THROMBOTIC COMPLICATIONS of cardiovascular disease are a main cause of death and disability and, consequently, thrombolysis could favorably influence the outcome of such life-threatening diseases as myocardial infarction, cerebrovascular thrombosis, and venous thromboembolism. Thrombolytic agents are plasminogen activators that convert plasminogen, the inactive proenzyme of the fibrinolytic system in blood, to the proteolytic enzyme plasmin. Plasmin dissolves the fibrin of a blood clot, but may also degrade normal components of the hemostatic system and induce the so-called "lytic state." However, physiologic fibrinolysis is fibrin-oriented as a result of specific molecular interactions between tissue-type plasminogen activator (t-PA), fibrin, plasminogen, and z2-antiplasmin.1

Currently, six thrombolytic agents are either approved for clinical use or under clinical investigation in patients with acute myocardial infarction. These include streptokinase, urokinase, recombinant t-PA (rt-PA), anisoylated plasminogen streptokinase activator complex (APSC), recombinant single-chain urokinase-type plasminogen activator (scu-PA; recombinant prourokinase), and recombinant staphylocinase (Sak).2 In patients with acute myocardial infarction, reduction of infarct size, preservation of ventricular function, and/or reduction in mortality has been observed after treatment with either streptokinase, rt-PA, or APSC.3

This review will focus on the biochemical and thrombolytic properties of staphylokinase, a bacterial protein with profibrinolytic properties that would appear to have potential for treatment of acute myocardial infarction.

HISTORICAL OVERVIEW

Staphylokinase, a protein produced by certain strains of Staphylococcus aureus,4 was shown to have profibrinolytic properties more than 4 decades ago.5,6 Natural staphylokinase has been purified from S aureus strains that were transformed with bacteriophages containing the staphylokinase gene, or that had undergone lysogenic conversion to staphylokinase production.6 Natural staphylokinase has been purified by precipitation with ammonium sulphate and chromatography on CM-cellulose7 or by affinity chromatography on plasmin-Sepharose8 or on plasminogen-Sepharose.9 Its in vitro fibrinolytic properties were evaluated in the 1950s and 1960s10,11 and its in vivo thrombolytic properties in dogs in 196412 and in 1986.13

Sweet et al10 reported that staphylokinase is a rapid and potent activator of the human plasminogen-plasmin system. However, using a clot lysis assay, a wide range of staphylokinase-neutralizing activity was detected. Therefore, the investigators concluded that, in view of the variation in loading dosage that would be required with staphylokinase and the anticipation of a marked rise in inhibitor level after an initial infusion, it would be unlikely that staphylokinase could be of use as a thrombolytic agent. Lewis et al11,12 obtained intravascular clot lysis with staphylokinase in 4 of 6 dogs. However, this was associated with severe hemorrhage and high toxicity. After these discouraging results, interest in the development of staphylokinase as a thrombolytic agent apparently faded away. In 1986, Kanai13 performed another study in dogs with experimental thrombi in the femoral artery using systemic or intra-arterial bolus administration of staphylokinase. An extreme prolongation of the prothrombin and partial thromboplastin times and a remarkable elevation of the serum fibrinogen degradation products were observed. Kanai suspected that "staphylokinase decomposed sitoply fibrinogen as well as fibrin." However, in retrospect, these in vivo studies in dogs appear to have been misleading because the dog is unusually sensitive to fibrinolytic activation with staphylokinase (see below).

PRODUCTION OF STAPHYLOKINASE

We have recently purified natural staphylokinase from Trypontone Soy broth conditioned by a selected S aureus strain by batch adsorption to SP-Sephadex and chromatography on insolubilized plasminin, which was alkylated with the active site histidine titrant D-Val-Phe-Lys-Cl.14 This yielded highly purified preparations with a yield of 40 μg/L of culture broth. However, the purification of staphylokinase from lysogenic S aureus strains for detailed physical and biochemical studies as well as for the evaluation of its in vivo thrombolytic potential appeared to be elusive, mainly because of low expression levels and concomitant secretion of potent exotoxins.11,14

