administration. Particularly useful formulations may display or attain gel consistency upon administration, whereby pharmaceutical active ingredients included in the formulations are retained in the gel *in situ* and are gradually released from the gel, i.e., sustained or slow release. Also, where the formulations contain therapeutic cells, gel consistency may provide cell-supportive environment and may ensure proximity of the cells and optional beneficial substances, such as growth factors that stimulate survival, proliferation (propagation) and/or differentiation of the cells.
Fresh frozen plasma (FFP) is prepared in blood banks worldwide mainly as a by-product of red blood cell concentrate preparation. With view of improving safety of FFP, solvent/detergent (S/D) treatment of plasma has been developed in the course of 1980's, resulting in a manufactured product in 1992. S/D treatment and S/D-treated plasma are described *inter alia* in Horowitz et al. 1992; US 4,764,369; EP 0 322 786; and US 2002/018777. S/D treatment of plasma disrupts the membranes of lipid-enveloped viruses, cells and most protozoa, while leaving the labile coagulation factors intact. The treatment has variable efficacy against bacteria and is substantially ineffective against non-lipid-enveloped viruses. Compared to FFP, S/D-treated plasma displays extremely high safety with respect to transfusion related acute lung injury (TRALI), significantly lower likelihood of provoking allergic reactions, and low batch to batch variation in plasma level coagulation factors. JP2011229508 (abstract) concerns a cell composition comprising skeleton myoblasts embedded in gel including plasma.
WO 2009/016451 concerns the use of a homologous or autologous blood derived substance alone or in combination with hyaluronic acid to treat an articular disease, articular pain or skin. Park et al. 2009 concerns the combination of fibrin and hyaluronic acid as a cell delivery vehicle for rabbit chondrocytes with applications in cartilage repair.

Summary

The present inventors have found pharmaceutical formulations addressing one or more of the above-mentioned problems in the art.

An aspect of the ~~invention~~ present disclosure relates to a pharmaceutical formulation comprising solvent/detergent-treated plasma (S/D plasma) and a glycosaminoglycan.

A further aspect of the present disclosure relates to the pharmaceutical formulation as described above for use in the treatment of a musculoskeletal disease, preferably wherein the musculoskeletal disease is a bone disease or a joint disease.

Another aspect of the present disclosure relates to the use of a formulation comprising S/D plasma and a glycosaminoglycan as a pharmaceutical excipient.

As evidenced in the Examples section, formulations applying the principles of the present disclosure~~invention~~ have the advantageous property to gelify *in vitro* in contact with body fluids of subjects, such as

human subjects, especially serum or synovial fluids, for example from patients suffering from knee osteoarthritis or bone diseases. Such formulations applying the principles of the present disclosure~~invention~~ are shown to gelify *in vitro* in contact with body fluids such as whole blood, and hence to have the property to gelify *in situ (in situ* coagulation) when contacted with body fluids such as whole blood. For example, the present formulation may advantageously provide a natural environment of

In certain embodiments, the pharmaceutical formulation may comprise one or more other ingredients in addition to the S/D plasma and glycosaminoglycan. In other embodiments, the S/D plasma and glycosaminoglycan may be the only components of the formulation; hence, in such embodiments the pharmaceutical formulation may consist of or consist essentially of the S/D plasma and glycosaminoglycan. In yet further embodiments, the pharmaceutical formulation may comprise one or more other ingredients in addition to the S/D plasma and glycosaminoglycan, but such additional ingredients are not pharmaceutical active ingredients.

In certain embodiments, the pharmaceutical formulation may advantageously further comprise one or more pharmaceutical active ingredients.

