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(54) Title: AGENTS TARGETING FIDGETIN-LIKE 2 AND USES THEREOF

(57) Abstract: Nucleic acid molecules and compositions thereof targeted to fidgetin-like 2, and methods of their use in treating a pathological condition in a human subject are described.

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AGENTS TARGETING FIDGETIN-LIKE 2 AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to U.S. Provisional Patent Application Serial No. 63/600,001, filed November 16, 2023, and is incorporated herein by reference in its entirety.

INCORPORATION BY REFERENCE OF SEQUENCE LISTING

[002] The instant application contains a Sequence Listing conforming the rules of WIPO Standard ST.26 which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. The XML copy, created on November 14, 2024, is named P-622979-PC_SQL_ST26_14NOV24.xml and is 17,605 bytes in size.

BACKGROUND

[003] The development of safe and effective therapies for treating acute and chronic wounds among other pathologies is an issue currently of great interest to clinical scientists and industry, alike. For example, wound healing is an intricate, multi-stage process that relies heavily on the delivery of new cells to the wound zone. Two key elements of the wound healing response are fibroplasia and epithelialization when fibroblasts and epithelial cells, respectively, enter the wound to form a protective barrier from the external environment. This is stimulated by cell proliferation and migration from the wound edge. The identification of agents that increase the rate at which cells invade and close a wound would represent a major advance in wound healing therapeutics. Ideally, this would be a topically or locally applied agent that stimulates the proliferation and migration of fibroblasts and wound edge epithelial cells. Such agents may also be useful for treating other pathologies.

[004] The disclosures of all publications, patents, patent application publications and books referred to in this application are hereby incorporated by reference in their entirety into the subject application to more fully describe the art to which the present disclosure pertains.

SUMMARY

[005] In one aspect, a nucleic acid molecule is provided comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1). In one aspect, a nucleic acid molecule is provided comprising the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2). In some embodiments, the nucleic acid molecule comprises no more than 52 nucleotides.

[006] In one aspect, a double stranded nucleic acid molecule is provided wherein one strand comprises the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1). In some embodiments, the sequence comprising GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) comprises no more than 52 nucleotides.

[007] In one aspect, a double stranded nucleic acid molecule is provided wherein one strand comprises the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2). In some embodiments, the sequence comprising AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2) comprises no more than 52 nucleotides.

[008] In one aspect, a double stranded nucleic acid molecule is provided comprising a strand comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and a strand comprising the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2). In some embodiments, each sequence comprises no more than 52 nucleotides.

[009] In one aspect, a nucleic acid molecule is provided consisting of the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

[0010] In one aspect, a nucleic acid molecule is provided consisting of the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0011] In one aspect, a double stranded nucleic acid molecule is provided wherein one strand consists of GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

[0012] In one aspect, a double stranded nucleic acid molecule is provided wherein one strand consists of AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2)

[0013] In one aspect, a double stranded nucleic acid molecule is provided consisting of GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0014] In any of the foregoing aspects, SEQ ID NO:1 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21; and SEQ ID NO:2 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21.

[0015] In any of the foregoing aspects, the nucleic acid has at least one modification selected from a 3' overhang, a 5' overhang, a 5' phosphorylation, a 2' sugar modification, a nucleic acid base modification, a phosphate backbone modification, a phosphodiester cap, or any combination of one or more of any of the foregoing. In any of the foregoing aspects, the one or more modification is 2'-O-methyl-adenosine, 2'-O-methyl-uridine, 2'-O-methyl-cytosine, 2'-O-methyl-guanosine, 2'-O-methyl-thymidine, 2'-fluoro-adenosine, 2'-fluoro-cytidine, 2'-fluoro-guanosine, 2'-fluoro-uracil, 2'-fluoro-thymidine, deoxycytosine, deoxyguanosine, deoxyadenosine, deoxythymidine, deoxyuridine, a locked adenosine, a locked uridine, a locked guanosine, a locked cytidine, a phosphorothioate, a phosphodiester cap, or any combination thereof.

[0016] In one aspect, a composition is provided comprising any of the foregoing nucleic acid molecules or double-stranded nucleic acids, and a pharmaceutically acceptable carrier, vehicle, excipient or diluent.

[0017] In some embodiments, the carrier comprises at least one of the following: saline, a sugar, a polypeptide, a polymer, a lipid, a cream, a gel, a micelle material, a wafer, a liposome or a nanoparticle. In some embodiments, the carrier comprises at least one of the following: a glucose solution, a polycationic binding agent, a cationic lipid, a cationic micelle, a cationic polypeptide, a hydrophilic polymer grafted polymer, a non-natural cationic polymer, a cationic polyacetal, a hydrophilic polymer grafted polyacetal, a ligand functionalized cationic polymer, a nucleic acid delivery vehicle, a ligand functionalized-hydrophilic polymer grafted polymer, or a ligand functionalized liposome. In some embodiments, the carrier comprises a cationic polymer-nucleic acid complex. In some embodiments, the hydrophilic polymer is polyethylene glycol (PEG).

[0018] In some aspects, the nanoparticle is a liposomal nanoparticle.

[0019] In some embodiments, the carries comprises collagen. In some embodiments the composition is collagen microparticles. In some embodiments the nucleic acid molecule is adsorbed to the collagen. In some embodiments, the collagen microparticles are provided in a surfactant polymer dressing. In some embodiments the polymer comprises a poloxamer.

[0020] In some embodiments, the nucleic acid is provided in a liposome, microparticle or nanoparticle.

[0021] In one aspect, a method is provided for treating a pathological process in a subject comprising administering to the subject a therapeutically effective amount of any of the foregoing nucleic acids or compositions thereof. Non-limiting examples of pathological processes include healing for example from a wound, burn, neuropathy, vasculopathy, or cardiopathy, whether as a result of external injury or trauma, or as a result of a disease process. In one embodiment, the disease process may be induced by an external injury or wound, or an infection, metabolic disorder, and the like. In some embodiments, the method is directed to treating the disease process that occurs after an initial disease induction event. In some embodiments the pathological process or disease is acute. In some embodiments the pathological process or disease is chronic.

[0022] In one aspect, a method is provided for treating a wound, injury or other pathological process, or inhibiting, reducing or preventing a scar or other pathological process in a subject comprising administering to the subject a therapeutically effective amount of any of the foregoing nucleic acids or compositions thereof. In some embodiments, the wound, injury or scar is of the skin, eye, central nervous system, peripheral nervous system, cardiac tissue, blood vessel, tendon, ligament, muscle, oral cavity, lips, palate, internal organs, surgical wounds, abdominal cavity, pelvic cavity or thoracic cavity. In some embodiments, the wound, injury or scar of the eye is of the cornea or lens capsule. In some embodiments, the wound or scar results from eye surgery, LASIK surgery, LASEK surgery, PRK surgery, glaucoma filtration surgery, cataract surgery, and corneal cicatrisation.

[0023] In some embodiments, the wound, injury or scar of the central nervous system is a wound, injury or scar of the brain. In some embodiments, the wound, injury or scar of the central nervous

system is a wound, injury or scar of the spinal cord. In some embodiments, the wound, injury or scar is traumatic brain injury. In some embodiments, the wound, injury or scar is spinal cord injury.

[0024] In some embodiments, inhibition of scarring reduces the number of incidences of adhesion formation and/or the size of adhesions formed. In some embodiments, the where the prevention, reduction or inhibition of scarring enhances neuronal reconnection and/or neuronal function. In some embodiments, the cardiac tissue wound is from a myocardial infraction. In some embodiments, the wound is a neuronal wound. In some embodiments, the wound results in a capsular contraction. In some embodiments, the wound is a surgical wound. In some embodiments, the wound is from a cosmetic procedure or a scar revision. In some embodiments, skin graft healing is enhanced using a composition of the disclosure.

[0025] In some embodiments, a nucleic acid disclosed herein of composition thereof is used to treat or ameliorate a pathological condition in addition to those described above. Such other pathological processes include the sequelae from a wound or injury, such as but not limited to nerve damage or chronic neuropathy, chronic pain resulting from an initial wound, injury or disease process, and neurotrophic keratitis resulting from, for example, an initial injury to the cornea.

[0026] In some embodiments, a method is provided for accelerating or improving the healing of a skin graft or skin grafting site in a subject comprising administering to the subject an effective amount of any pharmaceutical composition as described herein to accelerate healing of the skin graft or skin grafting site.

[0027] In some embodiments, a method is provided for accelerating or improving the healing of a spinal cord injury in a subject comprising administering to the subject an effective amount of any pharmaceutical composition disclosed herein to accelerate healing of the spinal cord injury.

DETAILED DESCRIPTION

[0028] The present subject matter may be understood more readily by reference to the following detailed description which forms a part of this disclosure. It is to be understood that this disclosure is not limited to the specific products, methods, conditions or parameters described and/or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of the claimed disclosure.

[0029] Unless otherwise defined herein, scientific and technical terms used in connection with the present application shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0030] As employed above and throughout the disclosure, the following terms and abbreviations, unless otherwise indicated, shall be understood to have the following meanings.

[0031] In the present disclosure, the singular forms "a," "an," and "the" include the plural reference, and reference to a particular numerical value includes at least that particular value, unless the context clearly indicates otherwise. Thus, for example, a reference to "a compound" is a reference to one or more of such compounds and equivalents thereof known to those skilled in the art, and so forth. The term "plurality", as used herein, means more than one. When a range of values is expressed, another embodiment includes from the one particular and/or to the other particular value.

[0032] Similarly, when values are expressed as approximations, by use of the antecedent "about," it is understood that the particular value forms another embodiment. All ranges are inclusive and combinable. In the context of the present disclosure, by "about" a certain amount it is meant that the amount is within ± 20% of the stated amount, or preferably within ± 10% of the stated amount, or more preferably within ± 5% of the stated amount.

[0033] As used herein, the terms “treat”, “treatment”, or “therapy” (as well as different forms thereof) refer to therapeutic treatment, including prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change associated with

a disease or condition. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of the extent of a disease or condition, stabilization of a disease or condition (i.e., where the disease or condition does not worsen), delay or slowing of the progression of a disease or condition, amelioration or palliation of the disease or condition, and remission (whether partial or total) of the disease or condition, whether detectable or undetectable. Those in need of treatment include those already with the disease or condition as well as those prone to having the disease or condition or those in which the disease or condition is to be prevented.

[0034] As used herein, the terms "component," "composition," "formulation", "composition of compounds," "compound," "drug," "pharmacologically active agent," "active agent," "therapeutic," "therapy," "treatment," or "medicament," are used interchangeably herein, as context dictates, to refer to a compound or compounds or composition of matter which, when administered to a subject (human or animal) induces a desired pharmacological and/or physiologic effect by local and/or systemic action. A personalized composition or method refers to a product or use of the product in a regimen tailored or individualized to meet specific needs identified or contemplated in the subject.

