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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 Hematopoietic Cell Kinase inhibitor.

# METHOD AND MEDICAMENT FOR TREATING ENDOMETRIOSIS

## CROSS REFERENCE TO RELATED APPLICATION

This application claims the priority benefit of PCT International Application No. PCT/CN2023/112275, filed 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 pelvic 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 (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, 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 not being lethal, chronic pain and infertility pose significant impacts on the quality of life. The economic burden of endometriosis is estimated to reach $80 billion annually in the US alone (PMID: 35620300). Moreover, mounting evidence suggests endometriosis is a systemic disease that disturbs 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 novel druggable targets for treating endometriosis. As shown in FIG. 1A, *Hematopoietic Cell Kinase* was identified as top-ranked potential therapeutic targets by PandaOmics using 11 endometriosis transcriptomics datasets. Upregulation of Hematopoietic Cell Kinase was further confirmed at both mRNA and protein levels in the human endometriosis samples, and validated by *in vitro* and *in vivo* experiments. This study is the first demonstration of applying AI in exploring therapeutic targets for 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 Hematopoietic Cell Kinase inhibitor.

In certain embodiments, the Hematopoietic Cell Kinase inhibitor is one or more selected from the group consisting of Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

Another aspect of the present invention provides use of a Hematopoietic Cell Kinase inhibitor in manufacture of a medicament for treating endometriosis.

In certain embodiments, the Hematopoietic Cell Kinase inhibitor is one or more selected from the group consisting of Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

Another aspect of the present invention provides a medicament for use in treatment of endometriosis, wherein the medicament comprises a Hematopoietic Cell Kinase inhibitor.

In certain embodiments, the S1PR1 antagonist is one or more selected from the group consisting of Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

## BRIEF DESCRIPTION OF THE DRAWINGS

**FIGs. 1A-1B. PandaOmics identified Hematopoietic Cell Kinase as potential therapeutic targets for endometriosis.** (FIG. 1A) The pipeline of therapeutic target identification for endometriosis using PandaOmics. With the input of 11 endometriosis datasets, PandaOmics utilized a combination of Omics and text scores to prioritize targets for endometriosis (Target ID). DEG and pathway analyses were performed using the platform. After Target ID, proposed targets were subjected to IHC validation. Only validated targets were proceeded to *in vitro* and *in vivo* validation using siRNA approach. The downstream effectors were then predicted for the validated targets *via* both computational and experimental methods. (FIG. 1B) Screenshot of the Target ID page of PandaOmics for endometriosis meta-analysis. Hematopoietic Cell Kinase was revealed as novel druggable

targets for endometriosis. Data for gene expression, genetics, drugs, and text were available for the current analysis.

**FIGs. 2A-2C. Consistent dysregulation of Hematopoietic Cell Kinase in endometriosis.** (FIG. 2A) The expressions of Hematopoietic Cell Kinase in the eleven endometriosis-related comparisons were displayed in box plots. (FIG. 2B) Representative image of the paraffin-embedded human endometriotic and normal endometrial stromal tissues stained with anti-Hematopoietic Cell Kinase antibodies. (FIG. 2C) Protein expressions of Hematopoietic Cell Kinase in IHC were assessed by H-score. Data are represented as mean ± SEM. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. $P < 0.05$ is considered as statistically significant.

**FIGs. 3A-3E. Knockdown of Hematopoietic Cell Kinase inhibited proliferation and promoted apoptosis of endometriotic stromal cells.** Endometriotic stromal cells were transiently transfected with non-target siRNA control (Control) and siRNA targeting Hematopoietic Cell Kinase (siHCK). mRNA and protein expressions of (FIGs. 3A, 3B) Hematopoietic Cell Kinase in the transfected cells were examined by quantitative PCR and immunofluorescence staining with anti-Hematopoietic Cell Kinase antibodies, respectively. Representative images of the transfected cells stained with anti-Hematopoietic Cell Kinase were shown. Viability and proliferative ability of the transfected cells were assessed by (FIG. 3C) CCK8 assay and (FIG. 3D) Ki67 immunofluorescence staining, respectively. (FIG. 3E) The transfected cells were also subjected to TUNEL assay to examine their apoptotic status. The mean percentage of apoptotic cells were shown in the bar chart. Data are represented as mean ± SEM. $*P < 0.05$, $**P < 0.01$. $P < 0.05$ is considered as statistically significant.

**FIGs. 4A-4L. Knockdown of Hematopoietic Cell Kinase suppressed endometriosis *in vivo*.** (FIG. 4A) Timeline illustrating the establishment of the *in vivo* endometriosis models and siRNA treatment for investigating the effect of Hematopoietic Cell Kinase. (FIG. 4B) To assess the safety of the siRNA treatment, body weights of the mice were measured before (T0) and after (T7) the treatment. The effect of knocking down HCK in endometriosis was assessed by both subcutaneous (FIGs. 4C-4G) and intraperitoneal (FIGs. 4H-4L) endometriosis mouse models (n=5). (FIGs. 4C, 4H) The volume and weight of the excised lesions were recorded and compared. mRNA and protein expression of (FIGs. 4D-4E, FIGs. 4I-4J) Hematopoietic Cell Kinase in the murine endometriotic xenograft were analyzed by quantitative PCR and IHC. Representative images of the paraffin-embedded murine endometriotic xenografts stained with anti-Hematopoietic Cell Kinase antibodies were shown. (FIGs. 4F, 4K) Proliferation and (FIGs. 4G, 4L) apoptosis status of the xenograft treated with siRNA against Hematopoietic Cell Kinase were analyzed by Ki-67 IHC staining and TUNEL assay, respectively. Representative images of each experimental group were displayed. Data are represented as mean ± SEM. $*P < 0.05$, $**P < 0.01$. $P < 0.05$ is considered as statistically significant.

**FIG. 5. Potentiality of Hematopoietic Cell Kinase as immune targets in endometriosis.** Dysregulated pathways associated with Hematopoietic Cell Kinase 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. Pathways labeled in blue are immune-associated.

**FIG. 6. Expressions of Hematopoietic Cell Kinase were dysregulated in endometriosis proteomics datasets.** Protein expression boxplots for Hematopoietic Cell Kinase in the endometriosis proteomics dataset PDX006553, retrieved from the ProteomeXchange Consortium.

## 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). As used herein, “inhibitor” and “antagonist” can also be refereed to an “active agent”.

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.

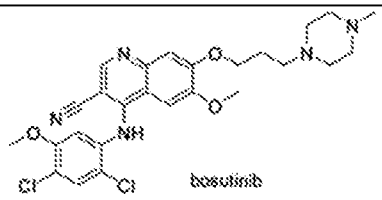
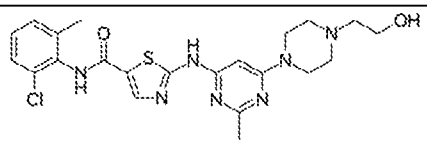
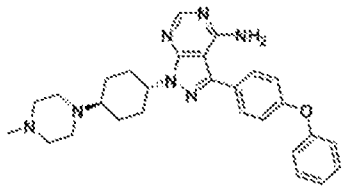
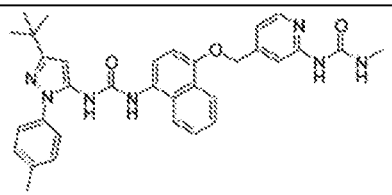
**Active agents for treating endometriosis**

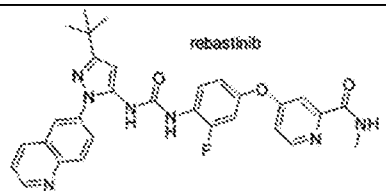
The inventor discovered through extensive research a target, Hemopoietic Cell Kinase (HCK), for treating endometriosis. An antagonist or agonist of the target may be used to treat endometriosis.

The hematopoietic cell kinase is a member of the SRC family of cytoplasmic tyrosine kinases (SFKs), and is expressed in cells of the myeloid and B-lymphocyte cell lineages. Excessive Hematopoietic Cell Kinase activation is associated with several types of leukemia and enhances cell proliferation and survival by physical association with oncogenic fusion proteins, and with functional interactions with receptor tyrosine kinases. Elevated activity of the Hematopoietic Cell Kinase is also observed in many solid malignancies, including breast and colon cancer, and correlates with decreased patient survival rates. Hematopoietic Cell Kinase enhances the secretion of growth factors and pro-inflammatory cytokines from myeloid cells, and promotes macrophage polarization towards a wound healing and tumor-promoting alternatively activated phenotype.

