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(54) Title: METHOD AND MEDICAMENT FOR TREATING ENDOMETRIOSIS

(57) Abstract: Provided is a method and a medicament for treating endometriosis in a subject in need thereof, comprising administering to the subject an effective amount of a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist.

METHOD AND MEDICAMENT FOR TREATING ENDOMETRIOSIS

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority from PCT international application PCT/CN2023/112244 filed on August 10, 2023, which is incorporated herein by reference in its entirety.

FIELD

The present invention relates to the field of medicine, in particular, to a method for treating endometriosis.

BACKGROUND

Endometriosis is a chronic inflammatory gynecological disease characterized by the presence of ectopic endometrial glands and stroma, predominantly on the pelvic peritoneum, ovaries and the rectovaginal septum. About 5 - 15% of women at reproductive age are estimated to suffer from endometriosis worldwide (PMID: 27159755), and the prevalence can reach 35 - 80% in women with pain and/or infertility (PMID: 32212520, 33640070). Owing to the variability in symptoms and confusion between signs of endometriosis and other disorders, delayed disease diagnosis, with the means ranging from 4 - 12 years, is frequently reported (PMID: 8671344, 22990516, 12790847, 28440744). The etiology of endometriosis remains obscure, and therefore several hypotheses are proposed to explain the origin of the disease (reviewed by PMID: 30026507). Pathologically, genetics, the environment, immune dysfunction, and estrogen perturbation may contribute to the implantation and maintenance of endometriotic lesions (PMID: 30026507). Among these, dysregulated steroidogenesis is the most studied mechanism in endometriosis pathology, which can be reflected by hormonal variation as a prevalent risk factor for the disease.

Due to the heterogeneous nature of its pathogenesis, endometriosis remains incurable. Multiple therapeutic approaches, such as surgery, medical treatment, and acupuncture, have been adopted in managing endometriosis and infertility. Hormone therapy is regarded as the first line therapy for endometriosis. Elagolix and Myfembree, two approved hormonal medications, collectively demonstrated their efficacy in reducing endometriosis-induced pain without any safety concerns in various phase III trials (PMID: 28525302, 29889764, 34134684, 33066973, 35717987).

Despite endometriosis itself not a lethal disease, chronic pain and infertility pose significant impacts on the quality of life. It is estimated that the economic burden of endometriosis could reach $80 billion annually in the US alone (PMID: 35620300). Nevertheless, mounting evidence suggests endometriosis is a systemic disease that alters cardiovascular, neurological, metabolic, and immune functions (PMID: 33640070). Patients

may have increased risks of developing several chronic diseases, such as adenomyosis (PMID: 24532217), ovarian cancer (PMID: 28240000) and autoimmune diseases (PMID: 31260048). These altogether urge the need to innovate effective therapeutics for the disease. To tackle this issue, we utilized an artificial intelligence (AI)-driven target discovery platform, PandaOmics, to identify S1PR1 as a repurposing candidate for treating endometriosis.

SUMMARY

The purpose of the present invention is to provide a therapy or a medicament for the treatment of endometriosis.

One aspect of the present invention provides a method for treating endometriosis in a subject in need thereof, comprising administering to the subject an effective amount of a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist.

In certain embodiments, the the S1PR1 antagonist is one or more selected from the group consisting of Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

Another aspect of the present invention provides use of a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist in manufacture of a medicament for treating endometriosis.

In certain embodiments, the the S1PR1 antagonist is one or more selected from the group consisting of Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

Another aspect of the present invention provides a medicament for use in treatment of endometriosis, wherein the medicament comprises a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist.

In certain embodiments, the the S1PR1 antagonist is one or more selected from the group consisting of Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs. 1A-1D show *in silico* analysis of the association between S1PR1 and endometriosis. (FIG. 1A) Screenshot of the Target ID page of PandaOmics for endometriosis meta-analysis. S1PR1 was revealed as a druggable target for endometriosis. Data for gene

expression, genetics, drugs, and text were available for the current analysis. (FIG. 1B)Thirty-one uterine endometrial samples in GSE179640 were categorized into five groups: Ovarian endometriotic tissue, Peritoneal endometriotic tissue and its adjacent tissue, eutopic endometrium, and Control. Cells identified by scRNA-seq data were combined and then clustered into 18 clusters. The intensity of the expression of (FIG. 1C) S1PR1 in each cell cluster was displayed in the t-SNE plots. (FIG. 1D) Dysregulated pathways associated with S1PR1 in endometriosis comparisons were displayed. Pathways were annotated by the Reactome database, and the degree of pathway dysregulation was determined by iPANDA algorithm. Bar colored in green and red indicates the number of comparisons with significant activation and inactivation of the corresponding pathway, respectively.

FIGs. 2A-2B show expression of S1PR1 in GSE203191. (FIG. 2A) Based on disease diagnosis and symptom observation, 33 menstrual effluent samples were classified into three groups: Diagnosed, Symptomatic, and Control. Cells identified by scRNA-seq data from each group were combined and then clustered into 19 clusters. Expression intensities of (FIG. 2B) S1PR1 in the cell clusters were displayed in the t-SNE plots.

DETAILED DESCRIPTION

It should be understood that this invention is not limited to particular embodiments described herein. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can also be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are to disclose and describe the methods and/or materials in connection with which the publications are cited.

Where a range of values with one or two limits is provided, it is understood that a smaller range between any stated intervening value in that stated range and either limit of that stated range is encompassed within the invention. Where the stated range includes one or two limits, ranges excluding either or both of the limits are also included in the invention.

Terminology

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely," "only" and the like in connection with the recitation of claim elements, or use of a "negative" limitation.

Unless otherwise stated, the term “comprise”, “include”, “contain” and variations of

these terms, such as comprising, comprises and comprised, are not intended to exclude further members, components, integers or steps. These terms also encompass the meaning of "consist of" or "consisting of". The term "consist of" or "consisting of" is a particular embodiment of the term "comprise", wherein any other non-stated member, component, integer or step is excluded.

The term "about" refers to a range equal to the particular value plus or minus ten percent (+/- 10%).

The term "and/or" refers to any one, several or all of the elements connected by the term.

The term "endometriosis" as used herein refers to a condition in which tissue containing typical endometrial granular and stromal elements occurs aberrantly in various locations in the pelvic cavity or some other area of the body (most commonly the peritoneal cavity).

The term "treat", "treating" or "treatment", as used herein, refers to alleviating, inhibiting and/or reversing the progress of a disease (such as endometriosis). The term "treating" is inclusive of any indicia of success in the treatment or amelioration of the disease, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the subject; delaying or slowing in the rate of progression, etc. Measurement of the treatment or amelioration may be based on, e.g., the results of a physical examination, a pathological test and/or a diagnostic test as known in the art. Treating may also refer to reducing the incidence or onset of a disease, or a recurrence thereof (such as a lengthening in time of remission), as compared to that which would occur in the absence of the measure taken. Clinically, such a treatment can also be called prevention.

