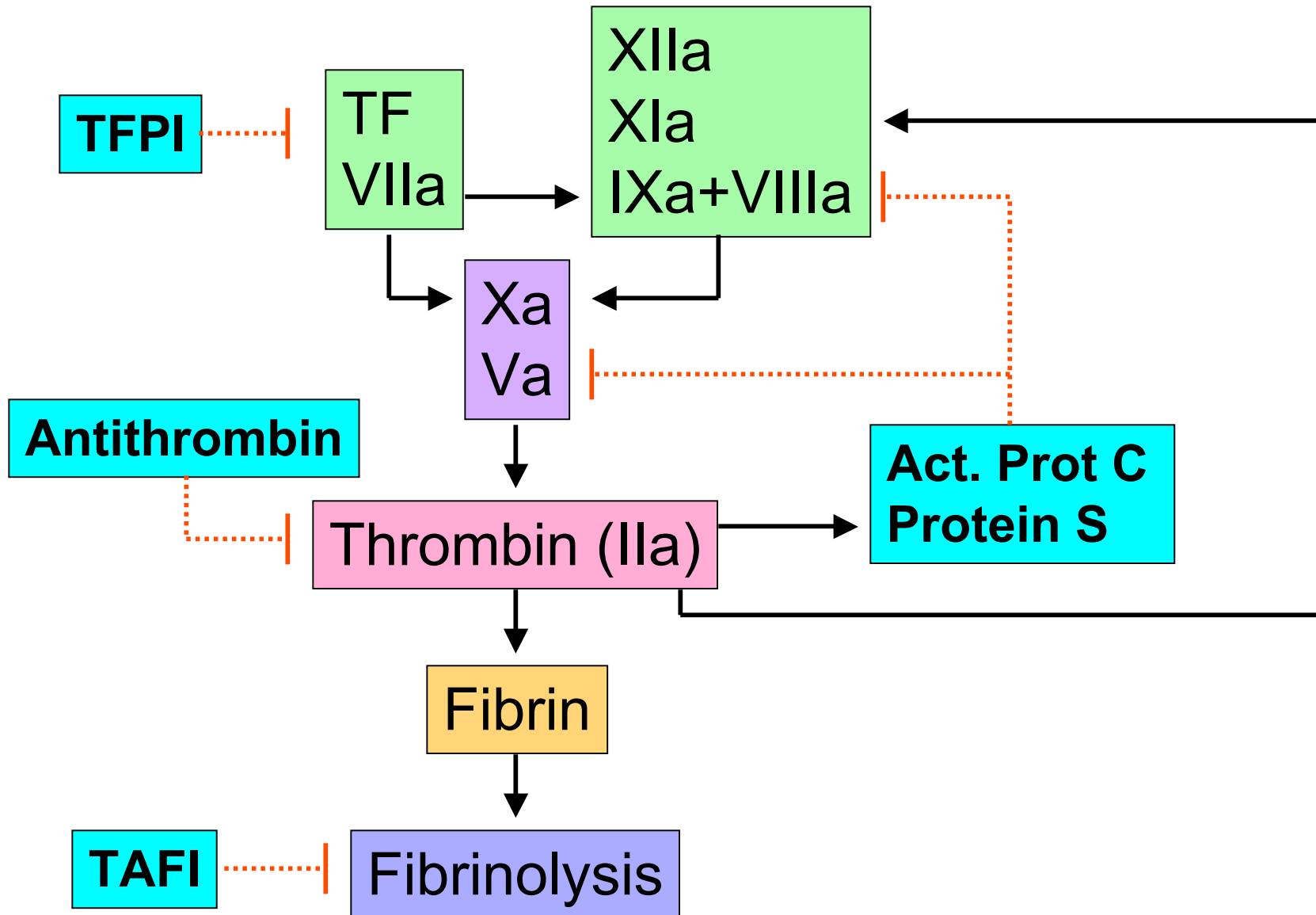


# **Anticoagulation Armamentarium: Update on drugs and mechanisms**

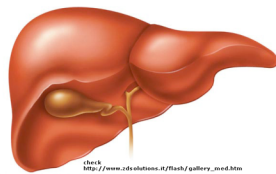
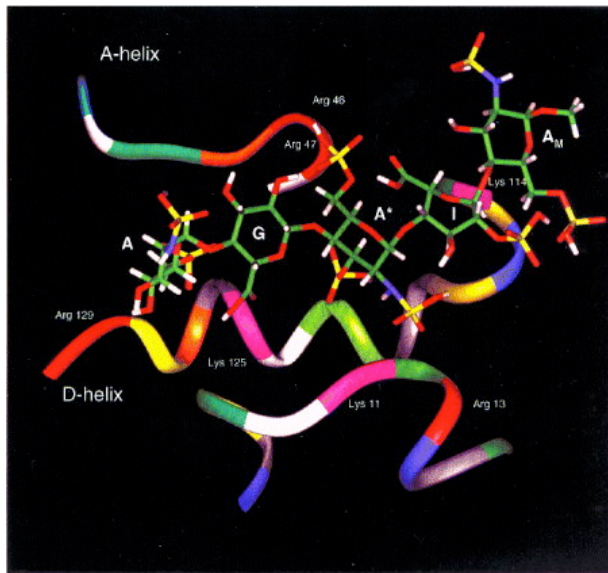
**Sudha Parasuraman, M.D.  
Brigham and Women's Hospital  
Children's Hospital Boston  
February 15, 2007**