The active agent used to treat endometriosis can be any one selected from the group consisting of inhibitor of Hematopoietic Cell Kinase, including but not limited to Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

The structures of the exemplified inhibitors of Hematopoietic Cell Kinase are shown below.

| | |
|---|---|
| Bosutinib |  |
| Dasatinib |  |
| KIN-8194 |  |
| RV568 |  |

| | |
|---|---|
| Rebastinib |  |

The amount of each of the active agents in a unit dosage form may be 1-1000 mg, 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 0.1 μg/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 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 8 mg/kg, 10 mg/kg, 20 mg/kg, 25 mg/kg, 40 mg/kg, 50 mg /kg, 60 mg/kg, 75 mg/kg, 100 mg/kg, 120 mg/kg, 150 mg/kg, 175 mg/kg, 200 mg/kg, 225 mg/kg, 250 mg/kg or 300 mg/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.

#### 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.

**Experimental validation of the potential targets**

Following the identification of potential therapeutic targets based on PandaOmics and expression analysis, the targets were subjected to immunohistochemistry (IHC) analysis in the human paraffin-embedded ovarian endometrial stromal (EMS), peritoneal EMS and normal EMS tissue to confirm their protein expressions using anti-Hematopoietic Cell Kinase antibody.

Functional analysis of the confirmed targets was first performed in the EMS cells using siRNA knockdown approach. EMS cells were transfected with 10nM of non-target control siRNA or siRNA targeting Hematopoietic Cell Kinase, and expression of Hematopoietic Cell Kinase was confirmed by quantitative PCR (qPCR) and immunofluorescence (IF) staining with anti-Hematopoietic Cell Kinase antibody. Three functional assays were performed subsequently, including CCK8 assay for cell viability, IF staining against anti-Ki-67 antibody for cell proliferation, and TUNEL assays for apoptosis assay. Both CCK8 and TUNEL assays were conducted according to the manufacturer's instructions.

Endometriosis mimic mouse models were established by the subcutaneous and intraperitoneal transplantation of the endometrial tissue dissected from the uterus horns of a healthy female mouse in another healthy female mouse, respectively. 2 weeks following the transplantation, the mice were divided into two groups, and subjected to either of the treatments: intraperitoneal administration of siRNA of Hematopoietic Cell Kinase or non-target siRNA control, for a week. Body weight of the mice was monitored daily. At day 7, mice were sacrificed and the peritoneal lesions were excised. Lesion volume and weight were recorded. The xenografts underwent expression validation of Hematopoietic Cell Kinase by qPCR and IHC, followed by Ki-67 IHC staining and TUNEL assay.

**2. Results**

**Identification of Hematopoietic Cell Kinase as potential therapeutic targets 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, 141 unique genes with three levels of novelties 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. Hematopoietic Cell Kinase was identified as potential therapeutic candidates for endometriosis. It ranked as the top-50 targets under novel settings in the meta-analysis, and had 6 Omics score models having 6 models scored 0.8 or above (FIG. 1B).

**Consistent upregulation of Hematopoietic Cell Kinase in endometriotic samples**

To investigate the functional correlation of Hematopoietic Cell Kinase with endometriosis, expression profiles between samples collected from the endometriosis lesions and control endometrium were analyzed. Regarding the bulk transcriptomics profiles, Hematopoietic Cell Kinase were upregulated in 8 out of 11 comparisons, with 3 of the upregulations reaching statistically significant (FDR < 0.05), respectively (FIG. 2A).

Immunohistochemistry (IHC) staining was performed to evaluate the protein expression dysregulation of the targets in the paraffin-embedded ovarian and peritoneal EMS tissue samples, and revealed Hematopoietic Cell Kinase was significantly overexpressed in the ovarian EMS tissues in contrast to the normal endometrial stroma (FIG. 2B and 2C). We also observed the expression dysregulation of the targets in three endometriosis proteomics datasets. Hematopoietic Cell Kinase was observed in one of the comparisons. Despite not reaching statistical significance, it was upregulated in the endometriotic samples when compared to the healthy controls (FIG. 6). Taken altogether, consistent upregulations of Hematopoietic Cell Kinase were observed in mRNA and protein levels in endometriosis samples, supporting its potential in driving endometriosis.

**Knockdown of *Hematopoietic Cell Kinase* diminished endometriosis *in vitro* and *in vivo***

To delineate the functional roles of Hematopoietic Cell Kinase in endometriosis, knockdown of Hematopoietic Cell Kinase (siHCK) was conducted in endometriotic stromal cells through transient transfection of siRNAs. Both quantitative PCR (qPCR) analysis and immunofluorescence (IF) staining confirmed the silencing of Hematopoietic Cell Kinase in siHCK cells (FIG. 3A and 3B). Functionally, knockdowns of Hematopoietic Cell Kinase significantly diminished viability (FIG. 3C) and immunofluorescence intensity of Ki-67 (FIG. 3D) of the transfected stromal cells. In addition, the percentage of apoptotic cells increased by at least 3 fold upon knockdown of Hematopoietic Cell Kinase (FIG. 3E).

Functional characterization of Hematopoietic Cell Kinase in the endometriosis mouse model was performed in a similar manner. After successful subcutaneous and intraperitoneal implantation of endometrial tissue respectively, the mice were subjected to siRNA treatments for a week (FIG. 4A). As reflected by the steady increase in body weight, treatment with siHCK demonstrated no deleterious effect on the mice (FIG. 4B). In contrast to those treated with control siRNA, both the volume and weight were significantly reduced in subcutaneous

lesions treated with siHCK (FIG. 4C). Subcutaneous lesions treated with siHCK showed reduced Hematopoietic Cell Kinase expression at mRNA (FIG. 4D) and protein levels (FIG. 4E). Consistent with the *in vitro* results, siHCK treatment decreased Ki-67 IHC staining intensity in the endometriotic cells (FIG. 4F). Inhibition of Hematopoietic Cell Kinase also significantly promoted cell apoptosis (FIG. 4G). Similar to the subcutaneous treatment, intraperitoneal treatment of HCK significantly reduced ectopic lesion growth (FIG. 4H). Target knockdown was confirmed for siHCK (FIG. 4I). siHCK tended to decrease the proliferative ability of the endometriotic cells (FIG. 4K) and significantly induced apoptosis in the ectopic lesions (FIG. 4L). Taking both the *in vitro* and *in vivo* results into account, inhibition of Hematopoietic Cell Kinase exhibited protection against endometriosis through suppression of cell proliferation and activation of apoptosis, suggesting its possibility as therapeutics for endometriosis.

**Hematopoietic Cell Kinase as an immune target in endometriosis**

Subsequent to the functional characterization, dysregulated pathway analysis was performed to address the mechanistic explanation of the effect of Hematopoietic Cell Kinase on endometriosis. As shown in FIG. 5, the number of comparisons having significant dysregulation of each pathway ($P < 0.05$) was indicated by the length of the bar, by which green and red represent activation and inhibition, respectively. The majority of the altered pathways associated with Hematopoietic Cell Kinase was linked to immune and infection (*lower panel*). Four out of eight Hematopoietic Cell Kinase-associated immune pathways (labeled in blue) were activated. These spotted the potential for developing Hematopoietic Cell Kinase as immune targets.

## CLAIMS

1. A method for treating endometriosis in a subject in need thereof, comprising administering to the subject an effective amount of a Hematopoietic Cell Kinase inhibitor.

2. The method according to claim 1, wherein the Hematopoietic Cell Kinase inhibitor is one or more selected from the group consisting of Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

3. Use of a Hematopoietic Cell Kinase inhibitor in manufacture of a medicament for treating endometriosis.

4. The use according to claim 3, wherein the Hematopoietic Cell Kinase inhibitor is one or more selected from the group consisting of Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

5. A medicament for use in treatment of endometriosis, wherein the medicament comprises a Hematopoietic Cell Kinase inhibitor.

6. The medicament for use according to claim 5, wherein the Hematopoietic Cell Kinase inhibitor is one or more selected from the group consisting of Bosutinib, Dasatinib, KIN-8194, RV568, Rebastinib, and a derivative thereof.