The term "active agent", as used herein, refers to a pharmaceutically active chemical that provides some pharmacologic effect and is used for treating or preventing a disease, such as endometriosis.

The term "inhibitor" and "antagonist", as used herein, can be used interchangeably and refer to any molecule that partially or fully blocks or inhibits an activity of a target (such as the protein used as a target in the present invention).

The term "derivative" of a compound, as used herein, refers to any pharmaceutically acceptable molecule that is derived from (i.e., structurally related to) the compound and has similar or substantially the same activity as the compound, which upon administration to a subject is capable of providing (directly or indirectly) a compound of the active agent or an active metabolite thereof. Examples of the derivatives include, but are not limited to, pharmaceutically acceptable salt, hydrate, solvate, prodrug or metabolite.

The term "pharmaceutically acceptable salt", as used herein, refers to a relatively nontoxic, inorganic or organic acid salt of a compound of the invention. These salts may be prepared *in situ* during the final isolation and purification of the compounds or by reacting the purified compound in its free form separately with a suitable organic or inorganic acid and isolating the salt thus formed. Representative acid salts include, but are not limited to,

acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinafoate salts. In one embodiment, the pharmaceutically acceptable salt is a hydrochloride/chloride salt.

The term “solvate”, as used herein, refers to a complex of variable stoichiometry formed by a solute (e.g., the active agent of the present invention) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid.

The term “prodrug” of a compound, as used herein, refers to a precursor, which when administered to a biological system, generates said compound as a result. For example, prodrugs can have the structure X-drug wherein X is an inert carrier moiety and drug is the active compound,

The term “metabolite” of a compound, as used herein, refers to a molecule which results from a modification or processing of the compound after administration to a subject. The term “metabolite” may designate a modified or processed drug that retains at least part of the activity of the parent compound.

The term “pharmaceutically acceptable”, as used herein, refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of a subject without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio.

The term “pharmacologically acceptable carrier”, as used herein, refers to any carrier that has substantially no long term or permanent detrimental effect when administered to a subject, such as a stabilizer, diluent, additive, auxiliary, excipient and the like. “Pharmaceutically acceptable carrier” should be a pharmaceutically inert material that has substantially no biological activity and constitutes a substantial part of the formulation.

The term “subject”, as used herein, refers to any organism to which the active agent of the composition of the present invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates such as chimpanzees and other apes and monkey species, and humans). The subject may be a mammal, particularly a human, including a male or female, and including a neonatal, infant, juvenile, adolescent, adult or geriatric, and further is inclusive of various races and ethnicities.

The term “therapeutically effective dose” or “effective dose”, as used herein, which can be used interchangeably with "therapeutically effective amount" or “effective amount”, refers

to an amount that is effective for treating a disease (such as endometriosis) as noted through clinical testing and evaluation, patient observation, and/or the like. An "effective amount" can further designate an amount that causes a detectable change in biological or chemical activity. The detectable changes may be detected and/or further quantified by one skilled in the art for the relevant mechanism or process. Moreover, an "effective amount" can designate an amount that maintains a desired physiological state, i.e., reduces or prevents significant decline and/or promotes improvement in the condition.

The term “unit dosage form”, as used herein, refers to physically discrete units (such as capsules, tablets, or loaded syringe cylinders) suitable as unitary dosages for a subject, each unit containing a predetermined quantity of active agent calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier.

The term “unit dose”, as used herein, refers to a dose of a substance (such as an active agent of the present invention) in a unit dosage form.

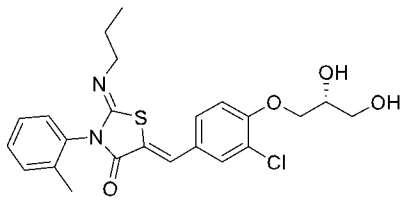
Active agents for treating endometriosis

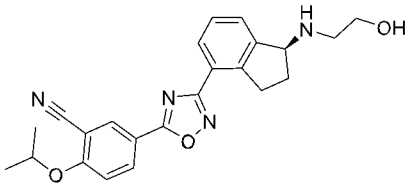
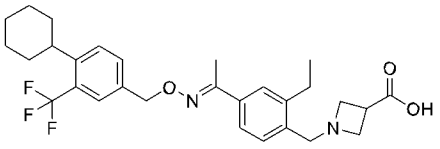
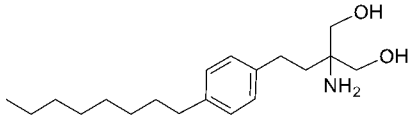
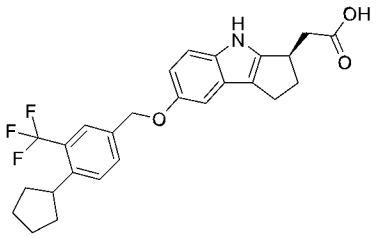
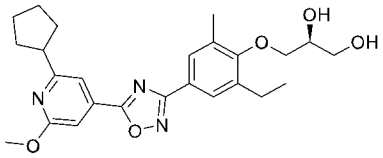
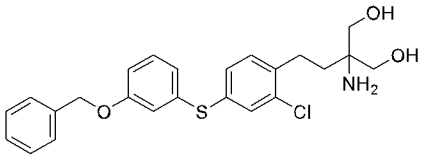
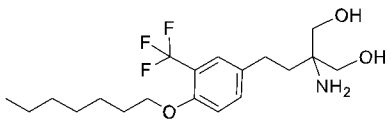
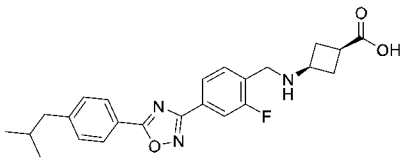
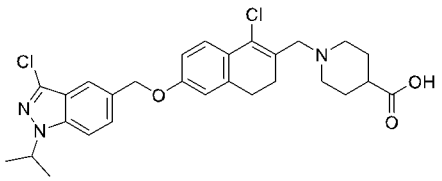
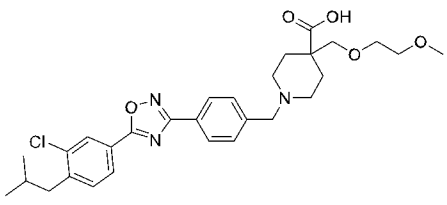
The inventor discovered through extensive research a target, sphingosine-1-phosphate receptor 1 (S1PR1), for treating endometriosis. An antagonist or agonist of the target may be used to treat endometriosis.

