A61K A61P

Title: COMPOSITIONS AND METHODS OF TREATING SKIN FIBROTIC DISORDERS

(57) Abstract: A method for preventing and/or modulating formation of a dermal fibrotic disorder includes administering a therapeutically effective amount of a multi-phase modulator to a subject in need thereof. The multi-phase modulator is selected from the group consisting of axitinib, nintedanib, sorafenib, sunitinib, lenvatinib, panitumib, pazopanib, regorafenib, and riociguat. The dermal fibrotic disorder is acne scars, skin scars such as keloids and hypertrophic scars, wrinkles, cellulite and dermal neoplastic fibrosis, scarring alopecia, various vasculopathy, vasculitis, burn wound healing, diabetic foot syndrome, scleroderma, arthrofibrosis, Peyronie's disease, dupuytren's contracture, or adhesive capsulitis.
COMPOSITIONS AND METHODS OF TREATING SKIN FIBROTIC DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This claims the benefits of U.S. Provisional Patent Application No. 62/238,309, filed on October 7, 2015, the disclosure of which is incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] This invention relates to compositions and methods for preventing or treating formation of fibrotic lesions, including skin scars such as keloids and hypertrophic scars.

BACKGROUND

[0003] Dermal wound healing involves several phases: hemostasis, inflammation, proliferation, and tissue maturation. The overall process is induced and regulated by a complex array of factors, such as growth factors and cytokines.

[0004] The initial hemostasis controls the release of a variety of growth factors and/or cytokines from activated platelets to promote blood clotting. The hemostasis phase is followed by the inflammation phase.

[0005] The inflammation phase induces vasodilation and results in an influx of lymphocytes and macrophages. Macrophages will release growth factors, such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), interleukin-1 (IL-1), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF) that stimulate fibroblasts cells to promote the proliferation phase.

[0006] As the proliferative phase progresses, these growth factors stimulate angiogenesis and fibroplasias to rebuild blood flow to tissues after injury. Finally, the tissues mature to complete the wound healing processes. The tissue maturation phase also requires growth factors to control cell differentiation.

[0007] Because the wound healing processes involve multiple phases that require different factors at different times, any improper action of these factors in any phase
may result in improper wound healing. For example, excessive fibrosis may lead to undesirable scar formation.

[0008] Given these multiple factors and their spatial and temporal interactions, identifying an appropriate drug treatment strategy is challenging. For effective controls of dermal wound healing, a therapy may need to modulate more than one phase and target for a positive wound repair outcome.

SUMMARY OF THE INVENTION

[0009] Embodiments of the present invention relate to compositions and methods for preventing and/or modulating the formation of dermal fibrotic disorders. Embodiments of the invention are based on therapeutic utilities of compounds possessing certain spectrum of pharmacologic effects to modulate exuberant activities in various phases of wound healing, thereby preventing and/or alleviating aberrant fibrotic tissue formations (e.g., scar formations). Specifically, compounds of the invention include agents that can interfere with multiple phases (multiple targets) of wound healing processes. These agents will be referred to as "multi-phase modulators" or "multi-target modulators." The "multi-phase modulators" or "multi-target modulators" may include multikinase inhibitors that can inhibit multiple kinases, as well as soluble guanylate cyclase (SGC) stimulators that can stimulate the activities of soluble guanylate cyclase.

[0010] In one aspect, embodiments of the invention relate to methods for preventing and/or modulating formation of a dermal fibrotic disorder. A method in accordance with embodiments of the invention includes administering a therapeutically effective amount of a multi-phase modulator to a subject in need thereof. The subject may be a mammal, particularly a human.

