and lung infection in Covid-19 causes permanent fibrosis (P. Zhang *et al.* (2020), *Bone Res.* 8). Fibroproliferative diseases including any kind of fibrosis, scar formation, keloids as seen within organs, and fibrous adhesions, an extra-organ manifestation, also occurs in many other chronic diseases and injuries, and it is the most critical stage that tips the scale towards organ dysfunction, failure, and death.

[004] Although a fibroproliferative disease is thought to initiate by the immune system and inflammation, it is not clear how an injury of an internal organ such as an inflammation (e.g. pneumonia in the lung) causes connective tissue deposition, leading either to forms of fibrosis and scarring or chronic wounds.

[005] Thus, there is a need in the art to investigate the clinical situation behind having an injury of an internal organ of a subject, the ECM movement towards said site of injury and then resulting in a fibroproliferative disease or a chronic wound.

[006] Therefore, the objective of the present invention is to comply with this need.

[007] The solution of the present invention is described in the following, exemplified in the appended examples, illustrated in the figures and reflected in the claims.

SUMMARY

[008] The present disclosure deals with a novel mechanism of ECM movement and physical translocation of pre-existing matrix to areas of injury. This was found out by labelling the pre-existing extracellular matrix (ECM) of the surface of different internal organs with N-Hydroxysuccinimide-esters in chemical and viral models of fibrosis, as well as *ex-vivo* human samples. Basically, the inventors investigated that ECM is moving and that this movement plays a role in a pathogenic state. In particular, it was demonstrated that mesothelial cells are causative for ECM production and movement. In other words, targeting said mesothelial cells which produce the ECM and which form the surface as the outermost lining of each internal organ can modulate the movement of ECM towards a site of injury of said organ of a subject, thus either inhibiting ECM movement or promoting it. Knowing that mesothelial cells produce ECM which then forms with the mesothelial cell the surface of said organ, one can indirectly or directly affect / target said cells, preferably specifically targeting said cells, thus modulating ECM towards a site of injury of said organ of a subject suffering from or being at a risk of an injury of said organ. Even though a small portion of the ECM on the organ surface may also be contributed from other cell types other than mesothelial cells, the mesothelial cells are the main contributer for ECM production and movement of the ECM. This opens a new clinical situation,

which has not been defined yet.

[009] Thus, in one aspect, the present disclosure relates to the use of a compound in the manufacture of a medicament for the modulation of movement of extracellular matrix (ECM) produced by mesothelial cells forming the surface of an internal organ, towards a site of injury of said organ of a subject suffering from or being at a risk of an injury of said organ, wherein modulation is inhibition or promotion. In a first example the present disclosure relates to a compound for use in a method for the modulation of movement of extracellular matrix (ECM) produced by mesothelial cells forming the surface of an internal organ, towards a site of injury of said organ of a subject suffering from or being at a risk of an injury of said organ, wherein modulation is inhibition or promotion.

[0010] Additionally, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein modulation comprises that said compound is capable of specifically targeting mesothelial cells.

[0011] The present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein said compound is a transcription construct encoding a gene involved in the modulation of movement of ECM produced by mesothelial cells.

[0012] In addition, the present disclosure may also envisage the compound for the use as defined elsewhere herein, wherein said gene is selected from the group consisting of *csta, tgfb, tgfbr2, ctsb, aebp1, col1a1, adamTs1, dcn, sparc, timp1, c1, c2, c3, c4, saa3, hsf1,* and *dtr* or a combination thereof*.* Additionally or alternatively, the present disclosure may also envisage the compound for the use as defined elsewhere herein*,* wherein said gene is selected from the group consisting of *mgp, plac8, crip1, lgals1, and ifi27l2a* or a combination thereof*.*

[0013] Further, the present disclosure may also encompass the compound for the use as defined elsewhere herein, wherein the transcription construct comprises DNA or RNA.

