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(54) **Title:** TREATING INFLAMMATORY BOWEL DISEASE OR CHRONIC PANCREATITIS

(57) **Abstract:** Methods are provided for treating an individual with inflammatory bowel disease and/or chronic pancreatitis by ad-
ministering an effective amount of Fuzheng Huayu (FZHY).



TREATING INFLAMMATORY BOWEL DISEASE OR CHRONIC PANCREATITIS

BACKGROUND

[0001] Inflammatory bowel disease (IBD) is an increasingly common inflammatory disorder of the gastrointestinal tract, with symptoms including weight loss, watery diarrhea, rectal bleeding, abdominal cramps, abdominal pain, and fever. IBD affects both children and adults, and according to the Mayo Clinic, more than 1.5 million Americans have Crohn's disease or ulcerative colitis, the most common forms of inflammatory bowel disease. IBD may at times begin clinically with a more benign or milder presentation, resembling Irritable Bowel Syndrome (IBS) but can subsequently progress with increasing inflammation, which is distinct from IBS. The precise cause of IBD remains unknown. In some cases, IBD requires surgical intervention.

[0002] IBD is difficult to treat effectively, and treatment of IBD is varied. Treatment typically includes salicylate derivatives (e.g. 5-ASA) given orally or rectally, and/or corticosteroids, despite known problematic side-effects.

[0003] Chronic pancreatitis is commonly defined as a continuing, chronic, inflammatory process of the pancreas, characterized by irreversible morphologic changes. This chronic inflammation can lead to chronic abdominal pain and/or impairment of endocrine and exocrine function of the pancreas. Chronic pancreatitis usually is envisioned as an atrophic fibrotic gland with dilated ducts and calcifications. However, findings on conventional diagnostic studies may be normal in the early stages of chronic pancreatitis, as the inflammatory changes can be seen only by histologic examination. Based on estimates from hospital discharge data in the United States, approximately 87,000 cases of pancreatitis occur annually. Roughly half of the patients with chronic pancreatitis eventually require surgical intervention, which is indicated when an anatomical complication (e.g., pancreatic pseudocyst, abscess, fistula, ascites, fixed obstruction of the intrapancreatic portion of the distal common bile duct, stenosis of the duodenum with gastric outlet obstruction) that is correctable by a mechanical intervention exists.

[0004] There remains an unmet need in the art for improved methods for treating Inflammatory Bowel Disease and chronic pancreatitis.

[0005] Publications of interest include Xie et al. (2013) Evidence-Based Complementary and Alternative Medicine, Article ID 972863, entitled "Proteomic Analysis of the Effect of Fuzheng Huayu Recipe on Fibrotic Liver in Rats"; Liu et al. (2009) Chinese Medicine 4:12, entitled "Effect of *Fuzheng Huayu* formula and its actions against liver fibrosis".

[0006] Patent publications include CN101612205, entitled "Traditional Chinese medicine for treating ulcerative colitis"; US20130101553, entitled "Inducing inaction of fibrogenic myofibroblasts"; and

US20100285053 entitled "Immunosuppressive extract of *Cordyceps sinensis* and uses thereof".

SUMMARY

- [0007] Methods are provided for treating an individual with Inflammatory Bowel Disease (IBD) or chronic pancreatitis comprising administering an effective amount of Fuzheng Huayu (FZHY) to an individual. Methods are also provided for reducing IBD-associated complications such as weight loss, comprising administering an effective amount of FZHY to an individual with IBD. The symptoms relieved by the provided methods include weight loss, colon shortening, soft/loose stool (e.g., diarrhea, watery diarrhea, etc.), rectal bleeding (e.g., bloody stool), abdominal cramps, abdominal pain, vomiting, acute right lower quadrant pain, malaise, fatigue, fever, and/or anemia.
- [0008] Without being bound by theory, it is believed that most available agents for inflammatory bowel disease (IBD) target acute inflammatory responses, whereas FZHY can target the chronic inflammatory responses that are key to IBD pathogenesis.
- [0009] In some embodiments, FZHY is administered in combination with at least one other anti-IBD or gastrointestinal agent. Suitable anti-IBD agents for combination therapy with FZHY include: 5-aminosalicylic acid (5-ASA); 5-ASA derivatives (e.g., sulfasalazine, mesalamine, balsalazide, olsalazine); antibiotics (e.g., metronidazole, ciprofloxacin, rifaximin); corticosteroids (e.g., hydrocortisone, prednisone, methylprednisolone, prednisolone, entocort (budesonide), dexamethasone); immunosuppressants (e.g., azathioprine, 6-mercaptopurine, methotrexate, cyclosporine); DMARDs, TNF Inhibitors (e.g., infliximab, adalimumab, certolizumab pegol); monoclonal antibodies (e.g., natalizumab, ustekinumab); histamine h2 antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine); proton pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole magnesium, rabeprazole sodium, pantoprazole); antidiarrheals (e.g., diphenoxylate and atropine, loperamide, cholestyramine); anticholinergic, antispasmodic agents (e.g., dicyclomine, hyoscyamine); and the like.
- [0010] In some embodiments, FZHY is administered in combination with at least one other anti-chronic pancreatitis agent. Suitable anti-chronic pancreatitis agents for combination therapy with FZHY include: analgesics (e.g., acetaminophen, hydrocodone and acetaminophen, tramadol); nonsteroidal anti-inflammatory drugs (e.g., naproxen, diclofenac, ketorolac, ibuprofen, celecoxib); hormones (e.g., octreotide); antidepressants (e.g., amitriptyline hydrochloride, clomipramine, doxepin, nortriptyline, desipramine); pancreatic enzyme supplements (e.g., pancrelipase); and the like.
- [0011] Embodiments of the invention include treating a mammalian individual, including without limitation dog, cat, pig, sheep, cow, horse, human, etc. Embodiments of the invention include treating an individual for IBD. In particular embodiments the methods are used in the

treatment of chronic IBD. In some embodiments, the methods are used in the treatment of ulcerative colitis, Crohn's disease, radiation colitis, chronic radiation colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behçet's disease, or indeterminate colitis.