# REGULATION OF COAGULATION

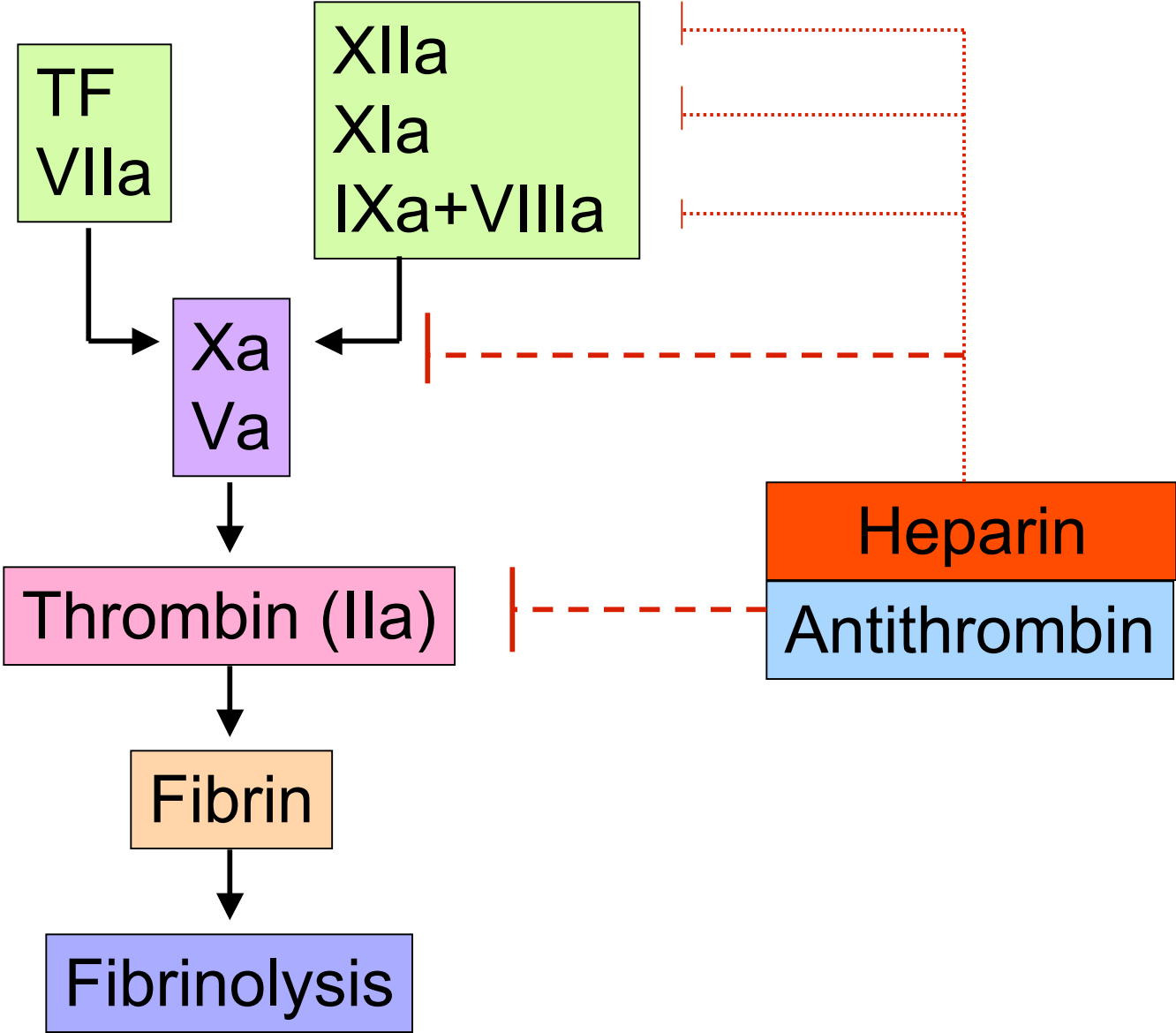


# Traditional Anticoagulants

- Unfractionated Heparin
- Low molecular heparins
- Warfarin



# Mechanism of action of heparin



## UFH vs LMWH

High Mol Wt (15,000)

Variable bioavailability

Anti-Xa = anti-IIa

Multiple targets

Short  $t_{1/2}$

IV or 2-3 times/d SQ

↑ HIT risk

Monitoring required

Antidote: protamine

Low Mol Wt (4500-6000)