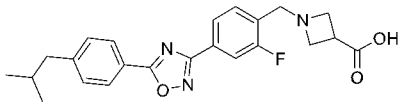
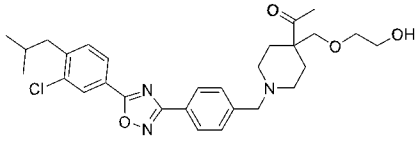
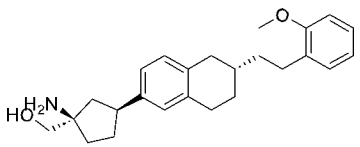
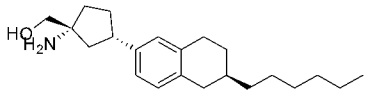
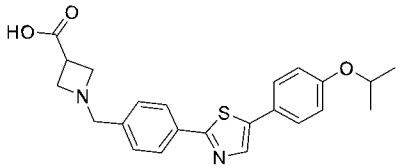
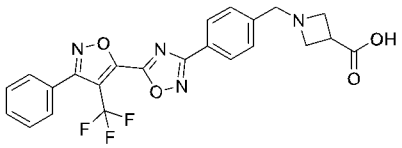
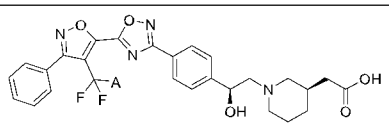
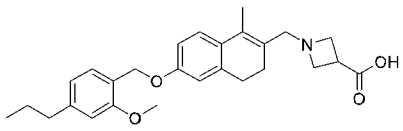
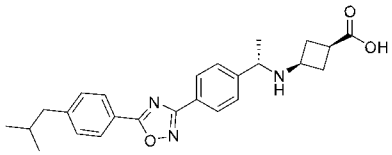
Sphingosine-1-phosphate receptor 1 (S1P receptor 1 or S1PR1), also known as endothelial differentiation gene 1 (EDG1) is a protein that in humans is encoded by the S1PR1 gene. S1PR1 is a G-protein-coupled receptor which binds the bioactive signaling molecule sphingosine 1-phosphate (S1P). S1PR1 belongs to a sphingosine-1-phosphate receptor subfamily comprising five members (S1PR1-5). S1PR1 was originally identified as an abundant transcript in endothelial cells and it has an important role in regulating endothelial cell cytoskeletal structure, migration, capillary-like network formation and vascular maturation. In addition, S1PR1 signaling is important in the regulation of lymphocyte maturation, migration and trafficking.

The active agent used to treat endometriosis can be any one selected from the group consisting of S1PR1 antagonists, including but not limited to Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

The structures of the exemplified S1PR1 antagonists are shown below.

Ponesimod	

Ozanimod	
Siponimod	
Fingolimod	
Etrasimod	
Cenerimod	
Mocravimod dihydrochloride	
Amiselimod hydrocholoride	
CBP-307	
TT-01688-CL	
Vibozilimod	

Icanbelimod	
SCD-044	
BMS-986166	
BMS-986104	
CP-1050	
BMS-520	
BMS-542	
Ceralifimod	
PF-04629991	

The amount of each of the active agents in a unit dosage form may be 1-1000mg, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 , 16, 17, 18, 19, 20, 25, 30, 35, 40, 50, 60, 70, 75, 80, 90, 100, 110, 120, 125, 130, 140, 150, 160, 170, 175 , 180, 190, 200, 250, 300, 350, 400, 450, 500, 600, 700, 750, 800, 900, 1000mg or any range between any two of the above specific values.

Administration

Each of the active agent of the present invention may be administered to the subject via

oral, buccal, sublingual, rectal, vaginal, parenteral, intradermal or intranasal or parenteral route. The parenteral administration includes intravenous, intraperitoneal, intradermal, subcutaneous, intramuscular, intracranial, intrathecal, intratumoral, transdermal, transmucosal intraarticular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional or intracranial injection or infusion.

The active agent(s) as used herein may be formulated for administration in a pharmaceutical composition in accordance with known techniques. See, for example, *Remington, The Science and Practice of Pharmacy (9th Ed. 1995)*. In the manufacture of a pharmaceutical composition according to the present invention, the active agent is typically admixed with, *inter alia*, a pharmaceutical acceptable carrier. The carrier must, of course, be acceptable in the sense of being compatible with any other ingredients in the formulation and must not be deleterious to the patient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the compound as a unit-dose formulation, for example, a tablet, which may contain from 0.01% or 0.5% to 95% or 99% by weight of the active agent. One or more active agents may be incorporated in the formulations of the invention, which may be prepared by any of the well-known techniques of pharmacy comprising admixing the components, optionally including one or more accessory ingredients and/or excipients. In some embodiments, any of the compositions, carriers, accessory ingredients excipients and/or the formulations of the invention comprise ingredients that are from either natural or non-natural sources. In other embodiments, any component of the compositions, carriers, accessory ingredients, excipients and/or the formulations of the invention may be provided in a sterile form. Non-limiting examples of a sterile carrier include endotoxin-free water or pyrogen-free water.

In some embodiments, the pharmaceutical composition of the invention is provided as part of a sterile composition/formulation comprising an active agent of the invention and a pharmaceutically acceptable carrier and/or excipient.

Dosage forms suitable for the oral administration include tablet, capsule, powder, pill, granule, suspension, solution or preconcentrate of solution, emulsion or preconcentrates of emulsion. Pharmaceutical acceptable carriers that can be used in an oral dosage form include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like. Carriers such as starches, sugars, microcrystalline cellulose, diluents, filler, glidants, granulating agents, lubricants, binders, stabilizers, disintegrating agents and the like can be used to prepare an oral solid preparation such as powder, capsule or tablet.

The diluent includes, but not limited to, microcrystalline cellulose, mannitol, powdered sugar, compressible sugar, dextran, dextrin, spinose, lactose, cellulose powder, sorbitol, sucrose and Talc powder or a combination thereof. The diluent may be 5% to 90% based on the total weight of the oral composition, preferably 10% to 80%, 20%-70%, 30%-60%, 40%-50%.

The disintegrating agent includes, but not limited to, cellulose, alginate, gum, cross-linked polymer, such as cross-linked polyvinylpyrrolidone or crospovidone, croscarmellose sodium, croscarmellose calcium, soybean polysaccharide, sodium starch glycolate, guar gum

or any combination thereof. The disintegrating agent may be present in an amount of about 1% to 15%, preferably 2% to 10%, based on the total weight of the oral composition.

The binder includes, but not limited to, starch, cellulose or derivatives thereof, such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose and hydroxypropyl methyl cellulose, sucrose, dextrose, corn syrup, polysaccharide, gelatin or any combination thereof. The binder may be present in an amount of 0.01 to 10%, preferably 1% to 10%, based on the total weight of the composition.

The glidant includes, but not limited to, colloidal silicon dioxide, magnesium trisilicate, cellulose powder, talc powder or a combination thereof can be selected. The glidant may be present in an amount of 0.1% to 10%, preferably 0.1% to 0.5%, based on the total weight of the composition.