[0011] In accordance with embodiments of the invention, a multi-phase modulator may be a multiple-kinase ("multikinase") inhibitor or a soluble guanylate cyclase (SGC) stimulator (e.g., riociguat). As used herein, the term a "multikinase inhibitor" refers to a compound that can inhibit multiple kinases, particularly multiple receptor tyrosine kinases. A soluble guanylate cyclase (SGC) stimulator can stimulate the activity of an SGC, leading to the formation of cyclic GMP (cGMP), which is a second messenger in various signal transduction pathways.
In accordance with embodiments of the invention, a multikinase inhibitor, for example, may include axitinib, nintedanib, sorafenib, sunitinib or lenvatinib, which can inhibit receptor tyrosine kinases, such as VEGFR receptors (VEGFR-1, VEGFR-2, and/or VEGFR-3) and PDGF receptors (PDGFR1 and/or PDGFR2). In addition, compounds of the invention (e.g., axitinib, nintedanib, sorafenib, sunitinib, and lenvatinib) also have various degrees of inhibitory potencies against fibroblast growth factor receptors (FGFR).

In accordance with embodiments of the invention, the multikinase inhibitors may include, but are not limited to, axitinib, nintedanib, sorafenib, sunitinib, lenvatinib, panatinib, pazopanib, regorafenib, and their stereoisomer, tautomer, prodrug, free base, analogs, metabolites, pharmaceutically acceptable salt, solvate or solvate of a salt thereof. These compounds have anti-multikinase activities, such as anti-VEGFR, anti-PDGFR, and/or anti-FGFR activities. As shown in this description, these multikinase inhibitors can inhibit exuberant tissue fibrosis or scar formation. They are effective in remedying undesired scar formation, presumably due to their abilities to inhibit multiple kinases, such as receptor tyrosine kinases that mediate signal transductions in the various phases of wound healing, thereby modulating the wound healing processes at multiple phases.

As used herein, a "pharmaceutically acceptable salt" refer to a compound that has been modified by adding an acid or base to make a salt thereof, wherein the compound may be a parent compound, or a prodrug, a derivative, a metabolite, or an analog of the parent compound.

In accordance with some embodiments of the invention, the multikinase inhibitor is axitinib. Axitinib is a tyrosine kinase inhibitor of VEGFR-1, VEGFR-2 and VEGFR-3. Axitinib has been shown to potently inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib also inhibits closely related receptor tyrosine kinases (RTKs), such as PDFGR-1, PDGFR-2, and KIT.

In accordance with some embodiments of the invention, the multikinase inhibitor is nintedanib. Nintedanib is tyrosine kinase inhibitor of various receptors, such as VEGFR, FGFR, PDGFR-a and PDGFR-β, and FGF.
In accordance with some embodiments of the invention, the multikinase inhibitor is sorafenib. Sorafenib is a tyrosine kinase inhibitor of several receptors, such as VEGFR-2, VEGFR-3 and PDGFR2.

In accordance with some embodiments of the invention, the multikinase inhibitor is sunitinib. Sunitinib is tyrosine kinase inhibitor of VEGFR and PDGFR.

In accordance with some embodiments of the invention, the multikinase inhibitor is lenvatinib. Lenvatinib is a tyrosine kinase receptor inhibitor of various receptors, such as VEGFR-1, VEGFR-2, VEGFR-3, FGFR-1, FGFR-2, FGFR-3, FGFR-4, and PDGFR-a.

In accordance with some embodiments of the invention, the multi-phase modulator is an SGC stimulator, such as riociguat. Riociguat, a soluble guanylate cyclase stimulator, may have effects on proliferation, fibrosis and inflammation in wound healing.

In accordance with embodiments of the invention, an agent for controlling exuberant activities in various phases of wound healing may be used with other types of agents that can interfere with one or more phases involved in wound healing. These other agents may include anti-angiogenic agents, anti-inflammatory agents, or anti-vascular permeability agents. Preferred anti-angiogenic agents include, but are not limited to, tyrosine kinase inhibitors, in particular, those targeting multiple receptors, such as those described in further detail herein: angiostatic cortisenes; matrix metalloprotease inhibitors; integrin inhibitors; PDGF antagonists; anti-proliferatives; hypoxia inducible factor-I inhibitors; fibroblast growth factor inhibitors; epidermal growth factor inhibitors; tissue inhibitor of metalloproteinases inhibitors; insulin-like growth factor inhibitors; tumor necrosis factor inhibitors; antisense oligonucleotides; anti-VEGF antibody, VEGF trap, anti-VEGF and/or anti-PDGF compounds, and their stereoisomer, tautomer, prodrug, free base, analogs, metabolites, pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