[0035] The terms "subject," "individual," and "patient" are used interchangeably herein, and refer to an animal, for example a human, to whom treatment with a composition or formulation in accordance with the present disclosure, is provided. The term "subject" as used herein refers to human and non-human animals. The terms "non-human animals" and "non-human mammals" are used interchangeably herein and include all vertebrates, e.g., mammals, such as non-human primates, (particularly higher primates), sheep, dog, rodent, (e.g., mouse or rat), guinea pig, goat, pig, cat, rabbits, cows, horses and non-mammals such as reptiles, amphibians, chickens, and turkeys. The compositions described herein can be used to treat any suitable mammal, including primates, such as monkeys and humans, horses, cows, cats, dogs, rabbits, and rodents such as rats and mice. In some embodiments, the mammal to be treated is human. The human can be any human of any age. In an embodiment, the human is an adult. In another embodiment, the human is a child. The human can be male, female, pregnant, middle-aged, adolescent, or elderly. According to any of the methods of the present disclosure and in some embodiments, the subject is human. In another embodiment, the subject is a non-human primate. In another embodiment,

the subject is murine, which in some embodiments is a mouse, and, in another embodiment is a rat. In another embodiment, the subject is canine, feline, bovine, equine, laprine or porcine. In another embodiment, the subject is mammalian. As will be noted herein, treatment of a non-human animals (e.g., non-human primate, non-human mammal) using the teachings of the disclosure may require use of a siRNAs directed to the orthologue of fidgetin-like 2 in the particular species.

[0036] Conditions and disorders in a subject for which a particular drug, compound, composition, formulation (or combination thereof) is said herein to be "indicated" are not restricted to conditions and disorders for which that drug or compound or composition or formulation has been expressly approved by a regulatory authority, but also include other conditions and disorders known or reasonably believed by a physician or other health or nutritional practitioner to be amenable to treatment with that drug or compound or composition or formulation or combination thereof.

[0037] The present disclosure is directed to nucleic acid sequences that inhibit human fidgetin-like 2 activity, pharmaceutical compositions thereof, and methods of their use for preventing or treating various injuries, wounds and diseases. In some embodiments the nucleic acid sequence is a small interfering RNA (siRNA) sequence. In some embodiments, the siRNA comprises ribonucleotides and deoxyribonucleotides.

[0038] Nucleic Acid Sequences

[0039] In one aspect, a nucleic acid molecule is provided comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1), AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2), or comprising a duplex comprising SEQ ID NO:1 and SEQ ID NO:2.

[0040] SEQ ID NO:1 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21. SEQ ID NO:2 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21.

[0041] In one aspect, a duplex nucleic acid molecule is provided comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1). SEQ ID NO:1 comprises

ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21.

[0042] In one aspect, a duplex nucleic acid molecule is provided comprising the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0043] In some embodiments, any nucleic acid molecule comprises no more than 52 nucleotides.

[0044] In some embodiments, the nucleic acid molecule comprises a single stranded sequence of GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) or AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0045] In some embodiments, a double stranded nucleic acid is provided comprising SEQ ID NO:1 and SEQ ID NO:2.

[0046] In some embodiments, one or both nucleic acids of a double stranded nucleic acid comprise no more than 52 nucleotides.

[0047] In one aspect, a nucleic acid molecule is provided consisting of the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1), AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2), or consisting of a duplex consisting of SEQ ID NO:1 and SEQ ID NO:2.

[0048] In one aspect, a duplex nucleic acid molecule is provided wherein one sequence consists of the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

[0049] In one aspect, a duplex nucleic acid molecule is provided wherein one sequence consists of the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0050] In some embodiments, the nucleic acid molecule consists of no more than 52 nucleotides.

[0051] In some embodiments, the nucleic acid molecule consists of a single stranded sequence of GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) or AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0052] In some embodiments, a double stranded nucleic acid is provided consisting of SEQ ID NO:1 and SEQ ID NO:2.

[0053] In some embodiments, SEQ ID NO:1 is referred to as a sense strand, and SEQ ID NO:2 is referred to as an antisense strand. In some embodiments the nucleic acids disclosed herein, and in particular double-stranded nucleic acids, are referred to as small interfering RNA or siRNA. In some embodiments, a siRNA comprises a sense strand and an antisense strand.

[0054] In some embodiments, the siRNA comprises deoxyribonucleotides at the 3' end. SEQ ID NO:1 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides dT at positions 20 and 21. SEQ ID NO:2 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides dT at positions 20 and 21.

[0055] In some embodiments, a nucleic acid comprises no more than 52 nucleotides. In some embodiments, a single strand component of a siRNA of the disclosure is from 14 to 50 nucleotides in length. In another embodiment, a single strand component of a siRNA of the disclosure is 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 nucleotides in length. In yet another embodiment, a single strand component of a siRNA of the disclosure is 20 nucleotides in length. In yet another embodiment, a single strand component of a siRNA of the disclosure is 21 nucleotides in length. In yet another embodiment, a single strand component of a siRNA of the disclosure is 22 nucleotides in length. In yet another embodiment, a single strand component of a siRNA of the disclosure is 23 nucleotides in length. In some embodiments, a siRNA of the disclosure is from 28 to 56 nucleotides in length. In another embodiment, a siRNA of the disclosure is 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52 nucleotides in length.

[0056] In some embodiments, one single strand component of a double-stranded siRNA of the disclosure is from 20 to 50 nucleotides in length. In another embodiment, one single strand component of a double-stranded siRNA of the disclosure is independently 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, or 28 nucleotides in length. In yet another embodiment, one single strand component of a double-stranded siRNA of the disclosure is 20 nucleotides in length. In yet another embodiment, one single strand component of a double-stranded siRNA of the disclosure is 21 nucleotides in length. In yet another embodiment, one single strand component of a double-stranded siRNA of the disclosure is 22 nucleotides in length. In yet another embodiment, one single strand component of a double-stranded siRNA of the disclosure is 23 nucleotides in length. In some embodiments, one single strand components of a double-stranded

siRNA of the disclosure is from 28 to 56 nucleotides in length. In another embodiment, one single strand component of a double-stranded siRNA of the disclosure is 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52 nucleotides in length.

[0057] In some embodiments, a nucleic acid embodied herein may have at least about 90%, or at least about 95%, sequence identity to SEQ ID NO:1 or SEQ ID NO:2, wherein a change or modification of any nucleotide as described herein may be provided.

[0058] In one embodiment, a nucleic acid embodied herein comprises or consists of 20 contiguous nucleotides within SEQ ID NO:1 or SEQ ID NO:2, in any single stranded or double stranded nucleic acid disclosed herein. Thus, in one embodiment, provided are nucleic acid sequences consisting of CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5), GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6), GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7), or AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8). SEQ ID NO:5 and SEQ ID NO:6 comprise ribonucleotides at positions 1-18, and deoxyribonucleotides at positions 19 and 20; and SEQ ID NO:7 and SEQ ID NO:8 comprise ribonucleotides at positions 1-19, and a deoxyribonucleotide at positions 20.

[0059] In one embodiment, a single stranded nucleic acid molecule is provided comprising CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5), GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6), GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7), or AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8). In some embodiments, the nucleic acid molecule comprises no more than 52 nucleotides.

[0060] In one embodiment, a single stranded nucleic acid molecule is provided consisting of CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5), GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6), GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7), or AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8).

[0061] In some embodiments, a double stranded nucleic acid molecule is provided wherein one strand comprises any one of sequences CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5), GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6), GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7), or AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8). In some

embodiments, the sequence comprises no more than 52 nucleotides.

[0062] In some embodiments, a double stranded nucleic acid molecule is provided wherein one strand consists of any one of CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5), GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6), GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7), or AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8).

[0063] In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand comprising the sequence CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5) and a strand comprising the sequence GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6). In some embodiments, a double stranded nucleic acid molecule is provided comprising the sequence GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7) and a strand comprising the sequence AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8). In some embodiments, each sequence comprises no more than 52 nucleotides.

[0064] In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand consisting of the sequence CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5) and a strand consisting of the sequence GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6). In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand consisting of the sequence GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7) and a strand consisting of the sequence AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8).

[0065] In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand consisting of the sequence CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5) and a strand consisting of the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2). In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand consisting of the sequence GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7) and a strand consisting of the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

[0066] In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand comprising the sequence CCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:5) and a strand comprising the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2). In some embodiments, a double stranded nucleic acid molecule is provided comprising the

sequences GCCAUAUGCGCCGUGUACU[dT] (SEQ ID NO:7) and AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2). In some embodiments, each sequence comprises no more than 52 nucleotides.

[0067] In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand consisting of the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and a strand consisting of the sequence GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6). In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand consisting of the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and a strand consisting of the sequence AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8).

[0068] In some embodiments, a double stranded nucleic acid molecule is provided comprising a strand comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and a strand comprising the sequence GUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:6). In some embodiments, a double stranded nucleic acid molecule is provided comprising the sequences GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and AGUACACGGCGCAUAUGGC[dT] (SEQ ID NO:8). In some embodiments, each sequence comprises no more than 52 nucleotides.

[0069] In one embodiment of any of the nucleic acids herein, any U is changed to dT.

[0070] Thus, any nucleic acid embodied herein have a length of 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, 30 nucleotides, 31 nucleotides, 32 nucleotides, 33 nucleotides, 34 nucleotides, 35 nucleotides, 36 nucleotides, 37 nucleotides, 38 nucleotides, 39 nucleotides, 40 nucleotides, 41 nucleotides, 42 nucleotides, 43 nucleotides, 44 nucleotides, 45 nucleotides, 46 nucleotides, 47 nucleotides, 48 nucleotides, 49 nucleotides, 50 nucleotides, 51 nucleotides, or 52 nucleotides.

[0071] In some embodiments, any nucleic acid sequence disclosed herein has at least one modification selected from a 3' overhang, a 5' overhang, a 5' phosphorylation, a 2' sugar modification, a nucleic acid base modification, a phosphate backbone modification, or any combination of one or more of any of the foregoing. Any of the sequences may have a

phosphodiester cap. Any of the sequences may have one or more than one of the same or different modifications.

[0072] Non-limiting examples of one or more modifications include 2'-O-methyl-adenosine, 2'-O-methyl-uridine, 2'-O-methyl-cytosine, 2'-O-methyl-guanosine, 2'-O-methyl-thymidine, 2'-fluoro-adenosine, 2'-fluoro-cytidine, 2'-fluoro-guanosine, 2'-fluoro-uracil, 2'-fluoro-thymidine, deoxycytosine, deoxyguanosine, deoxyadenosine, deoxythymidine, deoxyuridine, a locked adenosine, a locked uridine, a locked guanosine, a locked cytidine, a phosphorothioate, and a phosphodiester cap. In some embodiments, at least one additional nucleotide or modified nucleotide such as but not limited to those aforementioned is added to an end of the nucleic acid.

[0073] In some embodiment, any of the nucleic acid sequences disclosed herein may be modified or further modified with one or more nucleotide modifications as described herein. In some embodiments, any unmodified nucleotide in a sequence described herein may be modified to one of the modified nucleotides such as but not limited to those described herein. In some embodiments, a modified nucleotide in a sequence described herein may be changed to a different modified nucleotide such as but not limited to one of the modified nucleotides described herein. Modified nucleotide or modified nucleic acid encompasses modified nucleotides, bonds between nucleotides or any component of a nucleotide, and addition of one or more modified or unmodified nucleotides to one or both ends of a sequence, or addition of a cap, as described herein.

[0074] In an embodiment, the 5' terminal residue of a strand of the siRNA is phosphorylated. In an embodiment the 5' terminal residue of the antisense strand of the siRNA is phosphorylated. In an embodiment, the 5' terminal residue of a strand of the siRNA is not phosphorylated. In an embodiment the 5' terminal residue of the antisense strand of the siRNA is not phosphorylated.

