FVIIa also has been approved for the treatment of patients with congenital FVII deficiency, and is increasingly being utilized in off-label uses, such as the treatment of bleeding associated with other congenital or acquired bleeding disorders, trauma, and surgery in non-hemophilic patients.

The use of recombinant FVIIa to promote clot formation underlines its growing importance as a therapeutic agent. FVIIa therapy leaves significant unmet medical need. For example, based on clinical trial data, an average of 3 doses of FVIIa over a 6 hour or more time period are required to manage acute bleeding episodes in hemophilia patients. More efficacious variants of FVIIa are needed to reduce these requirements. Therefore, among the objects herein, it is an object to provide modified FVII polypeptides that are designed to have improved therapeutic properties.

SUMMARY

In one aspect, there is provided a modified factor VII (FVII) polypeptide, wherein the FVII polypeptide has only 1, 2, 3, 4, 5, 6 or 7 amino acid replacements, and optionally a replacement of all or part of the Gla domain, compared to an unmodified FVII polypeptide that comprises the sequence of amino acids set forth in any of SEQ ID NOS:1-3 and 18-74;

one amino acid replacement is at a position corresponding to position 286 in a FVII polypeptide having the sequence of amino acids set forth in SEQ ID NO:3; and

the replacement at position 286 is replacement by an arginine (Arg, R) that results in a modified FVII polypeptide that exhibits increased coagulant activity compared to the FVII polypeptide that does not have the modification at position 286.

In one aspect, there is provided a nucleic acid molecule, comprising a sequence of nucleotides encoding a modified FVII polypeptide as defined herein.

In one aspect, there is provided a vector, comprising the nucleic acid molecule as defined herein.

In one aspect, there is provided a cell, comprising the vector as defined herein.

In one aspect, there is provided a pharmaceutical composition, comprising a therapeutically effective concentration or amount of a modified FVII polypeptide as defined herein, or a nucleic acid molecule as defined herein or a vector as defined herein or a cell as defined herein, in a pharmaceutically acceptable vehicle.

Provided herein are modified Factor VII (FVII) polypeptides. In particular, provided herein are modified FVII polypeptides that exhibit procoagulant activities. The FVII polypeptides are modified in primary sequence compared to an unmodified FVII polypeptide, and can include amino acid insertions, deletions and replacements. Modified FVII polypeptides provided herein include FVII polypeptides that exhibit those that have increased resistance to inhibitors such as antithrombin III (AT-III) and tissue factor pathway inhibitor (TFPI), those that have increased resistance to the inhibitory effects of Zn^{2+}, those that have increased catalytic activity in the presence and/or absence of TF, those that have improved pharmacokinetic properties, such as increased half-life, those that have increased binding and/or affinity for the platelet surface, those that have increased binding and/or affinity for serum albumin, and those that have increased binding and/or affinity for platelet integrin $\alpha_{IIb}\beta_3$. The modified FVII polypeptides can contain any combination of modifications provided herein, whereby one or more activities or properties of the polypeptide are altered compared to an unmodified FVII polypeptide. Typically the modified FVII polypeptide retains procoagulant activity. Also provided herein are nucleic acid molecules, vectors and cells that encode/express modified FVII polypeptides. Pharmaceutical compositions, articles of manufacture, kits and methods of treatment