The extrinsic coagulation pathway in coronary artery disease and endotoxemia
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Recombinant Nematode Anticoagulant Protein c2 (rNAPc2), an inhibitor of tissue factor-factor VIIa, attenuates coagulation and the IL-10 response in human endotoxemia

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Abstract

Background
The tissue factor-factor VIIa complex (TF-FVIIa) is responsible for the initiation of blood coagulation under both physiologic and pathologic conditions. Recombinant Nematode Anticoagulant Protein c2 (rNAPc2) is a potent inhibitor of TF-FVIIa that is mechanistically distinct from tissue factor pathway inhibitor. The first aim of this study was to elucidate the pharmacokinetics (PK) and pharmacodynamics of a single intravenous (iv) dose of rNAPc2. The second aim was to study the effect of a single iv dose of rNAPc2 on endotoxin-induced coagulation and inflammatory responses.

Methods and results
In the first part of the study, three groups of healthy male volunteers received a single iv dose rNAPc2 of either 3.0, 5.0 or 7.5 μg/kg. There were no safety or tolerability concerns following the administration of rNAPc2. The PK elimination profile was consistent with previous studies in which rNAPc2 was administered subcutaneously. Maximum plasma concentrations of rNAPc2 were 47.2 ± 3.4, 66.3 ± 6.6 and 136.7 ± 30 ng/mL for the doses 3.0, 5.0 and 7.5 μg/kg, respectively. The respective elimination half lives were 56.4 ± 6.4, 56.7 ± 5.1 and 51.5 ± 8.7 hours. The iv administration of rNAPc2 resulted in a dose dependent TF-FVIIa inhibition, as reflected in a reduction of the endogenous thrombin potential and a selective prolongation of prothrombin time versus the activated partial thromboplastin time.

In the second part of the study, the effect of rNAPc2 on endotoxin-induced coagulation and inflammation was evaluated. The administration of a single iv dose of 7.5 μg/kg rNAPc2 completely blocked endotoxin-induced thrombin generation, as measured by plasma prothrombin fragment F1+2. rNAPc2 did not affect the endotoxin-induced increase of on fibrinolytic parameters such as plasmin-antiplasmin complexes and plasminogen activator inhibitor type I. The endotoxin-induced rise in tumor necrosis factor alpha (TNF-α), interleukin (IL)-6 and IL-8 was not affected by rNAPc2 iv. However, rNAPc2 attenuated the endotoxin-induced rise in IL-10.

Conclusions
rNAPc2, a potent inhibitor of TF-FVIIa, was well tolerated and could safely be used intravenously up to a dose of 7.5 μg/kg in this Phase I study in healthy male volunteers. A single iv dose rNAPc2 of 7.5 μg/kg completely blocked endotoxin induced thrombin generation, without affecting the fibrinolytic response. In addition, rNAPc2 attenuated the endotoxin-induced rise in IL-10 without affecting the rises in TNF-α, IL-6 and IL-8.
Effect of rNAPc2 on coagulation and inflammation in human endotoxemia

Introduction
Tissue factor (TF), a 47 kDa transmembrane glycoprotein, is the major cellular trigger of blood coagulation under physiologic conditions. The tissue factor–factor VIIa catalytic complex (TF-FVIIa) is able to generate factor Xa via direct activation of factor X, and indirectly through the activation of factor IX, thus initiating thrombin generation. It has been well established that tissue factor also plays an important role in disease processes resulting from the activation of the coagulation pathway. For example, as TF is present in atherosclerotic plaques, acute coronary syndromes are believed to be the consequence of pathological plaque rupture with subsequent thrombus formation initiated by TF-FVIIa. In addition, TF plasma levels are elevated during sepsis and this is believed to contribute directly to the pathogenesis of multiple organ failure. A variety of inflammatory stimuli, including bacterial cell products and cytokines, are known to induce the expression of TF on the surface of endothelial cells and monocytes, thereby activating the coagulation pathway. In view of the central role of TF-FVIIa in the activation of coagulation, novel therapeutic strategies aimed at inhibiting this complex and are currently being evaluated in experimental and clinical trials.

