tissue permeability and therefore can be used to increase the dispersion and delivery of therapeutic agents. Various hyaluronidases have been used therapeutically (*e.g.* Hydase™, Vitrase™ and Wydase™), typically as dispersing and spreading agents in combination with other therapeutic agents. Many of these are ovine or bovine forms, which can be immunogenic for treatment of humans. Improved compositions of hyaluronidases that can be used for treatment are needed.

SUMMARY

Provided herein are soluble PH20 polypeptides, including extended soluble PH20 (esPH20) polypeptides, and compositions. The PH20 polypeptides provided herein are soluble proteins that are truncated at the C-terminus and include those that lack all of the GPI-anchor attachment signal sequence (e.g. are truncated at amino acid positions 450 to 490). Soluble PH20 polypeptides also include extended soluble PH20 polypeptides that retain one or more residues located in the GPI-anchor attachment signal sequence of the corresponding full length wild-type PH20 polypeptide. Also provided herein are other modified PH20 polypeptides that contain C-terminal truncations. Partially deglycosylated forms of any of the polypeptides also are provided. Also provided are methods of treatment using the PH20 polypeptides provided herein.

Provided herein is a truncated PH20 hyaluronidase that consists of the sequence of amino acids set forth as amino acids 36-469, 36-470 or 36-471 of SEQ ID NO: 107, or contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-469, 36-470 or 36-471 of SEQ ID NO: 107, whereby the amino acid-substituted PH20 hyaluronidase consists of a sequence of amino acids that has at least 95% sequence identity with the sequence of amino acids set forth as amino acids 36-469, 36-470 or 36-471 of SEQ ID NO: 107, whereby the amino-acid substituted hyaluronidase activity at neutral pH of the PH20 hyaluronidase that consists of amino acid residues 36-469, 36-470 or 36-471 of SEQ ID NO: 107.

Provided herein is a conjugate, comprising the PH20 as defined above.

Provided herein is a nucleic acid molecule encoding the PH20 as defined above, wherein the nucleic acid molecule does not encode a full-length PH20 but a encodes a truncated PH20.

Provided herein is an expression vector, comprising a polynucleotide that consists of the sequence of nucleotides encoding a PH20 as defined above each including or immediately followed by a stop codon operatively inserted into the vector for expression of the PH20 as defined above.

Provided herein is a vector, comprising the nucleic acid as defined above.

Provided herein is a cell, comprising a vector as defined above.

Provided herein is a cell, comprising a nucleic acid molecule as defined above.

Provided herein is a composition, comprising a PH20 polypeptide as defined above.

Provided herein is a composition, comprising a plurality of PH20 polypeptides as defined above.

Provided herein is a composition as defined above, that is a pharmaceutical composition.

Provided herein is the use of a PH20 as defined above or a composition as defined above in the formulation of a medicament for treating a hyaluronan-associated disease or condition.

Provided herein is a pharmaceutical composition, comprising a polypeptide as defined above for use for treating a hyaluronan-associated disease or condition.

Provided herein is a pharmaceutical composition as defined above for use in treating an excess of glycosaminoglycans; for treating a tumor; for treating glycosaminoglycan accumulation in the brain; for treating a cardiovascular disorder; for treating an ophthalmic disorder; for treating pulmonary disease; for increasing penetration of chemotherapeutic agents into solid tumors; for treating cellulite; for treating a proliferative disorder; or for increasing bioavailability of drugs and other therapeutic agents.

Provided herein are isolated substantially purified extended soluble PH20 (esPH20) hyaluronidases, that can be N-glycosylated or N-partially glycosylated. In some examples, the N-partially glycosylated esPH20 polypeptide contains at least an N-acetylglucosamine moiety linked to each of at least two N-linked moieties, such as, for example, amino acid residues 368 and 393 of SEQ ID NO:107 or residues corresponding to amino acid residues 368 and 393 of SEQ ID NO:107. In some aspects, the N-partially glycosylated esPH20 polypeptide contains at least two N-acetylglucosamine moieties linked to each of at least two N-linked moieties. The N-partially glycosylated esPH20 polypeptide provided herein also can contain a branched sugar.

Provided herein are esPH20 polypeptides that have the sequence of amino acids set forth in any of SEQ ID NOS: 60-63 and 102-104 or an allelic or species variant thereof. Also provided are esPH20 polypeptide variants having at least 40%,