BRIEF DESCRIPTION OF THE DRAWINGS

- [0012] Figure 1 demonstrates that FZHY reduces weight loss in mice with chronic colitis.
- [0013] Figure 2 demonstrates that FZHY reduces gross features of colitis (disease severity is associated with soft stool (diarrhea), bloody stool, shortened colon, and thickened colon). Depicted are the colons of control (water) and FZHY treated mice (treated via oral gavage).
- [0014] Figure 3 demonstrates that FZHY reduces shrinkage of the pancreas in an animal model of acute pancreatitis.

DETAILED DESCRIPTION

- [0015] The present disclosure relates to methods of treating an individual for Inflammatory Bowel Disease (IBD) and/or chronic pancreatitis by administering to the individual an effective amount of Fuzheng Huayu (FZHY), optionally combined with a second therapeutic agent.
- [0016] *Inflammatory Bowel Disease.* As used herein, the term “inflammatory bowel disease” or “IBD” refers to any of a variety of diseases characterized by inflammation of all or part of the intestines (e.g., colon and/or small intestine). Non-limiting examples of “IBD” include: Crohn's Disease, Ulcerative Colitis, radiation colitis, Collagenous colitis, Lymphocytic colitis, Ischaemic colitis, Diversion colitis, Behçet's disease, and Indeterminate colitis. While radiation colitis is a progressive form of colitis that begins after radiotherapy (e.g., to treat malignancy) in some patients, radiation colitis is considered herein to be a form of IBD. As will be understood by one of ordinary skill in the art, the two IBD types that account for the majority of IBD clinical cases are Crohn's Disease and Ulcerative Colitis. While IBD symptoms vary from patient to patient and some may be more common than others, the symptoms can include weight loss, colon thickening, soft/loose stool (e.g., diarrhea, watery diarrhea, etc.), rectal bleeding (e.g., bloody stool), abdominal cramps, abdominal pain, vomiting, acute right lower quadrant pain, malaise, fatigue, fever, and/or anemia.
- [0017] Different forms of IBD differ in the location and nature of the inflammatory changes. For example Crohn's disease can affect any part of the gastrointestinal tract, from mouth to anus, although a majority of the cases start in the terminal ileum. Crohn's disease can also affect the entire thickness of the bowel wall. In addition, in Crohn's disease, the inflammation of the intestine can “skip” leaving normal areas in between patches of diseased intestine (sometimes referred to as skip lesions). In more severe cases, Crohn's can lead to tears

(fissures) in the lining of the anus, which may cause pain and bleeding, especially during bowel movements. Inflammation may also cause a fistula to develop. In contrast, ulcerative colitis is restricted to the colon and the rectum. Microscopically, ulcerative colitis is restricted to the mucosa (epithelial lining of the gut), while Crohn's disease can affect the whole bowel wall ("transmural lesions"). In patients with ulcerative colitis, the lining of the colon can become inflamed and develop tiny open sores, or ulcers, that produce pus and mucous. The combination of inflammation and ulceration can cause abdominal discomfort and frequent emptying of the colon. Crohn's disease and ulcerative colitis can present with extra-intestinal manifestations (e.g., liver problems, arthritis, skin manifestations, eye problems, etc.). Rarely, a definitive diagnosis of neither Crohn's disease nor ulcerative colitis can be made because of idiosyncrasies in the presentation. In this case, a diagnosis of indeterminate colitis may be made.

[0018] IBD is associated with inflammation of the gastrointestinal tract, and encompasses acute and chronic inflammatory conditions. Acute inflammation is generally characterized by a short time of onset and infiltration or influx of neutrophils. Chronic inflammation is generally characterized by a relatively longer period of onset and infiltration or influx of mononuclear cells. Chronic inflammation can also typically characterized by periods of spontaneous remission and spontaneous occurrence. "Mucosal layer of the gastrointestinal tract" is meant to include mucosa of the bowel (including the small intestine and large intestine), rectum, stomach (gastric) lining, oral cavity, and the like.

[0019] "Chronic IBD" refers to IBD that is characterized by a relatively longer period of onset, is long-lasting (e.g., from several days, weeks, months, or years and up to the life of the subject), and is associated with infiltration or influx of mononuclear cells and can be further associated with periods of spontaneous remission and spontaneous occurrence. Thus, subjects with chronic IBD may be expected to require a long period of supervision, observation, or care.

[0020] In some embodiments of the invention, an individual is diagnosed with a chronic inflammatory disease of the bowels prior to administration of FZHY. In some embodiments a patient is diagnosed with ulcerative colitis. In other embodiments a patient is diagnosed with Crohn's disease.

