Table S1: Categories, examples and properties of ATAs. Within each of the three main categories of ATAs (targeting platelets, coagulation and fibrinolysis), there are numerous types of small molecule biological drugs with distinct mechanisms of action, routes of administration and pharmacological properties. Generally, oral ATAs have longer onset and duration time and are used for chronic thromboprophylaxis. Injectable ATAs with faster onset and shorter duration are used for therapy. Fibrinolytic plasminogen activators (PA) and translational anticoagulants APC and TM have practically immediate onset and exhibit the shortest duration.

Category	Subclass	Actions	Examples	Route	Onset	Duration	Antidote
Antiplatelet	Arachadonic Acid Metabolism Inhibitors	Irreversible COX inhibition – ↓ platelet activation and aggregation	Aspirin	Oral	~2 hrs	~7 days	None
	ADP Receptor Antagonists	P2Y12 inhibition – reduction of platelet activation and aggregation	Clopidogrel, prasugrel, etc	Oral	1-2 hours	~7 days	None
	Glycoprotein Antagonists	GPIIb/IIIa inhibition – ↓ platelet aggregation	Abciximab, eptifibatide, etc	Parenteral	~30 min	4-6 hours	None
Anticoagulant	Vitamin K antagonists	Inhibition of Vitamin K recycling – ↓ synthesis of multiple coagulation factors	Warfarin	Oral	Several days	Several days	Plasma derivatives
	Antithrombin activators	Activation of Antithrombin III – inhibition of Factor Xa +/- thrombin	Heparin, LMWH, fondaparinux	Parenteral	30 min-2hr	Few hours (longer for fondaparinux)	Protamine (except fondaparinux)
	Direct thrombin inhibitors	Direct, competitive inhibition of thrombin	Hirudin, dabigatran, etc	Parenteral or oral	~1 hr	~24 hours	None available
	Direct Xa inhibitors	Direct competitive inhibition of Factor Xa	Rivaraoxaban, apixiban	Oral	~1 hr	~24 hours	None available
	Activated Protein C	Inactivates Factor Va, VIIIa	Drotrecogin alfa (withdrawn from market)	Parenteral	Minutes	Minutes	None
	Thrombomodulin	Inhibits thrombin (cleavage of fibrinogen, activation of platelets), activates protein C	ART-123, Solulin (clinical trials)	Parenteral	Minutes	From less 1 hour to 24 hours	None
Fibrinolytic	Tissue Plasminogen Activators	Conversion of plasminogen to plasmin -- proteolysis of fibrin clot	Altelpase, tenectaplase, etc	Parenteral	Minutes	From ~ 5min to ~ 30min	Tranexamic acid, aminocaproic acid
	Urinary Plasminogen Activators		Urokinase	Parenteral	Minutes	From ~ 5min to ~ 30min	

Figure S1. Prevention and therapy of thrombosis. Blood clots form upon activation of platelets and the coagulation cascade, which in a simplistic interpretation, dominate arterial and venous clotting, respectively (i.e., "white" and "red" clots). However, these pathways are closely intertwined: e.g., activated platelets support coagulation, while thrombin activates platelets. Blocking either pathway with anti-thrombotic agents (ATA) inhibits the other to some extent. Inhibition of both pathways provides greater protection against thrombosis but increases the risk of bleeding. Anti-platelet agents and anticoagulants are used most commonly to prevent clotting (chronic prophylaxis, usually using orally administered drugs) and, in some acute settings, to inhibit ongoing thrombosis (therapy, usually using injectable drugs). Fibrinolytic agents are used as an emergency therapy in acute settings to lyse occlusive thrombi. Tissue type and urokinase type plasminogen activators (PAs) (tPA and uPA) are serine proteases (MW ~50-60kD) that cleave plasminogen into a broad specificity serine protease, plasmin, that cleaves fibrin (among other substrates). The enzymatic activity of PAs and plasmin are inhibited by "suicide substrates" (primarily PAI-1 and a_s-PI, respectively) by forming inactive complexes that are cleared rapidly from the circulation.