In accordance with embodiments of the invention, the dermal fibrotic disorders include but not limited to acne scars, skin scars such as keloids and hypertrophic scars, wrinkles, cellulite and dermal neoplastic fibrosis, scarring alopecia, various vasculopathy, vasculitis, burn wound healing, diabetic foot syndrome, scleroderma, arthrodysplasia, Peyronie’s disease, dupuytren’s contracture, or adhesive capsulitis.
In accordance with embodiments of the invention, compounds/molecules of the present invention may be administered by oral, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingual, intramuscular, intradermal, subcutaneous, topical, intranasal, intraperitoneal, intrathoracic, intralesional, paralesional, intravenous, epidural, intrathecal, or intracerebroventricular routes, or by injection into the tissue and/or joints.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows TGF-βI mRNA expression levels in wound sites treated with compounds of the invention relative to those in an untreated unwounded site on the dorsum of pigs.

FIG. 2 shows images of pig dermal tissues from histologic slides after hematoxylin and eosin staining. There was a decrease in neovascularization and fibrosis in drug treatment groups as compared to the untreated wound control. Panel (A) unwounded normal skin. Panel (B) untreated wound tissue, showing more neovascularization and fibrosis. Panel (C) axitinib treated wound, showing neovascularization and reduced fibrosis.

FIG. 3 shows results of nintedanib (labeled as AIV002) treatment of rabbit ear hypertrophic scar. Nintedanib treatment decreased neovascularization and dermal fibrosis. Panel (A) shows H&E staining (left: untreated; right: treated wound), wherein the untreated site has substantial neovascularization (left), relative to the treated site (right). Panel (B) shows Mason’ s Trichrome staining (left: untreated; right treated wound).

DETAILED DESCRIPTION

Embodiments of the present invention relate to compositions (multi-phase modulators) and methods for preventing and/or modulating the formation of dermal fibrotic disorders. Dermal wound healing involves several phases: hemostasis, inflammation, proliferation, and tissue maturation. The overall process is induced and regulated by a complex array of factors, such as growth factors and cytokines. Effective approaches to the control of exuberant activities in wound healing likely require controls and modulations in multiple phases.
[0028] Factors involved in wound healing exert their functions by binding to their respective receptors to activate various signaling pathways. These receptors include tyrosine kinases. Therefore, receptor tyrosine kinase inhibitors (particularly multikinase inhibitors) can be used to regulate the exuberant wound healing processes. Embodiments of the invention are based on therapeutic utilities of compounds that possess a certain spectrum of pharmacologic effects to modulate exuberant activities in various phases of wound healing, thereby preventing and/or alleviating aberrant fibrotic tissue formations (e.g., scar formations).

[0029] Because various kinases are involved in different phases of the wound healing processes, compounds of the invention include multikinase inhibitors that can inhibit multiple kinases, thereby interfering with multiple kinase-mediated signaling pathways. By inhibiting multiple kinases, one can achieve overall effects that may not be achievable by inhibiting a single kinase. In other words, by inhibiting multiple kinases in multiple phases of the wound healing processes, one may be able to achieve therapeutically effective effects to have a meaningful control of the undesirable fibrosis.

[0030] Compounds of the invention, for example, may include axitinib, nintedanib, sorafenib, sunitinib, lenvatinib, panatinib, pazopanib, and regorafenib, which can potently inhibit receptor tyrosine kinases, such as VEGFR receptors (VEGFR-1, VEGFR-2, and/or VEGFR-3) and/or PDGF receptors (PDGFR1 and/or PDGFR2). In addition, these compounds also have different extents of inhibitory potencies against fibroblast growth factor receptors (FGFR). Having the abilities to inhibit multiple receptor tyrosine kinases (e.g., VEGFR, PDGFR, and/or FGFR), these compounds can produce effective controls of undesirable fibrosis, such as in scar formation.