[0021] Diagnosis is suggested by typical symptoms and signs, particularly when accompanied by extraintestinal manifestations or a history of previous similar attacks. UC should be distinguished from Crohn disease but more importantly from other causes of acute colitis (eg, infection; in elderly patients, ischemia). In all patients, stool cultures for enteric pathogens should be done, and *Entamoeba histolytica* should be excluded by examination of fresh stool specimens. Sigmoidoscopy allows visual confirmation of colitis and permits direct sampling of stool or mucus for culture and microscopic evaluation, as well as biopsy of affected areas.

Although visual inspection and biopsies may be nondiagnostic, because there is much overlap in appearance among different types of colitis, acute, self-limited, infectious colitis can usually be distinguished histologically from chronic idiopathic UC or Crohn colitis. Severe perianal disease, rectal sparing, absence of bleeding, and asymmetric or segmental involvement of the colon indicate Crohn disease rather than UC.

[0022] X-rays are not diagnostic but occasionally show abnormalities. Plain x-rays of the abdomen may show mucosal edema, loss of haustration, and absence of formed stool in the diseased bowel. Barium enema shows similar changes, albeit more clearly, and may also show ulcerations. A shortened, rigid colon with an atrophic or pseudopolypoid mucosa is often seen after several years of illness. X-ray findings of thumbprinting and segmental distribution are more suggestive of intestinal ischemia or possibly Crohn colitis rather than of UC.

[0023] Although Crohn disease and UC are similar, they can be distinguished in most cases.

Differential Diagnosis of Crohn's Disease and Ulcerative Colitis:

Crohn's Disease	Ulcerative Colitis
Small bowel is involved in 80% of cases.	Disease is confined to the colon.
Rectosigmoid is often spared; colonic involvement is usually right-sided.	Rectosigmoid is invariably involved; colonic involvement is usually left-sided.
Gross rectal bleeding is rare, except in 75–85% of cases of Crohn colitis.	Gross rectal bleeding is always present.
Fistula, mass, and abscess development is common.	Fistulas do not occur.
Perianal lesions are significant in 25–35% of cases. On x-ray, bowel wall is affected asymmetrically and segmentally, with skip areas between diseased segments.	Significant perianal lesions never occur. Bowel wall is affected symmetrically and uninterruptedly from rectum proximally.
Endoscopic appearance is patchy, with discrete ulcerations separated by segments of normal-appearing mucosa.	Inflammation is uniform and diffuse.
Microscopic inflammation and fissuring extend transmurally; lesions are often highly focal in distribution.	Inflammation is confined to mucosa except in severe cases.
Epithelioid (sarcoid-like) granulomas are detected in bowel wall or lymph nodes in 25–50% of cases (pathognomonic).	Typical epithelioid granulomas do not occur.

[0024] *Chronic Pancreatitis.* The term “chronic pancreatitis” is used herein as commonly defined: a continuing, chronic, inflammatory process of the pancreas, characterized by irreversible morphologic changes. This chronic inflammation can lead to chronic abdominal pain and/or impairment of endocrine and exocrine function of the pancreas. Chronic pancreatitis is usually seen as an atrophic fibrotic gland with dilated ducts and calcifications. However, findings on conventional diagnostic studies may be normal in the early stages of chronic pancreatitis, as the inflammatory changes can be seen only by histologic examination. Based on estimates from hospital discharge data in the United States, approximately 87,000 cases of pancreatitis occur annually. Roughly half of the patients with chronic pancreatitis eventually require surgical intervention, which is indicated when an anatomical complication

(e.g., pancreatic pseudocyst, abscess, fistula, ascites, fixed obstruction of the intrapancreatic portion of the distal common bile duct, stenosis of the duodenum with gastric outlet obstruction) that is correctable by a mechanical intervention exists.

[0025] *Fuzheng Huayu*. The inventors have discovered the Fuzheng Huayu (FZHY) can be used to treat IBD and/or chronic pancreatitis. FZHY is used as a traditional medicine in Asia for liver fibrosis. FZHY can be taken orally, and has a good safety profile relative to current therapies for IBD. The term "Fuzheng Huayu" or "FZHY" is known in the art and is used herein to mean a combination of six traditional Chinese drugs in the following proportions:

- (i) Radix Salviae Miltiorrhizae (dan shen) (4 parts);
- (ii) Cordyceps sinensis (chong cao)(Fermentation Mycelium Powder) (2 parts);
- (iii) Fructus Schisandrae Chinensis (wu wei zi)(1 part);
- (iv) Semen Persicae (peach kernel) (1 part);
- (v) Pollen Pini (song hua fen) (1 part); and
- (vi) Gynostemma Pentaphyllum (Jiaogulan) (3 parts)

For example see Liu et al, Chin Med. 2009 Jun 29;4:12: "Effect of Fuzheng Huayu formula and its actions against liver fibrosis," which is incorporated herein by reference in its entirety.

[0026] As described in more detail below, FZHY can be formulated in any convenient way. In some cases, FZHY is formulated as a capsule, for example as a unitary dose in a capsule containing from about 100 mg to about 2.5 g. FZHY, including for example 200 mg FZHY, 400 mg FZHY, 800 mg FZHY; 1 g FZHY, 1.5 g FZHY, 2 g FZHY, 2.5 g FZHY, etc.