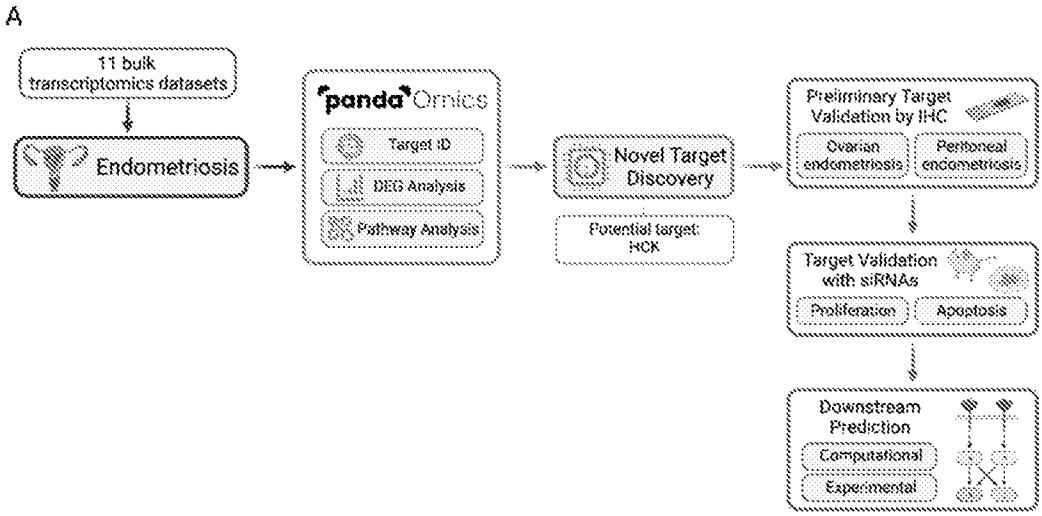

A
11 bulk transcriptomics datasets
Endometriosis
pandaOmics
Target ID
DEG Analysis
Pathway Analysis
Novel Target Discovery
Potential target: HCK
Preliminary Target Validation by IHC
Ovarian endometriosis
Peritoneal endometriosis
Target Validation with siRNAs
Proliferation
Apoptosis
Downstream Prediction
Computational
Experimental

FIG. 1A

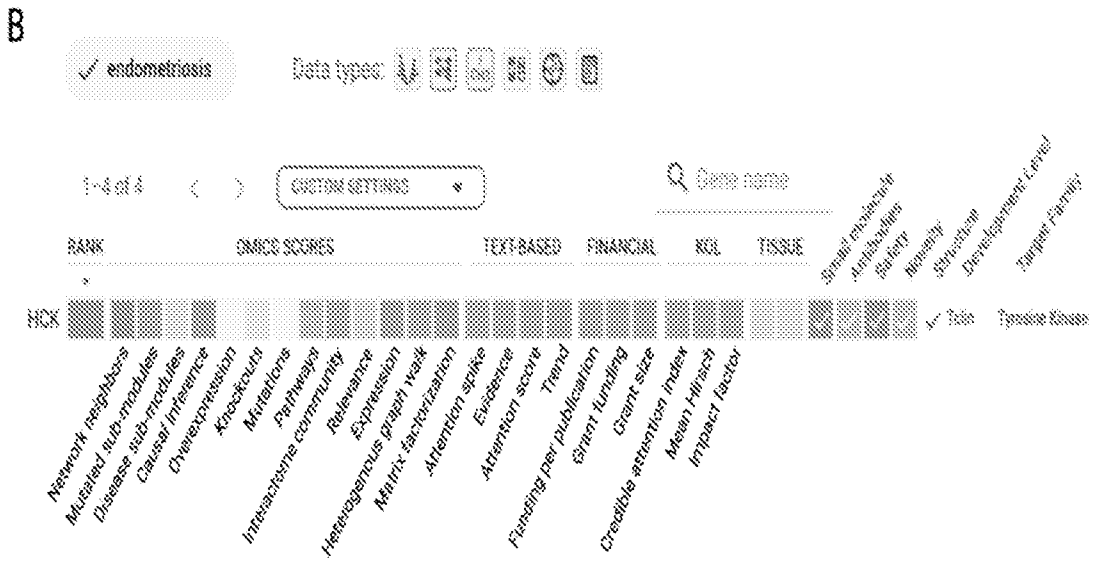

B
endometriosis
Data types
RANK
OMICS SCORES
TEXT-BASED
FINANCIAL
KOL
TISSUE
HCK
Network neighbors
Mutated sub-modules
Disease sub-modules
Causal interface
Overexpression
Knockouts
Mutations
Pathways
Interactome community
Relevance
Expression
Heterogeneous graph walk
Matrix factorization
Attention spike
Evidence
Attention score
Trend
Funding per publication
Grant funding
Grant size
Credible attention index
Mean H-index
Impact factor

FIG. 1B

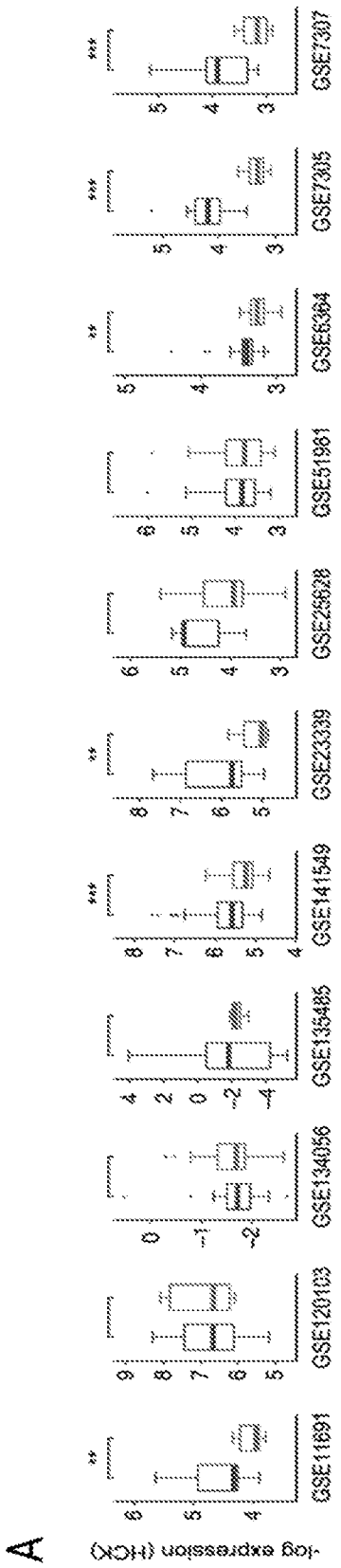

A
-log expression (HCK)
GSE11691
GSE120103
GSE134056
GSE135485
GSE141549
GSE23339
GSE25628
GSE51961
GSE6364
GSE7305
GSE7307