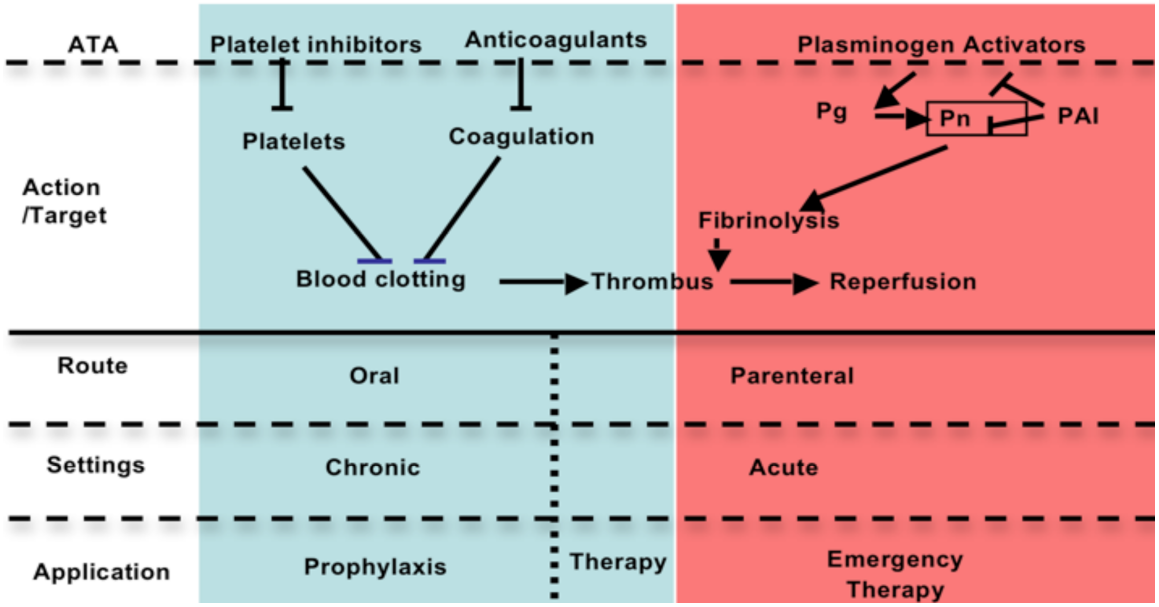

Figure S2. Local release and thrombolysis by flow-sensitive nanocarriers. Intravenously injected shear-activated nanotherapeutics (SA-NTs) dissociate into NPs at the thrombus site due to the enhanced shear stress. Accumulation of tPA-coated nanoparticles at the occlusion site leads to progressive dissolution of the clot. Due to the high local drug concentration achievable with the SA-NTs, this strategy may be suitable for dissolving partially occlusive clots, though it remains unlikely that any currently available drug/DDS will be able to dissolve fully occlusive clots.