[0027] The terms "treatment", "treating", "treat" and the like are used herein to generally refer to obtaining a desired pharmacologic and/or physiologic effect. The effect can be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. "Treatment" as used herein covers any treatment of inflammatory bowel or chronic pancreatitis disease in a mammal, particularly a human, and includes: (a) preventing the disease or symptom (e.g., weight loss; colon shortening; soft stool, e.g., diarrhea; bloody stool; abdominal pain; vomiting; rectal bleeding; internal cramps/muscle spasms in the region of the pelvis; and/or anemia) from occurring in a subject which may be predisposed to the disease or symptom but has not yet been diagnosed as having it; (b) reducing the progression of the disease symptom, i.e., arresting its development; or (c) relieving the disease symptom, i.e., causing regression of the disease or symptom.

[0028] The terms "recipient", "individual", "subject", "host", and "patient", are used interchangeably herein and refer to any mammalian subject for whom diagnosis, treatment, or therapy is desired, particularly humans. "Mammal" for purposes of treatment refers to any

animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, sheep, goats, pigs, etc. Preferably, the mammal is human.

[0029] An "effective amount" is an amount sufficient to effect beneficial or desired clinical results. An effective amount can be administered in one or more administrations, and may be administered for a period of time sufficient to effect a therapeutic results, e.g. for up to about one week, up to about 2 weeks, up to about 3 weeks, or more. For purposes of this invention, an effective amount of FZHY is an amount that is sufficient to palliate, ameliorate, stabilize, reverse, prevent, slow or delay the progression of the disease state (e.g., IBD and/or chronic pancreatitis) by decreasing IBD-associated clinical symptoms (e.g., weight loss, colon shortening, soft/loose stool (e.g., diarrhea, watery diarrhea, etc.), rectal bleeding (e.g., bloody stool), abdominal cramps, abdominal pain, vomiting, acute right lower quadrant pain, malaise, fatigue, fever, and/or anemia) and/or clinical symptoms associated with chronic pancreatitis (e.g., chronic abdominal pain and/or symptoms associated with impairment of endocrine and exocrine function of the pancreas).

[0030] The term "sample" with respect to a patient encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents; washed; or enrichment for certain cell populations, such as cancer cells. The definition also includes sample that have been enriched for particular types of molecules, e.g., nucleic acids, polypeptides, etc.

[0031] The term "biological sample" encompasses a clinical sample, and also includes tissue obtained by surgical resection, tissue obtained by biopsy, cells in culture, cell supernatants, cell lysates, tissue samples, organs, bone marrow, blood, plasma, serum, and the like. A "biological sample" includes a sample obtained from a patient's cell, e.g., a sample comprising polynucleotides and/or polypeptides that is obtained from a patient's cell (e.g., a cell lysate or other cell extract comprising polynucleotides and/or polypeptides); and a sample comprising cells from a patient.

Methods

[0032] Methods are provided for treating an individual with Inflammatory Bowel Disease (IBD) or chronic pancreatitis, comprising administering an effective amount of FZHY to an individual for a period of time sufficient to effect a therapeutic result.

[0033] Effective doses of the therapeutic entity of the present invention vary depending upon many different factors, including the means of administration, target site, physiological state of the patient, the severity and course of the disease, the disease being treated (e.g., IBD,

chronic pancreatitis, radiation colitis, Crohn's disease, ulcerative colitis, etc.), whether the patient is human or an animal, other medications administered, whether treatment is prophylactic or therapeutic, the patient's clinical history and response to FZHY, and the discretion of the attending physician. The FZHY is suitably administered to the patient (i.e., the individual) at one time or over a series of treatments.

[0034] Usually, the patient is a human, but nonhuman mammals may also be treated, e.g. companion animals such as dogs, cats, horses, *etc.*, laboratory mammals such as rabbits, mice, rats, *etc.*, and the like. Treatment dosages can be titrated to optimize safety and efficacy.

[0035] In some embodiments, the FZHY is administered orally (e.g., via capsule) and the effective daily dose can range from about 1g to about 30g (e.g., from about 1.25g to about 24g, from about 3g to about 24g, from about 3.2g to about 24g, from about 4g to about 24g, from about 4.8g to about 24g, from about 5g to about 24g, from about 5.6g to about 24g, from about 6g to about 24g, from about 6.4g to about 24g, from about 2.4g to about 10g, from about 3g to about 10g, from about 3.2g to about 10g, from about 4g to about 10g, from about 4.8g to about 10g, from about 5g to about 10g, from about 5.6g to about 10g, from about 6g to about 10g, from about 6.4g to about 10g, from about 2.4g to about 6.4g, from about 3g to about 6.4g, from about 3.2g to about 6.4g, from about 4g to about 6.4g, from about 4.8g to about 6.4g, from about 5g to about 6.4g, from about 5.6g to about 6.4g, from about 6g to about 6.4g, from about 2.4g to about 6g, from about 3g to about 6g, from about 3.2g to about 6g, from about 4g to about 6g, from about 4.8g to about 6g, from about 5g to about 6g, from about 5.6g to about 6g, about 2g, 2.4g, about 3g, about 3.2g, about 4g, about 4.8g, about 5g, about 5.6g, about 6g, or about 6.4g). In some embodiments, the effective daily dose is provided in a unit dosage formulation in any increment. As non-limiting illustrative examples: administration of 1.6g (e.g., one 1.6 g capsule, two 800 mg capsules, etc.) can be performed twice in one day to deliver a daily dose of 3.2 g; or thrice in one day to deliver a daily dose of 4.8 g. As another non-limiting example, the use of 800 mg capsules facilitates any dose (e.g., a daily dose) with a multiple of (0.8g) (e.g., 2.4g, 3.2g, 4g, 4.8g, 5.6g, 6.4g, etc.).