FIG. 2A

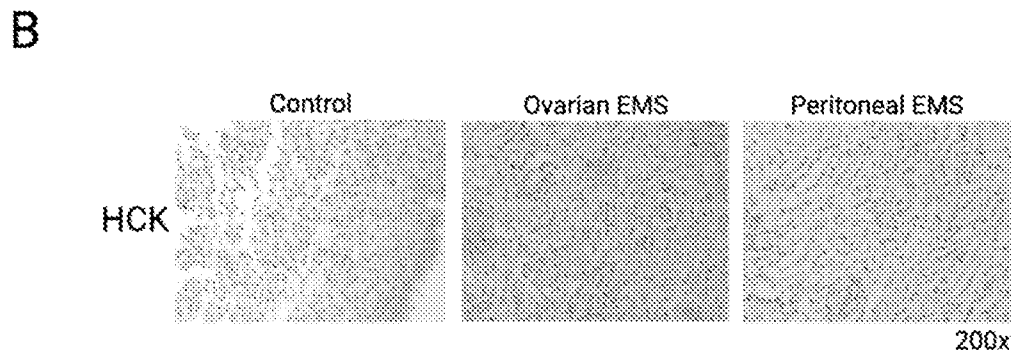

B
Control
Ovarian EMS
Peritoneal EMS
HCK
200x

FIG. 2B

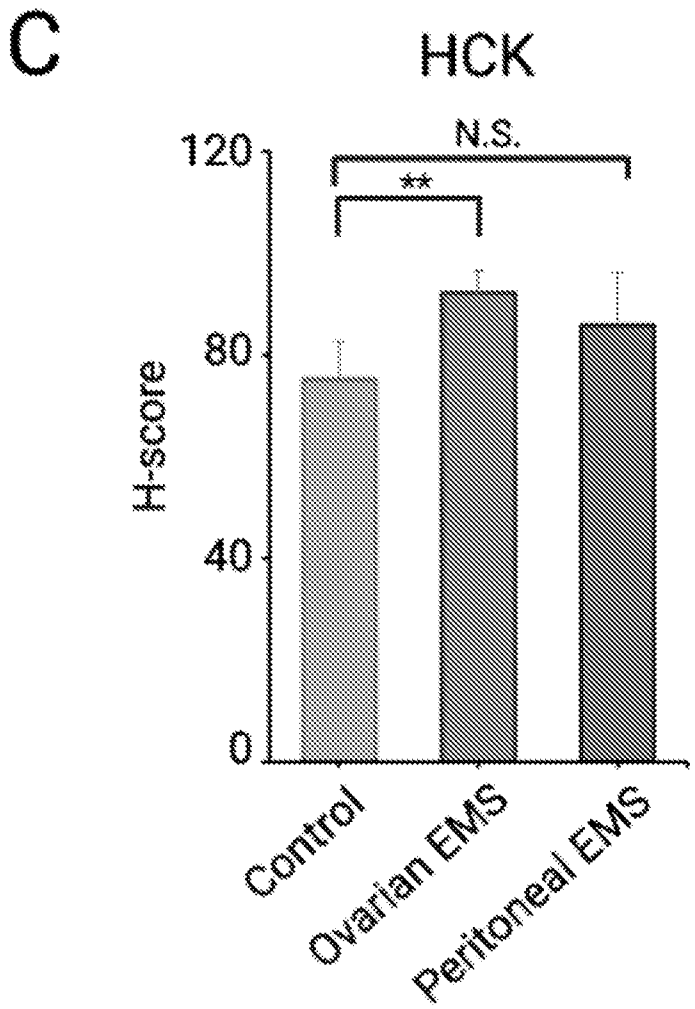

C
HCK
N.S.
**
120
80
40
0
H-score
Control
Ovarian EMS
Peritoneal EMS

FIG. 2C

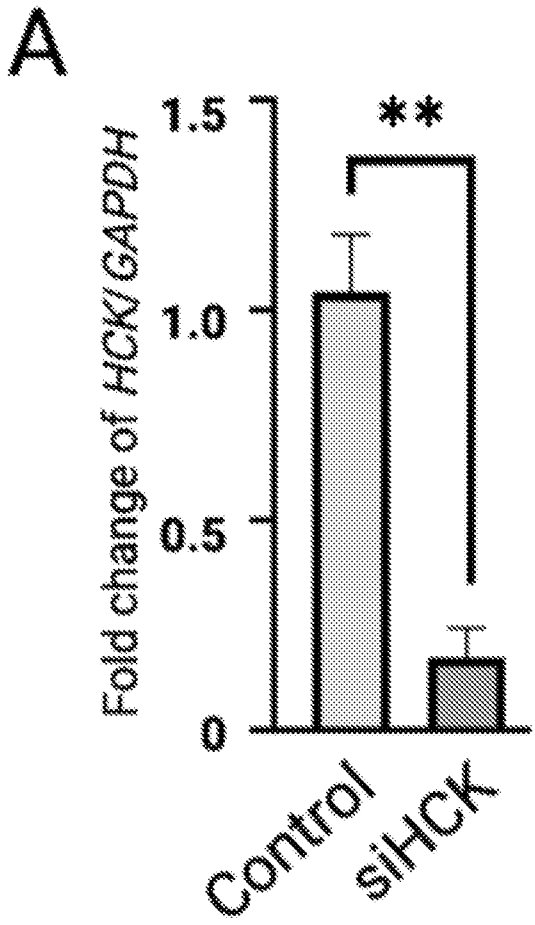

A
Fold change of HCK/GAPDH
1.5
1.0
0.5
0
**
Control
siHCK

FIG. 3A

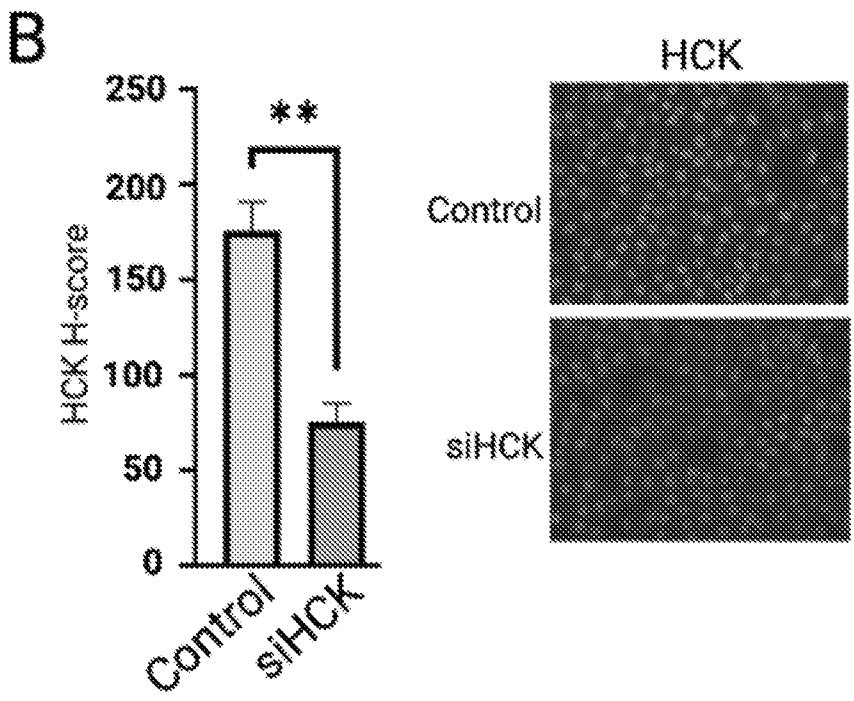

B
HCK H-score
250
200
150
100
50
0
**
Control
siHCK
HCK
Control
siHCK

FIG. 3B

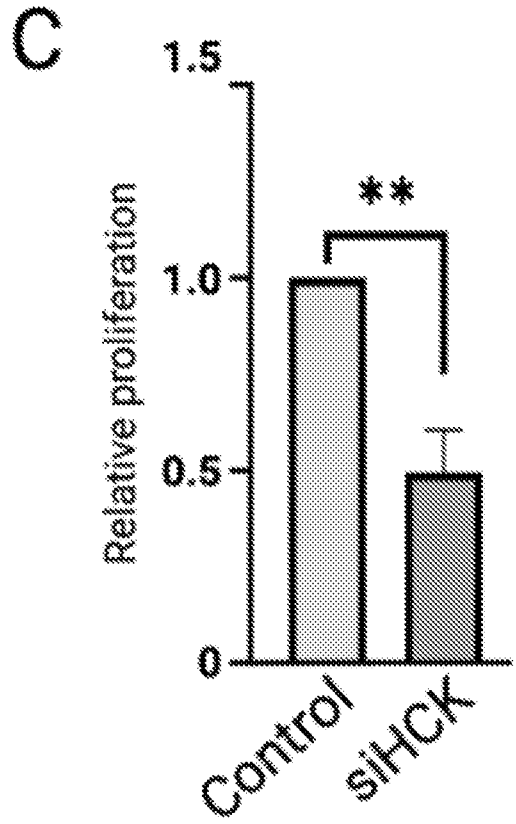

C
1.5
1.0
0.5
0
Relative proliferation
**
Control
siHCK

FIG. 3C

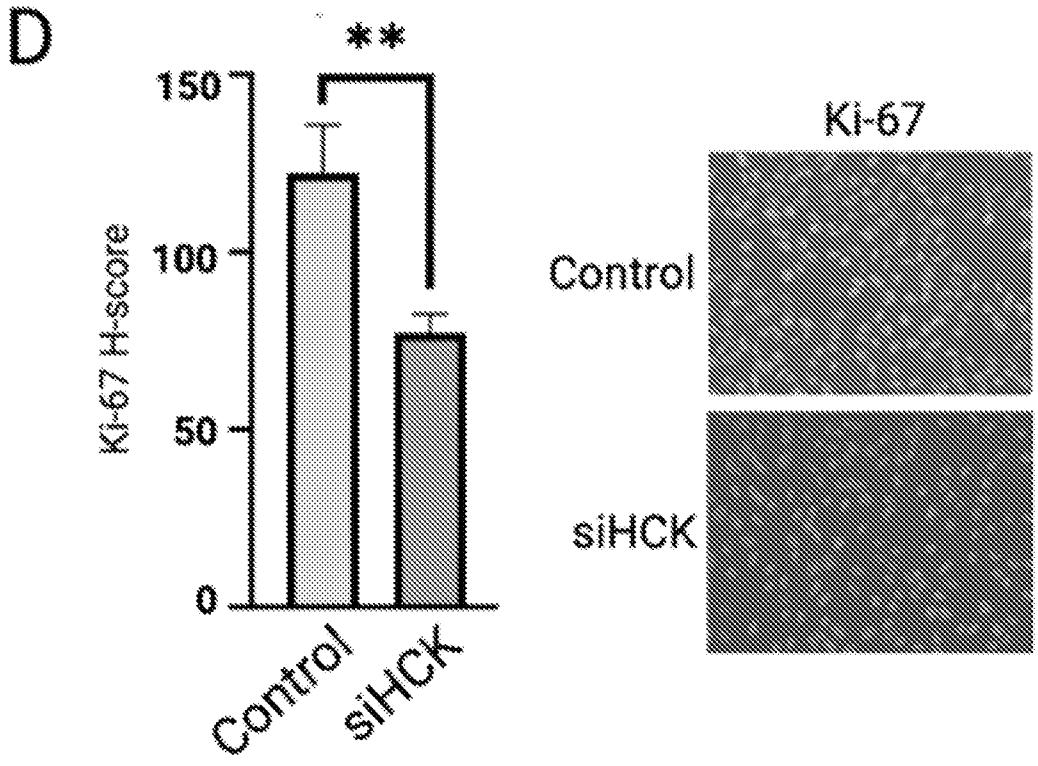