The staphylokinase gene has been cloned from the bacteriophages sak3C15 and sak42D16 as well as from the genomic DNA (sakSTAR) of a lysogenic S aureus strain.14 It has been expressed under the control of the XPR promoter and its own translation signals in Escherichia coli17 and also under the control of its natural promoter and translation signals in Bacillus subtilis14,18 or E coli.14 resulting in accumulation of the gene product in the periplasmic space or in the culture medium, respectively. This mode of expression led to two problems complicating the high yield production of mature staphylokinase: (1) proteolytic degradation in the NH2-terminal region that rendered purification attempts more laborious;14,16 and (2) reduced growth of recombinant E coli cells overexpressing staphylokinase, possibly as a result of oversaturation of the export pathway.14 Furthermore, the processing, translocation, and stability of the staphylokinase gene products was found to be suboptimal19 and the endo-

From the Center for Molecular and Vascular Biology, University of Leuven, Belgium.

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Address reprint requests to D. Collen, MD, PhD, Center for Molecular and Vascular Biology, University of Leuven, Campus Gasthuisberg, O & N, Herestraat 49, B-3000 Leuven, Belgium.

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In solution, the mutual positions of the two domains are consistently reduced to levels admissible for human administration.

In an effort to improve the production procedure, recombinant plasmids were constructed, with the signal sequence of the sak42D and the sakSTAR staphylokinase genes replaced by an ATG start codon, which express staphylokinase under the control of a tac promoter and two Shine-Dalgarno sequences in tandem. Induction of transfected E. coli TG1 cells in a bacterial fermenter produced intracellular staphylokinase (sak42D or sakSTAR) representing 10% to 15% of total cell protein. Highly purified recombinant staphylokinase was purified from cytosol fractions by chromatography, at room temperature, on SP-Sepharose and on phenyl-Sepharose columns, with yields of 50% to 70% (approximately 200 mg/L of fermentation broth). Because Sak42D appeared to have a somewhat lower temperature stability than SakSTAR, the latter molecule was selected for further evaluation of its thrombolytic properties in humans. The purified material was devoid of human pathogenic viruses and, at a dose of 4 mg/kg, did not produce acute reactions or affect body weight in mice.

GENE STRUCTURE OF STAPHYLOKINASE

The staphylokinase gene encodes a protein of 163 amino acids, with amino acid 28 corresponding to the NH2-terminal residue of full-length mature staphylokinase. This coding sequence is preceded upstream by canonical Shine-Dalgarno, and by -10 and -35 prokaryotic promoter sequences. Staphylokinase shows no significant homology with streptokinase. Only four nucleotide differences were found in the coding regions of the sakΔC, sak42D, and sakSTAR genes, one of which constituted a silent mutation. These affect the codons for amino acids 38, 61, 63, and 70 (amino acids 11, 34, 36, and 43, respectively, of the mature protein). Amino acid 38 is Lys in all three staphylokinase moieties, amino acid 61 is Ser in SakSTAR but Gly in SakΔC and Sak42D, amino acid 63 is Gly in SakSTAR and in SakΔC, but Arg in Sak42D, and amino acid 70 is His in SakSTAR and in SakΔC, but Arg in Sak42D. In the 3' region of the staphylokinase molecule, approximately 160 nucleotides downstream of the stop codon, all reported sequences diverged markedly, suggesting that this region is unimportant for expression of the protein.

PROTEIN STRUCTURE OF STAPHYLOKINASE

Mature staphylokinase consists of 136 amino acids in a single polypeptide chain without disulfide bridges. The solution structure of staphylokinase has been analyzed by x-ray scattering, dynamic light scattering, ultracentrifugation, and UV circular dichroism spectroscopy. Staphylokinase has a radius of gyration of 2.3 nm, a Stokes radius of 2.12 nm, and a maximum dimension of 10 nm. The sedimentation coefficient is 1.71 S. These physical parameters indicate that the shape of staphylokinase is very elongated. The molecule consists of two folded domains of similar size. The mean distance of the centers of gravity of the domains is 3.7 nm. In solution, the mutual positions of the two domains are variable, suggesting that the molecule is shaped like a flexible dumbbell.