[0014] Further, the present disclosure may also encompass the compound for the use as defined elsewhere herein, wherein if the transcription construct is a DNA construct, said construct further comprises a mesothelium specific control element and/or promoter element and/or enhancer element. Preferably, the present disclosure may also encompass the compound for the use as defined elsewhere herein wherein, if the transcription construct is a DNA construct, the mesothelium specific promoter element is any one of a CRIP1, LGALS1, MGP, SAA3 or a SEPP1 promoter, preferably CRIP1.

[0015] Additionally, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein if the transcription construct is a DNA construct, said construct further comprises a RNA or protein target sequence.

[0016] Further, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein if the transcription construct is a RNA construct, said construct further comprises a RNA or protein target sequence.

[0017] Additionally, the present disclosure may also encompass the compound for the use as defined elsewhere herein, wherein the compound is an agonist or antagonist of a mesothelium specific receptor.

[0018] Further, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein the agonist or antagonist is selected from an antibody, a siRNA, a nucleic acid, an aptamer, a peptide, a protein, a lipid, or a small organic molecule.

[0019] Additionally, the present disclosure may also encompass the compound for the use as defined elsewhere herein, wherein the mesothelium specific receptor is selected from the group consisting of MSLN1, GPM6A, PDPN, TGF-β receptor, LTB4 receptor BLT2, Podoplanin, and Procr.

[0020] Further, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein the compound is administered via injection or infusion.

[0021] Additionally, the present disclosure may also encompass the compound for the use as defined elsewhere herein, wherein the administration is performed intravenously, intraperitoneally, intrapleurally, intrathecally, via pericardiocentesis or via the lymphatic system.

[0022] Further, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein the compound is administered via a viral vector, a liposome, a transfection reagent, an extracellular vesicle or directly.

[0023] Further, the present disclosure may also envisage the compound for the use as defined elsewhere herein, wherein the viral vector is an adeno-associated virus (AAV) vector and/or an adeno-virus (AV) vector.

[0024] Additionally, the present disclosure may also encompass the compound for the use as defined elsewhere herein, wherein the vector, which is an AAV vector or an AV vector comprises a peptide comprising a RGD motif.

[0025] Additionally, the present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein said internal organ is any one of a lung, a kidney, a heart, a

liver, a stomach, a bladder, a peritoneum, a brain, a uterus, a spleen, a pancreas or an intestine.

[0026] The present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein if the modulation of ECM movement is inhibition, said injury of said organ is associated with a chronic wound.

[0027] The present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein if the modulation of ECM movement is promotion, said injury of said organ is associated with a fibroproliferative disease.

[0028] The present disclosure may also comprise the compound for the use as defined elsewhere herein, wherein if the modulation of ECM movement is promotion, said injury of said organ is associated with a fibroproliferative disease, which is fibrosis, preferably any one of lung fibrosis, liver fibrosis, kidney fibrosis, cardiac fibrosis, bladder fibrosis, brain fibrosis, uterus fibrosis, spleen fibrosis, pancreas fibrosis or stomach fibrosis.

[0029] In a second example the present disclosure relates to a compound for use in a particular *in vivo* screening method for identifying a modulator of movement of extracellular matrix (ECM) produced by mesothelial cells towards a site of injury of an internal organ of a subject, the method comprising

a) contacting ECM of an internal organ of a subject with a label;

b) introducing to said organ an injury;

c) contacting mesothelial cells, which form the surface of said organ with a compound of interest;

d) determining whether said compound of interest modulates movement of ECM towards a site of injury of said organ using a detection method in comparison to a control subject having ECM of said organ labelled, but not having mesothelial cells of said organ contacted with said compound of interest,

wherein modulation of movement of ECM towards said site of injury of said organ is indicative for said compound of interest to be a modulator of said ECM movement and wherein step b) and step c) can be switched.