[0036] An exemplary treatment regime entails administration daily (e.g., once, twice, thrice, etc. daily), every other day (e.g., once, twice, thrice, etc. every other day), semi-weekly, weekly, once every two weeks, once a month, *etc.* In another example, treatment can be given as a continuous infusion. Unit doses are usually administered on multiple occasions. Intervals can also be irregular as indicated by monitoring clinical symptoms. Alternatively, the unit dose can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency may vary depending on the patient. It will be understood by one of skill in the art that such guidelines will be adjusted for localized administration, e.g. intranasal, inhalation, rectal, *etc.*, or for systemic administration, e.g. oral,

rectal (e.g., via enema), i.m. (intramuscular), i.p. (intraperitoneal), i.v. (intravenous), s.c. (subcutaneous) and the like.

[0037] FZHY can be provided in pharmaceutical compositions suitable for therapeutic use, e.g. for human treatment. In some embodiments, pharmaceutical compositions of the present invention include one or more therapeutic entities of the present invention or pharmaceutically acceptable salts, esters or solvates thereof. In some other embodiments, the use of FZHY includes use in combination with another therapeutic agent, e.g., another anti-IBD agent. Therapeutic formulations comprising FZHY can be prepared for storage by mixing the FZHY with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. The FZHY composition will be formulated, dosed, and administered in a fashion consistent with good medical practice. The "effective amount" of FZHY to be administered will be governed by considerations such as those cited above (e.g., severity of disease etc.), and is the minimum amount necessary to prevent and/or reduce the symptoms of the targeted disease (e.g., IBD, chronic pancreatitis, ulcerative colitis, Crohn's disease, radiation colitis, etc.).

[0038] FZHY can be administered by any suitable means, including topical, oral (e.g., pill, capsule, gel, etc.), rectal (e.g., enema), parenteral, subcutaneous, intraperitoneal, intrapulmonary, and intranasal. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, intrathecal or subcutaneous administration. In addition, FZHY is suitably administered by pulse infusion, particularly with declining doses of the agent.

[0039] In a subject method, an active agent (e.g., FZHY) may be administered to the host using any convenient means capable of resulting in the desired degree of reduction of symptoms. Thus, an active agent can be incorporated into a variety of formulations for therapeutic administration. For example, an active agent can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols. In an exemplary embodiment, an active agent is formulated as a gel, as a solution, or in some other form suitable for intravaginal administration. In a further exemplary embodiment, an active agent is formulated as a gel, as a solution, or in some other form suitable for rectal (e.g., intrarectal) administration.

[0040] Treatment with FZHY may be combined with other therapies (including dietary changes, medications and surgery) and FZHY need not be, but is optionally formulated with one or more agents that potentiate activity, or that otherwise increase the therapeutic effect. These are generally used in the dosages recommended by the manufacturer, and dosages

can readily be optimized. Agents that can be used in combination with FZHY include anti-IBD agents and/or anti-pancreatitis agents.

[0041] Examples of suitable anti-IBD agents for combination therapy with FZHY include, but are not limited to: 5-aminosalicylic acid (5-ASA); 5-ASA derivatives (e.g., sulfasalazine, mesalamine, balsalazide, olsalazine); antibiotics (e.g., metronidazole, ciprofloxacin, rifaximin); corticosteroids (e.g., hydrocortisone, prednisone, methylprednisolone, prednisolone, entocort (budesonide), dexamethasone); immunosuppressants (e.g., azathioprine, 6-mercaptopurine, methotrexate, cyclosporine); DMARDs, TNF Inhibitors (e.g., infliximab, adalimumab, certolizumab pegol); monoclonal antibodies (e.g., natalizumab, ustekinumab); histamine H2 antagonists (e.g., cimetidine, ranitidine, famotidine, nizatidine); proton pump inhibitors (e.g., omeprazole, lansoprazole, esomeprazole magnesium, rabeprazole sodium, pantoprazole); antidiarrheals (e.g., diphenoxylate and atropine, loperamide, cholestyramine); anticholinergic, antispasmodic agents (e.g., dicyclomine, hyoscyamine); and the like.

[0042] Examples of suitable anti-pancreatitis agents for combination therapy with FZHY include, but are not limited to: analgesics (e.g., acetaminophen, Hydrocodone and acetaminophen, tramadol); nonsteroidal anti-inflammatory drugs (e.g., naproxen, diclofenac, ketorolac, ibuprofen, celecoxib); hormones (e.g., octreotide); antidepressants/TCAs (e.g., amitriptyline hydrochloride, clomipramine, doxepin, nortriptyline, desipramine); pancreatic enzyme supplements (e.g., pancrelipase); and the like.

[0043] FZHY is often administered as a pharmaceutical composition as the active therapeutic agent combined with a pharmaceutically acceptable excipient. The preferred form depends on the intended mode of administration and therapeutic application. The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[0044] In still some other embodiments, pharmaceutical compositions can also include large, slowly metabolized macromolecules such as proteins, polysaccharides such as chitosan, polylactic acids, polyglycolic acids and copolymers (such as latex functionalized SepharoseTM, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes).

[0045] A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group, and non-covalent associations. Suitable covalent-bond carriers

include proteins such as albumins, peptides, and polysaccharides such as aminodextran, each of which have multiple sites for the attachment of moieties. A carrier may also bear FZHY by non-covalent associations, such as non-covalent bonding or by encapsulation. The nature of the carrier can be either soluble or insoluble for purposes of the invention. Those skilled in the art will know of other suitable carriers for binding FZHY, or will be able to ascertain such, using routine experimentation.