The major physiologic inhibitor of TF-FVIIa is the serine protease inhibitor, tissue factor pathway inhibitor (TFPI). TFPI binds to and inhibits factor Xa directly, prior to forming a quaternary inhibitory complex with TF-FVIIa, thereby inhibiting thrombin generation. Experimental settings where animals were depleted of TFPI, have demonstrated a sensitivity to TF and endotoxin and a propensity to develop intravascular coagulation. In a lethal E. coli sepsis model in baboons, treatment with TFPI attenuated the procoagulant and interleukin (IL)-6 response and prevented mortality. However, in healthy human volunteers administered endotoxin, blocking TF-FVIIa with TFPI had no impact on inflammatory cytokines, but completely prevented endotoxin-induced activation of coagulation. A phase II clinical trial of recombinant TFPI (rTFPI) in patients with severe sepsis, demonstrated accelerated decrease of IL-6 plasma levels in the rTFPI group. However, the recently completed, still unpublished phase III trial of rTFPI in severe sepsis, OPTIMIST, failed to show a reduction in the primary end-point of 28-day all cause mortality.

Recombinant Nematode Anticoagulant Protein c2 (rNAPc2) is an 85 amino acid protein that was originally isolated from the hematophagous hookworm *Ancylostoma caninum*. It specifically inhibits TF-FVIIa by a unique mechanism of action that requires the initial binding of rNAPc2 to the serine protease factor Xa or its circulating
zymogen factor X prior to formation of the quaternary inhibitory complex with TF-FVIIa. The utilization of zymogen factor X as an inhibitory scaffold obviates the need of generating activated factor X to inhibit TF-FVIIa. In addition, the formation of a complex between rNAPc2 and factor X results in an elimination half-life of more than 50 hours in man. In a model of endotoxin-induced coagulation activation in chimpanzees, rNAPc2 completely inhibited factor Xa-mediated thrombin generation. Clinically, rNAPc2 was shown to be effective in the prevention of postoperative venous thromboembolism in patients undergoing total knee replacement. In addition, TF-FVIIa inhibition with rNAPc2 was also shown to be a safe and potentially effective strategy to prevent thrombin generation in patients undergoing elective coronary interventions. In all these studies, rNAPc2 was administered subcutaneously. The current study had two aims: the first aim was to study the pharmacokinetics of a single intravenous (iv) dose of rNAPc2, the second aim was to study the effect of a single iv dose of rNAPc2 on endotoxin-induced coagulation and inflammatory responses in healthy human volunteers.

**Methods**

**Study design**

The study protocol was conducted according to the International conference on Harmonisation Good Clinical Practice Guideline and was approved by the institutional scientific and ethics committee. Twenty-eight healthy men (age 18-35 years) volunteered to participate in the study. Written informed consent was obtained from each subject before the start of the study. None of the subjects had abnormalities on physical examination or routine laboratory investigation. The subjects did not take any medication and did not smoke or use illicit drugs. The study was performed in two parts. First, the safety and pharmacokinetics (PK) of rNAPc2 were studied in three groups of four healthy male volunteers (group 1-3). All subjects fasted overnight before administration of rNAPc2. At 7 AM two intravenous cannulas were inserted, one for the administration of rNAPc2 and the other for blood sample collection. Each group of volunteers received rNAPc2 (Corvas International, San Diego CA, USA) as a single intravenous (iv) dose of 3.0, 5.0 or 7.5 μg/kg, respectively. Following analysis of the safety and PK data, the dose of 7.5 μg/kg was chosen for the second part of the study, in which sixteen healthy male volunteers participated. Eight subjects were examined after the administration of endotoxin alone (group 4), and eight
subjects after the administration of endotoxin and a single iv dose of rNAPc2 (group 5). All subjects fasted overnight before endotoxin administration. At 7 AM two intravenous cannulas were inserted, one for the administration of endotoxin and rNAPc2 and the other for blood sample collection. In group 4, endotoxin (Escherichia coli lipopolysaccharide, lot G-1, US Pharmacopeia, Rockville, MD) was administered at 9 AM as a single iv dose of 4 ng/kg bodyweight. Group 5 received rNAPc2 as a single iv dose of 7.5 μg/kg bodyweight, immediately followed by endotoxin as a single iv dose of 4 ng/kg bodyweight. Oral temperature, blood pressure, heart rate and oxygen saturation were measured at hourly intervals (Dinamap 1846 SX; Criticon, Tampa FL). Clinical symptoms such as headache, shivering, nausea, vomiting, tiredness and malaise were recorded throughout the study period using a graded scale (0=absent, 1=weak, 2=moderate, 3=severe).