Dosage forms can be in the form, e.g., of tablets or capsules, and the effective dose may be provided in one or more tablets, capsules or the like, and be provided once a day or throughout the day at intervals, e.g., of 4, 8 or 12 hours. Tablets or capsules, for example, could contain, e.g., 10, 25, 50, 75, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1,000, 1,100, or 1,250 mg of the active agent. For example, administration to a human subject of the active agent of the present invention may comprise a daily dosage in the range of 100-1,250, 150-1,000, 200-800, or 250-750 mg, which daily dosage can be administered either once a day in its entirety or fractions of which are administered throughout the day in intervals. Liquid formulations can also be prepared so that any dosage may readily and conveniently be dispensed.

Parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a subject. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable carrier for injection, suspensions ready for injection, and emulsions.

Some suitable carriers that can be used to provide parenteral dosage forms provided herein include, but are not limited to: water for injection; aqueous vehicles such as, but not limited to, sodium chloride injection, Ringer's injection, dextrose injection; water-miscible carriers such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous carriers such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Compounds that increase the solubility of one or more of the active agents disclosed herein can also be incorporated into the parenteral dosage forms provided herein. For example, cyclodextrin and its derivatives can be used to increase the solubility of an active agent of the present invention.

It should be understood that a therapeutically effective dose may be determined by a physician, according to such as the type, stage and/or severity of the disease, the condition, age, body weight, sex and response of the subject to be treated, as well as the route of administration.

A therapeutically effective amount is an amount such that when administered to a

subject is sufficient to achieve a plasma concentration of from about 0.01μg/ml to about 100 μg/ml, from about 0.1μg/ml to about 10 μg/ml, from about 1 μg/ml to about 5 μg/ml.

When administering the active agent of the present invention to a subject, the therapeutically effective amount of each of the active agents generally may be in the range of about 0.5 to about 250 mg/kg, about 1 to about 250 mg/kg, about 2 to about 200 mg/kg, about 3 to about 120 mg/kg, about 5 to about 250 mg/kg, about 10 to about 200 mg/kg, or about 20 to about 120 mg/kg for each active agent of the present invention. In some embodiments, the therapeutically effective amount may be 0.5mg/kg, 1mg/kg, 2mg/kg, 3mg/kg, 4mg/kg, 5mg/kg, 6mg/kg, 8mg/kg, 10mg/kg, 20mg/kg, 25mg/kg, 40mg/kg, 50mg /kg, 60mg/kg, 75mg/kg, 100mg/kg, 120mg/kg, 150mg/kg, 175mg/kg, 200mg/kg, 225mg/kg, 250mg/kg or 300mg/kg.

Each of the active agents of the present invention may be administered once or twice one day; or once every 2, 3, 4, 5, 6, 7, 8, 9 or 10 days or once every 1, 2 or 3 weeks. In some embodiments, each of the active agents of the present invention may be administered in a five times weekly scheme. In the five times weekly scheme, the administration may be done on five consecutive days (once daily) followed by two consecutive days off.

The term "kit", as used herein, refers to a package and, as a rule, instruction for use. An active agent or a pharmaceutical composition in a kit can be in any of a variety of forms suitable for distribution in a kit. Such forms can include a liquid, powder, tablet, suspension and the like. Two or more active agents may be provided in separate containers suitable for administration separately, or alternatively may be provided in a composition in a single container in the package. The kit may contain an amount sufficient for one or more dosages of agents according to the treatment methods. The instruction for use generally comprises a literal statement of how to treat a disease (such as ALS) with the agents in the kit.

It should be understood that the combination or pharmaceutical composition of the present invention may include other therapeutic agents or therapies, such as biological therapeutic agents and/or chemotherapeutic agents in addition to the active agents of the present invention. The method may include administration of other therapeutic agents or therapies, such as biological therapeutic agents and/or chemotherapeutic agents in addition to administration of the active agents of the present invention. Other therapeutic agents or therapies may be administered simultaneously, separately or sequentially with the therapeutic agents of the present invention.

EXAMPLES

Example 1. Identification of Therapeutic Targets and Drug Repurposing Candidates for Endometrium Using PandaOmics™ – an AI-enabled Biological Target Discovery Platform

1. Methods

Data source and availability

Both bulk and single cell transcriptomics, and proteomics data were utilized in the current analysis. A total of thirty-six endometriosis-related bulk transcriptomics datasets, comprising microarray and RNA-sequencing series, of various tissue sources retrieved from Gene Expression Omnibus (GEO) and ArrayExpress were available for direct downstream analysis and target identification on PandaOmics. Two single cell transcriptomics datasets, GSE179640 and GSE203191, were also extracted from GEO.

Dataset and comparison selection

Since disease pathogenesis was initiated from eutopic endometrium, datasets with uterine endometrial tissue were selected for downstream analysis and target identification. eleven case-control comparisons were generated from eleven bulk transcriptomics datasets, which were listed in Table 1. Both normal endometrial tissue from healthy individuals and eutopic endometrial tissue from patients with endometriosis were chosen as the controls, which was labeled as 'Healthy' and 'Eutopic endometrium', respectively, in the column Experimental design in Table 1.

Table 1. Comparisons in Endometriosis meta-analysis for target selection

Serie	Type	Platform	Experimental design	# Control	# Case	Year	Reference
Endometriosis meta-analysis							
GSE11691	Microarray	GPL96	Eutopic endometrium vs Endometriosis	9	9	2008	18688027
GSE6364	Microarray	GPL570	Healthy vs Endometriosis	16	21	2006	17510236
GSE7305	Microarray	GPL570	Healthy vs Endometriosis	10	10	2007	17640886
GSE7307	Microarray	GPL570	Healthy vs Endometriosis	18	19	2007	-
GSE51981	Microarray	GPL570	Healthy vs Endometriosis	71	77	2013	25243856
GSE25628	Microarray	GPL571	Healthy vs Endometriosis	6	7	2010	23460397
GSE23339	Microarray	GPL6102	Healthy vs Endometriosis	9	10	2010	21436257
GSE120103	Microarray	GPL6480	Healthy (fertile) vs Endometriosis	9	16	2018	30760267
GSE141549	Microarray	GPL10558, GPL13376	Healthy vs Endometriosis	42	198	2019	32859947
GSE135485	RNA-seq	GPL21290	Healthy vs Endometriosis	4	54	2019	-
GSE134056	RNA-seq	GPL18573	Healthy vs Endometriosis	22	16	2019	31552087

Target identification by PandaOmics

PandaOmics was a cloud-based target discovery platform with multiple deep learning models and AI algorithms incorporated in the target prioritization process. Twenty-three target prioritization models covering Omics, Text-based, Financial, and Key Opinion Leader (KOL) data were developed to predict the association between the target genes and a particular indication. Scores of each of the models are given in a normalized scale from zero to one, with higher scores corresponding to better target-disease association as predicted by the model. These models were validated using a Time Machine approach to confirm their abilities in target identification. Adjustable filters for druggability, tissue specificity, target family, and developmental status were also available to refine the target list.