[0075] As defined herein, the abbreviation "d(nucleotide)" refers to the deoxy-nucleotide. The abbreviation "m(nucleotide)" refers to the 2'-O-methyl nucleotide. The abbreviation "T" refers to thymidine. The abbreviation f(nucleotide) refers to the 2'-fluorodeoxy nucleotide. The abbreviation "(Phos)" refers to a phosphodiester cap. A capital letter residue refers to an RNA residue. The abbreviation "l(nucleotide)" refers to a locked nucleotide. A locked nucleotide has an extra bridge connecting the 2' oxygen and 4' carbon. The abbreviation "(s)" refers to

phosphorothioate, i.e., a phosphorothioate bond between the adjacent nucleotides or modified nucleotides. Otherwise, the abbreviations for nucleotides and ribonucleotides have the meaning known in the art.

[0076] The abbreviations of the modifications of nucleotides described herein are as follows. mU refers to 2'-O-methyl-uridine. mA refers to 2'-O-methyl-adenosine. mC refers to 2'-O-methyl-cytidine. mG refers to 2'-O-methyl-guanosine. fA refers to 2'-fluoro-adenosine. fC refers to 2'-fluoro-cytidine. fG refers to 2'-fluoro-guanosine. fU refers to 2'-fluoro-uridine. dC refers to deoxycytidine. dG refers to deoxyguanosine. dA refers to deoxyadenosine. dT refers to deoxythymidine. The abbreviations for the bases of unmodified nucleotides include A refers to adenine; U refers to uracil; G refers to guanine; C refers to cytosine; T refers to thymine. lA (lower case L followed by A) refers to a locked adenosine. lU refers to a locked uridine. lG refers to a locked guanosine. lC refers to a locked cytidine.

[0077] In some embodiments, any of the nucleic acid sequences disclosed herein may be modified or further modified with one or more modifications or additional modifications as described herein. In addition to any modifications described above that may be present in a sequences listed herein, and may be further included in any of the nucleic acids at other positions not modified or replacements for those already modified, other nucleic acid modifications are fully encompassed herein. Such other modifications include 2'-O-methyl thymidine, 2'-fluoro thymidine, and deoxyuridine.

[0078] By way of non-limiting example, in SEQ ID NO:1, any G may be replaced by mG. In some embodiments, any of G in positions 1, 8, 10, 13 and/or 15 may be replaced by mG. In some embodiments any C may be replaced by fC or mC. In some embodiments, any of C in positions 2, 3, 9, 11, 12, and/or 18 may be replaced independently by fC or mC. In some embodiments, any A may be replaced by a mA. In some embodiments, any of A in positions 4, 6 and/or 17 may be replaced by mA. In some embodiments, any U may be replaced by fU or mU. In some embodiments, any of U in positions 5, 7, 14, 16 and/or 19 may be replaced independently by fU or mU.

[0079] In SEQ ID NO:1, in some embodiments, the G in position 1 is be replaced by mG. In some embodiments, C in position 2 is replaced fC. In some embodiments, C in position 2 is

replaced by mC. In some embodiments, C in position 3 is replaced fC. In some embodiments, C in position 3 is replaced by mC. In some embodiments, A in position 6 is replaced by mA. In some embodiments, A in position 6 is replaced by mA. In some embodiments, U in positions 5 is replaced fU. In some embodiments, U in position 7 is replaced by fU. In some embodiments, U in position 5 is replaced mU. In some embodiments, U in position 7 is replaced by mU.

[0080] By way of non-limiting example, in SEQ ID NO:2, any G may be replaced by mG. In some embodiments, any of G in positions 2, 8, 9, 11, 17 and/or 18 may be replaced by mG. In some embodiments any C may be replaced by fC or mC. In some embodiments, any of C in positions 5, 7, 10, 12 and/or 19 may be replaced independently by fC or mC. In some embodiments, any A may be replaced by a mA. In some embodiments, any of A in positions 1, 4, 6, 13 and/or 15 may be replaced by mA. In some embodiments, any U may be replaced by fU or mU. In some embodiments, any of U in positions 3, 14 and/or 16 may be replaced independently by fU or mU.

[0081] In SEQ ID NO:2, in some embodiments, the G in position 2 is be replaced by mG. In some embodiments, C in position 5 is replaced fC. In some embodiments, C in position 5 is replaced mC. In some embodiments, A in position 1 is replaced by mA. In some embodiments, A in position 4 is replaced by mA. In some embodiments, A in position 6 is replaced by mA. In some embodiments, U in position 3 is replaced fU. In some embodiments, U in position 3 is replaced by mU.

[0082] In some embodiments, in SEQ ID NO:1 or SEQ ID NO:2, a phosphorothioate bond (abbreviated as "(s)") may be present between the first and second nucleotide, and/or the second and third nucleotide. In some embodiments, SEQ ID NO:1 comprises G(s)CC, GC(s)C, or G(s)C(s)C as the first three nucleotides. In some embodiments, SEQ ID NO:2 comprises A(s)GU, AG(s)U, or A(s)G(s)UC as the first three nucleotides. Such phosphorothioate bonds are in addition to any nucleotide modifications as described above, for example, in SEQ ID NO:1, mG(s)CC, G(s)fCmC or G(s)fC(s)mC; in SEQ ID NO:2, mA(s)GU, A(s)mGU, or A9s)G(s)fU.

[0083] Any of the foregoing modifications may be made to the corresponding position(s) in any of SEQ ID Nos. 5-8.

[0084] It should be noted that the abbreviations herein of the unmodified and modified nucleic acid abbreviations may refer to the nucleic acid base, the nucleoside (i.e., the base and the sugar), or the nucleotide (the nucleoside and the phosphate group). One of skill in the art will recognize the unmodified or modified nucleic acid components therefrom. In some embodiments, a ribonucleotide that is modified is replaced with a modified ribonucleotide. In some embodiments, the ribonucleotide that is modified is replaced with a modified deoxyribonucleotide.

[0085] A locked nucleic acid (LNA), often referred to as inaccessible RNA, is a modified RNA nucleotide in which the ribose moiety is modified with an extra bridge connecting the 2' oxygen and 4' carbon. In some embodiments, a nucleic acid comprises a locked adenosine. In some embodiments a nucleic acid comprises a locked cytosine. In some embodiments a nucleic acid comprises a locked guanosine. In some embodiments a nucleic acid comprises a locked uridine. In some embodiments a nucleic acid comprises a locked thymidine.

[0086] In an embodiment, the 5' terminal residue of a strand of the siRNA is phosphorylated. In an embodiment the 5' terminal residue of the antisense strand of the siRNA is phosphorylated. In an embodiment, both are phosphorylated.

[0087] The nucleic acid sequences disclosed herein target the mRNA of fidgetin-like 2 (FL2). The NCBI reference sequence: NM 001013690.4 (SEQ ID NO:3), to the nucleic acid encoding human fidgetin-like 2, is:

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1  agtgagctat ggggacacta ctgcactgta gcctgggcaa cagagcaaga ccttgtctca
61 aaaatgtata tatattttgg gctttttttc ctaaaacggg aactacaaca gcatatttgc
121 gagctgatga gagtgaccca gcagagaggg aaatggatca gctctgttga agatgcactg
181 gacaccagaa cacgcccagc ccctcaacca gtggccagag cagcacctgg acgtctcctc
241 caccaccccg tcgccggccc acaagttgga gttgcccccc gggggtcgcc aacgctgcca
301 ctacgcttgg gcacacgacg acatctcagc cctcactgcc tccaacctcc taaagcgcta
361 tgcagagaag tactctgggg tcttggattc tccctacgag cgtccggccc tgggcgggta
421 cagcgacgcc tccttcctca acggcgccaa aggggatccc gagccctggc cagggccgga
481 gccaccctac cccttggcct cactccacga aggcctccca ggaaccaaat cgggcggtgg
541 cggcggllcc ggggccclgg ggggclcccc aglllagcc gggaacclcc clgaaccccl
601 ctacgccggc aatgcgtgcg ggggcccatc ggcggcgccc gagtacgcgg ccggctacgg
661 cggggggtac ctggcgccgg gttactgcgc gcagacgggc gccgcgctgc ccccgccgcc
721 cccggccgcg ctcctgcagc ccccaccgcc tccggggtac gggccctcag cgccgctgta
781 caactatccc gcaggggct acgcagcgca gcccggctat ggcgcgctcc cgccgccccc
841 aggcccaccc ccggcccccc acctgacccc gggcctgccc gcgcccacgc ccctgcccgc
901 gccggcaccg cccaccgcct atggcttccc cacggccgcg ccgggtgccg aatccgggct
961 gtcgctgaag cgcaaggccg ccgacgaggg gcccgagggc cgctaccgca agtacgcgta
1021 cgagcccgcc aaggcccccg tggctgacgg agcctcctac cccgccgcgg acaacggcga
1081 atgtcggggc aacgggttcc gggccaagcc gccaggagcc gcggaggagg cgtcgggcaa
1141 gtacggtggc ggcgtccccc tcaaggtcct gggctccccc gtctacggcc cgcaactgga
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1201 gccctttgaa aagttcccgg agcgggcccc ggctcctcgt ggggggttcg ccgtgccgtc
1261 gggggagact cccaaaggcg tggaccctgg ggccctggag ctggtgacga gcaagatggt
1321 ggactgcggg cccccggtgc agtgggcgga tgtggcgggc cagggcgcgc tcaaggcggc
1381 gctggaggag gagctggtgt ggcccctgct caggccgccc gcctacccgg gcagcctgcg
1441 cccgccgcgg accgtcctgc tctttgggcc gcggggcgcg ggcaaagcgc tgctgggccg
1501 ctgcctcgcc acgcagctgg gcgccacgct gttgcgcctg cgcggcgcga ccctggctgc
1561 gcccggcgcc gccgagggcg cgcgcctcct ccaggccgcc ttcgcggccg cgcgctgccg
1621 cccaccctcc gtactcctca tcagcgagct agaggcgctg ctccccgccc gggacgacgg
1681 cgcggcggca gggggcgcgc tgcaggtgcc gctcctggcc tgcctggacg ggggctgcgg
1741 cgcgggggct gacggcgtgc tggttgtggg caccacctcg cggcccgcgg ctctggacga
1801 ggcgacccgc cggcgcttct ctctccgctt ctacgtggcg ctgcccgaca gcccggcccg
1861 cgggcagatc ctgcagcggg cgctggccca gcagggctgc gcgctcagtg agcgggaact
1921 ggcggcgctg gtgcagggca cgcagggctt ctctgggggc gagctggggc agctgtgcca
1981 gcaggcggcg gccggggcgg gcctcccggg gctgcagcgc cccctctcct acaaggacct
2041 ggaggcggcg ctggccaagg tgggccctag ggcctctgcc aaggaactgg actcgttcgt
2101 ggagtgggac aaaatgtacg gctccggaca ctgacggcgc gcgggggagg ccgcgggagc
2161 cgcagtccct ccgtccccgc cgcctccgcg tgggagggat gtcactgact aaacccggct
2221 ggcaggggct ggagtggtga atgtgggatc ggggacagga ggggtctgcc ggtggatatt
2281 tttttttcg tgggaaggaa aatgcttctg ccaggcagat gccatatgcg ccgtgtactc
2341 aggtttttcc tatttattgt ggactggaag ctcgccatct ccgcccggca gaccgggcag
2401 atccggcatg ggctggcacc cggggcctta agaactcctg ctctcttgcc acaacgcttt
2461 tgtctcctcg ctatctgaat ggcaccctcc ttctccctca ctctctccat cccattctct
2521 gcattctctt ggttttctct ccctttgct ttgtcgctga cacccctgcc cacccccatgc
2581 tggccctgtt tctctcctgc ccctccctcc ccagctctcc atcctcacc ctctgtgctt
2641 ctgtctccat ccctggctct ccagcgtccc tggccttttg gtccctgagc tttaatgcct
2701 ttccctgcct tctgttctta tttggactgc agtggccctt tgcaggagct ctggaggccc
2761 aggggctgag gaggagggtt acccctctac ccatctgaaa cctagggtct aggggatca
2821 aggaaaaaaa gtccccaaag aaggggaatt ttttgtttgt ttttgagggg agatcccaga
2881 aatgtagctt gtttcatatt ttagtcttct tatttttgta aaatgtgtag aatttgctgt
2941 ttttcttttt cttttgacaa ctcaggaaga aactgacctc agaaagaatg ttagactttg
3001 gctgctctcc tgtgtgcccc tcacacctgc cccctccccc ccactccatc caggggacca
3061 aattctccca gacactcaaa aaatgagact tacggggaag gggagaggaa gacccagagg
3121 cctcagtgaa accccagcta ttcctggtca gaagcagaat gtattcctaa gggcttcctc
3181 cccagggccg aggcctaggc atgaatgtgg ggagtgggct gtggggtttg agagaaggga
3241 ggccttattc ctctcctgct gctccccacc ccctgcccca cccaacccct ccgctgagtg
3301 ttttctgtga agggctatcc agagttagga tgcccttgcc caattccttc ctgagaccca
3361 gaaggtaggg tgggagggcc caaatgggaa ggtgacctaa gcagaaagtc tccagaaagg
3421 tcatgtcccc tggccctgcc ttggcagagg tccccagtga cttatgctag gaggattcca
3481 tctgggtaga cagtctggcc acaaaatcag ctactggacc tcagccatct ctgctggagg
3541 ctctgaggag gagtgagcat ccctcacttg tgggggctct gtgaggaaat gtgccttccc
3601 cattcccccg gagtcctagg tctggagctc cagggctggg agagggtgag ggagatgggc
3661 aggggtgttt tctctgacct tgggggctta gtctcagtcc tgcctgaact ttccactagg
3721 cttggaaccc ttccaagaac catatttctc tccttcccac caatttccc ttgatgaggc
3781 tttagcagtt tgctcccacc acccccagcc catttcacaa ctctgatctt agtccaaagc
3841 aggggacacg ccccccccacc accacttttt ctctctccca tctcagcctc ctgtgcagtt
3901 ccttgcctgc ccgtgcattt cctagagtct actgcctccc ccctggctgg gagggtgtct
3961 gggggggatc tttcaggggc cctggcaccc agggcctgtg ctggcctagg agtgctgacc
4021 agaaggctgc tctgttcccc cccacccccg ttgctttctg gccccctctt tggagccagc
4081 cacccacagg gctttggtgc ctcagaagca gtgggctgcc gggtcacagc cgcaggctgc
4141 aaaagaccct cggagggagc atggagtgag gggttctctc tcaggtgtgt atgtattggg
4201 gggtgggggt gggtggaggg tgtcagggaa gttggggtgg gatcccagcc ttcccttcaa
4261 gaggcaggga gctctgggag gtggagtccc caccgctttc tctactaggc tcctcctgtt
4321 ccccaggctt ggggagcttt gcacaaggag actgccccca gcctagtggc acctacctca
4381 tgggctctgg ggcaggtagg ggaagggcca gtccagctct ggtaatgctg gggggaggca
4441 taccaaagaa tccaggggca gggagtgggg agggtgactt ccgagctggc ctctcccctt
4501 cctctaccca gactggggct gggatcctct cctcccgctg taaccatttc tacctcattt
4561 tgctgcgtgt tgtacatgga cgtatttatc tcctgtctga cgatgctctg cagttgtggt
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4621 ctgtctacct cagaagagac tgtattttaa aagaaagtat tacacagtat taaagcgatg
4681 acatgtggtt tgcaaaaaaa aaaaaaaaaa a (SEQ ID NO:3);