**Blood collection**

Blood was collected from an intravenous cannula at 10 minutes before, at 5, 15 and 30 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 hours after endotoxin administration. Blood for cytokine assays and leukocyte counts was collected in K3-EDTA-containing tubes. All other blood samples were collected in citrated vacutainer tubes and were immediately centrifuged at 3000 rpm for 20 minutes at 16°C. Plasma was stored at -20°C until assays were performed.

**Assays**

Leukocyte counts and differentials were assessed by a Cell-dyn 4000 analyzer (Abbott Laboratories, Abbott Park IL 60064, USA). The plasma concentration of rNAPc2 was analyzed by sandwich ELISA. The assay used affinity-purified polyclonal antibodies that were raised against rNAPc2. The detector antibody was the same antibody conjugated to horseradish peroxidase. Coagulation assays (prothrombin time (PT) and activated partial thromboplastin time (APTT)) were performed on an automated coagulation analyzer (Behring Coagulation System, BCS) with reagents and protocols from the manufacturer (Dade Behring, Marburg, Germany). Inhibition of TF-FVIIa activity was measured on the BCS according to a method for the determination of TFPI activity as described by Sandset et al. The plasma concentrations of prothrombin fragment F_{1+2} (F_{1+2}) and plasmin-antiplasmin complexes (PAP) were measured by ELISA (Dade Behring, Marburg, Germany). The endogenous thrombin potential (ETP, i.e. the time integral of thrombin generated in
plasma in which coagulation is initiated via TF-FVIIa) was determined as described by Rosing et al.\textsuperscript{14} Plasminogen activator inhibitor type I (PAI-1) antigen was assayed by ELISA (Innotest PAI-1, Hyphen BioMed, Andrésy, France). Tumor necrosis factor alpha (TNF-α), IL-6, IL-8 and IL-10 were measured using commercial ELISA kits (Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands).

**Statistical analysis**
Values are given as means ± SEM. Differences in results between the rNAPc2 and control experiments were tested by repeated measurement analysis of variance. Changes in time within the same group were analyzed by one-way analysis of variance. A p value of <0.05 was considered significant.

**Results**

**Safety and pharmacokinetics of rNAPc2**
There were no safety or tolerability concerns following the iv dosing of rNAPc2 over the dose range from 3.0-7.5 μg/kg. No adverse events attributable to rNAPc2 infusion were observed, and no episodes of increased bleeding occurred.

The PK elimination profile of rNAPc2 after iv administration is shown in Table 1. Maximum plasma concentrations of rNAPc2 dose dependently increased, and the elimination half lives were comparable between the three different rNAPc2 doses. Plasma concentration versus time is shown in Figure 1.

<table>
<thead>
<tr>
<th>Table 1. Pharmacokinetic parameters after intravenous (iv) administration of rNAPc2</th>
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<td>Parameter</td>
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<td>T last (hr): mean ± SD</td>
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rNAPc2=recombinant nematode anticoagulant protein c2. T max=period between iv administration and maximal rNAPc2 plasma concentration. C max=maximum rNAPc2 plasma concentration. T last=period between iv administration and last measurement. C last=rNAPc2 plasma concentration at last measurement.
Effects of rNAPc2 on coagulation and inflammation in human endotoxemia

Figure 1. Plasma levels of recombinant nematode anticoagulant protein c2 (rNAPc2) after administration of a single intravenous dose of 3.0 μg/kg, 5.0 μg/kg, or 7.5 μg/kg rNAPc2 to healthy male volunteers. Data represent mean ± SEM.

Clinical features and neutrophil response
Injection of endotoxin induced a febrile response, peaking after 4 hours (peak: 38.3 ± 0.2 °C) together with a tachycardia and transient flu-like symptoms including headache, nausea, malaise and chills. In addition, endotoxin administration elicited activation of neutrophilic granulocytes, as reflected by a biphasic change in neutrophil counts involving an initial neutropenia (nadir: 2.2 ± 0.1 x 10⁹/L), followed by neutrophilia (peak: 15.3 ± 1.3 x 10⁹/L). None of these changes were affected by rNAPc2.