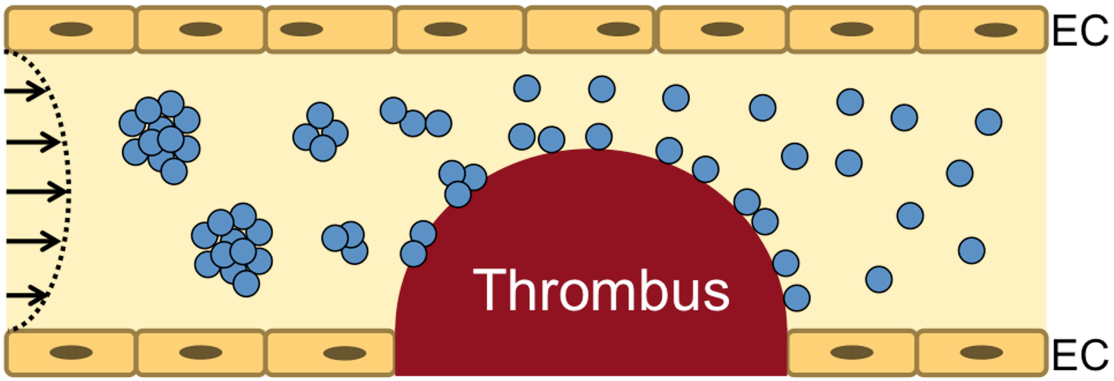

Figure S3. Recombinant ATA fusions with targeting scFv. (A) Constitutively active scFv/tPA fusion. Indicated are sequences of standard peptides connecting heavy and light chains and scFv with ATAs. (B) Clot-targeted scFv/hirudin fusion with Factor Xa - sensitive cleavage site in the connecting peptide. (C) Wild-type, plasmin-activated scFv/uPA fusion (uPA moiety is lmw scuPA). (D) Plasmin-resistant, thrombin-activated mutant of lmw scuPA fused with scFv targeted to RBC or endothelium (scFv/uPA-T).

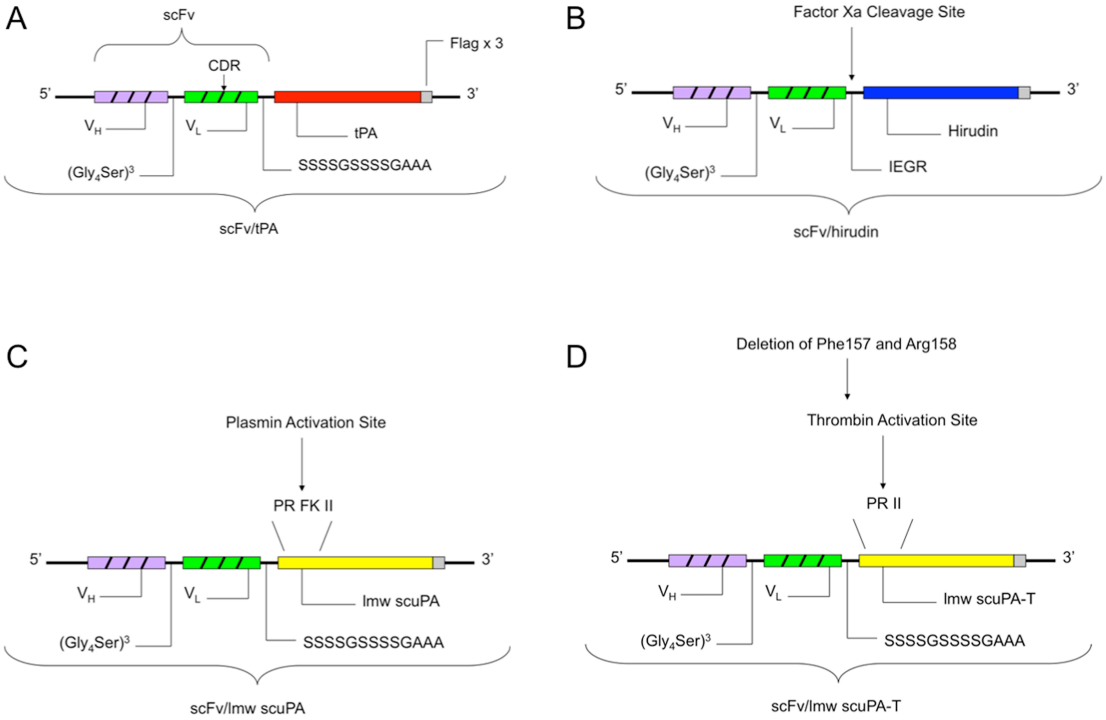

Figure S4: Proposed utility of RBC-targeted ATA for emergency management of NSTEMI and other forms of recurrent thrombosis. Recurrent cycles of partial thrombotic occlusion and incomplete clot lysis (time intervals T1-T5) typical of non-ST elevated myocardial infarction may eventuate in complete occlusion and transmural AMI. Rapid clearance and risk of side effects render fibrinolytic PAs ineffective in this setting (upper panel). A single injection of RBC-targeted scFv/pro-drug ATA fusion proteins (e.g., TM or thrombin-activated PA) would provide localized anti-thrombotic activity for the duration of highest risk (lower panel).