[0030] Finally, in another aspect the present disclosure relates to an *in vitro* screening method for identifying a modulator of the movement of extracellular matrix (ECM) towards an external stimulus in a single cell suspension derived from the mesothelium, the method comprising

CLAIMS

1. Use of a compound in the manufacture of a medicament for the modulation of movement of extracellular matrix (ECM) produced by mesothelial cells forming the surface of an internal organ, towards a site of injury of said organ of a subject suffering from or being at a risk of an injury of said organ, wherein modulation is inhibition or promotion.

2. The use of claim 1, wherein modulation comprises that said compound is capable of specifically targeting mesothelial cells.

3. The use of any one of the preceding claims, wherein said compound is a transcription construct encoding a gene involved in the modulation of movement of ECM produced by mesothelial cells.

4. The use of claim 3, wherein said gene is selected from the group consisting of *csta***,** *tgfb*, *tgfbr2, ctsb, aebp1, col1a1, adamTs1, dcn, sparc, timp1, c1, c2, c3, c4, saa3, hsf1,* and *dtr,* or a combination thereof.

5. The use of claim 3 or 4, wherein said gene is selected from the group consisting of *mgp, crip1, plac8, lgals1,* and *ifi27l2a,* or a combination thereof.

6. The use of any one of claims 3-5, wherein the transcription construct comprises DNA, preferably wherein if the transcription construct is a DNA construct, said construct further comprises a mesothelium specific control element and/or promoter element and/or enhancer element and/or wherein if the transcription construct is a DNA construct, said construct further comprises a RNA or protein target sequence.

7. The use of claim 6, wherein the mesothelium specific promoter element is any one of a CRIP1, LGALS1, MGP, SAA3 or a SEPP1 promoter, preferably CRIP1.

8. The use of any one of claims 3-5, wherein the transcription construct comprises RNA, preferably wherein if the transcription construct is a RNA construct, said construct further comprises a RNA or protein target sequence.

9. The use of any one of claims 1-8, wherein the compound is an agonist or antagonist of a mesothelium specific receptor, preferably wherein the agonist or antagonist is selected from an antibody, a siRNA, a nucleic acid, an aptamer, a peptide, a protein, a lipid or a small organic molecule.

10. The use of claim 9, wherein the mesothelium specific receptor is selected from the group consisting of MSLN1, GPM6A, PDPN, TGF-β receptor, LTB4 receptor BLT2, Podoplanin, and Procr.

11. The use of any one of the preceding claims, wherein the compound is to be administered via injection or infusion, preferably wherein the administration is performed intravenously, intrathecally, intraperitoneally, intrapleurally, via pericardiocentesis or via the lymphatic system.

12. The use of claim 11, wherein the compound is to be administered via a viral vector, a liposome, a transfection reagent, an extracellular vesicle or directly, preferably wherein the viral vector is an adeno-associated virus (AAV) vector and/or an adeno-virus (AV) vector.

13. The use of any one of the preceding claims, wherein said internal organ is any one of a lung, a kidney, a heart, a liver, a stomach, a bladder, a brain, a peritoneum, an uterus, a spleen, a pancreas or an intestine.

14. The use of any one of the preceding claims, wherein if modulation is inhibition, said injury of said organ is associated with a chronic wound or wherein if modulation is promotion, said injury of said organ is associated with a fibroproliferative disease.

15. An *in vitro* screening method for identifying a modulator of the movement of extracellular matrix (ECM) towards an external stimulus in a single cell suspension derived from the mesothelium, the method comprising

a) contacting said single cell suspension derived from the mesothelium with an already labeled ECM or placing said single cell suspension derived from the mesothelium under suitable conditions which allow said cells to produce ECM and then contacting of said produced ECM with a label;

b) exposing said single cells to an external stimulus;

c) contacting said single cells with a compound of interest;

d) determining whether said compound of interest modulates ECM movement towards said external stimulus using a detection method in comparison to a control single cell suspension, wherein said ECM has been labeled, but said single cells not contacted with said compound of interest,

wherein modulation of the movement of ECM towards said external stimulus is indicative for said compound of interest to be a modulator of said ECM movement and wherein step b) and step c) can be switched.