which encodes:

MHWTPEHAQPLNQWPEQHLDVSSTTPSPAHKLELPPGGRQRCHYAWAHDDISALTAS
NLLKRYAEKYSGVLDSPYERPALGGYSDASFLNGAKGDPEPWPGPEPPYPLASLHEGL
PGTKSGGGGGSGALGGSPVLAGNLPEPLYAGNACGGPSAAPEYAAGYGGGYLAPGYC
AQTGAALPPPPPAALLQPPPPPGYGPSAPLYNYPAGGYAAQPGYGALPPPPGPPPAPYL
TPGLPAPTPLPAPAPPTAYGFPTAAPGAESGLSLKRKAADEGPEGRYRKYAYEPAKAP
VADGASYPAADNGECRGNGFRAKPPGAAEEASGKYGGGVPLKVLGSPVYGPQLEPFE
KFPERAPAPRGGFAVPSGETPKGVDPGALELVTSKMVDCGPPVQWADVAGQGALKA
ALEEELVWPLLRPPAYPGSLRPPRTVLLFGPRGAGKALLGRCLATQLGATLLRLRGAT
LAAPGAAEGARLLQAAFAAARCRPPSVLLISELEALLPARDDGAAAGGALQVPLLACL
DGGCGAGADGVLVVGTTSRPAALDEATRRRFSLRFYVALPDSPARGQILQRALAQQG
CALSERELAALVQGTQGFSGGELGQLCQQAAAGAGLPGLQRPLSYKDLEAALAKVGP
RASAKELDSFVEWDKMYGSGH (SEQ ID NO:4) (human fidgetin-like 2).

[0088] The disclosure embraces modifications of the nucleic acid sequences disclosed herein that are useful for treatment of a non-human animals (e.g., non-human primate, non-human mammal). Such modifications of the nucleic acids disclosed herein comprise siRNAs directed to the orthologue of fidgetin-like 2 in the particular species.

Pharmaceutical Compositions

[0089] In some embodiments, a formulation, pharmaceutical composition, or delivery system of any of the nucleic acids described herein is provided. In some embodiments, the formulation, pharmaceutical composition, or delivery system comprises a nucleic acid consisting of or comprising any of those nucleic acids described herein, such as single stranded or double stranded (e.g., a duplex. In some embodiments, the formulation comprises one or more nucleic acids comprising those selected from among SEQ ID NO:1 or SEQ ID NO:2, or a duplex or double-stranded nucleic acid comprising a nucleic acid comprising two nucleic acid molecules selected from among SEQ ID NO:1 and SEQ ID NO:2. In some embodiments, the formulation comprises one or more nucleic acids consisting of those selected from among SEQ ID NO:1 and

SEQ ID NO:2, or a duplex or double-stranded nucleic acid consisting of two nucleic acid molecules selected from among SEQ ID NO:1 and SEQ ID NO:2. In some embodiments, the formulation comprises a duplex comprising SEQ ID NO:1 and any other nucleic acid. In some embodiments, the formulation comprises a duplex comprising SEQ ID NO:2 and any other nucleic acid. In some embodiments, the formulation comprises a duplex comprising a sequence consisting of SEQ ID NO:1 and any other nucleic acid. In some embodiments, the formulation comprises a duplex comprising a sequence consisting of SEQ ID NO:2 and any other nucleic acid. In other embodiments, any of SEQ ID NOs:5-8 may be used, as or part of single stranded nucleic acids, or consisting of or comprising one or both strands of a double stranded nucleic acids, in any formulation, pharmaceutical composition, or delivery system such as but not limited to those disclosed herein.

[0090] In one embodiment of the disclosure the inhibitor of fidgetin-like 2 by a nucleic acid disclosed herein is provided by a subcutaneous implant or depot medicament system for the pulsatile delivery of the inhibitor to a pathological site such as a wound or damaged nerve or to a site where a pathology is expected to be formed, for example, after surgery, to promote wound healing. The inhibitor can be provided, for example, in a therapeutically effective amount to each centimeter of a wound margin or each centimeter of a site at which a wound is expected to be formed.

[0091] A medicament in accordance with this aspect of the disclosure may be formulated in any appropriate carrier, vehicle, diluent, excipient or other delivery system. Suitable carriers are pharmaceutically acceptable carriers, preferably those consistent with administration topically or administration by injection, for example, intravenous administration or depot injection at a site.

[0092] It will be appreciated that, while the nucleic acid inhibitor of fidgetin-like 2 may be administered by the same route and in the same form in each incidence of treatment, different incidences of treatment may provide the inhibitor of fidgetin-like 2 by different formulations and/or different routes of administration. In embodiments of the disclosure the initial incidence of treatment may provide the inhibitor of fidgetin-like 2 by means of an injection, such as an intradermal injection, while the second (and any subsequent) incidences of treatment may involve provision of the inhibitor of fidgetin-like 2 by alternative routes, such as topical formulations, or

vice versa. In an embodiment, multiple administrations of the inhibitor of fidgetin-like 2 may be effected by the same means or route.

[0093] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising saline. In some embodiments the pharmaceutical composition is normal saline or phosphate-buffered saline.

[0094] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a sugar. In some embodiments, the pharmaceutical composition is a glucose solution.

[0095] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a polypeptide. In some embodiments the polypeptide is a cationic polypeptide. In some embodiments, the cationic polypeptide is a histidine-lysine copolypeptide.

[0096] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a polymer. In some embodiments, the hydrophilic polymer is polyethylene glycol (PEG). In some embodiments, the polymer is a hydrophilic polymer grafted polymer, a non-natural cationic polymer, a cationic polyacetal, a hydrophilic polymer grafted polyacetal, a ligand functionalized cationic polymer, or a ligand functionalized-hydrophilic polymer grafted polymer. In some embodiments the hydrophilic polymer is polyethylene glycol (PEG).

[0097] In some embodiments, the pharmaceutical composition comprises a polycationic binding agent.

[0098] In some embodiment, the pharmaceutical composition comprises a nucleic acid delivery vehicle.

[0099] In some embodiments, the pharmaceutical composition comprises a cationic polymer-nucleic acid complex.

[00100] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a lipid. In some embodiments the lipid is a cationic lipid.

[00101] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a cream.

[00102] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising an eye drop.

[00103] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a gel.

[00104] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a micelle material.

[00105] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a wafer. In some embodiments, a wafer comprises collagen, chondroitin sulfate, polyvinylpyrrolidone and polyethylene glycol 400. One non-limiting example of a wafer is described in an example herein.

[00106] In some embodiments, the inhibitor of fidgetin-like 2 is provided in or associated with a collagen particle. In some embodiments the collagen particle is a microparticle. In some embodiments the collagen particle is in a surfactant polymer dressing such as a poloxamer, such as but not limited to PluroGel®.

[00107] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a microemulsion of nanoparticles. One non-limiting example of a microemulsion is described in an example herein.

[00108] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a liposome. In some embodiments, the liposome is a ligand functionalized liposome. In some embodiments, the liposome is further functionalized with at least one 2' sugar modification.

[00109] In some embodiments the inhibitor of fidgetin-like 2 is provided in a pharmaceutical composition comprising a nanoparticle. In an embodiment, the inhibitor of fidgetin-like 2 is encapsulated in a nanoparticle. In an embodiment the nanoparticle is a liposomal nanoparticle. Such microparticles, nanoparticles or liposomes comprising a nucleic acid disclosed herein may

be provided in any of the aforementioned compositions, such as but not limited to a cream, eye drop, gel, wafer, parenterally administered formulation, wound dressing, collagen particle, poloxamer, depot-administrable gel, and the like. Thus, In any of the formulations disclosed herein or used for the nucleic acid disclosed herein, such nucleic acid may be disposed in the formulation as a nanoparticle or other particulate delivery system. Any description herein or nanoparticle is one intended form that may be used in any formulation disclosed herein.

