP inhibitor PJ34 (30mg/kg per day, administered in the drinking water) for the last 4 weeks of the experiment (5 mice per group) or were left untreated (8 mice). Three additional mice remained uninfected and either received PJ34 for the last 4 weeks or not. Giemsa-stained sections from every stomach were processed and the data are displayed as described for Figure 1. Representative sections are shown in A, and a comprehensive quantitative histopathological analysis is given in B.

Fig. 3: Stable reversal of Helicobacter*-induced gastric preneoplastic changes by oral administration of the PARP inhibitor PJ34 in combination with antibiotic eradication therapy.*
Myd88$^{-/-}$ mice were infected for 3 months with *Helicobacter felis*, and were either treated with the PARP inhibitor PJ34 (30mg/kg per day, administered in the drinking water) for the

second month of the experiment (5 mice per group) or were left untreated (6 mice). Five additional mice further received eradication therapy targeting the infection during weeks 5 and 6 of the experiment. This treatment consisted of metronidazole and tetracycline along with bismuth, and its efficacy was confirmed in a separate independent group (not shown) just after the end of the treatment. Two mice received only the eradication therapy, and no PJ34. Giemsa-stained sections from every stomach were processed and the data are displayed as described for Figure 1. Representative sections are shown in A, and a comprehensive quantitative histopathological analysis is given in B.

Detailed description of the invention

The present invention relates to a method of preventing and treating Helicobacter pylori induced gastric cancer comprising administering a PARP blocker, and the use of such blockers in said prevention and treatment and in the manufacture of medicaments for preventing and treating Helicobacter pylori induced gastric cancer.

The present invention is particularly useful for the prevention of Helicobacter pylori induced gastric cancer, because the administration of a PARP blocker inhibits the formation and leads to the regression of infection-induced gastric preneoplastic lesions, such as atrophy, epithelial hyperplasia, and intestinal metaplasia.

PARP blockers are compounds which reduce the enzyme activity of PARPs, e.g. PAR formation by PARP-1, PARP-2 and with reduced sensitivity also PARP10 or inhibit the production, expression or protein stability of PARP or the activation of PARP from its latent form (e.g. intramolecular domain interactions or inhibition of dimer formation), or inhibit binding of PARP to DNA.

For example, compounds which inhibit PARP enzyme activity bind to a DNA binding site of PARP or bind to a catalytic domain of PARP. PARP production can be inhibited by anti-sense oligodeoxynucleotides, siRNAs or shRNAs to the different PARP isoforms.

Gene therapy can make use of vectors harboring cDNA, which encode for proteins encoding for PARP or for genes involved in the activation or inactivation of PARP.

PARP blockers of the invention may belong to the class of inorganic compounds or organic compounds, and are e.g. polypeptides or small organic compounds, preferably

derived from templates for the design of novel PARP inhibitors as described in P. Jagtap and C. Szabo, Poly(ADP-Ribose) Polymerase and the therapeutic effect of its inhibitors, Nature Reviews 4, May 2005, 421-440.

PARP blockers are widely known. PARP blockers are, for example, disclosed in P. Jagtap and C. Szabo, Poly(ADP-Ribose) Polymerase and the therapeutic effect of its inhibitors, Nature Reviews 4, May 2005, 421-440 and in Patent Applications WO 05/097750, WO 05/123687, WO 2006/039545, WO 06/003146, WO 06/003148, and WO 06/003150, which are incorporated herewith by reference. However, the invention is not restricted to the PARP blockers disclosed therein, but extends to all PARP blockers.

Preferred PARP blockers according to the invention are (e.g. disclosed in P. Jagtap and C. Szabo, Poly(ADP-Ribose) Polymerase and the therapeutic effect of its inhibitors, Nature Reviews 4, May 2005, 421-440):