[0046] Acceptable carriers, excipients, or stabilizers are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 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 dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEENTM, PLURONICSTM or polyethylene glycol (PEG). Formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[0047] The active ingredients may also be entrapped in microcapsule prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsule and poly-(methylmethacrylate) microcapsule, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980).

[0048] Compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above. Langer, Science 249: 1527, 1990 and Hanes, Advanced Drug Delivery Reviews 28: 97-119, 1997. The agents of this invention can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient. The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance

with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[0049] Toxicity of FZHY can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., by determining the LD₅₀ (the dose lethal to 50% of the population) or the LD₁₀₀ (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of the proteins described herein lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition.

[0050] In some embodiments, the subject methods include monitoring the patient for efficacy of treatment. Monitoring may measure indicia of IBD (e.g. weight loss, colon thickening, soft/loose stool (e.g., diarrhea, watery diarrhea, etc.), rectal bleeding (e.g., bloody stool), abdominal cramps, abdominal pain, vomiting, acute right lower quadrant pain, malaise, fatigue, fever, and/or anemia; etc.) and/or monitoring for the presence or absence (either quantitatively or qualitatively) of a biomarker associated with the disease being treated. For example, diagnosis of IBD and/or chronic pancreatitis (as well as the assessment of treatment efficacy for IBD and/or chronic pancreatitis using the subject methods) can be determined by the presence or absence of biomarkers in a biological sample (e.g., blood, stool, etc.) from the patient followed by colonoscopy and/or any other suitable technique for assessing IBD and/or chronic pancreatitis.

[0051] Convenient biomarkers and ways to monitor/measure the biomarkers will be known to one of ordinary skill in the art and any convenient biomarker may be used. Examples of biomarkers that can be used to diagnose and/or determine the severity of IBD (and therefore to monitor the efficacy of the subject methods of treatment for IBD) include, but are not limited to: (i) biomarkers increased in patients with IBD (relative to patients without IBD): C-reactive protein (CRP), ESR, α 1 Antitrypsin, α 1 antichymotrypsin, α 2 macroglobulin, fibrinogen, prothrombin, factor VIII, plasminogen, tissue plasminogen activator antithrombin, lactoferrin, S100A12, C1s, C2, B, C3, C4, C5, C1INH inhibitor, C9 Haptoglobin, haemopexin, caeruloplasmin, calprotectin, serum amyloid A, ferritin, Fibronectin, and orosomucoid (α 1-acid glycoprotein). Useful antibodies include anti-OmpC, anti-CBir1, anti-I2, anti-A4-Fla2, anti-Fla-X, and antiglycan antibodies; and (ii) biomarkers decreased in patients with IBD (relative to patients without IBD): Factor XII, Albumin, transferrin, Insulin-like growth factor, α -fetoprotein, and cholinesterase.

[0052] For examples of IBD biomarkers, see (a) Iskandar et al., *Transl Res.* 2012 Apr;159(4):313-25: "Biomarkers in Inflammatory Bowel Disease: Current Practices and Recent Advances"; and (b) Vermeire et al., *Gut.* 2006 Mar;55(3):426-31; both of which are hereby incorporated by reference or their teachings on biomarkers of IBD.

[0053] Examples of biomarkers that can be used to diagnose and/or determine the severity of chronic pancreatitis can be found for example, in: Momi et al, *Minerva Gastroenterol Dietol.* 2012 Dec;58(4):283-97; Jin et al, *Intern Med.* 2011;50(15):1507-16; Paulo et al., *Proteomics Clin Appl.* 2011 Apr;5(3-4):109-20; Buxbaum et al., *JOP.* 2010 Nov 9;11(6):536-44; Carroll et al, *Am Fam Physician.* 2007 May 15;75(10):1513-20; Matull et al, *J Clin Pathol.* 2006 Apr;59(4):340-4; Cavestro et al, *JOP.* 2005 Jan 13;6(1 Suppl):53-9; and US patent applications 20100184662, 20100144850, 20100099615, and 20050166275; all of which are hereby incorporated by reference for their teachings on biomarkers of chronic pancreatitis.

[0054] The invention now being fully described, it will be apparent to one of ordinary skill in the art that various changes and modifications can be made without departing from the spirit or scope of the invention.

EXPERIMENTAL

[0055] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g. amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0056] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

[0057] The examples disclosed herein merely illustrate the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions.

Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of the present invention is embodied by the appended claims.

Examples

TNBS colitis with FZHY

[0058] Balb/c mice (~20g) were anesthetized with ketamine and rectally instilled with 2 mg Picrylsulfonic acid (2,4,6-Trinitrobenzenesulfonic acid solution (TNBS); Sigma-Aldrich; St. Louis, MO) in 100 μ L volume, as previously described (Wirtz S, Nat Protoc. 2007;2(3):541-6). Control mice received 100 μ L of vehicle (40% ethanol). Beginning 5 days prior to TNBS instillation, the mice were treated daily with FZHY (4g/kg) or water control (10 mL/kg) by oral gavage through the duration of the experiment, or otherwise noted. To induce chronic colitis, the mice were boosted with a similar dose of TNBS after >10 days. The animals were weighed and assessed daily for signs of colitis and general well being. They were sacrificed at 20% weight loss or earlier if moribund.