To identify potential targets for endometriosis, the case-control bulk transcriptomics comparisons created were allocated into a meta-analysis. To identify actionable targets with various novelty levels, settings of filters and scores were customized to reprioritize the targets. Only targets belonging to the druggable protein classes, and not regarded as essential

genes defined by the Therapeutic target database (TTD) were retained in the analysis. As a result, three lists of druggable targets with high confidence, medium novelty, and higher novelty were generated, and their top 50 targets were subjected to further analysis.

Single-cell transcriptomics data processing and analysis

For GSE203191, menstrual effluent samples were collected from 11 endometriosis (diagnosed), 13 symptomatic (not diagnosed but with chronic endometriosis symptoms), and 9 control subjects. Samples in GSE179640 were isolated from five regions: healthy uterine endometrium, eutopic endometrium from patients with endometriosis, ectopic endometriotic tissues from ovary and peritoneum, as well as tissue adjacent to the endometriotic lesion in the peritoneum.

For GSE203191, sample data matrices generated by Cell Ranger were retrieved from the GEO database, and subject to gene and cell filtrations as well as cell cluster annotations as defined in the original paper (PMID: 36104692). For GSE179640, the processed data that contains normalized expression, cell cluster annotations, sample metadata, as well as dimensionality reduction coordinates was readily provided by the authors and retrieved from https://singlecell.jax.org/datasets/endometriosis-2022. Differential gene expression between different cell clusters or different sample groups was calculated by Wilcoxon rank sum test using the log-normalized count data.

Pathway analysis

Signaling pathway activation status was assessed using PandaOmics proprietary single network model iPANDA (PMID: 27848968). With the combinational use of differential gene expression data and the degree of pathway topology decomposition, iPANDA robustly identified sets of biological relevant pathway signatures from the input data with significant noise reduction. iPANDA value of 1 and -1 indicated pathway activation and suppression, respectively. Hierarchical organization of signaling pathways were curated based on the Reactome database.

2. Results

Identification of S1PR1 as a potential therapeutic target by PandaOmics

Based on the expression correlation results, Endometriosis meta-analysis with 11 subtype and cycle nonspecific comparisons was utilized for target identification (Table 1). To identify potential therapeutic targets for endometriosis, high confidence targets associated with the disease were screened based on the ranking calculated by PandaOmics, the consistency of dysregulated expression across comparisons included in the meta-analysis, statistical significance of the dysregulation, as well as literature support in driving endometriosis or with potential roles in the underlying mechanisms promoting endometriosis. S1PR1 was ranked as the 223th target in the meta-analysis, and scored at least 0.8 in four Omics AI score models, i.e. Network neighbors, Expression, Heterogenous graph walk and Matrix factorization (Fig. 1A).

Upregulation of S1PR1 was observed in endometriosis transcriptomics datasets

To investigate the functional correlation of S1PR1 with endometriosis, expression profiles between samples collected from the endometriosis lesions and control endometrium were analyzed. Regarding the bulk transcriptomics profiles, S1PR1 was upregulated in 10 (90.9%) out of 11 comparisons, with 6 of the upregulations reaching statistically significant (FDR < 0.05) (Table 2). Two endometriosis single cell transcriptomics datasets, GSE179640 and GSE203191, were also extracted to study the cell-specific expression profile.

Table 2. Expression profile of S1PR1 in endometriosis bulk transcriptomics comparisons

Name	Type	Platforms	Source	Experimental design	# Case	# Control	Year	logFC	*p*-value	*q*-value
GSE7307	Microarray	GPL570	Uterine endometrium	Healthy vs Endometriosis	19	18	2007	0.75 ± 0.12	1.47E-07	2.81E-06
GSE51981	Microarray	GPL570	Uterine endometrium	Healthy vs Endometriosis	77	71	2013	-0.19 ± 0.06	1.54E-03	3.83E-03
GSE6364	Microarray	GPL570	Uterine endometrium	Healthy vs Endometriosis	21	16	2006	0.06 ± 0.06	3.49E-01	6.63E-01
GSE25628	Microarray	GPL571	Uterine endometrium	Healthy vs Endometriosis	7	15	2010	1 ± 0.28	1.42E-03	4.31E-02
GSE7305	Microarray	GPL570	Uterine endometrium	Healthy vs Endometriosis	10	10	2007	1.24 ± 0.12	9.80E-10	4.41E-08
GSE23339	Microarray	GPL6102	Uterine endometrium	Healthy vs Endometriosis	10	9	2010	1.18 ± 0.24	8.00E-05	3.88E-03
GSE135485	RNA-seq	GPL21290	Uterine endometrium	Healthy vs Endometriosis	54	4	2019	0.43 ± 0.93	6.46E-01	9.15E-01
GSE134056	RNA-seq	GPL18573	Uterine endometrium	Healthy vs Endometriosis	16	22	2019	0.02 ± 0.23	9.43E-01	9.91E-01
GSE120103	Microarray	GPL6480	Uterine endometrium	Healthy vs Endometriosis	16	9	2018	0.35 ± 0.4	3.90E-01	7.32E-01
GSE141549	Microarray	GPL10558...	Uterine endometrium	Healthy vs Endometriosis	198	42	2019	1.75 ± 0.12	2.85E-35	1.49E-32
GSE11691	Microarray	GPL96	Uterine endometrium	Eutopic endometrium vs endometriosis	9	9	2008	0.53 ± 0.13	5.87E-04	2.24E-02

GSE179640 is composed of control samples collected from uterine endometrium, eutopic endometrium of patients, ectopic endometriotic lesions from peritoneum and ovary, and tissue adjacent to the endometriotic lesions in the peritoneum. S1PR1 was specifically enriched in endothelial cells in GSE179640. It was significantly overexpressed in the endothelial cells and one of the myeloid cell clusters in the ovarian endometriosis samples. Its upregulation was also detected in the NK cells and a myeloid cell cluster in the peritoneal endometriosis lesions and adjacent tissue of the peritoneal endometriosis lesions, respectively (Fig. 1B and 1C). On the other hand, three groups of samples are available - menstrual effluent collected from endometriosis (diagnosed), symptomatic, and control subjects in GSE203191. No significant LFC of S1PR1 observed in the case-control comparisons in any cell types.

S1PR1 agonists as repurposing candidates for endometriosis

Using PandaOmics proprietary single network model iPANDA, S1PR1 mainly contributed to immune regulatory pathways, by which most of them are prominently activated in endometriotic samples (Fig. 1D). Literature has demonstrated the pivotal role of S1PR1 and its ligand, sphingosine-1-phosphate (S1P), in immune response. Information of the associations between S1PR1 variants and traits was retrieved from GWAS Catalog, and half of the traits are immune-related. Loss-of-function of S1PR1 in mice is lethal. Conditional mutations of S1PR1 drive severe phenotypic abnormalities in immune, cardiovascular, and neuronal systems (PMID: 22975327, 16314531, 12869509, 20584883, 21960637). Upregulation of S1PR1 has been reported in endometriosis (PMID: 30782093, 22277765). S1P increased the expression of IL-6 and proliferative ability of the endometriotic cells (PMID: 30782093). Inhibition of S1PR1 and S1PR3 suppressed S1P-induced endometriotic stromal cell proliferation (PMID: 30782093). S1P and its downstream pathway mediated the

induction of expression of COX-2 and PGE2 production, two important mediators of inflammation (PMID: 12890694, 26994820). As endometriosis is a chronic inflammatory disease and S1PR1 demonstrated a close linkage with endometriosis, targeting S1PR1 could be a therapeutic approach for endometriosis.