- GPI-6150 (Guilford)
- the phenanthridionone derivative PJ-34 (Inotek)
- 2,8 disubstituted quinazolin-4(3H)-one derivative (Fujisawa)
- the phthalazinone-based ONO-1924H, ONO2231 (Ono Pharmaceutical Co., Ltd.)
- thieno-phenanthridin-6-one, in which the thieno ring is attached to the isoquionlinone scaffold (GlaxoSmithKline)
- DR2313 (Meiji Seika Kaisha)
- compounds that contain aza-5[H]-phenanthridin-6-one and partially saturated aza-5 [H] phenanthridin 6-one scaffolds (Guilford)
- tricyclic lactam inhibitors AG140361 and AG140699 (Agouron/Pfizer)
- compounds using the tricyclic core of a PARP scaffold (Guilford; Farraris, D. et al., Bioorg. Med. Chem. 11, 3695-3707, 2003)
- indoloquinazolinone derivatives (Novartis, US 01/99505)
- the 3-aminomethyl carbazole imide CEP-6800 (Cephalon)
- INO-1001, INO-1002 and INO-1003 (Inotek)
- ABT472 and ABT888 (Abott Laboratories)
- KU58948 (Kudos Pharmaceuticals)
- BGP15 (Allos Therapeutics)
- ANG2864 (Angion Biomedica Corp.)
- AZD2281 (AstraZeneca)
- BSI401, BSI201 and BSI101 (BiPar Sciences, Inc.)

- CEP9722 (Cephalon, Inc.)
- CPH101 and CPH 102 (Crimson Pharma)
- GPI21016 (MGI Pharma, Inc.)
- AntiPARP 1 and AntiPARP 2 (Octamer, Inc.)
- Antibodies that bind to PARP, antigen binding fragments of an antibody (e.g. Fab fragments) or antibody-like molecules (e.g. repeat proteins) which by binding to PARP block its action or block the formation of dimers
- Virus-like particles loaded with PARP and therefore inducing an antibody response directed against these molecules with the effect to block their biological activity
- Antisense molecules for downregulation of PARP. These antisense molecules are 12-50 nucleotides in length and encode a given sequence found in the exons or introns of PARP genes. Moreover, antisense molecules containing a sequence of the PARP gene promoters and binding within the promoter region may be used. Finally, antisense molecules binding in the 3' UTR –non translated regions of the PARP genes are contemplated

Most preferred PARP blockers according to the invention are:
- INO-1001, INO-1002 and INO-1003 (Inotek);
- AG140699 (Pfizer)
- ABT472 and ABT888 (Abott Laboratories)
- KU58948 (Kudos Pharmaceuticals)
- ANG2864 (Angion Biomedica Corp.)
- AZD2281 (AstraZeneca)
- BSI401, BSI201 and BSI101 (BiPar Sciences, Inc.)
- CEP9722 (Cephalon, Inc.)
- GPI21016 (MGI Pharma, Inc.)
- AntiPARP 1 and AntiPARP 2 (Octamer, Inc.)
- ONO2231 (Ono Pharmaceutical Co., Ltd.).

One aspect of the invention relates to a method of preventing and treating Helicobacter pylori induced gastric cancer comprising administering PARP blockers as defined hereinbefore in a quantity effective against Helicobacter pylori induced gastric cancer or the gastric pre-cancerous lesions to a mammal in need thereof, for example to a human requiring such treatment. The treatment may be for prophylactic or therapeutic purposes. For the administration, the PARP blocker is preferably in the form of a pharmaceutical preparation comprising the PARP blocker in chemically pure form and optionally a

pharmaceutically acceptable carrier and optionally adjuvants. The PARP blocker is used in an amount effective against Helicobacter pylori induced gastric cancer or the gastric pre-cancerous lesions. The dosage of the active ingredient depends upon the species, its age, weight, and individual condition, the individual pharmacokinetic data, the mode of administration, and whether the administration is for prophylactic or therapeutic purposes. In the case of an individual having a bodyweight of about 70 kg the daily dose administered is from approximately 0.1 mg to approximately 5000 mg, preferably from approximately 1 mg to approximately 1000 mg, of a PARP blocker.

Pharmaceutical compositions for enteral administration, such as nasal, buccal, rectal or, especially, oral administration, and for parenteral administration, such as subcutaneous, intravenous, intramuscular or injections into the cerebrospinal fluid (CSF) compartment are especially preferred. The pharmaceutical compositions comprise from approximately 1% to approximately 95% active ingredient, preferably from approximately 20% to approximately 90% active ingredient.

For parenteral administration preference is given to the use of solutions of the PARP blockers, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example, can be made up shortly before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, viscosity-increasing agents, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known *per se*, for example by means of conventional dissolving and lyophilizing processes.

For oral pharmaceutical preparations suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, and also binders, such as starches, cellulose derivatives and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, flow conditioners and lubricants, for example stearic acid or salts thereof and/or polyethylene glycol. Tablet cores can be provided with suitable, optionally enteric, coatings. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient. Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The capsules

may contain the active ingredient in the form of granules, or dissolved or suspended in suitable liquid excipients, such as in oils.