[00110] In some embodiments, the nanoparticle comprises poly(lactic-co-glycolic acid) (PLGA, PLG), a copolymer, produced using methods known in the art. In some embodiments, the nanoparticle is sized between 1-100 nm. In some embodiments, the nanoparticle is biocompatible and/or biodegradable. This addition may in certain embodiments enhance purification of microparticles or nanoparticles using methods well known in the art. In one non-limiting example of nanoparticles are prepared as follows. Five hundred µl of tetramethyl orthosilicate (TMOS) was hydrolyzed in the presence of 100 µl of 1 mM HCl by sonication on ice for about 15 min, until a single phase formed. The hydrolyzed TMOS (100 µl) was added to 900 µl of 20 µM of siRNA solution containing 10 mM phosphate, pH 7.4. A gel was formed within 10 minutes. The gel was frozen at −80°C for 15 minutes and lyophilized. Such copolymer comprising a nucleic acid disclosed herein may be provided in any of the aforementioned compositions, such as but not limited to a cream, eye drop, gel, wafer, parenterally administered formulation, wound dressing, collagen particle, poloxamer, depot-administrable gel, and the like.

[00111] In a non-limiting embodiment, the inhibitor of fidgetin-like 2 is provided in a bulk-eroding system such as polylactic acid and glycolic acid (PLGA) copolymer-based microspheres or microcapsules systems containing the inhibitor of fidgetin-like 2. In an embodiment, blends of PLGA:ethylcellulose systems may be used as an appropriate carrier. A further medicament in accordance with this aspect of the disclosure may be formulated in a surface-eroding system wherein the inhibitor of fidgetin-like 2 is embedded in an erodible matrix such as the poly(ortho) ester and polyanhydride matrices wherein the hydrolysis of the polymer is rapid. Such bulk eroding system comprising a nucleic acid disclosed herein may be provided in any of the aforementioned compositions, such as but not limited to a cream, eye drop, gel, wafer, parenterally administered formulation, wound dressing, collagen particle, poloxamer, depot-administrable gel, and the like.

[00112] In some embodiments, the inhibitor of fidgetin-like 2 may also be formulated by combining a pulsatile delivery system as described above and an immediate release system such as a lyophilized injectable composition described above.

[00113] The inhibitor of fidgetin-like 2 may be used in a composition with additives. Examples of suitable additives are sodium alginate, as a gelatinizing agent for preparing a suitable base, or cellulose derivatives, such as guar or xanthan gum, inorganic gelatinizing agents, such as aluminum hydroxide or bentonites (termed thixotropic gel-formers), polyacrylic acid derivatives, such as Carbopol®, polyvinylpyrrolidone, microcrystalline cellulose and carboxymethylcellulose. Amphiphilic low molecular weight and higher molecular weight compounds, and also phospholipids, are also suitable. The gels can be present either as water-based hydrogels or as hydrophobic organogels, for example based on mixtures of low and high molecular weight paraffin hydrocarbons and vaseline. The hydrophilic organogels can be prepared, for example, on the basis of high molecular weight polyethylene glycols. These gelatinous forms are washable. Hydrophobic organogels are also suitable. Hydrophobic additives, such as petroleum jelly, wax, oleyl alcohol, propylene glycol monostearate and/or propylene glycol monopalmitostearate, in particular isopropyl myristate can be included. In an embodiment the inhibitor is in a composition comprising one or more dyes, for example yellow and/or red iron oxide and/or titanium dioxide for the purpose of matching as regards color.

[00114] Compositions may be in any suitable form including gels, lotions, balms, pastes, sprays, powders, wafers, bandages, wound dressing, emulsions, creams and ointments of the mixed-phase or amphiphilic emulsion systems (oil/water-water/oil mixed phase), liposomes and transfersomes or plasters/band aid-type coverings. Emulsifiers which can be employed in compositions comprising the inhibitor of fidgetin-like 2 include anionic, cationic or neutral surfactants, for example alkali metal soaps, metal soaps, amine soaps, sulphurated and sulphonated compounds, invert soaps, higher fatty alcohols, partial fatty acid esters of sorbitan and polyoxyethylene sorbitan, e.g. lanette types, wool wax, lanolin or other synthetic products for preparing the oil/water and/or water/oil emulsions.

[00115] Compositions comprising the inhibitor of fidgetin-like 2 can also comprise vaseline, natural or synthetic waxes, fatty acids, fatty alcohols, fatty acid esters, for example as

monoglycerides, diglycerides or triglycerides, paraffin oil or vegetable oils, hydrogenated castor oil or coconut oil, hog fat, synthetic fats (for example based on caprylic acid, capric acid, lauric acid or stearic acid, such as Softisan®), or triglyceride mixtures, such as Miglyol®, can be used as lipids, in the form of fatty and/or oleaginous and/or waxy components for preparing the ointments, creams or emulsions of the compositions comprising the inhibitor of fidgetin-like 2 used in the methods described herein.

[00116] In some embodiments, the pharmaceutical composition comprises an osmotically active acid or alkaline solution, for example hydrochloric acid, citric acid, sodium hydroxide solution, potassium hydroxide solution, sodium hydrogen carbonate, may also be ingredients of the compositions and, in addition, buffer systems, such as citrate, phosphate, tris buffer or triethanolamine, for adjusting the pH. It is possible to add preservatives as well, such as methyl benzoate or propyl benzoate (parabens) or sorbic acid, for increasing the stability.

[00117] Pastes, powders and solutions are additional forms of compositions comprising the inhibitor of fidgetin-like 2 which can be applied topically. As consistency-imparting bases, the pastes frequently contain hydrophobic and hydrophilic auxiliary substances, preferably, however, hydrophobic auxiliary substances containing a very high proportion of solids. In order to increase dispersity, and also flowability and slipperiness, and also to prevent agglomerates, the powders or topically applicable powders can, for example, contain starch species, such as wheat or rice starch, flame-dispersed silicon dioxide or siliceous earth, which also serve as diluent.

[00118] In an embodiment, the compositions comprise further active ingredients suitable for protecting or aiding in healing of the wound, for example one or more antibiotics, antiseptics, vitamins, anesthetics, antihistamines, anti-inflammatory agents, moisturizers, penetration-enhancing agents and/or anti-irritants.

[00119] In some embodiments, the carrier further comprises a targeting ligand. In some embodiments the targeting ligand is a protein. In some embodiments, the targeting ligand binds an epithelial cell, a vascular endothelial cell, a vascular smooth muscle cell, a myocardial (heart) cell or a passenger leukocyte cell resident in cutaneous tissue at a time of wound healing.

[00120] In some embodiments, the carrier comprises: (a) a histidine-lysine co-polymer; (b) a hydrophilic polymer comprising PEG; and, optionally, (c) a targeting ligand.

[00121] In an embodiment, the composition may further comprise one or more additional nucleic acid molecules that induce RNA interference and decrease the expression of a gene of interest. In an embodiment, the one or more additional nucleic acid molecules decrease the expression of a gene selected from the group consisting of fidgetin and fidgetin-like 2.

Methods of Use

[00122] In some embodiments, methods of use of any of the nucleic acids described herein and their pharmaceutical compositions are provided. In some embodiments, methods of use are provided using a nucleic acid comprising any of SEQ ID NO:1 or SEQ ID NO:2, or a duplex or double-stranded nucleic acid comprising either SEQ ID NO:1 or SEQ ID NO:2 or both. In some embodiments, methods of use are provided using a nucleic acid consisting of any one of SEQ ID NO:1 or SEQ ID NO:2, or a duplex or double-stranded nucleic acid consisting of SEQ ID NO: 1 or SEQ ID NO:2 or both. In other embodiments, any of SEQ ID NOs:5-8 may be used, consisting of or comprising single stranded nucleic acids, or in double stranded nucleic acids (consisting of or comprising one or both strands), for any methods disclosed herein. In some embodiments, modifications or additional modifications to the nucleic acid such as but not limited to those described herein is embraced herein. In any of the following descriptions of methods of use, any of the foregoing nucleic acids or those described elsewhere herein including modifications therein are embodied. The term "an inhibitor of fidgetin-like 2" is meant to encompass any of the nucleic acid sequences described herein or any modifications thereof. In some embodiments each individual strand within the double-stranded nucleic acid is no longer than 52 nucleotides. The disclosure embraces method of use for treatment of a human as well as non-human animals (e.g., non-human primate, non-human mammal) comprising modifications of the nucleic acid sequences disclosed herein. Such modifications of the nucleic acids disclosed herein comprise siRNAs directed to the orthologue of fidgetin-like 2 in the particular species. In some embodiments, the nucleic acids and siRNA disclosed herein are cross-reactive and therefore useful in at least one other species.

[00123] The following descriptions provide non-limiting guidance as to the various wounds,

injuries and diseases, among other conditions, that the compounds and compositions of the disclosure may benefit. The following descriptions are categorized by bodily system or site, with the recognition that such categorizations are for convenience only, and that certain aspects are shared among the categories and such categorization is not intended to be limiting to the particular conditions, diseases, wounds or injuries of any particular bodily system or site. The disclosure embraces any condition, disease, or biological process in a normal, injured or diseases human or other animal where targeting fidgetin-like 2 and/or blocking fidgetin-like 2 and/or inhibiting fidgetin-like 2 is beneficial.

Treatment of Skin

[00124] A method of treating a skin wound or injury in a subject is provided comprising administering to the subject an amount of an inhibitor of fidgetin-like 2 effective to treat the skin wound or injury.

[00125] In an embodiment, the amount of inhibitor of fidgetin-like 2 is effective to accelerate wound healing.

[00126] In an embodiment, the wound is an epidermal wound. In an embodiment, the wound is a skin wound. Non-limiting examples of specific wounds in which healing may be promoted using the medicaments and methods of the disclosure include, but are not limited to, the results of sun damage such as wrinkles, non-responsive skin after a facelift, lasabrasion, aged or sun-damaged skin, skin liver spots, birthmark, wart, enlarged oil glands, port wine stains, hemangiomas, telangiectasias, or to change the appearance of skin complexion. In an embodiment of the methods, the birthmark is a linear epidermal nevus. In some embodiments, the method is directed to enhancing skin health recovery from a skin procedure comprising laser application to the skin. In some embodiments, the method is directed to rejuvenating skin from a skin procedure comprising laser application to the skin.

[00127] In some embodiments, compounds of the disclosure are useful for improving or accelerating healing of skin grafting sites, such as on burns, scar revision, plastic surgery, or other procedures involving placement of a skin graft. As described elsewhere, the healing of the skin site from which a graft is taken is also a benefit of the compounds described herein.

[00128] In some embodiments, compounds of the disclosure are useful in enhancing healing of a skin graft or a skin grafting site. In some embodiments, the skin grafting is provided to treat a burn. In some embodiments the burn is a partial-thickness burn. In some embodiments the burn is a full-thickness burn. In some embodiments, the skin grafting is provided to treat an injury, such as from a large open wound. In some embodiments, the skin grafting is provided to treat an ulcer such as but not limited to a bedsore. In some embodiments, the skin grafting is provided to treat a skin infection. In some embodiments, the skin grafting is provided to treat a skin cancer surgery site. In some embodiments, the skin grafting is provided to cover a larger surface area than available from the supply of donor skin.