The launched agonists of S1PR1 - fingolimod, siponimod, ozanimod and ponesimod, functionally antagonize the action of S1PR1, and are indicated for treating multiple sclerosis. Binding of these compounds to S1PR1 induces receptor internalization and degradation. In particular, ponesimod acts specifically on the S1PR1 receptor. Besides the launched ones, sixteen additional compounds have been designed to target S1PR1 and tested in various indicators, i.e. Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrochloride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP1050, BMS520, BMS542, Ceralifimod, and PF-04629991.

CLAIMS

1. A method for treating endometriosis in a subject in need thereof, comprising administering to the subject an effective amount of a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist.

2. The method according to claim 1, wherein the S1PR1 antagonist is one or more selected from the group consisting of Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

3. Use of a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist in manufacture of a medicament for treating endometriosis.

4. The use according to claim 3, wherein the S1PR1 antagonist is one or more selected from the group consisting of Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

5. A medicament for use in treatment of endometriosis, wherein the medicament comprises a sphingosine-1-phosphate receptor 1 (S1PR1) antagonist.

6. The medicament for use according to claim 5, wherein the S1PR1 antagonist is one or more selected from the group consisting of Ponesimod, Ozanimod, Siponimod, Fingolimod, Etrasimod, Cenerimod, Mocravimod dihydrochloride, Amiselimod hydrocholoride, CBP-307, TT-01688-CL, Vibozilimod, Icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, Ceralifimod, PF-04629991 and a derivative thereof.

A
endometriosis
Data types:
1 - 20 of 100
ASSOCIATED GENES
RANK
OMICS SCORES
TEXT-BASED
FINANCIAL
KOL
TISSUE
S1PR1
Tclin
GPCR
Small molecule
Antibodies
Safety
Novelty
Structure
Development Level
Target Family
S1PR1
Network neighbors
Mutated sub-modules
Disease sub-modules
Causal inference
Overexpression
Knockouts
Mutations
Pathways
Relevance
Expression
Interactome community
Heterogeneous graph walk
Matrix factorization
Attention spike
Evidence
Attention score
Trend
Funding per publication
Grant funding
Grant size
Credible attention index
Mean Hirsch
Impact factor

FIG. 1A

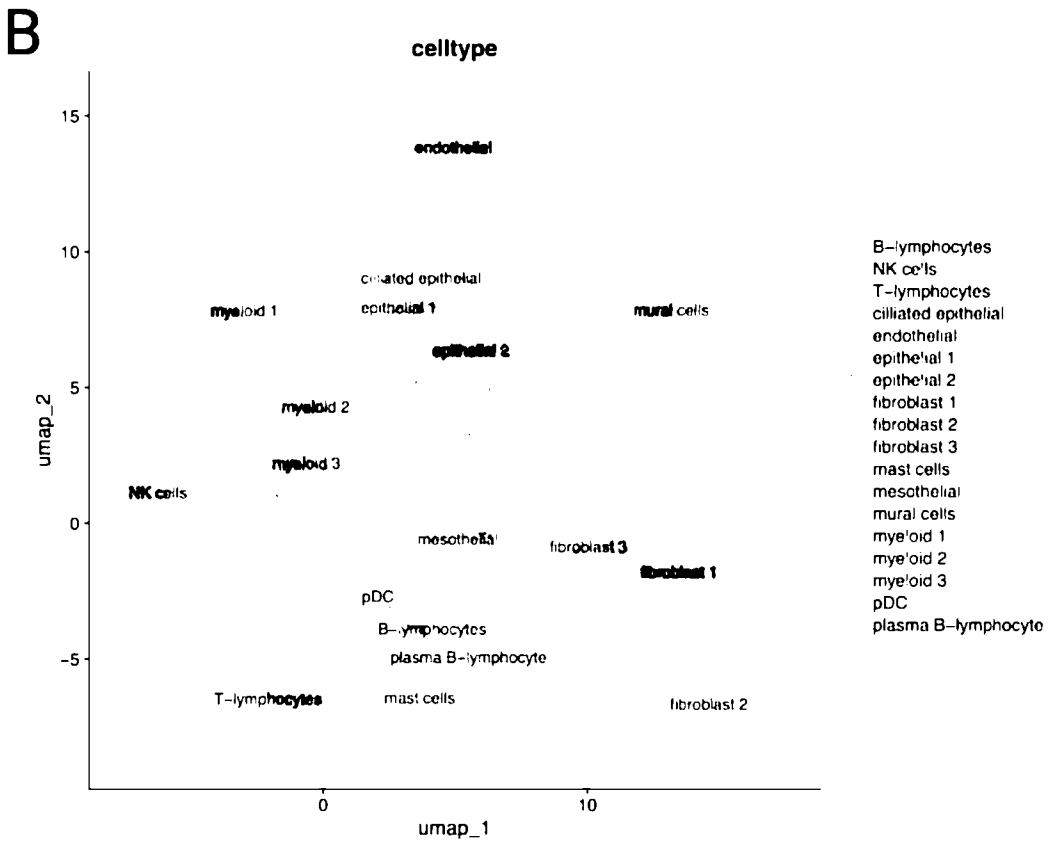

B
celltype
umap_2
umap_1
15
10
5
0
-5
0
10
endothelial
ciliated epithelial
myeloid 1
epithelial 1
mural cells
epithelial 2
myeloid 2
myeloid 3
NK cells
mesothelial
fibroblast 3
fibroblast 1
pDC
B-lymphocytes
plasma B-lymphocyte
T-lymphocytes
mast cells
fibroblast 2
B-lymphocytes
NK cells
T-lymphocytes
ciliated epithelial
endothelial
epithelial 1
epithelial 2
fibroblast 1
fibroblast 2
fibroblast 3
mast cells
mesothelial
mural cells
myeloid 1
myeloid 2
myeloid 3
pDC
plasma B-lymphocyte