[0031] In addition to multikinase inhibitors, soluble guanylate cyclase (SGC) stimulators may also be used in embodiments of the invention. SGC stimulators may also interfere with multiple phases of wound healing. Thus, in accordance with some embodiments of the invention, a compound of the invention may be an SGC stimulator, such as riociguat.

[0032] As used herein, the term "dermal fibrotic disorder" refers to exuberant activities in various phases of wound healing that would result in aberrant fibrotic tissue formations (e.g., scar formations).
As used herein, the term a "therapeutic effective amount" is an amount that would achieve the desired therapeutic effects. A therapeutic effective amount would depend on the patient conditions, routes of administration, administration regimes etc. One skilled in the art would be able to determine a therapeutic effective amount without inventive efforts.

The following describes some specific examples to illustrate embodiments of the invention. One skilled in the art would appreciate that these examples are for illustration only and other modifications and variations are possible without departing from the scope of the invention.

**EXPERIMENT #1**

Porcine skin resembles human skin in many aspects. Both species have a relatively thick epidermis, distinct rete pegs, dermal papillae, and dense elastic fibers in the dermis. Furthermore, unlike rodents and rabbits, porcine skin is adherent to the subcutaneous structures, similar to human skin. Because of these anatomical similarities and other parallelisms in wound healing, porcine models have emerged as important foundations for the study of pathophysiology and potential treatment paradigms for abnormal wound healing. It has also been observed in porcine full-thickness wound healing in Yucatan Minipigs that the spatial and temporal expressions of TGF-B1, PDGF and VEGF were similar to the patterns for the growth factors described above. Therefore, the full-thickness excision models in Yucatan minipigs are the models for human wound healing studies.

In this experiment, multiple full-thickness excision wounds were made to the dorsum of Yucatan minipigs, and the wound sites were allowed to re-epithelialized adequately. At four weeks post-wound, the wound sites had normal to pink vascularity and had pliability. Epidermal hyperplasia was observed, as expected for regenerative responses in the full-thickness wounds.

On Day 28 post-wound, a dose (e.g., 1%) of axitinib, nintedanib, riociguat, sorafenib, sunitinib, and/or lenvatinib was administered into the dermal tissue at or around the wound sites, once every two weeks on two occasions. One wound site was left untreated as the control for each pig. Please note that the particular parameters in this example are only for illustration. One skilled in the art would appreciate that the
dosages, administration methods, treatment regimen, and the administration sites may be varied to achieve similar results.

[0038] On Day 59 post wound, the minipigs were sacrificed and dermal tissues were collected for qualitative and quantitative evaluation using hematoxylin and eosin, and Mason's Trichrome staining. Dermal fibroplasia was characterized by increased numbers of fibroblasts in the dermis suspended in variable amounts of collagen in wounds.

[0039] In addition, total mRNA was isolated from skin biopsies of the treated wound sites and the untreated unwounded sites of the pigs. The mRNA samples were used to prepare cDNA and analyzed via qRT-PCR. The TGF-βI expression levels were assessed using beta actin as a reference gene.

[0040] Transforming-growth-factor (TGF)-β expression, following inflammatory responses, results in increased production of extracellular matrix (ECM) components, as well as mesenchymal cell proliferation, migration, and accumulation. Therefore, TGF-β has been found to induce fibrosis associated with chronic phases of inflammatory diseases. As shown in FIG. 1, compounds of the invention significantly reduced the expression levels of TGF-βI, suggesting that compounds of the invention can be used to control undesired fibrosis.

[0041] The histologic evaluation results, shown in Table 1, indicate that these compounds are effective in controlling the undesirable neovascular and fibrotic formation.

[0042] Among the various test compounds administered as two biweekly treatments, axitinib and nintedanib noticeably reduced neovascularization with a corresponding reduced dermal fibroplasia, as assessed by histopathologic examinations of the treated wounds relative to the untreated wound (Table. 1).