Transdermal application is also considered, for example using a transdermal patch, which allows administration over an extended period of time, e.g. from one to twenty days.

Another aspect of the invention relates to the use of PARP blockers as described hereinbefore in the prevention and treatment of Helicobacter pylori induced gastric cancer and in the manufacture of medicaments for the preventing or treating these diseases. Such medicaments are manufactured by methods known in the art, especially by conventional mixing, coating, granulating, dissolving or lyophilizing.

The PARP blocker can be administered alone or in combination with one or more other therapeutic agents, possible combination therapy taking the form of fixed combinations of a PARP blocker and one or more other therapeutic agents known in the prevention or treatment of Helicobacter pylori induced gastric cancer, the administration being staggered or given independently of one another, or being in the form of a fixed combination.

Possible combination partners considered are compounds effective against Helicobacter pylori infections, for example proton pump inhibitors and antibiotics.

The invention further relates to a method of screening for a compound effective in the prevention or treatment of Helicobacter pylori induced gastric cancer comprising contacting a candidate compound with a PARP and choosing candidate compounds which selectively reduce the activity of PARP. The invention further relates to compounds selected by these methods of screening.

Inhibitors of PARP activity are identified by contacting a PARP with a candidate compound. A control assay with the corresponding PARP – in the absence of the candidate compound – is run in parallel. A decrease in activity in the presence of the candidate compound compared to the level in the absence of the compound indicates that the compound is a PARP inhibitor.

Screening systems to be used for identification of candidate compounds comprise the following: To measure PAR formation, different PARPs can be incubated for different time

periods with 400 µM tritium labeled NAD and the reaction products are precipitated by TCA before they are analyzed using a beta-counter. Increasing PAR levels synthesized by PARPs can also be detected in a time- and DNA-dependent manner by western blot and vacuum slot blot using anti-PARPs or anti-PAR (e.g. LP96-10) antibodies. PAR formation can alternatively be detected by a pronounced shift of the coomassie-blue stained proteins in the denaturing gel due to a severly reduced migration velocity of the modified proteins when compared to unmodified. Finally, analysis of PAR formation can be verified by silver staining after separation of PAR products with a modified DNA sequencing gel electrophoresis.

Concepts and Evidence behind the Invention

The findings in three different preclinical models of *Helicobacter*-infection induced gastric cancer indicate that (1) oral administration of a PARP inhibitor (e.g. PJ34, 30 mg/kg body weight daily dose, dissolved in the drinking water) efficiently blocks the formation of preneoplastic lesions such as atrophic gastritis, epithelial hyperplasia and intestinal metaplasia. (2) The same treatment further leads to the regression of pre-existing lesions, a finding particularly promising as other treatments for these conditions are currently not available. (3) PARP inhibition induces stable regression of preneoplastic lesions (well beyond the end of therapy) if applied together with antibiotic eradication therapy targeting the *Helicobacter* infection.

Examples

1. PARP inhibition blocks the formation of Helicobacter-induced gastric preneoplastic lesions.

The C57Bl6 mouse represents an excellent model for studying gastric preneoplasia. Wild type mice of this background that are infected with the close *H. pylori* relative *H. felis* develop precancerous lesions within 2-3 months of infection. The process is accelerated further in C57Bl6 mice lacking the anti-inflammatory cytokine IL-10. These mice are characterized by an excessive, uncontrolled inflammatory and adaptive immune response to the infection. In this strain, atrophic, hyperplastic lesions appear as early as 2-3 weeks post infection. It was chosen to assess the effects of PARP inhibition in this model because it is fast, reproducible and consistent. Administration of the PARP inhibitor PJ34 at a daily dose of 30 mg/kg body weight in the drinking water efficiently blocked symptoms of chronic inflammation, epithelial atrophy and hyperplasia (Figure 1A and B). The

histopathological parameters were assessed in a quantitative fashion for every mouse (Figure 1B). We used the updated Sydney System for the classification and grading of gastritis initially published by Dixon et al. (1996), which remains the universally used method of histopathological classification of gastric specimens to date. While chronic inflammation was clearly reduced in PJ34 treated mice, the most significant effect was observed with regard to epithelial transformation (atrophy and hyperplasia). Interestingly, it made little difference in this scenario whether the inhibitor was applied for the entire duration of the experiment, or only during the last 2 of the 4 weeks of infection. The inhibitor had no effect on bacterial colonization (data not shown).