High bioavailability

Anti-Xa > anti-IIa

Multiple targets

Longer  $t_{1/2}$

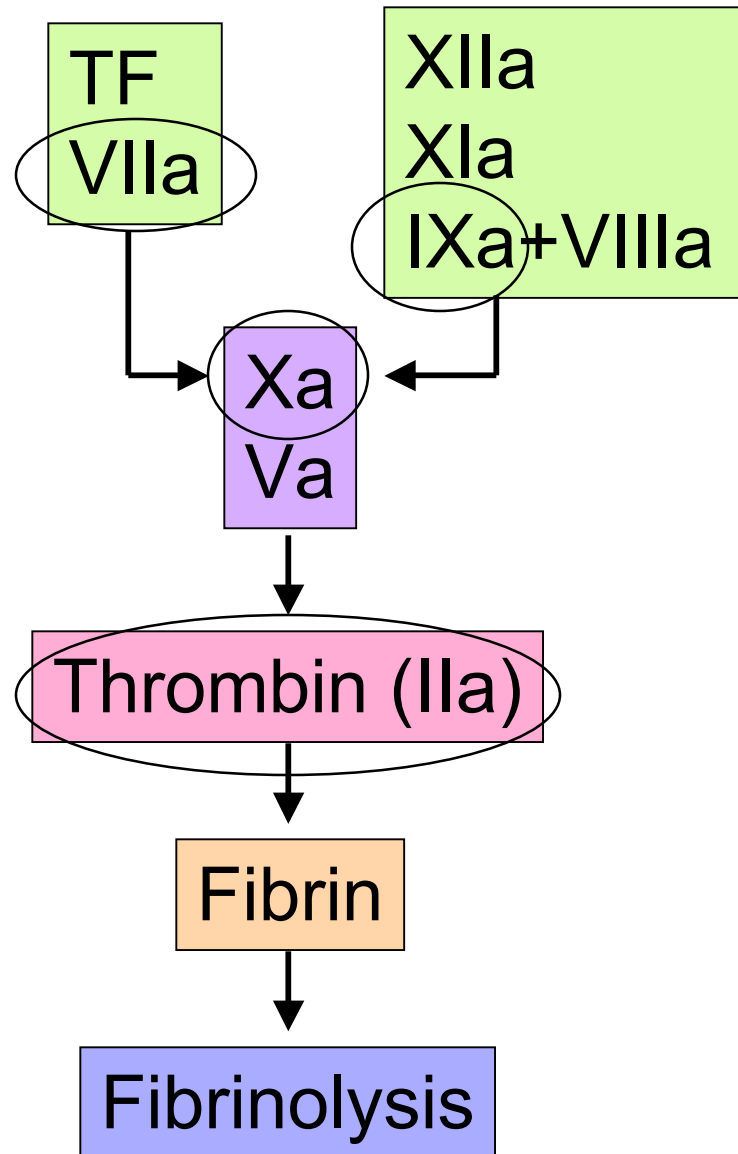
1-2 times/d SQ

↓ HIT risk

Monitoring usually not reqd

Antidote: protamine

## Sites of action for warfarin



# Limitations of warfarin

## LIMITATION

## CONSEQUENCE

Slow onset of action

Overlap with a parenteral anticoagulant

Genetic variation in metabolism

Variable dose requirements

Multiple food and Drug interactions

Frequent coagulation monitoring

Narrow therapeutic index

Frequent coagulation monitoring