FIG. 1B

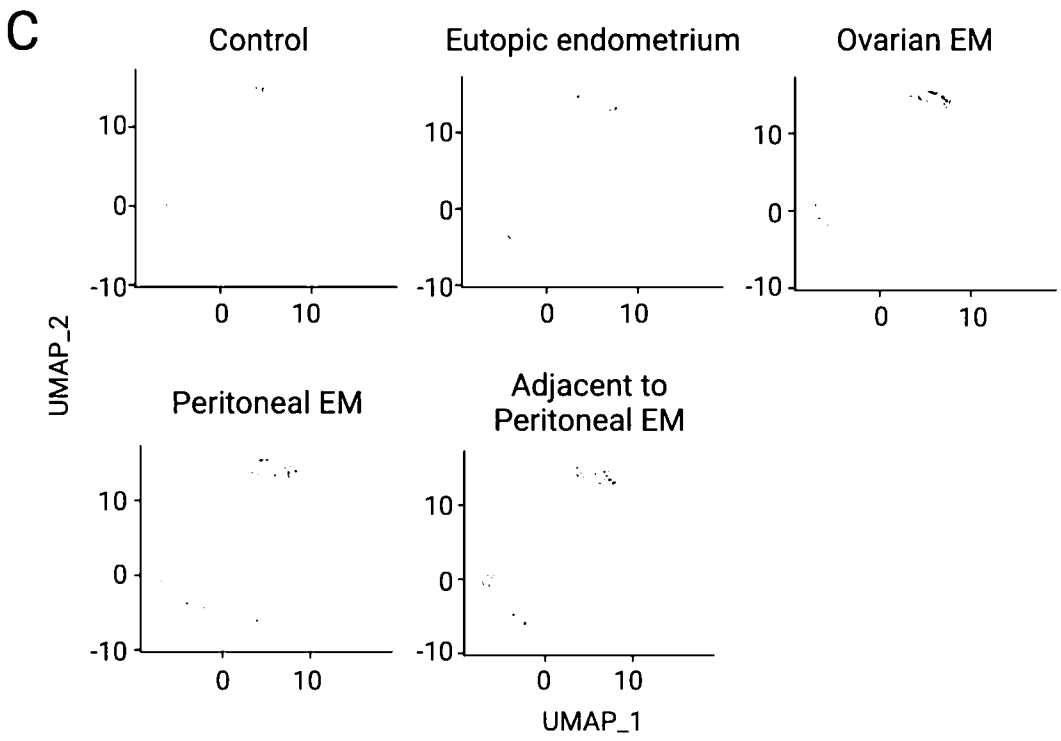

C
Control
Eutopic endometrium
Ovarian EM
Peritoneal EM
Adjacent to Peritoneal EM
UMAP_2
UMAP_1
10
0
-10
0
10

FIG. 1C

D

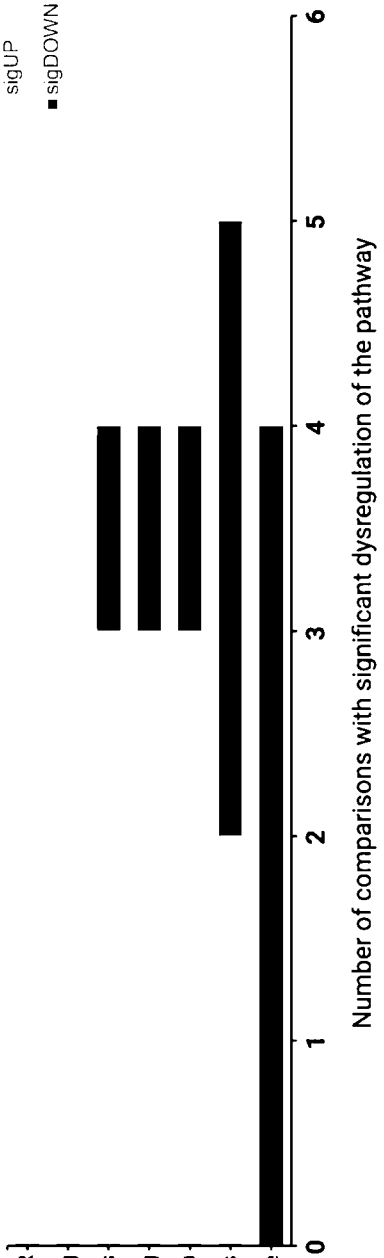

sigUP
sigDOWN
Signaling by GPCR
GPCR ligand binding
Signaling by Interleukins
Interleukin-4 and Interleukin-13 signaling
Cytokine Signaling in Immune system
Lysosphingolipid and LPA receptors
Infectious disease
0
1
2
3
4
5
6
Number of comparisons with significant dysregulation of the pathway

FIG. 1D

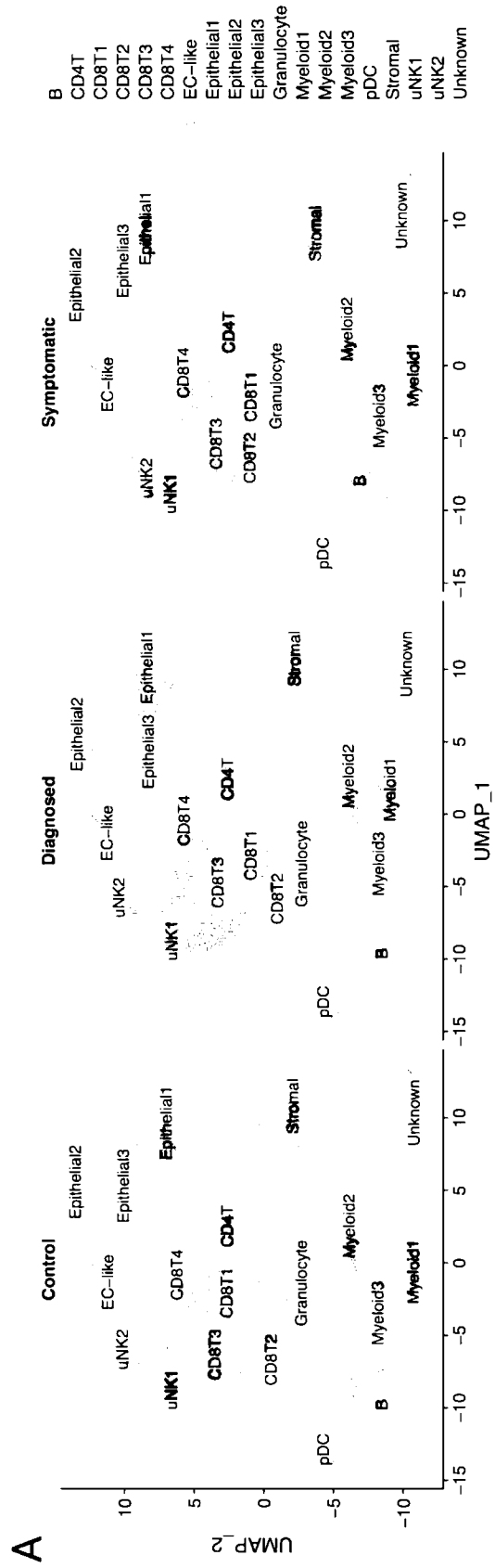

A
Control
Diagnosed
Symptomatic
Epithelial2
EC−like
Epithelial3
Epithelial1
uNK2
uNK1
CD8T4
CD8T3
CD4T
CD8T1
CD8T2
Granulocyte
Stromal
Myeloid2
Myeloid3
Myeloid1
pDC
B
Unknown
UMAP_1
UMAP_2
B
CD4T
CD8T1
CD8T2
CD8T3
CD8T4
EC−like
Epithelial1
Epithelial2
Epithelial3
Granulocyte
Myeloid1
Myeloid2
Myeloid3
pDC
Stromal
uNK1
uNK2
Unknown