2. PARP inhibition reverses the formation of Helicobacter-induced gastric preneoplastic lesions.

Based on the results obtained in the IL-$10^{-/-}$ model, it was speculated that PARP inhibition might be effective not only in preventing the formation of preneoplastic lesions, but might even reverse pre-existing lesions. To investigate this possibility, a C57Bl6 strain that lacks $CD4^+$ T-cells due to deletion of the *cd4* gene was used. This strain develops preneoplastic lesions with similar kinetics as wild type mice, but with higher uniformity (for unknown reasons, the responses of wild type mice vary even among very closely related individuals; wild type mice are therefore less suitable for pharmacological studies). For the "reversal" study shown in Figure 2, a total of 19 mice were either infected for 4 months, or were infected and treated with the PJ34 compound (at 30 mg/kg daily dose) for the last month of infection or remained uninfected with or without the compound. An additional infected control group was sacrificed after 3 months (just before the beginning of the PJ34 treatment of the respective study group), which confirmed the formation of preneoplastic lesions at this time (data not shown). As expected, the infected group that had not received PJ34 showed a high degree of pathology, with atrophic gastritis, hyperplasia and metaplasia readily detectable in all mice (Figure 2A and B). In contrast, the group that had been treated with PJ34 for the last month of the experiment had significantly reduced epithelial changes, with only minor if any symptoms of hyperplasia and metaplasia. In contrast, histopathological symptoms of chronic inflammation were only marginally reduced due to the treatment. The inhibitor treatment alone had no effects on the morphology of the stomachs in a control group (Figure 2A and B), and the inhibitor did not affect bacterial colonization.

3. PARP inhibition-induced reversal of preneoplastic lesions is stable after termination of the treatment, but only if Helicobacter is eradicated concomitantly.

To assess whether reversal of pre-existing lesions would also be achieved in yet another genetic background of C57Bl6 mice, and whether the reversal would be stable upon termination of the treatment, Myd88$^{-/-}$ mice were infected, which harbor a deletion of the innate immune adaptor gene *myd88*. Mice of this genotype are much more susceptible to *Helicobacter*-induced preneoplasia than wild type mice, and predominantly develop metaplasia, which is considered the more advanced lesion as compared to atrophy or epithelial hyperplasia. Infection of Myd88$^{-/-}$ mice typically results in complete atrophy and consistent development of metaplasia in all mice infected for more than 1 month. For the study shown in Figure 3, groups of mice were infected for 3 months (8 mice), or were infected and received PJ34 treatment for the second of the 3 months (8 mice). To verify the proper formation of lesions in the infected group, and the successful reversal of lesions in the PJ34-treated group, a small subset of each group (2 and 3 mice, respectively) was sacrificed just after the termination of PJ34 treatment at 2 months post infection. These groups showed that, indeed, metaplasia involving the entire corpus of the stomach was the dominant lesion in the infected group and that this lesion was completely absent in the PJ34 treated group. The data suggests that PJ34 induces reversal of preneoplasia also in this background. The remaining mice were maintained for another month without PJ34. An additional group of 5 mice, which had received the PJ34 treatment along with the other mice, was further treated with two antibiotics (metronidazone and tetracycline) along with bismuth for a two week regimen in weeks 5 and 6 (overlapping with parts of the PJ34 treatment). This group, as well as a small group of mice that received only antibiotics, but no PJ34, were analyzed with all other mice at 3 months post infection. The result of this extensive study was as follows (Figure 3A and B): whereas the treatment with PJ34 successfully induced regression of the lesions also in this background (see above), this reversal was not stable unless the mice were simultaneously cleared of their infection. Mice that had received the inhibitor and were cleared of their infection were completely asymptomatic even one month after the end of PARP inhibition. In contrast, the group that had received the inhibitor but still harbored the bacteria for a month without receiving PJ34 had significantly less metaplasia, but all other scores were similar to those of infected controls. From this result, it was concluded that PARP inhibition efficiently induces regression of preneoplastic lesions, but should be administered together with eradication therapy to avoid relapse. Continued presence of the bacteria will reactivate those elements of the immune system that cause epithelial transformation, and this will lead to rapid recurrence of preneoplastic lesions after the end of PARP inhibition.

Claims

1. A blocker of Poly(ADP-ribose) polymerase (PARP) for use in the prevention and treatment of Helicobacter pylori induced gastric cancer.