# Characteristics of an ideal anticoagulant

- High efficacy-to-safety index
- Good bioavailability
- No food or drug interactions
- Rapid onset of action
- Wide therapeutic window
- Predictable response – no monitoring required
- Availability of an antidote
- Reasonable cost

# Newer Anticoagulants

Designed to target specific coagulation enzymes or steps in the coagulation pathway



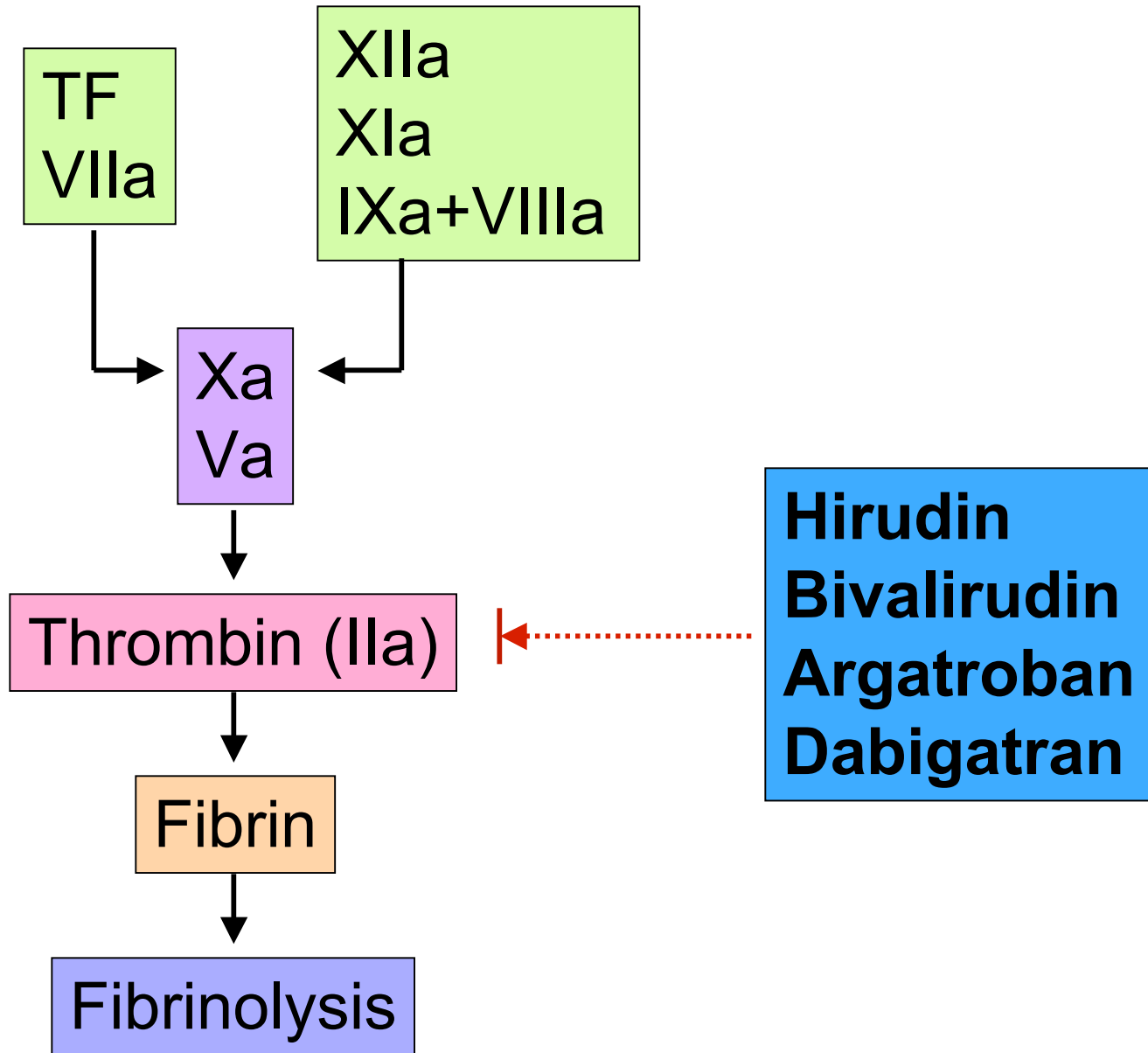
Developed from hematophagous organisms, by the application of recombinant DNA technology or by structure-based drug design