The applicability of the present disclosure ~~invention~~ is not limited to any pharmaceutical active ingredient or class of pharmaceutical active ingredients. The pharmaceutical active ingredient may be pharmacologically active itself, or may be converted into a pharmacologically active species by a chemical or enzymatic process in the body, i.e., the pharmaceutical active ingredient may be a prodrug. The present pharmaceutical formulations may be particularly useful for poorly-stable pharmaceutical active ingredients. Illustrative non-limiting examples of poorly-stable pharmaceutical active ingredients include peptides and proteins such as growth factors, peptide-like active ingredients, antibodies and vaccines, small interfering RNA (siRNA), DNA, hormones, etc. The term "pharmaceutical active ingredient" also encompasses any pharmacologically active salts, esters, N-oxides or prodrugs of the title compound or substance.

Moreover, combination of two or more pharmaceutical active ingredients or doses combinations may be included as the drug component. In this case, the release of each active ingredient may be identical or different such as for instance in case of a combination of two active ingredients in which the first one is presented as an immediate release form and the second one as a controlled release. Similarly, a combination of immediate release and controlled release form may also be obtained for the same active ingredient, in order to provide a rapid and sustained effect.

In certain embodiments, the pharmaceutical formulation may further comprise serum. The addition of serum to the present formulation may allow to a certain extent to improve the gelification of the formulation.

For example, the serum may be allogeneic or autologous with respect to the subject receiving the formulation. Preferably, the serum may be human serum, such that pharmaceutical formulations further comprising human serum are particularly suited for administration to human subjects. For example, the formulation may contain serum and S/D plasma such that the value calculated as (volume of serum in the formulation)/(volume of serum in the formulation + volume of S/D plasma

injection, or for intra-tendon, peri-tendon, intra-ligament or peri-ligament administration, such as, intra-tendon, peri-tendon, intra-ligament or peri-ligament injection.

A related ~~aspect~~ embodiment concerns the pharmaceutical formulation as described above for use in the treatment (including throughout the present specification therapeutic and/or preventative measures) of a musculoskeletal disease. Preferably, said musculoskeletal disease may be a bone disease or a joint disease. Alternatively or in addition, said musculoskeletal disease may affect tendons and/or ligaments.

Also intended is the use of the pharmaceutical formulation as described above for the manufacture of a medicament for the treatment of a musculoskeletal disease, preferably a bone disease or a joint disease. Alternatively or in addition, said musculoskeletal disease may affect tendons and/or ligaments.

Further intended is a method for treating a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments), in a subject in need of such treatment, comprising administering to said subject a therapeutically or prophylactically effective amount of the pharmaceutical formulation as described above.

Expanding on these findings, the present inventors have realised the use of the aforementioned formulations as a pharmaceutical excipient, more preferably as a sustained release or slow release pharmaceutical excipient. Accordingly, a related embodiment ~~aspect~~ provides the use of a formulation comprising S/D plasma and a glycosaminoglycan as a pharmaceutical excipient, preferably as a pharmaceutical excipient in a pharmaceutical formulation configured for parenteral administration, more preferably for intra-osseous, peri-osseous, intra-articular, or peri-articular administration, or for intra-tendon, peri-tendon, intra-ligament or peri-ligament administration.

Also disclosed is thus a formulation comprising S/D plasma and a glycosaminoglycan for use as a pharmaceutical excipient, more preferably for use as a sustained release or slow release pharmaceutical excipient, preferably for use as a pharmaceutical excipient for the treatment of a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments). Further disclosed is the use of a formulation comprising S/D plasma and a glycosaminoglycan for the manufacture of a pharmaceutical excipient, more preferably a sustained release or slow release pharmaceutical excipient, preferably for the manufacture of a pharmaceutical excipient for the treatment of a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments). Still further provided is a method for treating a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments) in a subject in need of such treatment, comprising administering to said

subject a formulation comprising S/D plasma and a glycosaminoglycan as a pharmaceutical excipient, more preferably as a sustained release or slow release pharmaceutical excipient.