D
**
150
100
50
0
Ki-67 H-score
Control
siHCK
Ki-67
Control
siHCK

FIG. 3D

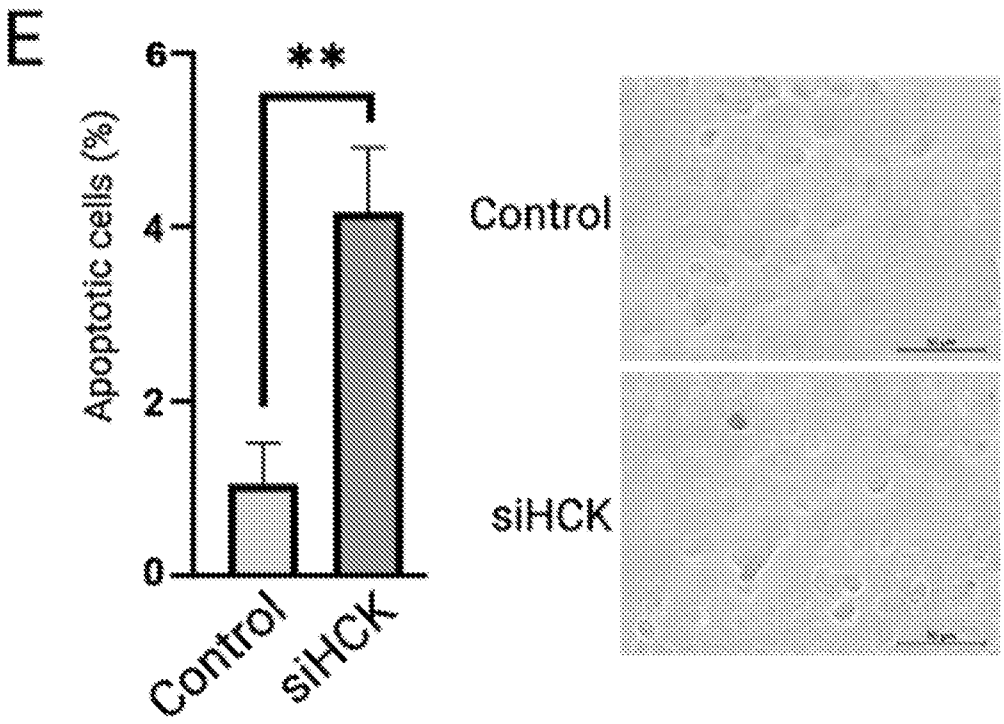

E
Apoptotic cells (%)
6
4
2
0
**
Control
siHCK
Control
siHCK

FIG. 3E

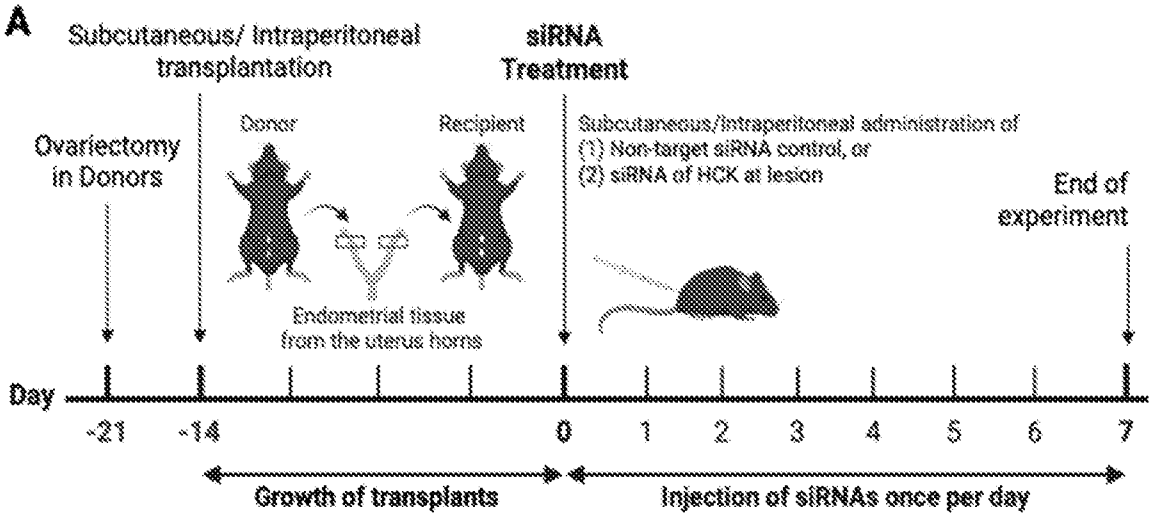

A
Subcutaneous/ Intraperitoneal transplantation
siRNA Treatment
Ovariectomy in Donors
Donor
Recipient
Endometrial tissue from the uterus horns
Subcutaneous/Intraperitoneal administration of
(1) Non-target siRNA control, or
(2) siRNA of HCK at lesion
End of experiment
Day
-21
-14
0
1
2
3
4
5
6
7
Growth of transplants
Injection of siRNAs once per day