[00129] In some embodiments, a method of enhancing hair follicle growth in skin comprises directly administering to the skin an amount of an inhibitor of fidgetin-like 2 effective to enhance hair follicle growth in skin. In some embodiments, the method increases hair growth in skin.

Treatment of the Heart

[00130] In an embodiment, the wound is a cardiac tissue wound. In an embodiment, the wound is a cardiovascular wound, for example resulting from a myocardial infarction. In some embodiments, a compound of the disclosure promotes cardiac angiogenesis. In some embodiments, a compound of the disclosure improves cardiac function post myocardial infarction. .

Treatment of the Nervous System

[00131] In an embodiment, the wound is a neuronal wound.

[00132] In an embodiment, the wound is a wound of the central nervous system. In some embodiments, the wound in a spinal cord injury. In some embodiments, the prevention, reduction or inhibition of scarring may enhance neuronal reconnection and/or neuronal function. In some embodiments, a compound of the disclosure promotes nerve growth. In some embodiments, a compound of the disclosure reduces neuronal inflammation. In some embodiments, a compound of the disclosure promotes recovery from nerve transection. In some embodiments, a compound of the disclosure promotes nerve regeneration after injury.

[00133] In some embodiments, the spinal cord injury is acute spinal cord injury or chronic spinal cord injury. In some embodiments, the chronic spinal cord injury is of a duration of about 1 month or longer, two months or longer, two months or longer, three months or longer, four months or longer, five months or longer, or six months or longer. In some embodiments, such durations are following an acute spinal cord injury or other traumatic or acute event. In some embodiments, the spinal cord injury is traumatic, surgically induced, congenital, inflammatory, infection related, degenerative, or cancer related.

[00134] In some embodiments, the wound is a wound of the peripheral nervous system. In some embodiments the wound is a cavernous nerve injury. In some embodiments, the prevention, reduction or inhibition of scarring may enhance neuronal reconnection and/or neuronal function. In some embodiments, a compound of the disclosure promotes peripheral nerve growth. In some embodiments, a compound of the disclosure reduces neuronal inflammation. In some embodiments, a compound of the disclosure promotes recovery from nerve transection. In some embodiments, a compound of the disclosure promotes nerve regeneration after injury. In some embodiments, a compound of the disclosure has anti-inflammatory activity in neuronal and other tissues.

[00135] In some embodiments, a compound of the disclosure treats or prevents neuropraxia.

[00136] In some embodiments, a compound of the disclosure treats or prevents adverse sequelae of nerve sparing surgery.

[00137] In some embodiments, a compound of the disclosure promotes recovery of erectile response after unilateral or bilateral cavernous nerve transection. In some embodiments, a compound of the disclosure recovery of erectile response within two weeks of cavernous nerve injury. In some embodiments, cavernous nerve injury is a result of a surgical procedure such as prostatectomy. In some embodiments, prostatectomy is radical prostatectomy.

[00138] In some embodiments, a wafer comprising a siRNA of the disclosure is implanted at the site of surgery. In some embodiments, siRNA concentrations of about 6.6, about 13.3 or about 26.6 micrograms per 100 mg wafer is implanted. In some embodiments, the wafer comprises about 2.5% collagen, about 7.5% chondroitin sulfate, about 82.5% polyvinylpyrrolidone, and

about 7.5% polyethylene glycol 400.

Treatment of a Wound to the Eye

[00139] In an embodiment, the wound is a wound of the eye (including the inhibition of scarring resulting from eye surgery such as LASIK surgery, LASEK surgery, PRK surgery, glaucoma filtration surgery, cataract surgery, or surgery in which the lens capsule may be subject to scarring) such as those giving rise to corneal cicatrisation; wounds subject to capsular contraction (which is common surrounding breast implants).

Treatment of Non-injury Eye Diseases

[0001] In an embodiment, a compound of the disclosure is useful for treating eye disease that are not a direct injury to the eye, such as a degenerative disease. In one embodiment, the methods and agents for uses disclosed herein are for use in patients with neurotrophic keratitis (NK) are directed to treating the degenerative disease of the cornea caused by damage to the trigeminal nerve, which may be triggered by any number of induction events that do not typically develop into NK. Thus, such methods and agents for are distinct from treatment of the causes of NK, and such treatment of NK typically would be initiated at diagnosis of NK as described herein, and not necessarily contiguous with any treatment of the causes or induction events.

Treatment of the Vasculature

[00140] In an embodiment, the wound is a wound of the circulatory system, such as but not limited to a blood vessel, venous or arterial valves, heart valves, or enhancing the integration of a replacement heart valve, bypass graft, vasculature of a transplanted organ, by way of non-limiting examples.

Treatment of the Musculoskeletal System

[00141] In an embodiment, the wound is a wound of tendons, ligaments or muscle.

Treatment of the Oral Cavity

[00142] In an embodiment, the wound is a wound of the oral cavity, including the gums, lips

and palate. In some embodiments, the method inhibits scarring resulting from treatment of cleft lip or palate.

Treatment of Organs and Cavities

[00143] In an embodiment, the wound is a wound of an internal organ such as but not limited to the liver, heart, brain, digestive tissues and reproductive tissues.

[00144] In an embodiment, the wound is a wound a body cavity such as but not limited to the abdominal cavity, pelvic cavity and thoracic cavity. In some embodiments, inhibition of scarring may reduce the number of incidences of adhesion formation and/or the size of adhesions formed.

Treatment of Surgical Wounds

[00145] In an embodiment, the wound is a surgical wound, such as but not limited to particular wounds associated with cosmetic procedures, such as scar revision. It is particularly preferred that the medicaments and methods of the disclosure be used to promote healing of wounds of the skin. Other non-limiting examples include surgical procedures to the eye and other parts of the body. As noted herein, the compound or composition of the disclosure may be applied to a site before the injury or wound occurs, such as a surgical incision.

Other Aspects of the Disclosure

[00146] In an embodiment of the methods and compositions described herein the subject is a mammal. In an embodiment the subject is human. As noted herein, a modification of the nucleic acid sequences disclosed herein to target a corresponding non-human FL2 is fully embraced herein.

[00147] As used herein, "promotion" of wound healing, or grammatical or syntactical equivalents thereof, means an acceleration in any one or more of visual appearance of wound recovery, reduction in wound size, reduction in distance between wound margins, scab formation, fibroplasia and re-epithelialization as compared to the corresponding parameter in an untreated wound.

[00148] As used herein, "wound" is a break or discontinuity in the structure of an organ or tissue

(including skin), which includes epithelium, connective tissue, and muscle tissue, caused by an external agent. Examples of wounds include, but are not limited to, skin wounds, ulcerations, bedsores, grazes, tears, cuts, punctures, tympanic membrane perforations, bums, and those that are a consequence of plastic surgery procedures.

Methods of Administration

[00149] The benefits that may be derived from the present disclosure may be applicable to pathological or biological processes occurring at any site, cells, tissue, organs, organ systems, or any component thereof, anywhere throughout the body. Non-limiting examples of such pathologies are described elsewhere herein. Non-limiting examples include treating a wound, for example the wound for which healing is promoted is a skin wound. For illustrative purposes, the embodiments of the disclosure will generally be described with reference to skin wounds, although they remain applicable to other tissues and organs. Merely by way of example, in another preferred embodiment the wound may be a wound of the circulatory system, particularly of a blood vessel. Other wounds in which wound healing may be promoted in accordance with the present disclosure include as a result of surgery or as a result of a burn. Other wounds in which wound healing may be promoted in accordance with the present disclosure include skin ulcers caused by pressure, venous stasis, or diabetes mellitus. In some embodiments, the result of a wound is a scar, which may be treated as described herein to prevent or reduce scarring of a wound at any site in or on the body. Other wounds include acute or chronic spinal cord injury.

[00150] In an embodiment, the inhibitor of fidgetin-like 2 is administered locally to the wound. In an embodiment, the inhibitor of fidgetin-like 2 is administered via a vein or artery. In an embodiment, the inhibitor of fidgetin-like 2 is administered by injection, catheterization or cannulation. In an embodiment, the inhibitor of fidgetin-like 2 is administered from an implant that elutes the inhibitor, for example an eluting wafer, gel, implant, stent or an eluting skin patch.

[00151] The dosage of the nucleic acid administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific nucleic acid and its mode and route of administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with the inhibitor and the desired therapeutic effect.

[00152] A dosage unit of the inhibitor may comprise a single compound, or a mixture of the compound with one or more anti-infection compound(s) or other wound healing-promoting compound(s).

[00153] In some embodiments, the inhibitor of fidgetin-like 2 is applied to the wound once. In some embodiments, the inhibitor of fidgetin-like 2 is applied to the wound more than once. In some embodiments, the inhibitor of fidgetin-like 2 is applied to the wound in the form of an controlled delivery device such as but not limited to a stent, wafer, implant, bandage, or any other slow or controlled release device. In some embodiments, the inhibitor of fidgetin-like 2 is applied to the wound each time the dressing is changed.

[00154] In some embodiments, the inhibitor of fidgetin-like 2 is applied to the wound until healing occurs. In some embodiments, the inhibitor of fidgetin-like 2 is applied to or maintained at the site for 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 days. In some embodiments, the inhibitor of fidgetin-like 2 is implanted or placed in a surgical site at the time of surgery. In some embodiments such placement is in the form of a controlled release composition such that the inhibitor of fidgetin-like 2 can act at the site for a period of time.

[00155] In an example of treating neurotrophic keratitis with an eye drop formulation of a nucleic acid disclosed herein, administration schedule may be determined by the concentration and volume administered, as well as the potency, half-life and other factors. In one embodiment, an eyedrop formulation of liposomes comprising a nucleic acid disclosed herein may be one drop in each eye every two days.

[00156] All combinations of the various elements described herein are within the scope of the disclosure unless otherwise indicated herein or otherwise clearly contradicted by context.

EXAMPLES

Example 1. siRNA Synthesis

Nucleic sequences SEQ ID NO:1 and SEQ ID NO:2 were prepared by conventional solid-phase oligonucleotide synthesis using phosphoramidite chemistry. Each cycle consists of 5´ deprotection, coupling, oxidation, and capping. Each coupling step is carried out by reaction of

the appropriate activated amidite with the free 5′ hydroxyl group of a support-immobilized protected nucleoside or oligonucleotide. The oligonucleotide is then deprotected and cleaved from the support. The 2′ TBDMS protecting group is then cleaved to yield the crude sense or antisense strand. The sense and antisense strands are then individually purified. The purified single strands are analyzed to confirm the correct molecular weight and impurity profile prior to annealing into the siRNA duplex. The annealed duplex is freeze-dried to yield the active pharmaceutical ingredient (API). The API is stored at –20°C.

Example 2. siRNA transfection of U2OS cells

[00157] The following methods are used to transfect U2OS cells in preparation for testing the efficacy of nucleic acids described herein.

[00158] siRNA transfection protocol (6 well plate). Seed 100,000 U2OS cells per well (6 well dish) and culture for 2 days (~80% confluency). Lipofectamine 3000: dilute 3.5 µL of siRNA (20 µM stock)/transfection (70 pmol) into 250 µL OptiMEM. Then dilute 3.5 µL of Lipofectamine 3000 into 250 µL of OptimMEM. Mix siRNA/OptiMEM into Lipofectamine/ OptiMEM solution. Incubate for 15 minutes at room temperature. Add mixture dropwise to wells.