2. A blocker according to claim 1 which is a compound selected from the group consisting of INO-1001, INO-1002, INO-1003, AG140699, ABT472, ABT888, KU58948, ANG2864, AZD2281, BSI401, BSI201, BSI101, CEP9722, GPI21016, AntiPARP1, AntiPARP2 and ONO2231.

3. A blocker according to anyone of claims 1 to 2 for use in the prevention and treatment of Helicobacter pylori induced gastric cancer.

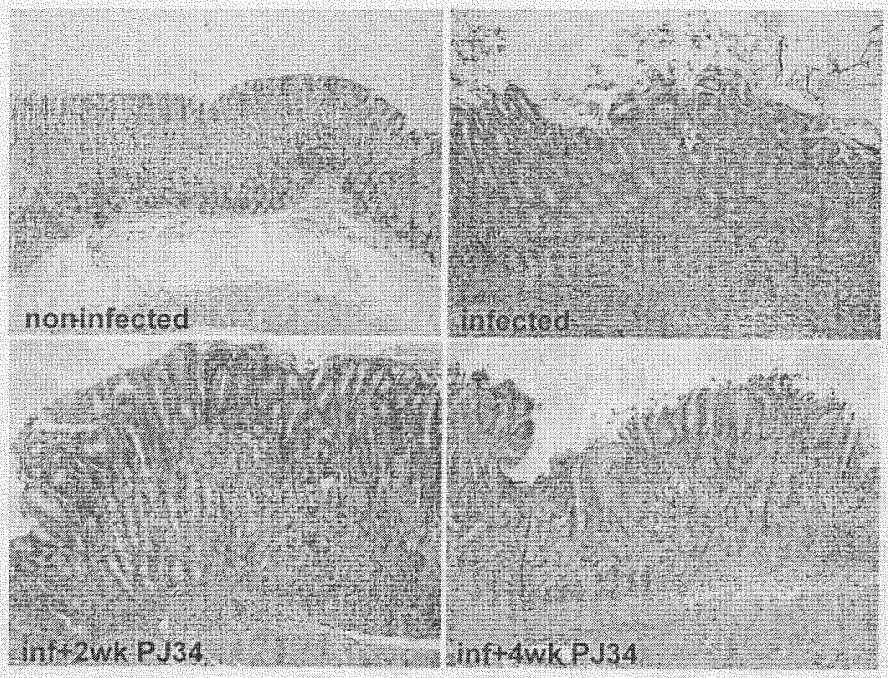
4. A method of screening for a compound effective in the prevention and treatment of Helicobacter pylori induced gastric cancer, comprising contacting a candidate compound with PARP and choosing candidate compounds which selectively reduce activity of PARP.

5. A compound selected according to the method of claim 4.

6. A method of preventing and treating Helicobacter pylori induced gastric cancer, comprising administering blockers of PARP in a quantity effective against Helicobacter pylori induced gastric cancer to a mammal in need thereof.

Fig. 1

A


non-infected
infected
inf+2wk PJ34
inf+4wk PJ34

B

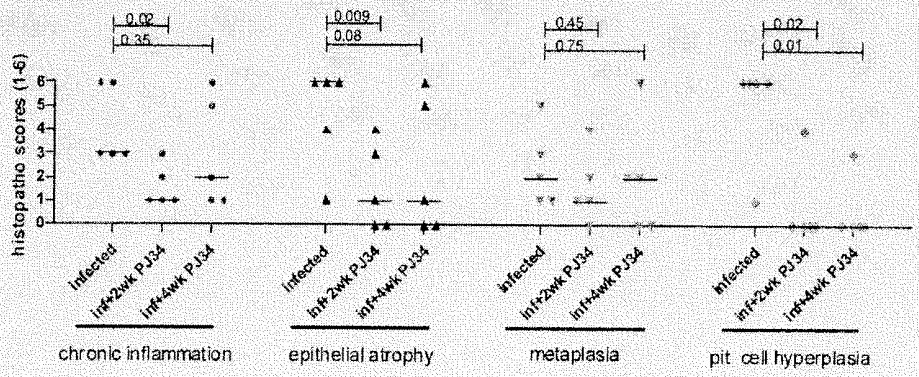

histopatho scores (1-6)
0
1
2
3
4
5
6
0.02
0.35
0.009
0.08
0.45
0.75
0.02
0.01
infected
inf+2wk PJ34
inf+4wk PJ34
chronic inflammation
epithelial atrophy
metaplasia
pit cell hyperplasia