[0043] FIG. 2 shows exemplary hematoxylin and eosin stainings of pig dermal tissues from treated and untreated wound sites. Panel (A) show a staining from an unwounded skin as a control. Panel (B) shows a staining of a sample from a wounded site without treatment with any compound of the invention. It is evident that the wounded tissue has substantial neovascularization and fibrosis. Panel (C) shows a staining of a sample from a wounded site treated with axitinib. Axitinib treatment results in significantly reduced neovascularization and reduced fibrosis, as compared
with the untreated wound (see Panel (B)). These results clearly show that compounds of the invention are effective in reducing neovascularization and fibrosis at the wounded sites. As a result, compounds of the invention may be used to reduce undesired fibrosis, such as scar formation.

**Table 1.** Qualitative assessments of dermal fibroplasia and neovascularization at wound sites after two doses, (minimal = 1, mild = 2, moderate = 3, marked = 4, and severe=5)

<table>
<thead>
<tr>
<th>Finding</th>
<th>Individual Scores &amp; Average Scores (bolded)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroplasia; dermis</td>
<td>axitinib</td>
</tr>
<tr>
<td></td>
<td>2,2,3</td>
</tr>
<tr>
<td></td>
<td>(2.33)</td>
</tr>
<tr>
<td>Neovascularization; dermis</td>
<td>1,2,2</td>
</tr>
<tr>
<td></td>
<td>(1.67)</td>
</tr>
</tbody>
</table>

As shown in Table 2, compounds of the invention also resulted in reduction of TGF-βI mRNA expression levels at the treated wounds, as compared to the expression level in unwounded normal skin, suggesting that compounds of the invention can be used to control the exuberant fibrosis. Among these compounds, axitinib, nintedanib, riociguat, sorafenib, and sunitinib are the most effective.

**Table 2.** TGF-βI mRNA expression in Yucatan pig skin wound sites after treatments.

<table>
<thead>
<tr>
<th>Animal Number</th>
<th>Duplicate Set</th>
<th>TGF-βI1 mRNA Expression Fold Relative to Untreated Unwounded Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>axitinib</td>
</tr>
<tr>
<td>7369</td>
<td>1</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.68</td>
</tr>
<tr>
<td>7370</td>
<td>1</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.89</td>
</tr>
<tr>
<td>7371</td>
<td>1</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.64</td>
</tr>
</tbody>
</table>

**EXPERIMENT #2**

In rabbits, wounds are created down to the bare cartilage on the ventral surface of the ear using a dermal biopsy punch. Because these wounds do not heal by
contraction, epithelialization is delayed and a raised scar is created. By both appearance and histological analysis, these scars resemble human hypertrophic scars. In this established model, it was shown that reduced TGF-β expression results in reduced scarring, which is consistent with the current understanding of the pathogenesis of excessive scarring/dermal fibrosis. Furthermore, excessive angiogenesis and vascularization have been shown to result in pathological hypertrophic scar in this model. Thus, this rabbit model was also used to assess the compounds of the invention.

Eight wounds were created on the ventral surface of the ears of each of New Zealand White rabbits using skin punch biopsies, and then the wounds were allowed to heal for approximately 2 weeks.

A dose (e.g., 1%) of axitinib, nintedanib, riociguat, sorafenib, sunitinib, and/or lenvatinib was administered into the dermal tissue, once every two weeks on two occasions. Again, the specific doses, treatment methods and schedules are for illustration only. One skilled in the art would appreciate that variations and modifications are possible to achieve similar results.

On Day 42 post wound, the rabbits were sacrificed and dermal tissues were collected for qualitative and quantitative evaluation using hematoxylin and eosin and Mason's Trichrome staining. In addition, TGF-β1 mRNA expression levels were measured using qRT-PCR.

Histologic slides for hematoxylin and eosin stainings were prepared from the wound sites. Tissues were evaluated qualitatively for inflammation, neovascularization, granulation tissue, degrees of re-epithelialization, and degrees of scarring (avascular collagen).

As compared with untreated wound and the vehicle-treated wound, the wounds treated with nintedanib had much less neovascularization and less scar tissues. As compared with the vehicle-treated wound, the mean TGFβ1 mRNA level was lower after intradermal treatment with nintedanib.