[0059] Repeated doses of intra-rectal TNBS were administered at days 0 and 10 (Acute model), and again on days 41, 64, and 70 (Chronic model). The mice were then treated with water (control) or FZHY via oral gavage. The efficacy of FZHY treatment was assessed in two ways: (1) body weight was measured over the entire experimental course (**Figure 1**); and (2) gross pathology was assessed for colon shortening, bloody stool, and/or soft stool (i.e., loss of defined stool pellets) at the completion of the experiment (**Figure 2**). Figure 1 shows that FZHY reduced weight loss in mice with TNBS-induced chronic colitis and Figure 2 shows that FZHY reduced gross pathological features of colitis.

Chronic Pancreatitis with FZHY

[0060] Experimental chronic pancreatitis (CP) was induced in mice (~20 g each) by repetitive caerulein stimulation. Mice were injected interperitoneally with 6 hourly doses of caerulein at 50 μ g/kg (Sigma-Aldrich) 3 days/week for 4 weeks to induce CP. The mice were treated with either FZHY (4g/kg) or water control (10 mL/kg) by oral gavage daily for 5 days/week. The animals were sacrificed and their tissues analyzed 4 weeks and 3 days after the last caerulein injection.

What is claimed is:

1. A method of treating an individual for Inflammatory Bowel Disease (IBD) or chronic pancreatitis, the method comprising:

administering to the individual an effective amount of Fuzheng Huayu (FZHY).

2. The method of Claim 1, wherein the individual is a mammal.

3. The method of Claim 2, wherein the individual is a human.

4. The method of Claim 1, wherein the individual is suspected of having Inflammatory Bowel Disease (IBD).

5. The method of Claim 1, wherein the individual has been diagnosed as having Inflammatory Bowel Disease (IBD).

6. The method of Claim 5, wherein the individual has ulcerative colitis.

7. The method of Claim 5, wherein the individual has Crohn's disease.

8. The method of Claim 5, wherein the individual has radiation colitis.

9. The method of Claim 5, wherein the IBD is chronic IBD.

10. The method of Claim 5, wherein the effective amount is effective at reducing at least one symptom associated with IBD selected from the group consisting of: weight loss, colon shortening, soft stool, diarrhea, bloody stool, abdominal cramps, abdominal pain, vomiting, acute right lower quadrant pain, malaise, fatigue, fever, and anemia.

11. The method of Claim 5, wherein FZHY is administered in combination with:

(i) an anti-IBD agent selected from the group consisting of: 5-aminosalicylic acid (5-ASA), a 5-ASA derivative, an antibiotic, a corticosteroid, an immunosuppressant, a TNF (tumor necrosis factor) inhibitor, natalizumab, ustekinumab, a histamine H2 antagonist, a proton pump inhibitor, an antidiarrheal, and an anticholinergic.

12. The method of Claim 1, further comprising monitoring the individual for symptoms associated with IBD and/or chronic pancreatitis.

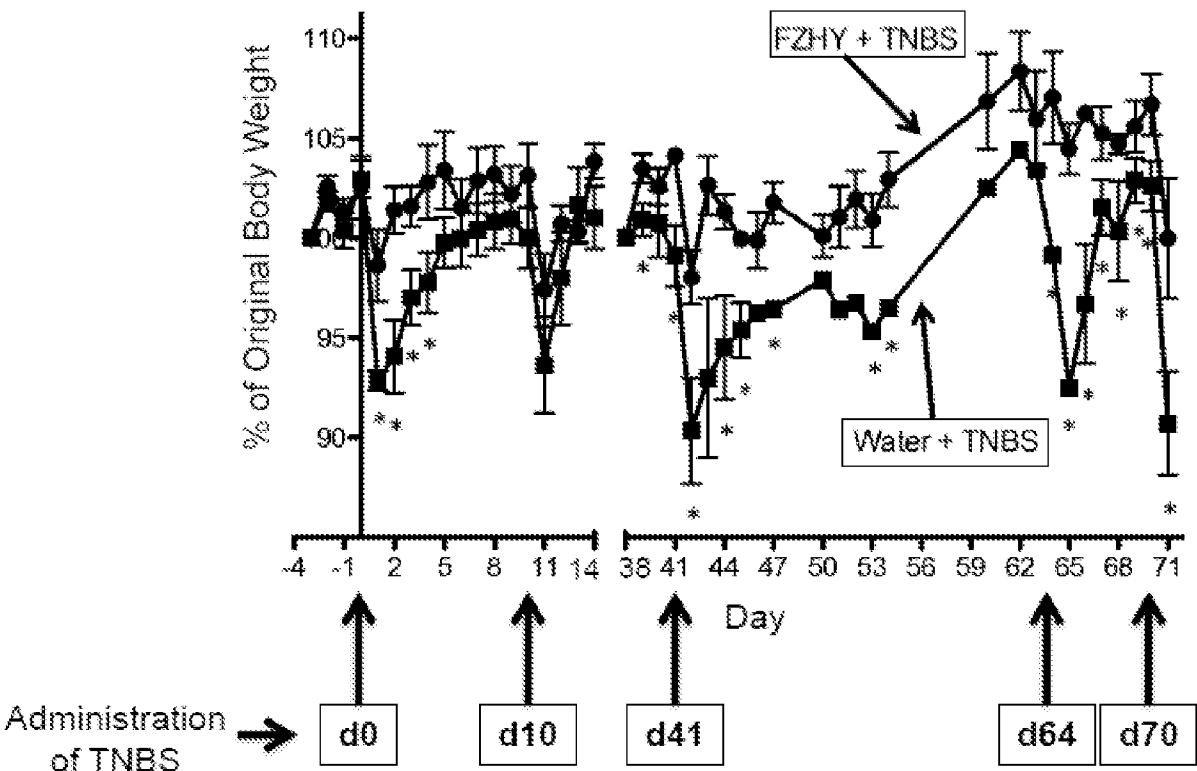
13. The method of Claim 1, further comprising monitoring the individual for biomarkers associated with IBD and/or chronic pancreatitis.