Preferably, the S/D plasma may be human S/D plasma, such that pharmaceutical formulations comprising human S/D plasma are particularly suited for administration to human subjects.
Also disclosed herein is the use of S/D plasma as a pharmaceutical excipient, preferably as a pharmaceutical excipient in a pharmaceutical formulation configured for parenteral administration, more preferably for intra-osseous, peri-osseous, intra-articular, or peri-articular administration, or for intra-tendon, peri-tendon, intra-ligament or peri-ligament administration.
Further disclosed is thus S/D plasma for use as a pharmaceutical excipient, more preferably for use as a sustained release or slow release pharmaceutical excipient, preferably for use as a pharmaceutical excipient for the treatment of a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments).
Further disclosed herein is the use of S/D plasma for the manufacture of a pharmaceutical excipient, more preferably a sustained release or slow release pharmaceutical excipient, preferably for the manufacture of a pharmaceutical excipient for the treatment of a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments). Still further provided is a method for treating a musculoskeletal disease, preferably a bone disease or a joint disease (alternatively or in addition, said disease may affect tendons and/or ligaments) in a subject in need of such treatment, comprising administering to said subject S/D plasma as a pharmaceutical excipient, more preferably as a sustained release or slow release pharmaceutical excipient.
Preferably, the S/D plasma may be human S/D plasma, such that pharmaceutical formulations comprising human S/D plasma are particularly suited for administration to human subjects.
Also disclosed herein is the use of the aforementioned formulations as a cell culture medium supplement. Accordingly, a related embodiment ~~aspect~~ provides the use of a formulation comprising S/D plasma and a glycosaminoglycan as a cell culture medium supplement. Such formulations may advantageously allow obtaining cells or cell cultures with improved properties.
Throughout this embodiment ~~aspect~~ of the disclosure ~~invention~~ and any of its embodiments, the S/D plasma may preferably be mammalian S/D plasma, more preferably human S/D plasma. Also throughout this embodiment ~~aspect~~ of the disclosure ~~invention~~ and any of its embodiments, the serum may be mammalian serum, more preferably human serum. Also preferably, the S/D plasma may be mammalian S/D plasma and the serum may be mammalian serum, or the S/D plasma may be human S/D plasma and the serum may be human serum. Human plasma and/or serum may be particularly advantageous for administration

to human subjects. Also throughout this embodiment ~~aspect~~ of the disclosure ~~invention~~ and any of its embodiments, the whole blood may be mammalian whole blood, more preferably human whole blood. Also preferably, the S/D plasma may be mammalian S/D plasma and the whole blood may be mammalian whole blood, or the S/D plasma may be human S/D plasma and the whole blood may be human whole blood. Human plasma and/or whole blood may be particularly advantageous for administration to human subjects.

Also disclosed herein are pharmaceutical formulations as taught above, and the corresponding uses thereof, wherein the glycosaminoglycan is omitted from the formulations. Hence, such formulations may in particular comprise S/D plasma (preferably human S/D plasma) and any one or more components as taught above, in particular, and any one or more of: the serum, the whole blood or the fractionated component thereof, the one or more pharmaceutical active ingredients (such as, each independently, selected from the group consisting of the cell composition, the pharmaceutical active compound, the protein, the peptide, and the small organic molecule. Such formulations may also display satisfactory gel-forming behaviour.

The above and further aspects and preferred embodiments of the disclosure ~~invention~~ are described in the following sections and in the appended claims. The subject-matter of appended claims is hereby specifically incorporated in this specification.

Brief Description of the Drawings

Fig. 1 illustrates X-ray view of bone tissue repair / formation 4 weeks after the administration of a formulation containing S/D plasma, IL-8 and $CaCl_2$ to a bone defect site in a immunocompetent mouse model of calvaria osteotomy. Bone repair can be clearly seen (mineralized areas) in the treated mice (B) compared to control without IL-8 (A).

Fig. 2 provides microscopic analysis of the newly formed tissue shown in Fig. 1B, at 20 times (A) and 40 times magnification. Four weeks after the administration of a formulation containing S/D plasma, IL-8 and $CaCl_2$ to a bone defect site in a immunocompetent mouse model of calvaria osteotomy, the empty collagen matrix presents broad areas of mineralized and non-mineralized osteoid and a large number of vessels.