Inhibition of TF-FVIIa activity
As shown in Figure 2A, there was a dose-dependent inhibition of TF-FVIIa activity following the administration of rNAPc2 alone. The extent of TF-FVIIa inhibition did not increase after endotoxin administration (Figure 2B). In contrast, TF-FVIIa inhibition rose significantly after 90 minutes, followed by a gradual decline out to 72 hours following the administration of endotoxin and rNAPc2.
Figure 2. Percentage of TF-FVIIa inhibition after administration of a single iv dose of 3.0 μg/kg, 5.0 μg/kg, or 7.5 μg/kg rNAPc2 (panel A), and after administration of a single iv dose of 4 ng/kg endotoxin or the combination of a single iv dose of 4 ng/kg endotoxin and a single iv dose of 7.5 μg/kg rNAPc2 (panel B) to healthy male volunteers. Data represent mean ± SEM.
TF-FVIIa = tissue factor-factor VIIa complex. iv = intravenous. rNAPc2 = recombinant nematode anticoagulant protein c2.

Endogenous thrombin potential
To evaluate the residual ability of thrombin generation in plasma after the administration of rNAPc2, we measured the endogenous thrombin potential (ETP). As shown in Figure 3A, administration of rNAPc2 alone resulted in a significant,
dose dependent reduction of ETP. The ETP remained stable after administration of endotoxin alone, whereas the ETP significantly reduced immediately after the administration of endotoxin and rNAPc2, followed by a gradual rise (Figure 3B).

**Figure 3.** Effect on endogenous thrombin potential (ETP) after administration of a single iv dose of 3.0 µg/kg, 5.0 µg/kg, or 7.5 µg/kg rNAPc2 (panel A), and after administration of a single iv dose of 4 ng/kg endotoxin or the combination of a single iv dose of 4 ng/kg endotoxin and a single iv dose of 7.5 µg/kg rNAPc2 (panel B) to healthy male volunteers. Data represent mean ± SEM. iv=intravenous. rNAPc2=recombinant nematode anticoagulant protein c2.
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Clotting times
As shown in Figure 4A, the administration of rNAPc2 alone resulted in a significant, dose dependent prolongation of the prothrombin time (PT). Administration of endotoxin did not result in a change of the PT (Figure 4B). After an initial significant rise, the PT gradually declined to baseline after 24 hours following administration of endotoxin and rNAPc2.

![Graph A](image)

**A**

![Graph B](image)

**B**

*Figure 4. Effect on prothrombin time (PT) after administration of a single iv dose of 3.0 µg/kg, 5.0 µg/kg, or 7.5 µg/kg rNAPc2 (panel A), and after administration of a single iv dose of 4 ng/kg endotoxin or the combination of a single iv dose of 4 ng/kg endotoxin and a single iv dose of 7.5 µg/kg rNAPc2 (panel B) to healthy male volunteers. Data represent mean ± SEM.*

iv=intravenous, rNAPc2=recombinant nematode anticoagulant protein c2.
Administration of endotoxin made the activated partial thromboplastin time (APTT) decline from $35.2 \pm 1.4$ to a nadir of $27.5 \pm 1.0$ sec after 3 hours, gradually returning to baseline after 12 hours. Five minutes after iv administration of endotoxin and rNAPc2, the APTT rose from $38.6 \pm 1.2$ to $43.4 \pm 1.2$ sec, declining to a nadir of $31.9 \pm 1.7$ sec after 3 hours and gradually returning to baseline after 12 hours.

**Thrombin generation**

As shown in Figure 5, the administration of endotoxin resulted in an enhanced thrombin generation, as reflected by the significant increase in the levels of prothrombin activation fragment $F_{1+2}$. The administration of rNAPc2 completely attenuated the endotoxin-induced rise in $F_{1+2}$ to baseline levels.

![Figure 5](image)

**Figure 5.** Effect on prothrombin fragment $F_{1+2}$ after administration of a single iv dose of 4 ng/kg endotoxin or the combination of a single iv dose of 4 ng/kg endotoxin and a single iv dose of 7.5 μg/kg rNAPc2 to healthy male volunteers. Data represent mean ± SEM. iv=intravenous. rNAPc2=recombinant nematode anticoagulant protein c2.