Fig. 2

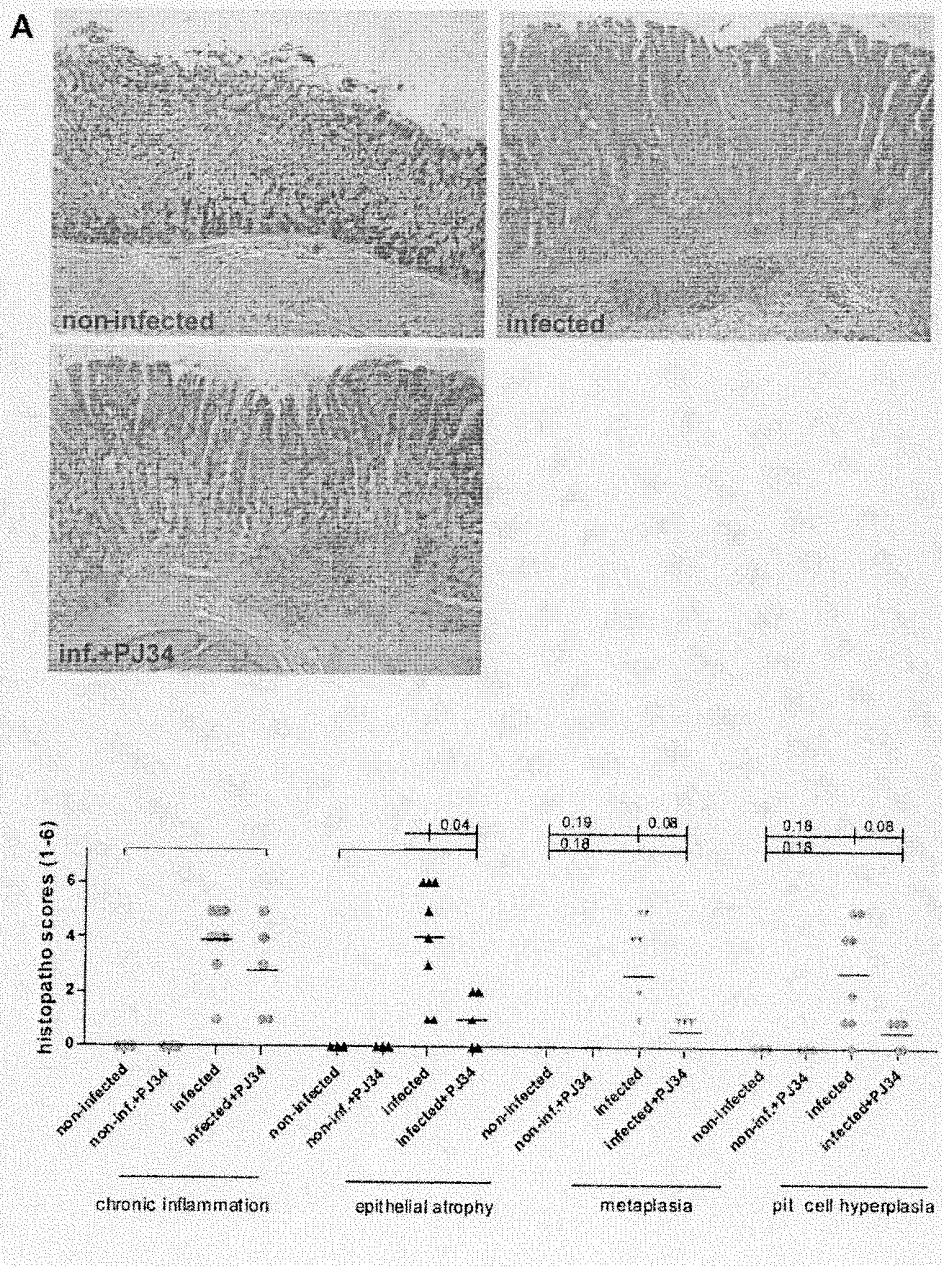
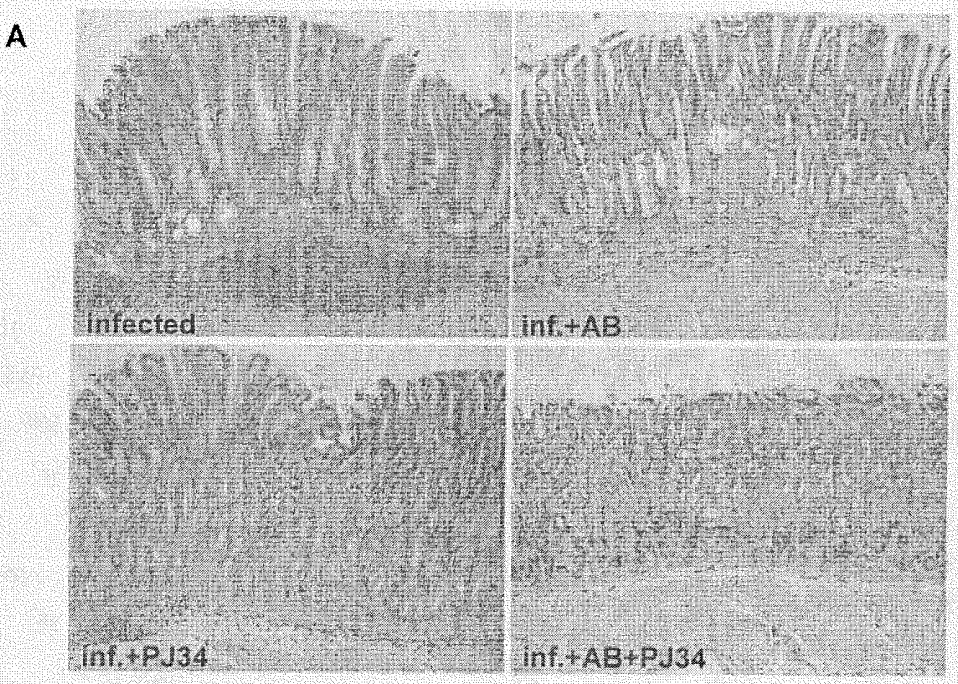
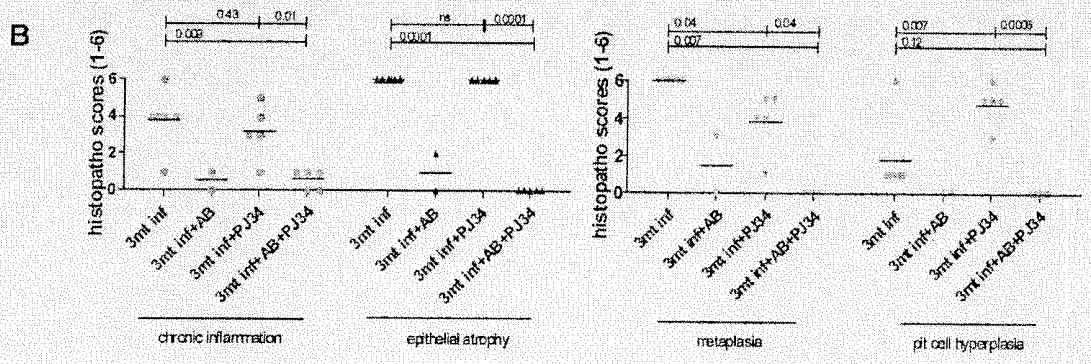