[00159] siRNA transfection protocol (24 well plate). Seed 20,000 U2OS cells per well (6 well dish) and culture for 2 days (~80% confluency). Follow Lipofectamine 3000 protocol. Dilute 0.7 µL of siRNA (20 µM stock)/transfection (70 pmol) into 125 µL OptiMEM. Dilute 0.7 µL of Lipofectamine 3000 into 125 µL of OptimMEM. Mix siRNA/OptiMEM into Lipofectamine/OptiMEM solution. Incubate for 15 minutes at room temperature. Add mixture dropwise to wells. Add 250 µL of serum free media.

Example 3. Activity Testing – Migration Assay

[00160] U2OS cells were seeded at a density of 100,000 cells per well in 6-well plates and cultured in DMEM supplemented with 10% FBS and 1% penicillin/streptomycin. The cells were grown for two days to approximately 80% confluency. Twelve hours prior to transfection, the culture media was replaced with serum-free DMEM to optimize transfection efficiency. Cells were transfected with 3.5 µL of 20 µM siRNA (70 pmol final concentration per well) using 3.75

μL of Lipofectamine 3000 in 250 μL of Opti-MEM. Transfection mixtures were prepared as per the manufacturer's protocol, allowed to incubate for 15 minutes at room temperature, and added dropwise to the cells. Post-transfection, 500 μL of serum-free DMEM was added to each well.

[00161] After 24 hours of incubation at 37°C with 5% CO_2, cells were washed twice with PBS and grown in complete DMEM (with 10% FBS) until harvest at 24, 48, or 72 hours. A scratch wound was introduced in the cell monolayer using a sterile 200 μL pipette tip, and the detached cells were removed by washing with PBS. Fresh media was added, and the migration of cells was monitored using the EVOS live-cell imaging system (Invitrogen). Time-lapse phase-contrast images were acquired every hour for up to 24 hours post-scratch.

[00162] Images were analyzed to measure cell migration distance. Directionality was quantified by calculating the ratio of the net displacement (D) to the total path length (L) of each cell trajectory. Data from three independent scratch assays were averaged, and representative images were included. Control cells were transfected with non-targeting siRNA, while experimental cells received FL2-targeting siRNA. The nucleic acids disclosed herein demonstrated significant activity in the migration assay by increasing cell motility in FL2 knockdown conditions, showing $\geq$ 50% scratch closure compared to a negative control.

Example 4. Activity Testing – Knockdown Assay

[00163] U2OS cells were transfected as described in Example 3. Cells were harvested at 24, 48, and 72 hours post-transfection for protein analysis. Cells were washed twice with ice-cold PBS, lysed with RIPA buffer containing protease and phosphatase inhibitors, and centrifuged at 14,000 rpm for 10 minutes at 4°C. The supernatant was collected, and protein concentration was determined using a BCA protein assay kit. Equal amounts of protein (20 μg) from each sample were resolved on a 10% SDS-PAGE gel and transferred to a PVDF membrane. The membrane was blocked with 5% non-fat dry milk in TBS-T for 1 hour at room temperature and incubated overnight at 4°C with primary antibodies against FL2 (1:1000 dilution) and GAPDH (1:5000 dilution) as a loading control. Following washes, membranes were incubated with HRP-conjugated secondary antibodies (1:3000 dilution) for 1 hour at room temperature. Protein bands were visualized using ECL chemiluminescent substrate and imaged on a gel documentation system (iBright Imaging Systems, Invitrogen).

[00164] Densitometric analysis using iBright Analysis Software (Invitrogen) of FL2 band intensity normalized to GAPDH confirmed efficient knockdown of FL2 by nucleic acids disclosed herein. Knockdown greater than 25% of a negative control was observed.

Example 5. siRNA compositions

[00165] Nanoparticles (np) comprising a siRNA of the disclosure are formulated using five hundred µl of tetramethyl orthosilicate (TMOS) hydrolyzed in the presence of 100 µl of 1 mM HCl by sonication on ice for about 15 min, until a single phase forms. The hydrolyzed TMOS (100 µl) is added to 900 µl of 20 µM of siRNA (or the negative control) solution containing 10 mM phosphate, pH 7.4. A gel is formed within 10 minutes. The gel is frozen at −80°C for 15 minutes and lyophilized. Such siRNA nanoparticles are formulated into an eye drop useful for the various eye conditions described herein.

[00166] A wafer comprising siRNA of the disclosure is made from 2.5% collagen, 7.5% chondroitin sulfate, 82.5% polyvinylpyrrolidone, and 7.5% polyethylene glycol 400. Such wafers are made to contain 6.6, 13.3 or 26.6 micrograms siRNA per 100 mg wafer. A wafer is implantable at a surgical site, such as during nerve-sparing surgery or procedures with high risk of neuronal dysfunction such as a radical prostatectomy.

Example 6. Nanoparticle Microemulsion Formulation

[00167] Constituents needed for the methodology: Zonyl FSO-100 (FSO), Poloxamer 188, perfluorodecalin (PFD), DNAse/RNAse free water, siRNA as described herein, or Control.

[00168] The protocol is performed in a sterile environment at room temperature using DNAse/RNAse free water. The containers necessary to process the formulation is pre- cleaned with RNAse zap, autoclaved and rinsed with DNAse/RNAse free water in a sterile laminar hood.

[00169] Preparation of organic phase. A 20% solution of PFD is made in FSO in a tissue culture laminar hood. For a batch formulation of 100mL, weigh 20 grams of FSO and add PFD to make the volume to 80 mL. The mixture was vortexed and sonicated in an ultrasonic water batch alternatively every 10 min for 1h followed by 4h stirring. Periodically the mixture should be checked for consistency since the FSO is sparingly soluble in PFD. In order to avoid big chunks

of FSO and entrapment of air, the mixture should be sonicated in an ultrasonic water batch making sure not to expose the mixture to moisture or water. The solubility could take somewhere between overnight stirring and 24hrs at room temperature. If large chunks of undissolved FSO are present it should be separated from the mixture by slow centrifugation at 300 g for 5 minutes at room temperature. The dissolved phase should be carefully decanted into sterile falcon tubes. Keep the supernatant aside, and add 10 mL of PFD to the larger chunks of FSO, vortex the mixture with the cap tightly closed followed by sonication in an ultrasonic water bath. The procedure should be repeated until the larger chunks of PFD are completely dissolved in PFD. Pool both the PFD mixtures to make it to 90mL. This should result in a homogeneous suspension.

[00170] An alternative scale-up process can be done by preparing the organic phase in smaller quantities and then pool all the fractions in the end to obtain a homogeneous suspension.

[00171] Characterization of particle size in the organic phase. The mixture of PFD should be of a specific particle size preferably below 5 microns. After overnight stirring of the FSO in PFD, an aliquot (10µL) of the mixture is diluted and is subjected to dynamic light scattering (DLS) to monitor the particle size optimized to have maximum stability. At higher particle sizes the stability of the formulation is less viable and to have the maximum efficiency, it is better to have the particle size around or less than 5 micrometers. If the particle size is larger than 5 microns by DLS measurements, an additional step of sonication using a probe is performed with slow pulse with 20 sec interval. Care should be taken not to exceed the sonication procedure for more than 10 minutes. If there are still larger particles more than 5 microns by DLS measurements, the mixture should be stirred overnight under sterile conditions to have a mixture of uniform particle size.

[00172] Preparation of aqueous phase. In a separate 50 mL Falcon tube, prepare 4% of Poloxamer solution in DNAse/RNAse free water. Weigh 400mg of Poloxamer in 9mL of DNAse/RNAse free water and mix in a nutator for 2 hours checking for consistency every 30 minutes. Poloxamer should dissolve completely in DNAse/RNAse free water. The Poloxamer solution should be chilled in an ice water bath till use or refrigerated. The Poloxamer solution should be made in the clean laminar hood and could be mixed using a nutator after tight capping outside the hood. (Note: The Poloxamer solution is made in 9mL of water and later 1mL of

siRNA mixed in DNAse/RNAse free water is added to make the aqueous phase of Poloxamer).

[00173] Addition of the siRNA/control in the aqueous phase. The siRNA powder or liquid is mixed in pre-chilled DNAse/RNAse free water and made up to 1mL. The siRNA is quickly thawed and diluted with DNAse/RNAse free water in an ice bucket just before making the formulation. Do not thaw the siRNA until everything is ready for the formulation. Gently add the 1mL of siRNA solution to the 9mL of pre-chilled Poloxamer solution in the laminar hood, and mix well to obtain homogeneous solution. This procedure should be performed in a certified biosafety hood.

[00174] Preparation of the emulsion formulation. Stir the PFD mixture at a constant speed of 1200rpm using a magnetic stir bar inside the laminar hood on an ice bath. The consistency and stability of the micro emulsion formation is checked by an optical microscope periodically. Gently add the aqueous phase of Poloxamer and siRNA mixture slowly using a micropipette. The slow addition of the aqueous phase is critical and faster addition may result in separation of the organic and the aqueous phase. The total 10 mL of the aqueous phase is added over a period of 20 minutes or more at the rate of 0.5mL/minute or less to obtain a stable emulsion. The stability of the emulsion should be tested by monitoring the phase separation while the solution stands for 1h at 4 °C.

Example 7. siRNA collagen – surfactant polymer dressing

[00175] A dressing for treating wounds, burns and other injuries using a collagen microparticle and surface polymer dressing (SPD) is made as follows: 10 g of sodium bis(2-ethylhexyl) sulfosuccinate (AOT) (Sigma-Aldrich) is dissolved in 34 ml of n-hexane and 2 ml of 5% collagen-I dissolved in acetic acid is added. The resulting microemulsion is stirred for 45 min until it becomes clear. This solution is then evaporated to remove the hexane. The residue is washed and is then suspended in nuclease free water and lyophilized. The 100 mg of lyophilized powder is then treated with 1000 µl of 25 µM siRNA solution and re-lyophilized. This material is then suspended in 1.25 mL of SPD, at 4 degrees for 2 hours, and is then lyophilized. The lyophilized powder is then added with 1.25mL of nuclease free water and 1.25mL of SPD.

Example 8. siRNA improves outcome of radical prostatectomy

[00176] A radical prostatectomy is performed on a prostate cancer patient. Such surgeries may have an up to 50% risk of erectile dysfunction. To reduce the possibility of erectile function and other neurologic complications post-surgery, a 100 mg wafer prepared as described herein comprising 10 micrograms of duplex siRNA of SEQ ID NOs:7/8 is implanted at the surgical site proximal to the cavernous nerves. The patient recovers erectile function post-surgery.

Example 9. siRNA improves excisional wound healing

[00177] A double blind, placebo controlled, randomized excisional wound clinical trial in normal healthy volunteers is conducted to evaluate the rate of wound healing in split thickness skin graft (STSG) donor sites. In normal volunteers, a 0.08 inch thickness STSG of dimension one inch by one inch will be taken using a calibrated microdermatome from the upper outer aspect of each buttock. Subjects will receive initial hemostasis management using standard techniques (pressure, thrombin spray, epinephrine). A wound photograph will be taken to fill 80% of the camera frame with a calibration ruler within the field of the photo. Using a side by side randomization designation, a Telfa® pad saturated with fixed dose of SEQ ID NOs: 1/2 will be applied to one side STSG donor site. In addition, a Telfa® pad saturated with the vehicle will be administered to the opposite side. A sterile, non-adhesive film will be placed over the Tegaderm™, followed by a gauze bolster that will be taped in place. During repeat dosing, the dressing will be taken down to include the film but not the Telfa pad. Repeat doses will be used to saturate the Telfa pad, as did the first dose. The dressing will then be restored, as above. One day after the final dose is administered, the bolster will be removed, and both Telfa® pads will be gently soaked away from the donor sites using saline irrigation. A second, similar photograph will be taken. The wound will then be dried and covered with a transparent, breathable filmic dressing, allowing visualization of wound healing thereafter. Photographs will be taken daily for two weeks or until complete epithelialization has occurred. The filmic dressing will be removed when the clinician deems that 100% wound epithelialization has occurred or if otherwise clinically indicated. Photographic planimetry will be performed by a blinded observer and rates of wound healing at all time points and time to complete epithelialization will be measured and reported.