14. A method of reducing Inflammatory Bowel Disease (IDB)-associated weight loss in an individual, the method comprising:

administering to the individual an effective amount of Fuzheng Huayu (FZHY) to reduce IDB-associated weight loss.

15. The method of Claim 14, further comprising monitoring the individual for weight loss.

FIGURE 1

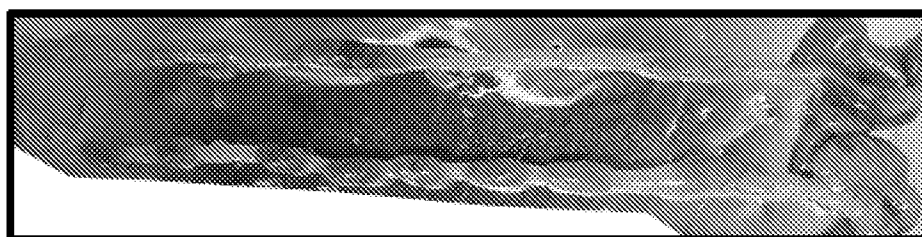


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FIGURE 2

Water

FZHY



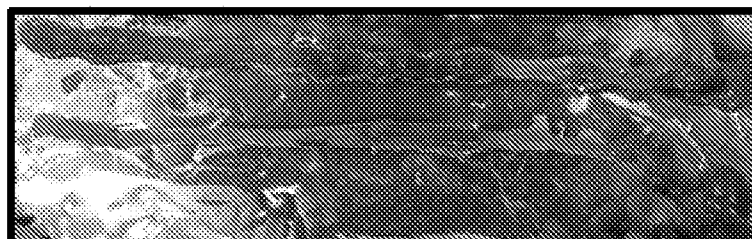
Water

FZHY



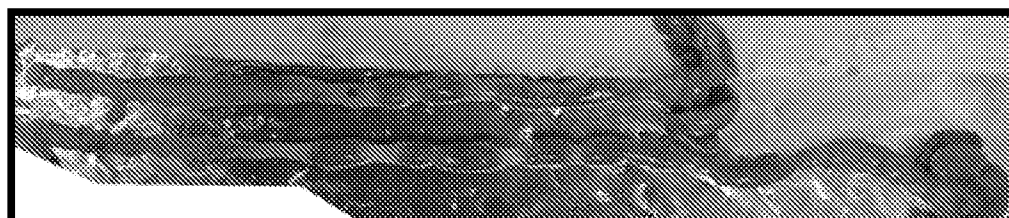
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FZHY



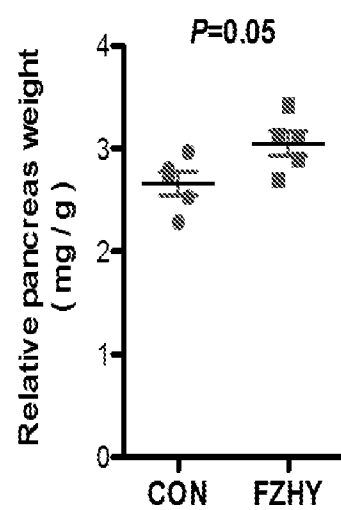
Water

FZHY



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FIGURE 3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 14/41771

A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 39/00 (2014.01) CPC - A61K 2039/505; C07K 2317/24 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) CPC -A61K2039/505; C07K2317/24				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 424/134.1, 133.1 (see search terms below)				
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase, PubWest, ProQuest Dialog, Google Scholar, Google Search Terms: Inflammatory, bowel, pancreatitis, Fuzheng Huayu, FZHY, ulcerative colitis, Crohn's disease, radiation colitis				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Y	US2011/0183948 A1 (Levine et al.) 28 July, 2011 (28.07.2011) para [0015], [0017], [0038], [0112], [0117], [0198], [0213], [0317], [0364]	1-15		
Y	Liu et al. Effect of Fuzheng Huayu formula and its actions against liver fibrosis. Chinese Medicine. 2009, 4:12, pp1-11	1-15		
Y	Jia et al. Fuzheng Huayu recipe prevents nutritional fibrosing steatohepatitis in mice. Lipids in Health and Disease 2012, 11:45, pp1-10	1		
Y	US 2013/0053362 A1 (Castro et al.) 28 February, 2013 (28.02.2013), para [0128], [0572], [0655], [0670]	1		
Y	CN101612205 A (Deng) 30 December 2009 (30.12.2009) abstract	1		
☐ Further documents are listed in the continuation of Box C. ☐				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; border: none;"> * 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 "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 </td> <td style="width: 50%; vertical-align: top; border: none;"> "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 </td> </tr> </table>			* 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 "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
* 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 "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 12 September 2014 (12.09.2014)		Date of mailing of the international search report 23 SEP 2014		
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774		