## New anticoagulants & their targets

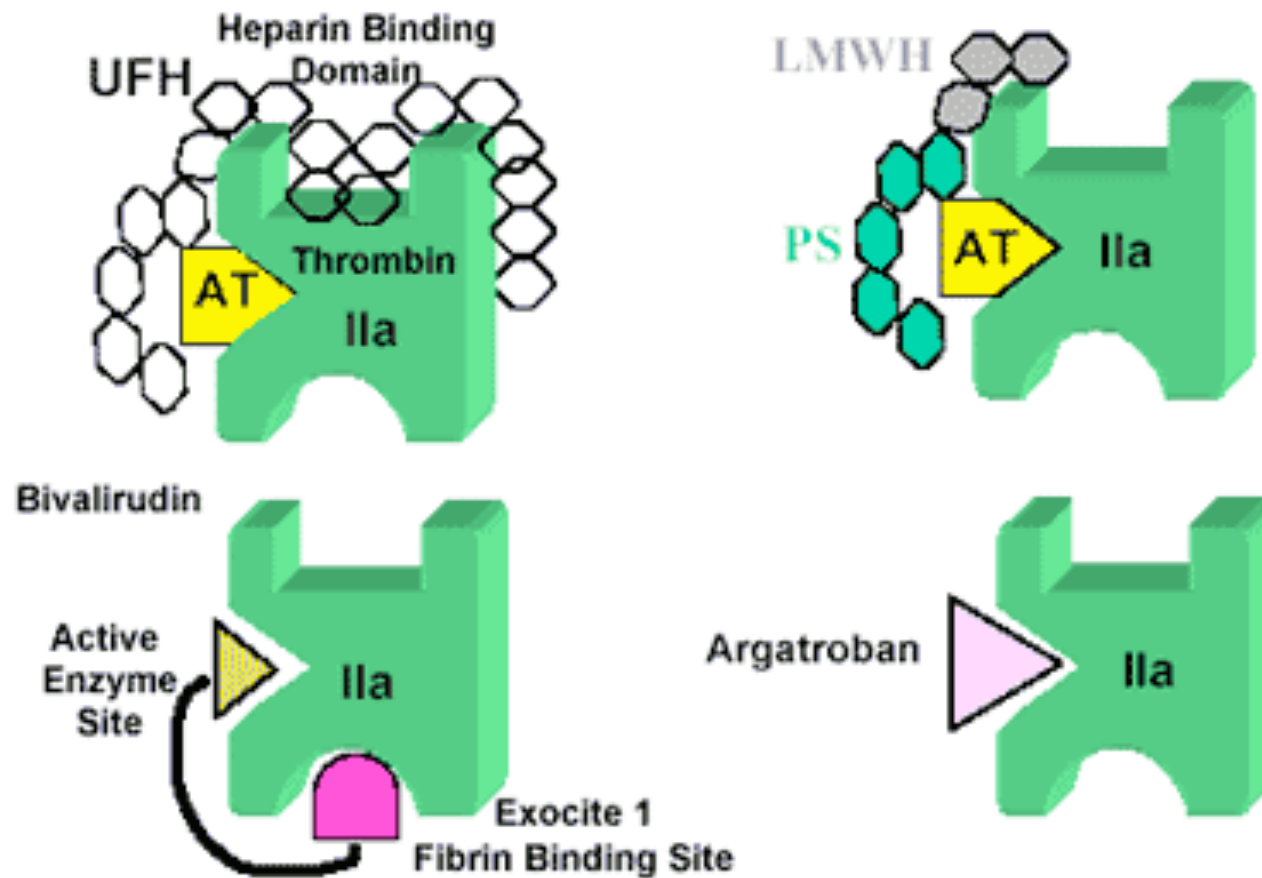
Steps in coag pathway	Site	Drug
Initiation	TF/VIIa	Tifacogin
		NAPc2
		FVIIai
Propagation	IXa	TTP889
	VIIIa/Va	Protein C ART-123
	Xa	Fondaparinux Idraparinux Apixaban Rivaroxaban
Fibrin formation	Thrombin	Dabigatran