FIG. 4A

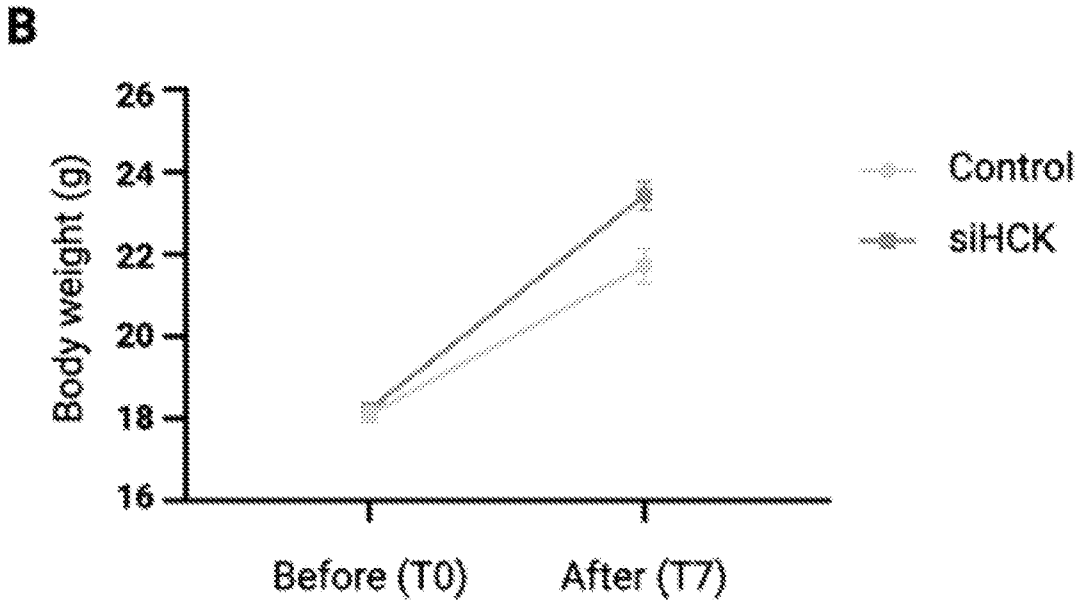

B
Body weight (g)
26
24
22
20
18
16
Before (T0)
After (T7)
Control
siHCK

FIG. 4B

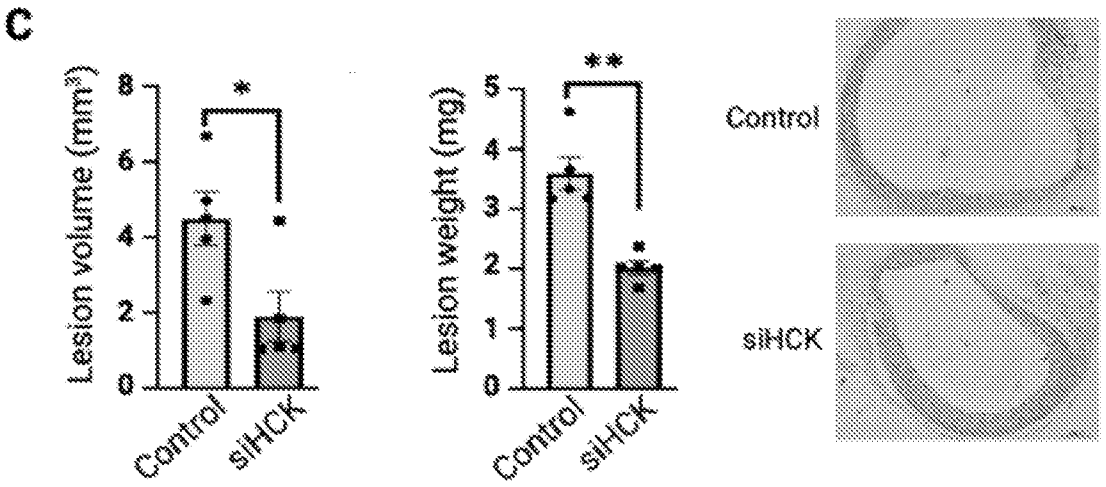

C
Lesion volume (mm³)
Lesion weight (mg)
Control
siHCK
Control
siHCK

FIG. 4C

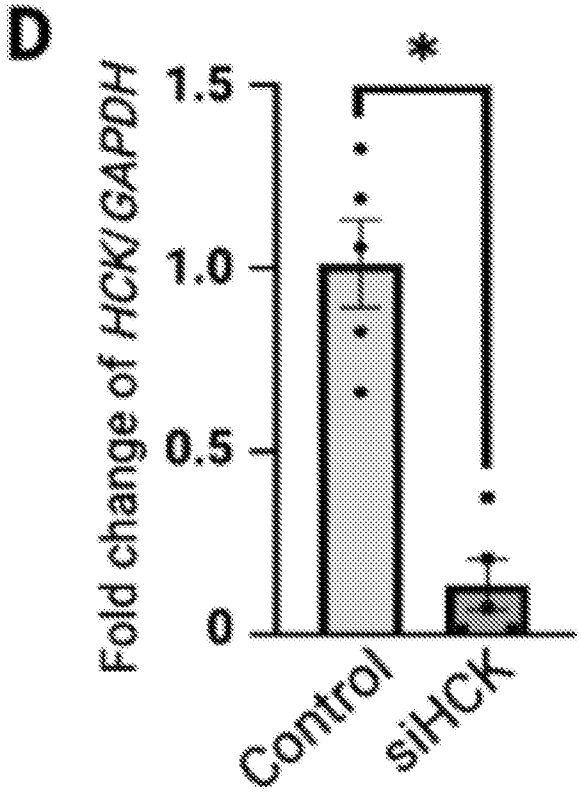

D
Fold change of HCK/GAPDH
1.5
1.0
0.5
0
*
Control
siHCK

FIG. 4D

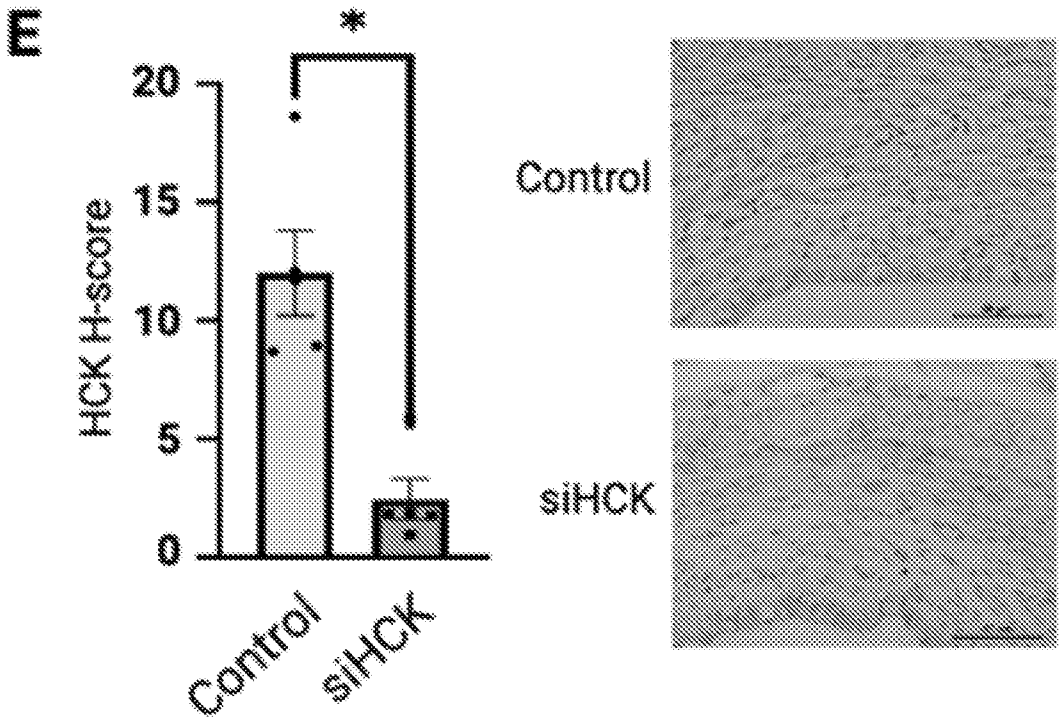

E
HCK H-score
20
15
10
5
0
*
Control
siHCK
Control
siHCK

FIG. 4E

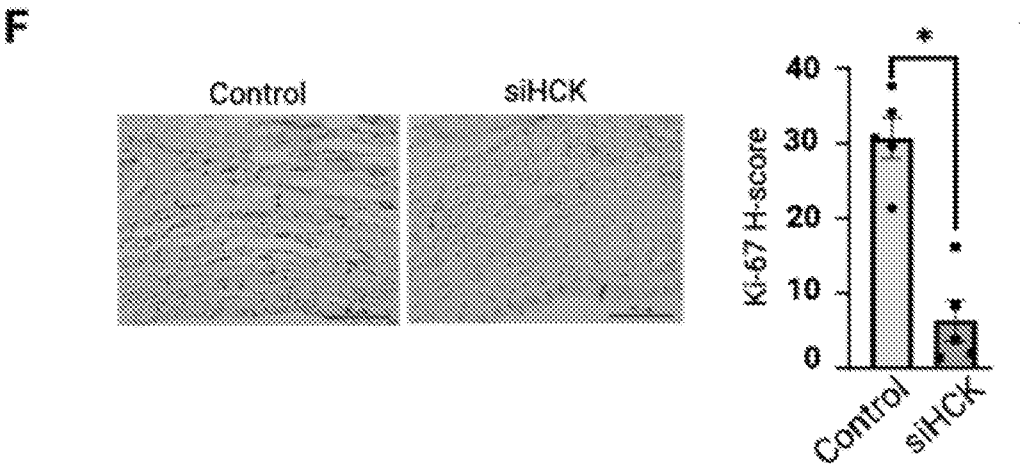



FIG. 4F

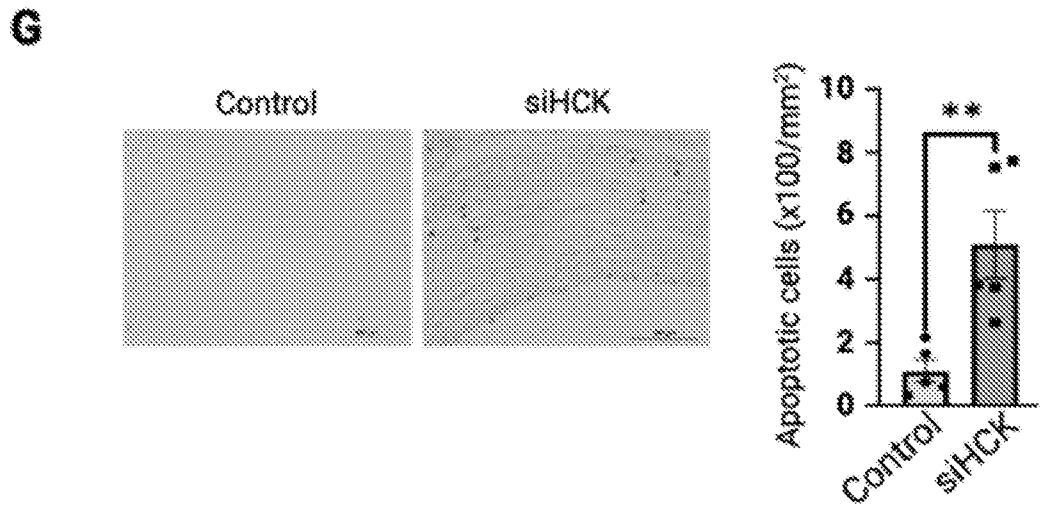



FIG. 4G

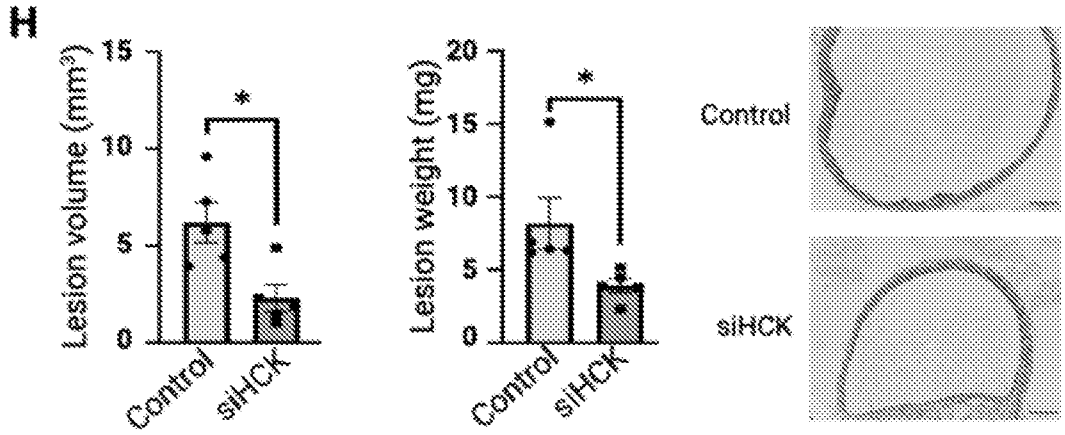



FIG. 4H

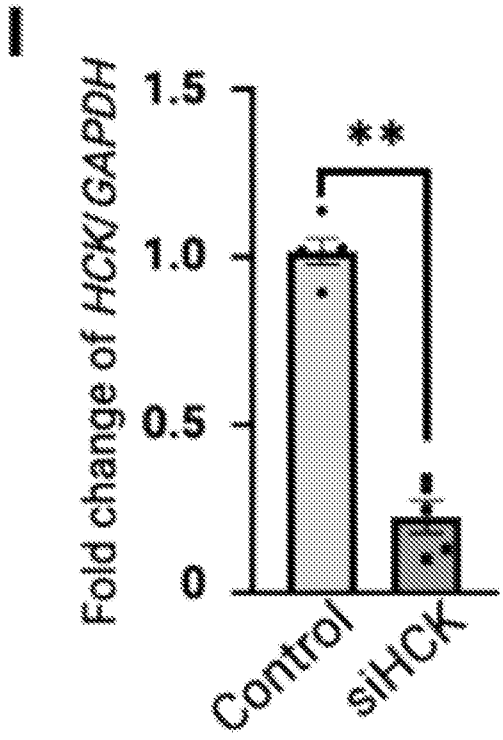

I
Fold change of HCK/GAPDH
1.5
1.0
0.5
0
**
**
Control
siHCK

FIG. 4I

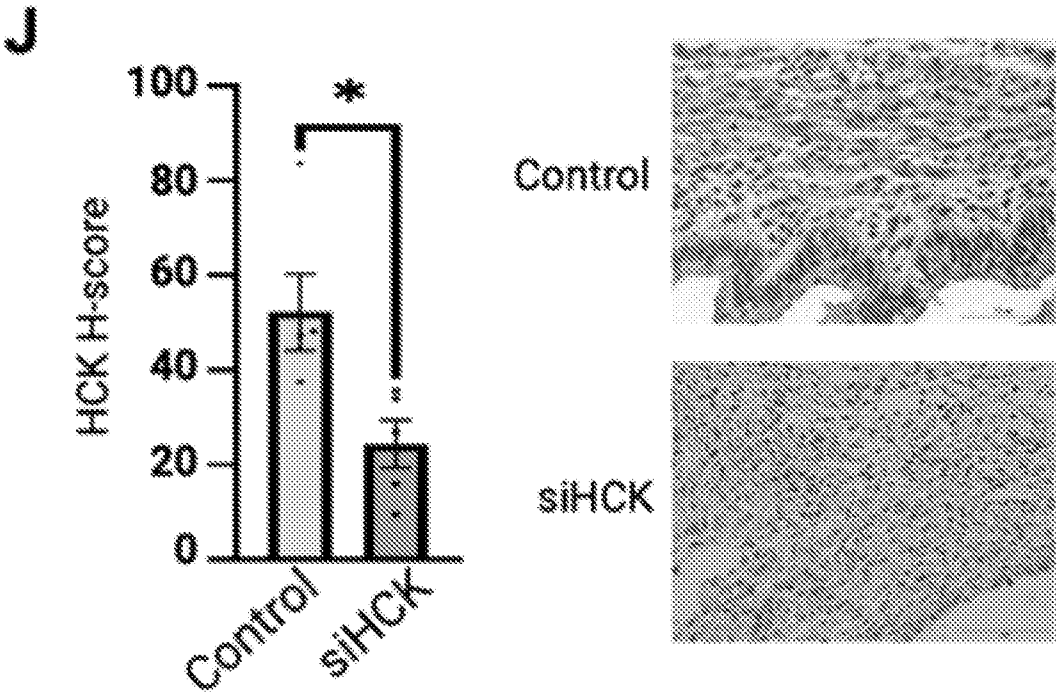

J
HCK H-score
100
80
60
40
20
0
*
Control
siHCK
Control
siHCK

FIG. 4J

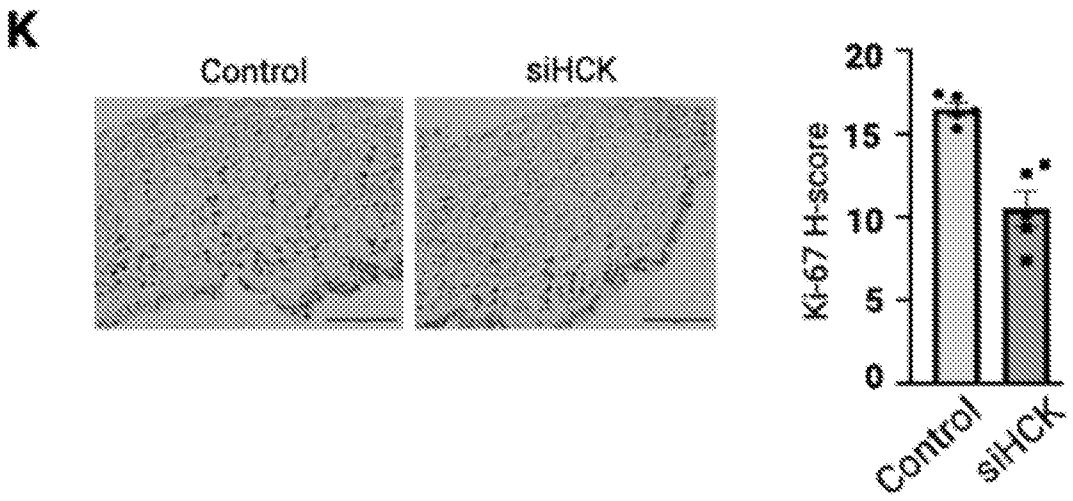

K
Control
siHCK
Ki-67 H-score
20
15
10
5
0
Control
siHCK

FIG. 4K

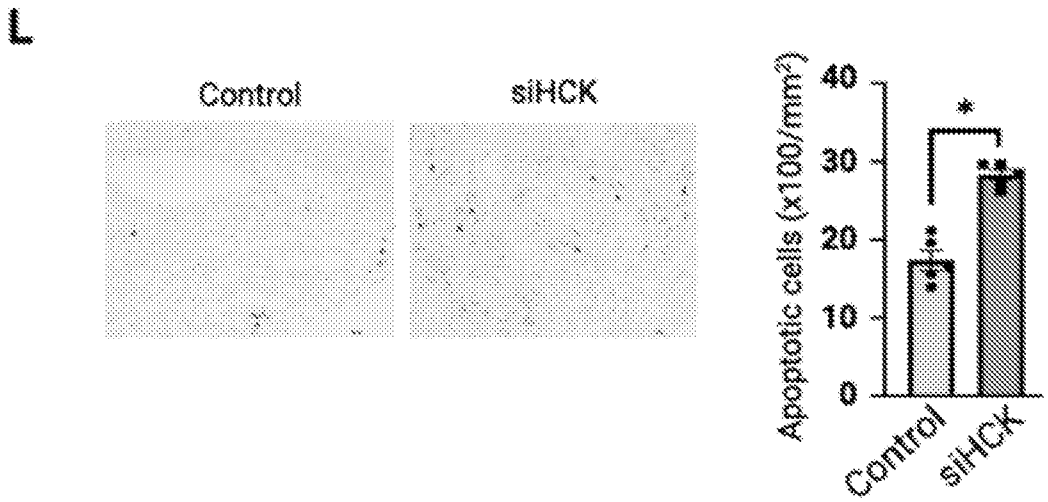

L
Control
siHCK
Apoptotic cells (x100/mm²)
40
30
20
10
0
*
Control
siHCK

FIG. 4L

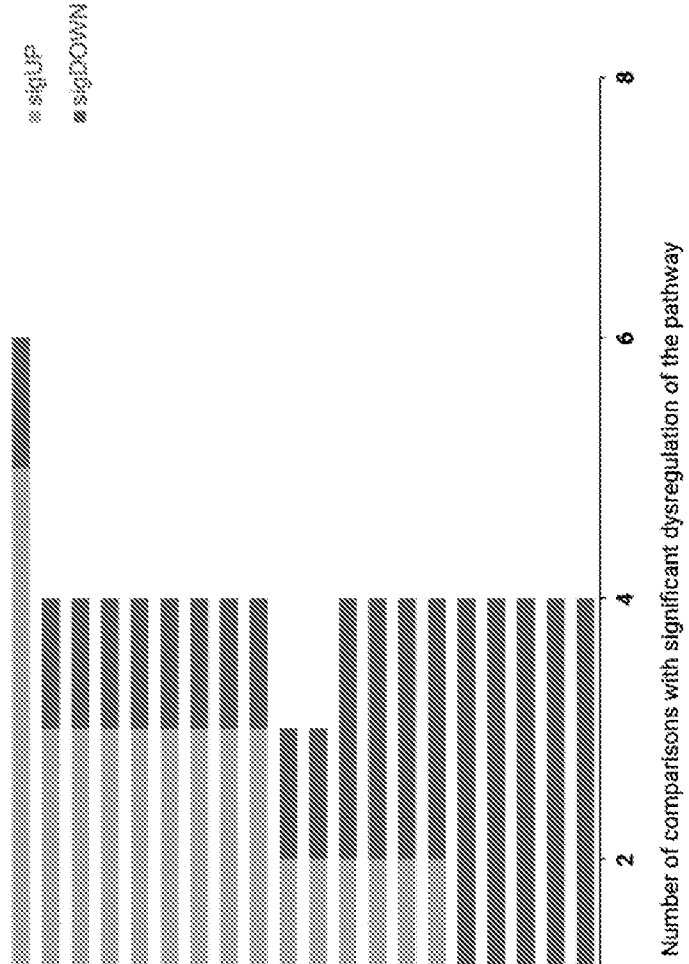

sigUP
sigDOWN
Nef and signal transduction
Anti-inflammatory response favoring Leishmania parasite infection
FCGR3A-mediated IL10 synthesis
Leishmania infection
Leishmania parasite growth and survival
Cytokine signaling in immune system
FLT3 signaling
Interleukin-3, Interleukin-5 and GM-CSF signaling
Signaling by Interleukins
FCGR3A-mediated phagocytosis
Leishmania phagocytosis
Parasite infection
Fcgamma receptor (FCGR) dependent phagocytosis
FCGR activation
Innate immune system
The role of Nef in HIV-1 replication and disease pathogenesis
Regulation of signaling by CBL