A
non-infected
infected
inf.+PJ34
B
histopatho scores (1-6)
0
2
4
6
0.04
0.19
0.18
0.08
0.18
0.18
0.08
non-infected
non-inf.+PJ34
infected
infected+PJ34
chronic inflammation
epithelial atrophy
metaplasia
pit cell hyperplasia

Fig. 3


A
infected
inf.+AB
inf.+PJ34
inf.+AB+PJ34


B
histopatho scores (1-6)
0.43
0.01
0.009
ns
0.0001
0.0001
0.04
0.04
0.007
0.007
0.0005
0.12
3mt inf
3mt inf+AB
3mt inf+PJ34
3mt inf+AB+PJ34
chronic inflammation
epithelial atrophy
metaplasia
pit cell hyperplasia

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/050194

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/00 A61K31/166 A61K31/366 A61K31/4184 A61K31/473
A61K31/502 A61K31/55 G01N33/50 A61P35/00

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)
A61K G01N

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 practical, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/90077 A1 (GUILFORD PHARM INC [US]; LI JIA HE [US]; KALISH VINCENT J [US]; ZHANG) 29 November 2001 (2001-11-29) compound 7 page 64, lines 17-30 page 69, line 27 - page 70, line 2 claims 9,12	1,3-6
X	US 6 514 983 B1 (LI JIA-HE [US] ET AL) 4 February 2003 (2003-02-04) column 34, line 35 column 39, lines 45-64 claim 16; examples 3,11	1,3-6