Several molecular forms of staphylokinase have been purified with slightly different molecular weights (Mw; 18,000 to 18,000 on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE)) and iso-electric points. Lower M, derivatives of mature staphylokinase were obtained lacking the 6 (Sak-Δ6) or the 10 (Sak-Δ10) NH2-terminal amino acids. On interaction with plasminogen in a buffer milieu, mature staphylokinase (NH2-terminal Ser-Ser-Ser-) is rapidly and quantitatively converted to Sak-Δ10 (NH2-terminal Lys-Gly-Asp-). Mature staphylokinase and Sak-Δ10 were shown to have the same fibrinolytic activity and a comparable plasminogen-activating and fibrinolytic potential in human plasma.

The amino acid in position 26 appears to be of crucial importance for the activation of plasminogen by staphylokinase. Indeed, substitution of the unique Met residue in position 26 with either Arg or Val results in loss of the functional activity, whereas substitution with Leu or Cys has little or no effect on the activity. These amino acid exchanges cause no significant changes of the solution structure of the mutant proteins. A detailed knowledge of the three-dimensional structure of the molecule will be required to elucidate these observations at the molecular level.

FUNCTIONAL PROPERTIES OF STAPHYLOKINASE

Interaction with plasminogen. Like streptokinase, staphylokinase is not an enzyme but it forms a 1:1 stoichiometric complex with plasminogen that activates other plasminogen molecules.

Streptokinase and plasminogen produce a complex that exposes the active site in the plasminogen molecule without proteolytic cleavage, whereas generation of plasmin is required for exposure of the active site in the complex with staphylokinase. Indeed, the active site titrant p-nitrophenyl-p'-guanidinobenzoate (NPGB) prevented active site exposure in equimolar mixtures of plasminogen and staphylokinase, but reacted stoichiometrically with mixtures preincubated in the absence of titrant.

The following model has been proposed for the activation of plasminogen (Plg) by staphylokinase (Sak):

\[ \text{Plg + Sak} \rightleftharpoons \text{Plg.Sak} \leftarrow \text{Pli.Sak} \]

\[ \text{Plg} \rightarrow \text{Pli} \]

According to this model, plasminogen and staphylokinase produce an inactive complex (Plg.Sak) in which active plasmin, staphylokinase (Pli.Sak) is generated in a rate-limiting step that is accelerated by plasminogen activators (eg, Pli.Sak itself) and delayed by plasmin inhibitors (eg, α2-antiplasmin). In mixtures with excess plasminogen over staphylokinase, the generated Pli.Sak complex converts the excess plasminogen to plasmin (Pli). In contrast to the indirect mechanism of plasminogen activation with streptokinase and staphylokinase, the physiologic plasminogen activators, t-
PA and urokinase, are enzymes that directly activate plasminogen by cleavage of a single Arg→Val peptide bond.

Activation of plasminogen by the preformed PII.Sak complex obeys Michaelis-Menten kinetics with $K_m = 7.0 \mu\text{mol/L}$ and $k_2 = 1.5 s^{-1}$. Staphylokinase does not bind to fibrin, and fibrin stimulates the initial rate of plasminogen activation by staphylokinase only fourfold, as compared with twofold by streptokinase. Studies on the interaction of staphylokinase with different molecular forms of plasminogen have shown that the lysine-binding sites in kringle 1 through 4 of plasminogen are not required for formation of the complex with staphylokinase, nor for the enzymatic activity of the complex.

Interaction of plasmin-staphylokinase complex with $\alpha_2$-antiplasmin. In purified systems, $\alpha_2$-antiplasmin rapidly inhibits the plasmin-staphylokinase complex (second-order inhibition rate constant of approximately $2 \times 10^6 \text{mol}^{-1} \cdot \text{L} \cdot \text{s}^{-1}$), although it does not inhibit the plasminogen(staphylokinase)streptokinase complex. Addition of 6-aminohexanoic acid or of fibrin-like substances (eg, CNBr-digested fibrinogen) induces a more than 100-fold reduction of the inhibition rate of the plasmin-staphylokinase complex by $\alpha_2$-antiplasmin. Rapid inhibition by $\alpha_2$-antiplasmin indeed requires the availability of the lysine-binding sites in the plasminogen moiety of the complex. Fibrin, but not fibrinogen, reduces the inhibition rate by $\alpha_2$-antiplasmin by competing for interaction with the lysine-binding site(s).