FIG. 3 shows results of nintedanib (labeled as AIV002) treatment of rabbit ear hypertrophic scar. Nintedanib treatment decreased neovascularization and dermal fibrosis. Panel (A) shows H&E staining (left: untreated; right: treated wound),
wherein the untreated site has substantial neovascularization (left), relative to the treated site (right). Panel (B) shows Mason’s Trichrome staining (left: untreated; right treated wound).

[0052] In addition to nintedanib, other compounds of the invention also have similar effects. For example, As compared with the untreated wound and the vehicle-treated wound, the wounds treated with axitinib had less neovascularization, less fibrosis, and less scar tissues. As compared with the vehicle-treated wound, the mean TGFβ1 mRNA level was lower after intradermal treatment with axitinib.

[0053] As compared with untreated wound and the vehicle-treated wound, the wounds treated with riociguat had slightly decreased neovascularization and fibrosis.

[0054] As compared with untreated wound and the vehicle-treated wound, the wounds treated with sorafenib had slightly increased neovascularization, and similar or decreased fibrosis. As compared with vehicle-treated wound, the mean TGFβ1 mRNA level was lower after intradermal treatment with sorafenib.

[0055] As compared with untreated wound and the vehicle-treated wound, the wounds treated with sunitinib had more neovascularization, and similar fibrosis. As compared with the vehicle-treated wound, the mean TGFβ1 mRNA level was lower after intradermal treatment with sunitinib.

[0056] As compared with untreated wound and the vehicle-treated wound, intradermal treatment with lenvatinib had similar neovascularization, fibrosis, and re-epithelialization. As compared with the vehicle-treated wound, the mean TGFβ1 mRNA level was lower after intradermal treatment with lenvatinib.

**Table 3.** TGF-β1 mRNA expression in rabbit ear wound sites after intradermal treatments.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Rabbit TGFβ1 mRNA Expression Fold by Treatment Relative to Untreated Wounded (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>axitinib</td>
</tr>
<tr>
<td>Normal skin</td>
<td>3</td>
<td>0.61 ± 0.15</td>
</tr>
<tr>
<td>Untreated (all rabbits)</td>
<td>7</td>
<td>1.00</td>
</tr>
</tbody>
</table>
[0057] While the invention has been described with respect to a limited number of embodiments, those skilled in the art, having benefit of this disclosure, will appreciate that other embodiments can be devised which do not depart from the scope of the invention as disclosed herein. Accordingly, the scope of the invention should be limited only by the attached claims.

<table>
<thead>
<tr>
<th>Treated (each drug)</th>
<th>5 or 6</th>
<th>0.87 ± 0.28</th>
<th>0.73 ± 0.13</th>
<th>1.14 ± 0.14</th>
<th>0.87 ± 0.13</th>
<th>0.76 ± 0.23</th>
<th>0.66 ± 0.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (each drug)</td>
<td>1 or 2</td>
<td>1.09</td>
<td>1.03 ± 0.19</td>
<td>1.01 ± 0.22</td>
<td>0.87 ± 0.20</td>
<td>1.26 ± 0.79</td>
<td>0.73 ± 0.09</td>
</tr>
</tbody>
</table>
CLAIMS

What is claimed is:

1. A method for preventing and/or modulating formation of a dermal fibrotic disorder, comprising:
   administering a therapeutically effective amount of a multi-phase modulator to a subject in need thereof.

2. The method according to claim 1, wherein the multi-phase modulator is a multi-kinase inhibitor or a soluble guanylate cyclase stimulator.

3. The method according to claim 1, wherein the multi-phase modulator is a multi-kinase inhibitor.

4. The method according to claim 3, wherein the multi-kinase inhibitor is selected from the group consisting of axitinib, nintedanib, riociguat, sorafenib, sunitinib, lenvatinib, panatinib, pazopanib, regorafenib, and a combination thereof.