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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 document but 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	Date of mailing of the international search report
26 March 2010	15/04/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Gradassi, Giulia

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/033006 A2 (PFIZER [US]; CANCER REC TECH LTD [GB]; STEINFELDT HEIDI MARIE [US]; BO) 30 March 2006 (2006-03-30) page 29, line 36 - page 31, line 28; claims 13-16	1-6
X	WO 2008/146035 A1 (ASTRAZENECA AB [SE]; ASTRAZENECA UK LTD [GB]; O'CONNOR MARK JAMES [GB]) 4 December 2008 (2008-12-04) page 3, lines 1-13 compound 168 claim 9; examples	1-3,5-6
X	US 2007/015837 A1 (KUN ERNEST [US] ET AL KUN ERNEST [US] ET AL) 18 January 2007 (2007-01-18) paragraph [0144]; claim 7	1-3,5-6
X	WO 2008/020180 A2 (KUDOS PHARM LTD [GB]; CANCER RES INST [GB]; ASHWORTH ALAN [GB]; LORD C) 21 February 2008 (2008-02-21) page 9, line 32 - page 10, line 6 page 23, line 24 - page 24, line 12 claims	1-6
X	ALANO C C ET AL: "Minocycline inhibits poly(ADP-ribose) polymerase-1 at nanomolar concentrations" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA 20060620 US, vol. 103, no. 25, 20 June 2006 (2006-06-20), pages 9685-9690, XP002575409 ISSN: 0027-8424 figures 3, 4B page 9686, right-hand column, paragraph 1 page 9688, right-hand column, paragraph 2	4-5
X	US 2007/021508 A1 (YEN RONG-LANG [TW] ET AL) 25 January 2007 (2007-01-25) paragraphs [0002], [0007], [0008], [0010], [0014], [0024], [0025], [0029]; claims 1,13,14	1,3,5-6
X	US 2008/176261 A1 (NOTTBOHM AMANDA C [US] ET AL) 24 July 2008 (2008-07-24) paragraph [0044]; claims 10-11	4-5
X,P	WO 2009/051815 A1 (BIPAR SCIENCES INC [US]; OSSOVSKAYA VALERIA [US]; SHERMAN BARRY [US]) 23 April 2009 (2009-04-23) page 49, line 11 - page 55, line 40 page 68, line 40 - page 69, line 17 claims 217-224	1-6

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/050194

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2009/114459 A2 (TRUSTEES OF THE UNIVERSITY OF [US]; O'MALLEY BERT W [US]; ABUZEID WALE) 17 September 2009 (2009-09-17) page 12, lines 12-16; claims	1-6
A	CAI L ET AL: "Helicobacter pylori infection and risk of gastric cancer in Changle County, Fujian Province, China" WORLD JOURNAL OF GASTROENTEROLOGY 200006 CN, vol. 6, no. 3, June 2000 (2000-06), pages 374-376, XP002575410 ISSN: 1007-9327 the whole document	1-6
A	"Stomach Cancer" In: Beers M. H.: "The Merck Manual 18th Edition" 2006, Merck Research Laboratories , Whitehouse Station, NJ , XP002575411 , pages 171-172 the whole document	1-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2010/050194

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0190077 A1	29-11-2001	AU 6459501 A	03-12-2001
US 6514983 B1	04-02-2003	NONE	
WO 2006033006 A2	30-03-2006	AR 051099 A1	20-12-2006
		AU 2005286190 A1	30-03-2006
		BR PI0515567 A	29-07-2008
		CA 2581200 A1	30-03-2006
		EP 1793830 A2	13-06-2007
		JP 2008513435 T	01-05-2008
		KR 20070046183 A	02-05-2007
		KR 20090130156 A	17-12-2009
		RU 2361592 C2	20-07-2009
WO 2008146035 A1	04-12-2008	AU 2008256562 A1	04-12-2008
		CA 2687786 A1	04-12-2008
US 2007015837 A1	18-01-2007	US 2008319054 A1	25-12-2008
WO 2008020180 A2	21-02-2008	NONE	
US 2007021508 A1	25-01-2007	NONE	
US 2008176261 A1	24-07-2008	NONE	
WO 2009051815 A1	23-04-2009	US 2009149417 A1	11-06-2009
WO 2009114459 A2	17-09-2009	NONE	