The activation rate of plasminogen by a mixture of plasmin-staphylokinase and $\alpha_2$-antiplasmin, which has no residual enzymatic activity, is indistinguishable from that by staphylokinase alone. Furthermore, on gel-filtration of the mixture of plasmin-staphylokinase and $\alpha_2$-antiplasmin, staphylokinase elutes with its own apparent $M_r$ whereas without addition of $\alpha_2$-antiplasmin it elutes as a complex with plasmin. These data indicate that neutralization of the plasmin-staphylokinase complex by $\alpha_2$-antiplasmin results in the formation of an inactive plasm(staphylokinase) complex, and dissociation of functionally active staphylokinase from the complex. Staphylokinase, which is converted to Sak-Δ10 on interaction with plasmin, is then recycled to other plasminogen molecules.

Fibrinolytic potency in a plasma milieu in vitro. Staphylokinase induces dose-dependent lysis of $125\text{I}$-fibrin-labeled human plasma clots submerged in citrated human plasma. Fifty percent lysis in 2 hours of a 0.12 mL clot in 0.5 mL plasma is obtained with 17 nmol/L staphylokinase, and is associated with only 5% plasma fibrinogen degradation. Corresponding values for streptokinase are 68 nmol/L and more than 90% fibrinogen degradation. In the absence of a fibrin clot, 50% fibrinogen degradation in human plasma in 2 hours requires 790 nmol/L staphylokinase, but only 4.4 nmol/L streptokinase. These results confirm and extend previous findings that, in a human plasma milieu in vitro, staphylokinase is more fibrinogen-sparing than streptokinase.

The different $M_r$ forms of staphylokinase (mature staphylokinase, Sak-Δ6 and Sak-Δ10) have the same fibrinolytic and fibrinogenolytic potential in human plasma in vitro. Furthermore, the fibrinolytic potency and fibrin-specificity in plasma of staphylokinase and of its preformed complex with plasmin are indistinguishable, most likely because, after neutralization of the complex by $\alpha_2$-antiplasmin, active staphylokinase is recycled to other plasminogen molecules.

The fibrinolytic activity of staphylokinase towards platelet-rich plasma (PRP; $4 \times 10^9$ platelets/μL) and platelet-poor plasma (PPP; < $5 \times 10^9$ platelets/μL) was compared in a human plasma milieu in vitro, which consisted of a 0.06 mL $125\text{I}$-fibrin-labeled plasma clot submerged in 0.5 mL plasma. Fifty percent clot lysis in 2 hours (C50) was obtained with 40 and 23 nmol/L staphylokinase, respectively. With streptokinase, no significant lysis of PRP clots was obtained with 440 nmol/L, whereas the C50 for PPP clots was 47 nmol/L. This differential sensitivity might result from alteration of the $\alpha_2$-antiplasmin to plasminogen ratio in the clot during retraction. Sabovic et al have indeed previously shown that, in a plasma milieu in vitro, retracted blood clots are more sensitive to lysis with the fibrin-specific plasminogen activators t-PA and scu-PA than with the nonfibrin specific agents streptokinase and urokinase. This phenomenon was explained by an enhanced systemic plasminogen activation with the non-fibrin-specific agents, which precluded recruitment of plasminogen from the surrounding plasma and thereby resulted in reduced clot lysis. Extrusion of non-fibrin-bound plasminogen from the clot, as a result of platelet-mediated retraction, also results in a reduced concentration of plasminogen, whereby the ratio of $\alpha_2$-antiplasmin to plasminogen associated with the clot increases.

MECHANISM OF THE FIBRIN-SPECIFICITY OF STAPHYLOKINASE

The fibrin-specificity of staphylokinase in human plasma has been explained by rapid inhibition of generated plasmin-staphylokinase complex by $\alpha_2$-antiplasmin, and by a more than 100-fold reduced inhibition rate at the fibrin surface, which may allow preferential plasminogen activation at the fibrin clot. However, staphylokinase also dissociates in active form from the plasmin-staphylokinase complex after neutralization by $\alpha_2$-antiplasmin, and is recycled to other plasminogen molecules. Thus, extensive systemic plasminogen activation with staphylokinase would be expected in plasma, which is clearly in contradiction with its well-established fibrin-specificity.