[00178] Subjects will return for photographs at one, three, and six months to ascertain durability

of healing and quality of scar using Category 1 of the Hamilton Scar Assessment Scale.

[00179] Frequency of dosing (qd, bid, and tid) will be explored among three cohorts.

[00180] Primary Objective: Demonstrate that STSG donor site treatment with SiFi2 supports more rapid wound healing than STSG donor site areas treated with vehicle alone.

[00181] Secondary Objectives: Demonstrate that wound healing after treatment of STSG donor sites with SiFi2 endures and is not associated with hypertrophic scarring as determined by the Hamilton Scar Assessment Scale, as compared to STSG donor site areas treated with vehicle.

[00182] Primary Endpoint: Rate and completion of STSG donor site wound healing, as determined by interpretation of standardized photography at Days 5-19.

[00183] Secondary Endpoints: (1) Maintenance of healed wound at one, three, and six months; (2) Degree of hypertrophic scarring in each treatment arm as assessed by Category 1 of the Hamilton Scar Assessment Scale6 score on photographs of the STSG donor sites at one, three, and six months as interpreted by three independent expert wound care surgeon reviewers; (3) Degree of pain and pruritus on the treated and untreated sides.

[00184] Inclusion Criteria: (1) Male and female healthy subjects of all races; (2) Age Range: 21-65 inclusive; (3) Basal Metabolic Index between 18 and 30; (4) Willing and able to provide Informed Consent and to participate in scar evaluation postoperatively; (5) Willingness to adhere to the follow up evaluation schedule. Exclusion Criteria: (1) Inability to provide Informed Consent; (2) Unwillingness to participate in scar evaluation postoperatively; (3) Cutaneous disease (scleroderma or other collagen vascular disease, prior keloid, severe skin thinning with prior skin tears); (4) The use of systemic steroids or dermatological steroids in the last six months; (5) Pregnancy or trying to become pregnant; (6) On anticoagulants; (7) Immune deficiency state; (8) Diabetes mellitus; (9) Malnourished; (10) Platelet or NSAID use in the prior two weeks; (11) Known hypersensitivity to suture or bandage materials; (12) Known hypersensitivity to epinephrine or thrombin; (13) Infection within the previous two weeks; (14) Any condition that in the opinion of the investigator will not allow the subject to successfully complete the clinical trial.

[00185] Safety: All adverse events, clinically significant laboratory abnormalities from baseline, abnormal bleeding, infection, and hypertrophic scar formation will be monitored.

[00186] Number of Subjects: Approximately 15 completed subjects across three cohorts (five subjects per cohort). One cohort would receive the treatment once per day (qd), the second cohort twice per day (bid), and the third cohort three times per day (tid).

[00187] Study Participation: Six months

[00188] Each subject would receive four days of drug applied on Telfa® absorptive pad beneath a tie over bolster at STSG donor sites either qd (cohort 1), bid (cohort 2), or tid (cohort 3) on Days 1, 2, 3, and 4. Total surgical time in any instance is estimated to be less than 2 hours.

[00189] Estimated Time to Complete Enrollment: Three months.

[00190] The results will show that STSG donor site treatment with SEQ ID NOs:1/2 supports more rapid wound healing than STSG donor site areas treated with vehicle alone, and that wound healing after treatment of STSG donor sites with SiFi2 endures and is not associated with hypertrophic scarring as determined by the Hamilton Scar Assessment Scale, as compared to STSG donor site areas treated with vehicle.

[00191] While certain features of the disclosure have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended claims are intended to cover all such modifications and changes as fall within the true spirit of the disclosure.

What is claimed is:

1. A nucleic acid molecule comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

2. A nucleic acid molecule comprising the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

3. The nucleic acid molecule of claim 1 or 2, wherein the nucleic acid molecule comprises no more than 52 nucleotides.

4. A double stranded nucleic acid molecule wherein one strand comprises the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

5. The double stranded nucleic acid molecule of claim 4, wherein the sequence comprising GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) comprises no more than 52 nucleotides.

6. A double stranded nucleic acid molecule wherein one strand comprises the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

7. The double stranded nucleic acid molecule of claim 6, wherein the sequence comprising AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2) comprises no more than 52 nucleotides.

8. A double stranded nucleic acid molecule comprising a strand comprising the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and a strand comprising the sequence AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

9. The nucleic acid of claim 8, wherein each sequence comprises no more than 52 nucleotides.

10. A nucleic acid molecule consisting of the sequence GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

11. A nucleic acid molecule consisting of the sequence

AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

12. A double stranded nucleic acid molecule wherein one strand consists of GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1).

13. A double stranded nucleic acid molecule wherein one strand consists of AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2)

14. A double stranded nucleic acid molecule consisting of GCCAUAUGCGCCGUGUACU[dT][dT] (SEQ ID NO:1) and AGUACACGGCGCAUAUGGC[dT][dT] (SEQ ID NO:2).

15. The nucleic acid molecule of any one of claims 1-14, wherein SEQ ID NO:1 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21; and SEQ ID NO:2 comprises ribonucleotides at positions 1-19, and deoxyribonucleotides at positions 20 and 21.

16. The nucleic acid of any one of claims 1-15 wherein the nucleic acid has at least one modification selected from a 3' overhang, a 5' overhang, a 5' phosphorylation, a 2' sugar modification, a nucleic acid base modification, a phosphate backbone modification, a phosphodiester cap, or any combination of one or more of any of the foregoing.

17. The nucleic acid of claim 16 wherein the one or more modification is 2'-O-methyl-adenosine, 2'-O-methyl-uridine, 2'-O-methyl-cytosine, 2'-O-methyl-guanosine, 2'-O-methyl-thymidine, 2'-fluoro-adenosine, 2'-fluoro-cytidine, 2'-fluoro-guanosine, 2'-fluoro-uracil, 2'-fluoro-thymidine, deoxycytosine, deoxyguanosine, deoxyadenosine, deoxythymidine, deoxyuridine, a locked adenosine, a locked uridine, a locked guanosine, a locked cytidine, a phosphorothioate, a phosphodiester cap, or any combination thereof.

18. A pharmaceutical composition comprising a nucleic acid of any one of claims 1-17 and a pharmaceutically acceptable carrier, vehicle, excipient or diluent.

19. The pharmaceutical composition of claim 18, wherein said carrier comprises at least

one of the following: saline, a sugar, a polypeptide, a polymer, a lipid, a cream, a gel, a micelle material, a wafer, a liposome or a nanoparticle.

20. The pharmaceutical composition of claim 18, wherein said carrier comprises at least one of the following: a glucose solution, a polycationic binding agent, a cationic lipid, a cationic micelle, a cationic polypeptide, a hydrophilic polymer grafted polymer, a non-natural cationic polymer, a cationic polyacetal, a hydrophilic polymer grafted polyacetal, a ligand functionalized cationic polymer, a nucleic acid delivery vehicle, a ligand functionalized-hydrophilic polymer grafted polymer, or a ligand functionalized liposome.

21. The pharmaceutical composition of claim 18, wherein the carrier comprises a cationic polymer-nucleic acid complex.

22. The pharmaceutical composition of claim 21, wherein the hydrophilic polymer is polyethylene glycol (PEG).

23. The pharmaceutical composition of claim 19 or 20, wherein the nanoparticle is a liposomal nanoparticle.

24. The pharmaceutical composition of claim 19, wherein the liposome is further functionalized with at least one 2' sugar modification.

25. A method of treating a pathological condition in a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 18.

26. A method of treating a wound, or inhibiting, reducing or preventing a scar in a subject comprising administering to the subject a therapeutically effective amount of the pharmaceutical composition of claim 18.

27. The method of claim 25, wherein the pathological condition is of the skin, eye, central nervous system, peripheral nervous system, cardiac tissue, blood vessel, tendon, ligament, muscle, oral cavity, lips, palate, internal organs, surgical wounds, abdominal cavity, pelvic cavity or thoracic cavity.

28. The method of claim 25, wherein the pathological condition is spinal cord injury.

29. The method of claim 25, wherein the pathological condition of the eye is of the cornea or lens capsule.

30. The method of claim 26, wherein the wound or scar is of the skin, eye, central nervous system, peripheral nervous system, cardiac tissue, blood vessel, tendon, ligament, muscle, oral cavity, lips, palate, internal organs, surgical wounds, abdominal cavity, pelvic cavity or thoracic cavity.

31. The method of claim 26, wherein the wound or scar results from eye surgery, LASIK surgery, LASEK surgery, PRK surgery, glaucoma filtration surgery, cataract surgery or corneal cicatrisation.

32. The method of claim 26, wherein the inhibition of scarring reduces the number of incidences of adhesion formation and/or the size of adhesions formed.

33. The method of claim 26, wherein the where the prevention, reduction or inhibition of scarring enhances neuronal reconnection and/or neuronal function.

34. The method of claim 30, wherein the cardiac tissue wound is from a myocardial infraction.

35. The method of claim 30, wherein the wound is a neuronal wound.

36. The method of claim 30, wherein the wound results in a capsular contraction.

37. The method of claim 30, wherein the wound is a surgical wound.

38. The method of claim 30, wherein the wound is from a cosmetic procedure or a scar revision.

39. A method of accelerating or improving the healing of a skin graft or skin grafting site in a subject comprising administering to the subject an amount of the pharmaceutical composition of claim 18 effective to accelerate healing of the skin graft or skin grafting site.

40. A method of accelerating or improving the healing of a spinal cord injury in a subject comprising administering to the subject an amount of the pharmaceutical composition of claim 18 effective to accelerate healing of the spinal cord injury.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/056211

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/7115*** (2024.01); ***A61K 31/712*** (2024.01); ***A61K 31/7125*** (2024.01); ***A61P 17/02*** (2024.01); ***A61P 25/00*** (2024.01); ***C07H 21/00*** (2024.01); ***C12N 15/113*** (2024.01)

CPC: ***A61K 31/7115; C12N 15/113; C07H 21/00; A61K 31/712; A61K 31/7125; A61P 17/02; A61P 25/00***

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0287974 A1 (BENVENISTY et al.) 24 November 2011 (24.11.2011) entire document	1-14
A	WO 2022/049295 A1 (CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE et al.) 10 March 2022 (10.03.2022) entire document	1-14
A	US 8,853,181 B2 (SHARP et al.) 07 October 2014 (07.10.2014) entire document	1-14
A	US 2008/0220983 A1 (TRINKLEIN et al.) 11 September 2008 (11.09.2008) entire document	1-14

☐ 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
23 December 2024 (23.12.2024)	**14 January 2025 (14.01.2025)**

Name and mailing address of the ISA/US	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/056211

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
   a. ☑ forming part of the international application as filed.
   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
      ☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.

2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/056211

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: **15-40**
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).