FIG. 2A

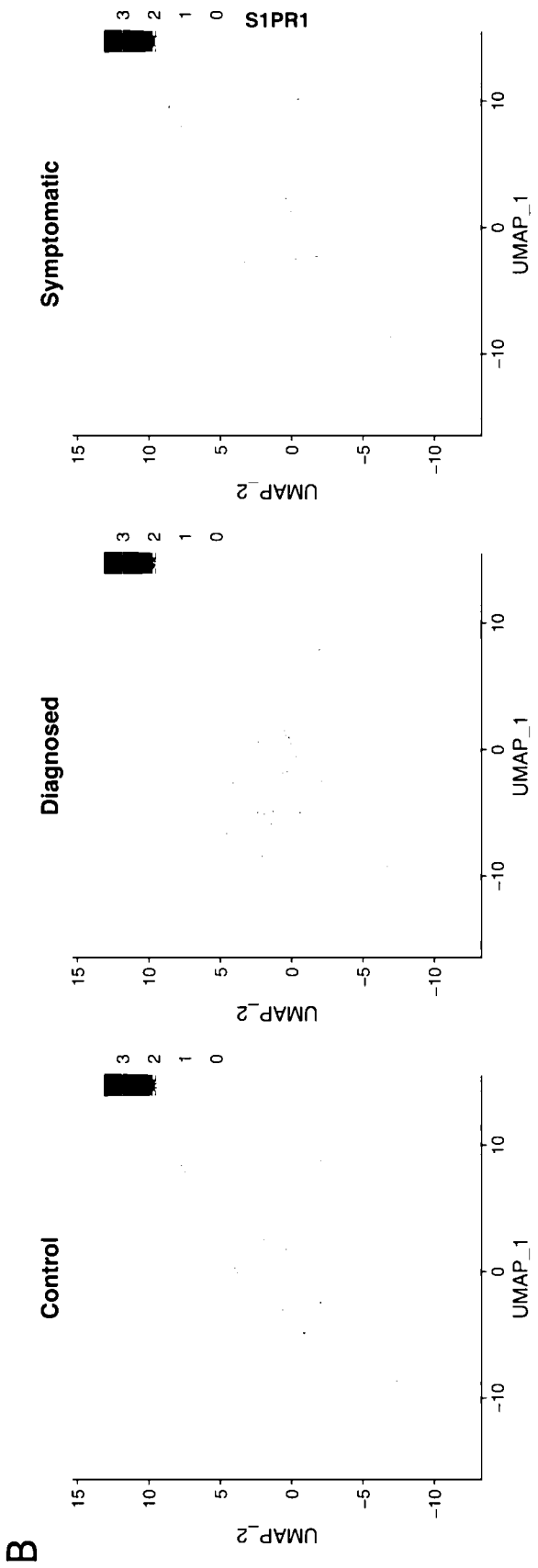


FIG. 2B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/110958

A. CLASSIFICATION OF SUBJECT MATTER

A61K45/00(2006.01)i; A61K31/137(2006.01)i; A61P15/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPABSC, CNTXT, CNABS, WPABS, DWPI, ENTXTC, ISI_Web of Science, NCBI, CNKI: sphingosine-1-phosphate receptor 1 antagonist, S1PR1 antagonist, endothelial differentiation gene 1, EDG1, ponesimod, ozanimod, siponimod, fingolimod, etrasimod, cenerimod, mocravimod dihydrochloride, amiselimod hydrocholoride, CBP-307, TT-01688-CL, vibozilimod, icanbelimod, SCD-044, BMS-986166, BMS-986104, CP-1050, BMS-520, BMS-542, ceralifimod, PF-04629991, endometriosis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 4212156 A1 (ABIVAX) 19 July 2023 (2023-07-19) the abstract, description paragraphs 21, 151-152, 191	1-6
X	US 2018217154 A1 (SAINT LOUIS UNIVERSITY) 02 August 2018 (2018-08-02) the abstract, claims 16-17, description paragraph 221	1-6
X	CN 110536694 A (ATYR PHARMA, INC.) 03 December 2019 (2019-12-03) claims 1, 12-13	5-6
X	CN 111265504 A (ZHEJIANG ZHENGXI BIOMEDICINE CO., LTD.) 12 June 2020 (2020-06-12) claim 3, description paragraph 3	5-6
X	ZHANG, F. et al. "Blocking sphingosine 1-phosphate receptor 1 with modulators reduces immune cells infiltration and alleviates endometriosis in mice" *Reprod Biomed Online*, Vol. 47, No. 5, 22 July 2023 (2023-07-22), Article 103304 (pages 1-14) the abstract, Experimental protocol	1-4

☑ Further documents are listed in the continuation of Box C. ☑ 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
"D" document cited by the applicant in the international application
"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	Date of mailing of the international search report
30 October 2024	**07 November 2024**

Name and mailing address of the ISA/CN	Authorized officer
CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China**	**WANG,SiTing** Telephone No. **(+86) 010-53962074**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YOSHINO, O. et al. "Sphingosine I Phosphate (S1P) Increased IL-6 Expression and Cell Growth in Endometriotic Cells" *Reproductive Sciences,* Vol. 26, 25 February 2021 (2021-02-25), pages 1460-1467 the abstract	1-4
X	ZHANG, F. et al. "The Sphingosine 1-Phosphate Axis: an Emerging Therapeutic Opportunity for Endometriosis" *Reproductive Sciences,* Vol. 30, No. 7, 20 January 2023 (2023-01-20), pages 2040-2059	1-4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2024/110958

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **1-2**
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 1-2 relate to a method for treating endometriosis in a subject, which fall within the criteria set out in PCT Rule 39.1(iv). The search has been carried out and based on the subject-matter of the manufacture of a medicament correspondingly.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2024/110958

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
EP	4212156	A1	19 July 2023	AU	2023207795	A1	01 August 2024
				WO	2023135207	A1	20 July 2023
				KR	20240135643	A	11 September 2024
				IL	314197	A	01 September 2024
				MX	2024008504	A	19 July 2024
US	2018217154	A1	02 August 2018	US	10877045	B2	29 December 2020
				WO	2017015334	A1	26 January 2017
CN	110536694	A	03 December 2019	CA	3060514	A1	25 October 2018
				JP	2023052761	A	12 April 2023
				EP	3612215	A1	26 February 2020
				EP	3612215	A4	26 May 2021
				EP	3612215	B1	28 August 2024
				JP	2020517638	A	18 June 2020
				WO	2018195338	A1	25 October 2018
				US	2020377874	A1	03 December 2020
				US	11767520	B2	26 September 2023
				AU	2018256435	A1	07 November 2019
CN	111265504	A	12 June 2020	None			