To elucidate this apparent paradox, the rate and extent of generation of plasmin-staphylokinase complex in human plasma was monitored, both in the absence and the presence of fibrin. When plasmin-staphylokinase complex is formed in the absence of fibrin, it is rapidly neutralized and staphylokinase is recycled to other plasminogen molecules. However, conversion of plasminogen-staphylokinase to plasmin-staphylokinase does not occur at a significant rate because it is prevented by $\alpha_2$-antiplasmin; without plasmin-staphylokinase complex, no significant plasminogen activation occurs. In the presence of fibrin, generation of the plasminogen(staphylokinase) complex is facilitated and inhibition of plasmin-staphylokinase by $\alpha_2$-antiplasmin at the clot surface is delayed more than 100-fold. Recycling of staphylokinase to fibrin-bound plasminogen, after neutralization of the plas-
plasminogen, by the catalytic efficiencies of the complexes. The results indicate that this variability is determined mainly by the extent of complex formation of staphylokinase with plasminogen. In the response of plasma fibrinolytic systems to activation of autologous plasminogen, and by the specificity of staphylokinase was studied using purified plasminogens in the plasma milieu. (A) In a buffer milieu, plasminogen (Plg) and staphylokinase (Sak) form an equimolar complex (Plg:Sak) in which the Plg moiety is converted to plasmin (Pll:Sak). Generated Pll:Sak accelerates the conversion of Plg:Sak to Pll:Sak, resulting in efficient activation of Plg to Pll. (B) In a plasma milieu in the absence of fibrin, α2-antiplasmin (α2-AP) inhibits the activation of Plg by Sak by impairing generation of active Pll:Sak complex. Inhibition of any generated Pll:Sak complex by α2-AP results in formation of the inactive plasmin-α2-antiplasmin complex (PAP) and dissociation of functionally active Sak, which can be recycled to other Plg molecules. (C) In a plasma milieu in the presence of fibrin, Plg activation by Sak is stimulated via a mechanism involving the lysine-binding sites of Plg. The effect of fibrin is probably mediated via enhanced generation of Pll:Sak complex and delayed inhibition of the clot-bound complex by α2-AP.

SPECIES VARIABILITY IN FIBRINOLYTIC RESPONSE

Species differences in reactivity of the plasma fibrinolytic system to plasminogen activators have been documented in vitro systems with several plasminogen activators, including streptokinase, urokinase, and t-PA. Therefore, the comparative fibrinolytic and fibrinogenolytic properties of staphylokinase and streptokinase were studied in human, baboon, rabbit, hamster, rat, and dog plasma in vitro. The plasma fibrinolytic systems of baboons, rabbits, and hamsters reacted comparably to the human system to staphylokinase; the rat system appeared to be very resistant, whereas in the dog system staphylokinase was very potent, but not fibrin-specific. The molecular basis of the marked interspecies variability in the response of plasma fibrinolytic systems to activation by staphylokinase was studied using purified plasminogens and α2-antiplasmins from different mammalian species. The results indicate that this variability is determined mainly by the extent of complex formation of staphylokinase with plasminogen, by the catalytic efficiencies of the complexes for the activation of autologous plasminogen, and by the rate of inhibition of these complexes by α2-antiplasmin. The comparably high reactivity of staphylokinase with both human and canine plasminogen may explain its high potency for clot lysis in these species, whereas the 10-fold lower reactivity of the canine plasmin-staphylokinase complex with α2-antiplasmin may explain its markedly lower fibrin-specificity in the dog. Thus, the choice of the canine species for the initial in vivo evaluation of staphylokinase may have produced misleading conclusions, in view of the unusually high sensitivity of the canine plasma fibrinolytic system to activation with staphylokinase.

THROMBOLYTIC PROPERTIES OF STAPHYLOKINASE IN ANIMAL MODELS OF THROMBOSIS

The thrombolytic properties of staphylokinase were compared with those of streptokinase in hamsters with a pulmonary embolus produced from human plasma or from hamster plasma, and in rabbits with a jugular vein blood clot produced from rabbit blood. Intravenous infusion of staphylokinase (SakSTAR) and streptokinase induced dose-dependent progressive clot lysis in the absence of significant systemic activation of the fibrinolytic system. On a molar basis, staphylokinase and streptokinase were equipotent in the rabbit model, whereas staphylokinase was less potent in the hamster model. The comparative thrombolytic properties of natural and recombinant staphylokinase (SakSTAR) and of streptokinase were also studied in hamsters with a pulmonary embolus consisting of a platelet-poor, a platelet-rich (300,000 platelets/μL), or a platelet-enriched (1,500,000 platelets/μL)
human plasma clot.