**Activation of the fibrinolytic system**

Administration of endotoxin resulted in activation of the fibrinolytic system, as confirmed by a transient increase in plasma concentrations of PAP, peaking from $195 \pm 23$ to $7116 \pm 2173$ μg/L after 2 hours. The rise in PAP was followed by a transient increase in PAI-1, peaking from $75.0 \pm 43.9$ μg/L to $281.5 \pm 54.3$ μg/L after 6 hours. rNAPc2 did not affect the endotoxin-induced release of PAI-1 or PAP.
Cytokines

All measured cytokines (TNF-α, IL-6, IL-8 and IL-10) rose in response to endotoxin. TNF-α rose from below the detection limit (1.4 pg/mL) to 1706 ± 356 pg/mL 90 minutes after endotoxin administration. IL-8 rose from below the detection limit (1 pg/mL) to 2562 ± 235 pg/mL 2 hours after endotoxin administration. IL-6 rose from below the detection limit (0.6 pg/mL) to 4345 ± 991 pg/mL 3 hours after endotoxin administration. The administration of rNAPc2 did not affect the rise in TNF-α, IL-6 and IL-8. As shown in Figure 6, IL-10 was significantly elevated, peaking at 3 hours following endotoxin administration. The administration of rNAPc2 with endotoxin resulted in an attenuated IL-10 response, which reached statistical significance 3 hours following the challenge.

![Figure 6](image)

**Figure 6.** Effect on interleukin (IL)-10 after administration of a single iv dose of 4 ng/kg endotoxin or the combination of a single iv dose of 4 ng/kg endotoxin and a single iv dose of 7.5 μg/kg rNAPc2 to healthy male volunteers. Data represent mean ± SEM.

iv=intravenous. rNAPc2=recombinant nematode anticoagulant protein c2.

Discussion

In the present clinical study, we examined the pharmacokinetics (PK) and pharmacodynamics (PD) of a single iv administration of rNAPc2, as well as its effect on endotoxin-induced coagulation and inflammatory responses in healthy human volunteers. We demonstrated that the PK and PD of intravenously and subcutaneously administered single doses of rNAPc2 are comparable. rNAPc2 iv completely prevented endotoxin-induced thrombin generation, without affecting fibrinolysis. In
addition, rNAPc2 iv attenuated the endotoxin-induced IL-10 response, without affecting the endotoxin-induced rise in TNF-α, IL-6 and IL-8.

The administration of rNAPc2 was well tolerated and there were no safety concerns or episodes of bleeding. We demonstrated that the elimination profile of a single iv dose of rNAPc2 is comparable to the elimination profile of a single subcutaneous dose, with a half-life of more than 50 hours\(^{15,16}\). The administration of a single iv dose of rNAPc2 resulted in a dose dependent inhibition of TF-FVIIa and a reduction of the ETP. It also elicited a dose dependent prolongation of PT, with a maximum elevation of approximately 1.5 fold over the baseline value at a dose of 7.5 μg/kg. This dose dependent, selective prolongation of the PT is consistent with the results of Vlasuk et al., who found a maximum PT elevation of approximately 1.8 fold over baseline values after a single subcutaneous dose of 5.0 μg/kg rNAPc2\(^{15}\).

We did not observe an effect on TF-FVIIa inhibition after administration of endotoxin alone. However, a significant increase of TFPI levels was found in patients with severe sepsis\(^{17}\). Possibly, the dose of endotoxin used in this study was insufficient to elicit an endogenous TFPI response.

Following the administration of both endotoxin and rNAPc2, the APTT rose to a maximum of 12% above the baseline value, then declined to a nadir approximately 17% below the baseline value and gradually returned to baseline within 12 hours. These findings are similar to those of de Jonge et al., comparing a single iv dose of endotoxin to the combination of iv endotoxin and rtTFPI in healthy human subjects\(^{18}\). The decline in APTT after the administration of endotoxin, is believed to be due to the rise in factor VIII, accompanying the acute phase reaction\(^{19}\).

The present results demonstrate that a single iv dose rNAPc2 of 7.5 μg/kg prevents endotoxin-induced thrombin generation, as reflected by the complete attenuation of the increase of F\(_{1-2}\). This finding is in accordance with two earlier studies showing that inhibition of TF-VIIa by rtTFPI\(^{18}\) and active site inactivated recombinant factor VIIa (FVIIai)\(^{20}\) dose dependently inhibited the endotoxin-induced thrombin generation in healthy humans. The ability of rNAPc2 to prevent endotoxin-induced thrombin generation has previously been shown in chimpanzees\(^{10}\).