HIV infection
Host interactions of HIV factors
Infectious disease
0
2
4
6
8
Number of comparisons with significant dysregulation of the pathway

FIG. 5

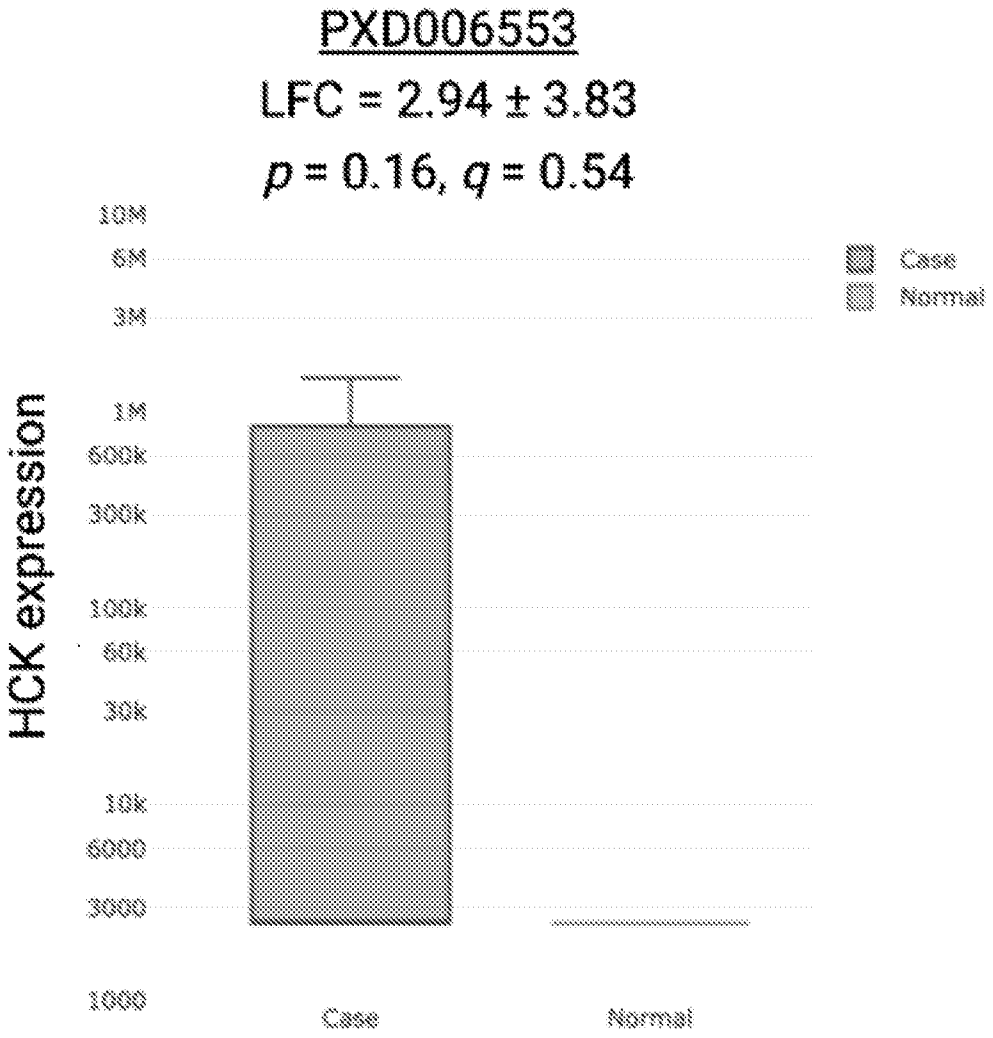

PXD006553
LFC = 2.94 ± 3.83
p = 0.16, q = 0.54
HCK expression
10M
6M
3M
1M
600k
300k
100k
60k
30k
10k
6000
3000
1000
Case
Normal
Case
Normal

FIG. 6

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/CN2024/110949**

## A. CLASSIFICATION OF SUBJECT MATTER

A61K45/00(2006.01)i; A61K31/495(2006.01)i; A61K31/505(2006.01)i; A61P37/00(2006.01)i; A61P43/00(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)

CNTXT,DWPI,WPABSC,ENTXTC,VCN,CJFD,CNKI,BAIDU, Bing, PubMed, ISI-Web of Science,endometriosis, Hematopoietic Cell Kinase,Bosutinib, Dasatinib, KIN-8194, RV568, JIN-49095397,Rebastinib,DCC-2036,EGFR,Sunitinib, Bruton tyrosine kinase

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | HE Ying, et al. "Receptor Tyrosine Kinase Inhibitor Sunitinib as Novel Immunotherapy to Inhibit Myeloid-Derived Suppressor Cells for Treatment of Endometriosis" *Immunotherapy of Endometriosis,* Vol. 12, 22 July 2021 (2021-07-22), pages 1-12 | 1-4 |
| X | CN 107530298 A (YALE UNIVERSITY) 02 January 2018 (2018-01-02) claims 18-23 | 5-6 |
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☑ 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 |
|---|---|
| **24 October 2024** | **30 October 2024** |
| Name and mailing address of the ISA/CN<br>**CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION**<br>**6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** | Authorized officer<br>**DU,Jun**<br>Telephone No. **(+86) 010-53960623** |