The relative thrombolytic potencies, on a weight base, of the staphylokinase preparations versus streptokinase were comparable in the platelet-poor clot model and in the platelet-rich clot model, but were fivefold higher in the platelet-enriched clot model. Intravenous infusion in baboons of streptokinase or staphylokinase (SakSTAR) induced a similar dose-dependent lysis of a 125I-fibrin-labeled autologous jugular vein clot, without systemic fibrinogen depletion. The thrombolytic potency towards platelet-rich arterial thrombus of streptokinase and staphylokinase (SakSTAR) was studied in a femoral arterial eversion graft model in baboons. Arterial recanalization with staphylokinase was more frequent and more persistent than with streptokinase.

In aggregate, these data confirm and establish that staphylokinase is a potent thrombolytic agent, in vivo, and that staphylokinase may be more potent than streptokinase for the dissolution of platelet-rich clots such as observed in the coronary arteries of patients with acute myocardial infarction.

**CORONARY THROMBOLYSIS WITH RECOMBINANT STAPHYLOKINASE IN PATIENTS WITH EVOLVING MYOCARDIAL INFARCTION**

The encouraging results obtained with staphylokinase in animal models of thrombosis have formed the basis for its evaluation, on a pilot scale, in patients with acute myocardial infarction. In four of five patients with acute myocardial infarction, 10 mg recombinant staphylokinase (SakSTAR), administered intravenously over 30 minutes, was found to induce angiographically documented coronary artery recanalization within 40 minutes. Plasma fibrinogen and α2-antiplasmin levels were unaffected (residual levels at 40 minutes coronary occlusion, intravenous administration of 10 mg streptokinase over 30 minutes, neutralizing antibody titers against staphylokinase (SakSTAR) were low at baseline and up to 6 days after infusion, but high titers (staphylokinase-neutralizing titers of 12 to 42 μg/mL plasma) of antibodies, which did not cross-react with streptokinase, were consistently demonstrable in plasma at 14 to 35 days. These observations were fully confirmed in the second pilot trial in five patients.

Thus, with respect to immunogenicity, the initial observations in man are not as encouraging as the experience in experimental animals. Although the restriction to single use as a result of immunogenicity would probably apply to both streptokinase and staphylokinase, the absence of cross-reactivity of induced antibodies suggests that the use of both substances would not be mutually exclusive.

**CONCLUSIONS**

Staphylokinase is a profibrinolytic agent that forms a 1:1 stoichiometric complex with plasminogen that, after conversion to plasmin, activates other plasminogen molecules to plasmin. The plasmin-staphylokinase complex, unlike the plasmin-streptokinase complex, is rapidly inhibited by α2-antiplasmin. In a plasma milieu, staphylokinase is able to dissolve fibrin clots without associated fibrinogen degradation. This fibrin-specificity of staphylokinase is the result of reduced inhibition by α2-antiplasmin of plasmin-staphylokinase complex bound to fibrin, recycling of staphylokinase from the plasmin-staphylokinase complex after inhibition by α2-antiplasmin, and prevention of the conversion of plasminogen-staphylokinase to plasmin-staphylokinase by α2-antiplasmin. In several experimental animal models, staphylokinase appears to be equipotent to streptokinase for the dissolution of whole blood or plasma clots, but significantly more potent for the dissolution of platelet-rich or retracted thrombi.

The feasibility of fibrin-specific coronary thrombolysis with an intravenous infusion over 30 minutes of 10 mg recombinant staphylokinase was demonstrated in two small pilot studies in patients with acute myocardial infarction with angiographically confirmed total occlusion of the infarct-related coronary artery. However, neutralizing antibodies against staphylokinase were demonstrable from the third week on in all patients. Definition of the therapeutic benefit...
of recombinant staphylokinase will require more detailed dose-finding studies followed by randomized efficacy studies against other thrombolytic agents.

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Staphylokinase, a fibrin-specific plasminogen activator with therapeutic potential?

D Collen and HR Lijnen