In accordance with earlier studies\(^{18,20}\), the endotoxin-induced thrombin generation was preceded by a short and rapid activation of the fibrinolytic system, as reflected by a rise in PAP levels, followed by a rise in PAI-1 levels. Recombinant NAPc2 did not affect this endotoxin-induced activation of the fibrinolytic system. This finding
confirms that during low-grade endotoxemia in humans, the fibrinolytic response occurs independent of thrombin generation. Tumor necrosis factor is considered to be the primary initiator of fibrinolysis activation in endotoxemia\textsuperscript{21-23}. Consistent with our finding that the endotoxin-induced activation of fibrinolysis was unaltered by rNAPc2 is the observation that the increased levels of TNF-\(\alpha\) after endotoxin administration were also unaffected by rNAPc2.

As observed for TNF-\(\alpha\), the rise in IL-6 and IL-8, induced by administration of low-dose endotoxin, was not influenced by rNAPc2 in these healthy human volunteers. This has also previously been demonstrated for rTFPI\textsuperscript{18} and FVIIa\textsuperscript{20}. Evidenced by the rises in TNF-\(\alpha\), IL-6 and IL-8, it appears that antagonizing the catalytic activity of TF-FVIIa with three inhibitors with different mechanisms of action does not attenuate these responses. In baboons with sepsis, rTFPI attenuated the IL-6 and IL-8 responses without affecting the early and transient TNF peaks\textsuperscript{4}. This was also observed in severe septic patients, showing an accelerated reduction of IL-6 levels in rTFPI treated patients\textsuperscript{6}. It is possible that cytokines are produced by different cell types during low-grade endotoxemia and severe sepsis. The prolonged IL-6 and IL-8 responses that are found during sepsis in primates\textsuperscript{4} could be produced by endothelial cells, that are known to predominantly produce these two cytokines upon stimulation\textsuperscript{24,25}, whereas the more transient rise in cytokines observed after low dose endotoxin injection could be attributed to monocytes. Hence, as suggested previously\textsuperscript{18}, the inhibition of TF-FVIIa may predominantly attenuate the cytokine response by endothelial cells, with a much smaller effect on endotoxin-induced cytokine production by monocytes. In addition, as TF-FVIIa has been shown to have direct pro-inflammatory effects independent of the activation of coagulation in man\textsuperscript{26}, our endotoxin model may not induce enough TF-FVIIa formation to contribute to inflammatory changes.

Compared to the well acknowledged proinflammatory cytokines such as TNF-\(\alpha\) and IL-6, rNAPc2 did attenuate the endotoxin-induced IL-10 response. To our knowledge, this is the first time IL-10 attenuation by inhibition of TF-FVIIa is demonstrated in vivo. The interplay of TF/FVIIa and IL-10 is largely unknown. Although IL-10 is able to reduce the TF-activity in vitro\textsuperscript{27}, no data are available on the effect of TF-FVIIa on the IL-10 response during infection. Generally, IL-10 is considered a potent anti-inflammatory cytokine. Anti-inflammatory cytokines such as IL-10 impair local antibacterial effector mechanisms\textsuperscript{28}. This explains why treatment with the IL-10 inhibitor AS101 significantly increased survival in septic mice after cecal ligation.
and puncture\textsuperscript{29}. Moreover, IL-10 is a major denominator of the immunosuppressive effect in septic plasma. It has been postulated that persistently high plasma levels of IL-10 reflect a state of immunoparalysis, caused by deactivation of monocytes\textsuperscript{28}. Several authors have described significantly higher IL-10 plasma levels in non-survivors of febrile illnesses as compared to survivors\textsuperscript{30,31}. In this respect, the attenuation of the IL-10 response by rNAPc2 might reflect a protective effect against immune suppression during endotoxemia. It is conceivable that the attenuation of the IL-10 response by rNAPc2 might play a role in human sepsis. Further studies are necessary to elucidate the role.

In summary, this study establishes the safety, tolerability and biological activity of intravenous rNAPc2 in healthy human volunteers. A single iv dose rNAPc2 of 7.5 µg/kg, completely blocks endotoxin-induced thrombin generation without affecting the fibrinolytic response. In addition, iv rNAPc2 attenuates the endotoxin-induced IL-10 response. The role of IL-10 suppression by rNAPc2 needs further investigation in human endotoxemia and sepsis.

Acknowledgement
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References