Description of Embodiments

As used herein, the singular forms "a", "an", and "the" include both singular and plural referents unless the context clearly dictates otherwise.

The terms "comprising", "comprises" and "comprised of' as used herein are synonymous with "including", "includes" or "containing", "contains", and are inclusive or open-ended and do not

~~Claims (Retyped)~~

1. A pharmaceutical formulation comprising solvent/detergent-treated plasma (S/D plasma) and a glycosaminoglycan.

2. The pharmaceutical formulation according to claim 1, wherein the pharmaceutical formulation comprises the glycosaminoglycan in a concentration ranging from about 0.10 mg/ml to about 200 mg/ml.

3. The pharmaceutical formulation according to claim 1, wherein the pharmaceutical formulation is produced by a method comprising combining the S/D-plasma and the glycosaminoglycan.

4. The pharmaceutical formulation according to any one of claims 1 to 3, wherein the S/D plasma is human S/D plasma.

5. The pharmaceutical formulation according to any one of claims 1 to 4, wherein the glycosaminoglycan is hyaluronic acid or a derivative thereof.

6. The pharmaceutical formulation according to any one of claims 1 to 5, further comprising one or more pharmaceutical active ingredients.

7. The pharmaceutical formulation according to any one of claims 1 to 6, further comprising serum, preferably human serum.

8. The pharmaceutical formulation according to any one of claims 1 to 6, further comprising whole blood or a fractionated component of whole blood, preferably wherein the whole blood is human whole blood.

9. The pharmaceutical formulation according to any one of claims 6 to 8, wherein the one or more pharmaceutical active ingredient is, each independently, selected from the group consisting of: a cell composition, a pharmaceutical active compound, a protein, a peptide, and a small organic molecule.

10. The pharmaceutical formulation according to claim 9, wherein the cell composition comprises mesenchymal stem cells (MSC), osteoprogenitors, osteoblastic cells, osteocytes, chondroblastic cells, and/or chondrocytes.

11. The pharmaceutical formulation according to claim 9, wherein the pharmaceutical active compound is an alpha-2 adrenergic receptor agonist, preferably the alpha-2 adrenergic receptor agonist is selected from the group consisting of clonidine and derivatives thereof.

12. The pharmaceutical formulation according to claim 9, wherein the pharmaceutical active protein or peptide is a growth factor, preferably a growth factor selected from the group consisting of a fibroblast growth factor (FGF), a transforming growth factor beta (TGFB), platelet-derived growth factor (PDGF), interleukin-8 (IL-8), a bone morphogenetic protein (BMP), parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrp), and stem cell factor (SCF); more preferably a growth

factor selected from the group consisting of FGF-2, TGFB-1, PDGF, IL-8, BMP-2, BMP-4, BMP-6, BMP-7, PTH, PTHrp, and SCF.

13. The pharmaceutical formulation according to any one of claims 1 to 12, which is configured for parenteral administration, preferably for intra-osseous, peri-osseous, intra-articular, or peri-articular administration, or for intra-tendon, peri-tendon, intra-ligament or peri-ligament administration.

14. The pharmaceutical formulation according to any one of claims 1 to 13 for use in the treatment of a musculoskeletal disease, preferably wherein the musculoskeletal disease is a bone disease or a joint disease.

15. The use of a formulation comprising S/D plasma and a glycosaminoglycan as a pharmaceutical excipient.

16. The use according to claim 15, wherein the formulation comprises the glycosaminoglycan in a concentration ranging from about 0.10 mg/ml to about 200 mg/ml.

17. The use according to claim 15, wherein the formulation is produced by a method comprising combining the S/D-plasma and the glycosaminoglycan.

18. The use according to any one of claims 15 to 17, wherein the S/D plasma is human S/D plasma.

19. The use according to any one of claims 15 to 18, wherein the pharmaceutical formulation is configured for parenteral administration, preferably for intra-osseous, peri-osseous, intra-articular, or peri-articular administration, or for intra-tendon, peri-tendon, intra-ligament or peri-ligament administration.