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| PX | CN 117338784 A (CHANG GENG UNIVERSITY) 05 January 2024 (2024-01-05)<br>claim 1 and paragraph 0003 | 5-6 |
| A | CHATTERJEE Kasturi, et al. "EGFR-mediated matrix metalloproteinase-7 up-regulation promotes epithelial-mesenchymal transition via ERK1-AP1 axis during ovarian endometriosis progression"<br>*The FASEB Journal,* 20 March 2018 (2018-03-20),<br>pages 4560-4572 | 3-6 |
| A | WO 0059901 A1 (BASF AKTIENGESELLSCHAFT) 12 October 2000 (2000-10-12)<br>description page 4 lines1-32,page 33 lines 1-26 | 3-6 |
| A | US 2018259533 A1 (SOMALOGIC, INC.) 13 September 2018 (2018-09-13)<br>table 11 | 3-6 |
| A | GUO Lulu, et al. "The Research Progress of VEGF-A in Endometriosis"<br>*Journal of International Obstetrics and Gynecology,* No. 01, 15 February 2018 (2018-02-15),<br>pages 112-113 | 3-6 |

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/CN2024/110949**

**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:

Claims1-2 direct to a method of treating endometriosis by using Hematopoietic Cell Kinase inhibitor. They do not meet the criteria set out in PCT Rules 39.1(iv). The search has been carried out and based on the use of claims 1-2 for Hematopoietic Cell Kinase inhibitor in manufacture of a medicament for treating endometriosis.

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/CN2024/110949**

| Patent document cited in search report | | | Publication date (day/month/year) | Patent family member(s) | | | Publication date (day/month/year) |
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**INTERNATIONAL SEARCH REPORT**
**Information on patent family members**

International application No.
**PCT/CN2024/110949**

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