5. The method according to claim 1, wherein the multi-phase modulator is a soluble guanylate cyclase stimulator.

6. The method according to claim 5, wherein the soluble guanylate cyclase stimulator is riociguat.

7. The method according to any one of claims 1-6, wherein said dermal fibrotic disorder is acne scar, skin scar, wrinkle, cellulite and dermal neoplastic fibrosis, scarring alopecia, vasculopathy, vasculitis, exuberant burn wound healing, diabetic foot syndrome, scleroderma, arthrofibrosis, Peyronie's disease, dupuytren's contracture, or adhesive capsulitis.

8. The method according to any one of claims 1-7, wherein the subject is a human.

9. The method according to any one of claims 1-8, wherein the administering is by oral, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingual, intramuscular,
subcutaneous, topical, intranasal, intraperitoneal, intrathoracic, intravenous, epidural, intrathecal, or intracerebroventricular route, or by injection into joint.

10. A composition for use in preventing and/or modulating formation of a dermal fibrotic disorder, comprising: a multi-phase modulator selected from the group consisting of a multikinase inhibitor and a soluble guanylate stimulator.

11. The composition according to claim 10, wherein the multikinase inhibitor is selected from the group consisting of axitinib, nintedanib, sorafenib, sunitinib, lenvatinib, panatinib, pazopanib, regorafenib, and a combination thereof.

12. The composition according to claim 10, wherein the soluble guanylate cyclase stimulator is riociguat.

13. The composition according to any one of claims 10-12, wherein the dermal fibrotic disorder is acne scar, skin scar, wrinkle, cellulite and dermal neoplastic fibrosis, scarring alopecia, vasculopathy, vasculitis, exuberant burn wound healing, diabetic foot syndrome, scleroderma, arthofibrosis, Peyronie's disease, dupuytren's contracture, or adhesive capsulitis.

14. The composition according to any one of claims 10-13, wherein the composition is formulated for administering by oral, parenteral, buccal, vaginal, rectal, inhalation, insufflation, sublingual, intramuscular, subcutaneous, topical, intranasal, intraperitoneal, intrathoracic, intravenous, epidural, intrathecal, or intracerebroventricular route, or by injection into joint.
Figure 1

TGF-β1 mRNA Expression Fold

- Duplicate Set 1
- Duplicate Set 2

Axitinib  Nintedanib  Riociguat  Sorafenib  Sunitinib  Lenvatinib  Untreated
Figure 2

(A) Control unwounded skin

(B) Untreated wound center section

(C) Axitinib-treated wound center section
Figure 3

A. H&E Staining, 10X

B. Mason’s Trichrome Staining, 10X
INTERNATIONAL SEARCH REPORT

International application No. PCT/US2016/055865

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61P 35/00; A61K 31/505; A61K 31/506; A61K 31/517; A61K 45/00; A61K 45/05 (2016.01)
CPC - A61K 31/505; A61K 31/506; A61K 31/517; A61K 45/00; A61K 45/05 (2016.1 1)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 31/505; A61K 31/506; A61K 31/517; A61K 45/00; A61P 35/00 (2016.01 )
CPC - A61K 31/505; A61K 31/506; A61K 31/517; A61K 45/00; A61K 45/05 (2016.1 1)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8) - A61K 31/505; A61K 31/506; A61K 31/517; A61K 45/00; A61P 35/00; CPC - A61K 31/505; A61K 31/506; A61K 31/517; A61K 45/00; A61K 45/05 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit.com, Google Patents, Google Scholar, Public AppFT and PatFT
Search terms used: riociguat, dermal, fibrotic, wrinkle, scar, Bay 63-2521, scleroderma

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>Y</td>
<td>US 2013/0210733 A1 (CYTOKINETICS INC) 15 August 2013 (15.08.2013) entire document</td>
<td>10-13</td>
</tr>
</tbody>
</table>

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
  "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
  "Z" document member of the same patent family

Date of the actual completion of the international search
28 November 2016

Date of mailing of the international search report
2-0 DEC 2016

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Form PCT/ISA/210 (second sheet) (January 2015)
INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/055865

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.: 8, 9, 14
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/2 to (continuation of first sheet (2)) (January 2015)