## Direct thrombin inhibitors

- Thrombin plays a central role in coagulation and hemostasis. Hence an attractive target for inhibition
- DTI inactivate fibrin-bound thrombin as well as fluid-phase thrombin
- Produce a more predictable anticoagulant effect by not binding to other proteins



## Thrombin Binding Sites



## Hirudin (lepirudin)

- Irreversible bivalent inhibitor
- Half-life: 60 min after IV ;120 min after SQ
- Monitored by aPTT at 1.5 – 2.0 x baseline
- Renal clearance
- Approved for use in HIT

# Argatroban

- Reversible monovalent inhibitor
- Given IV; Half-life: 45 min
- Monitored by aPTT at 1.5 – 3.0 x baseline
- Metabolized in the liver
- Approved for treatment of HIT +/- thrombosis

# Bivalirudin

- Reversible bivalent inhibitor
- Given IV; half-life: ~25 min
- Approved for pts undergoing Percutaneous Coronary Intervention (PCI) as an alternative to heparin and for those with HIT who require PCIs

# Dabigatran Etexilate

- Oral reversible thrombin inhibitor currently in three phase III trials
- Prodrug for dabigatran
- Half-life: 14-17 hours; twice daily dosing
- Renal excretion
- No monitoring required

## Factor Xa inhibitors

**Direct inhibitors:** inhibit free and platelet bound Xa

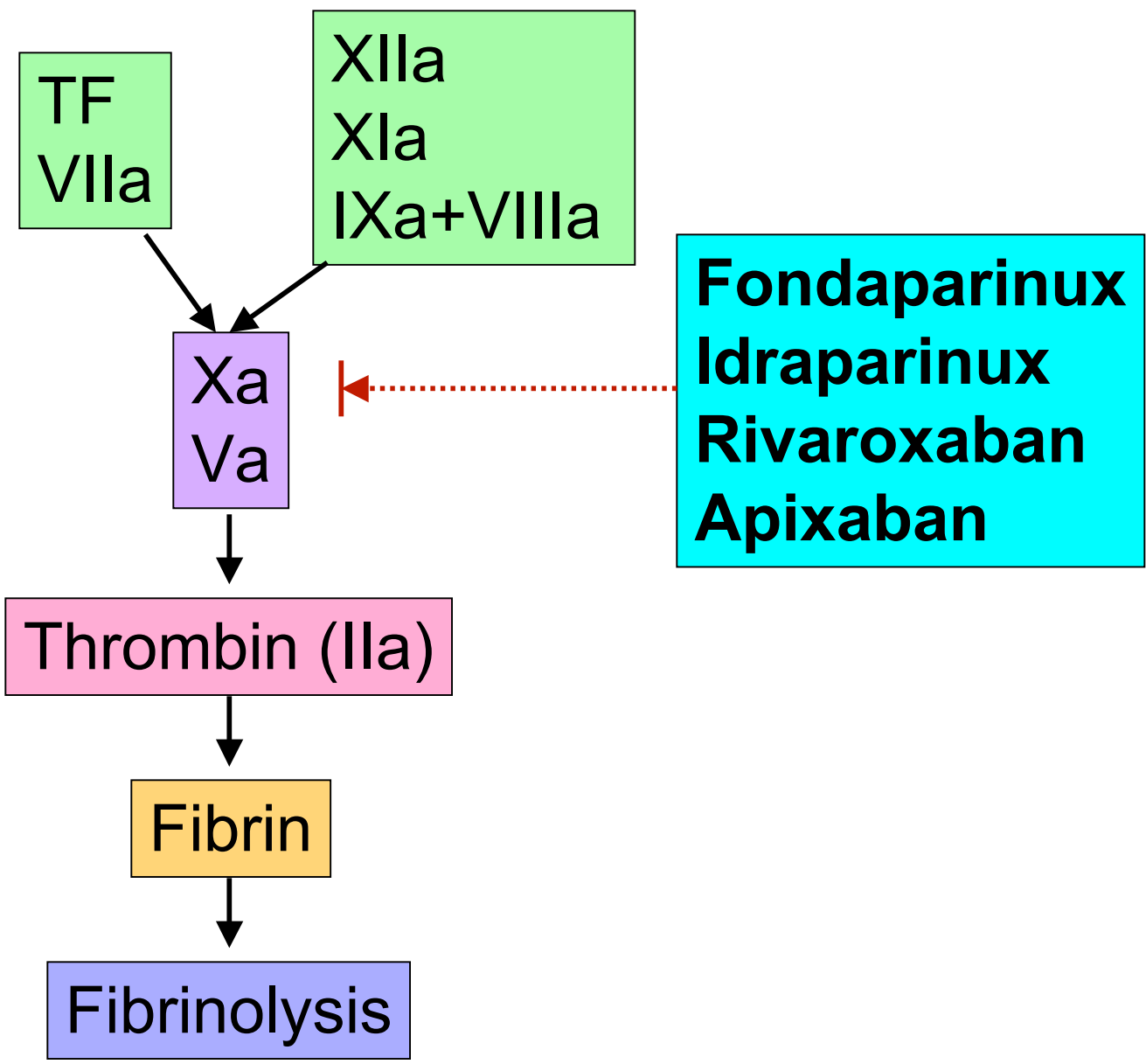
**Rivaroxaban**

**Apixaban**

**Indirect inhibitors:** bind to antithrombin and potentiate the natural inhibitory effect of antithrombin against Xa

**Fondaparinux**

**Idraparinux**



# Fondaparinux

- Synthetic pentasaccharide
- Single target – Xa
- Given once daily subcutaneously
- No cross-reactivity with HIT antibodies
- High bioavailability
- Half life: ~ 17 hours
- Renal excretion
- No antidote
- FDA approved for prevention and treatment of VTE

## Idraparinux

- Hyper-methylated derivative of fondaparinux
- Half-life: 80 – 130 hours; given once weekly as subcutaneous injection – No antidote
- When compared to placebo, very effective in extended treatment of VTE at the expense of an increased risk of bleeding
- Recent randomized trials confirm similar efficacy & safety when compared to standard therapy in treatment of DVT but not PE

# Oral factor Xa inhibitors

## Rivaroxaban:

- rapid onset of action; once daily dosing
- no monitoring required
- phase II and III trials in progress

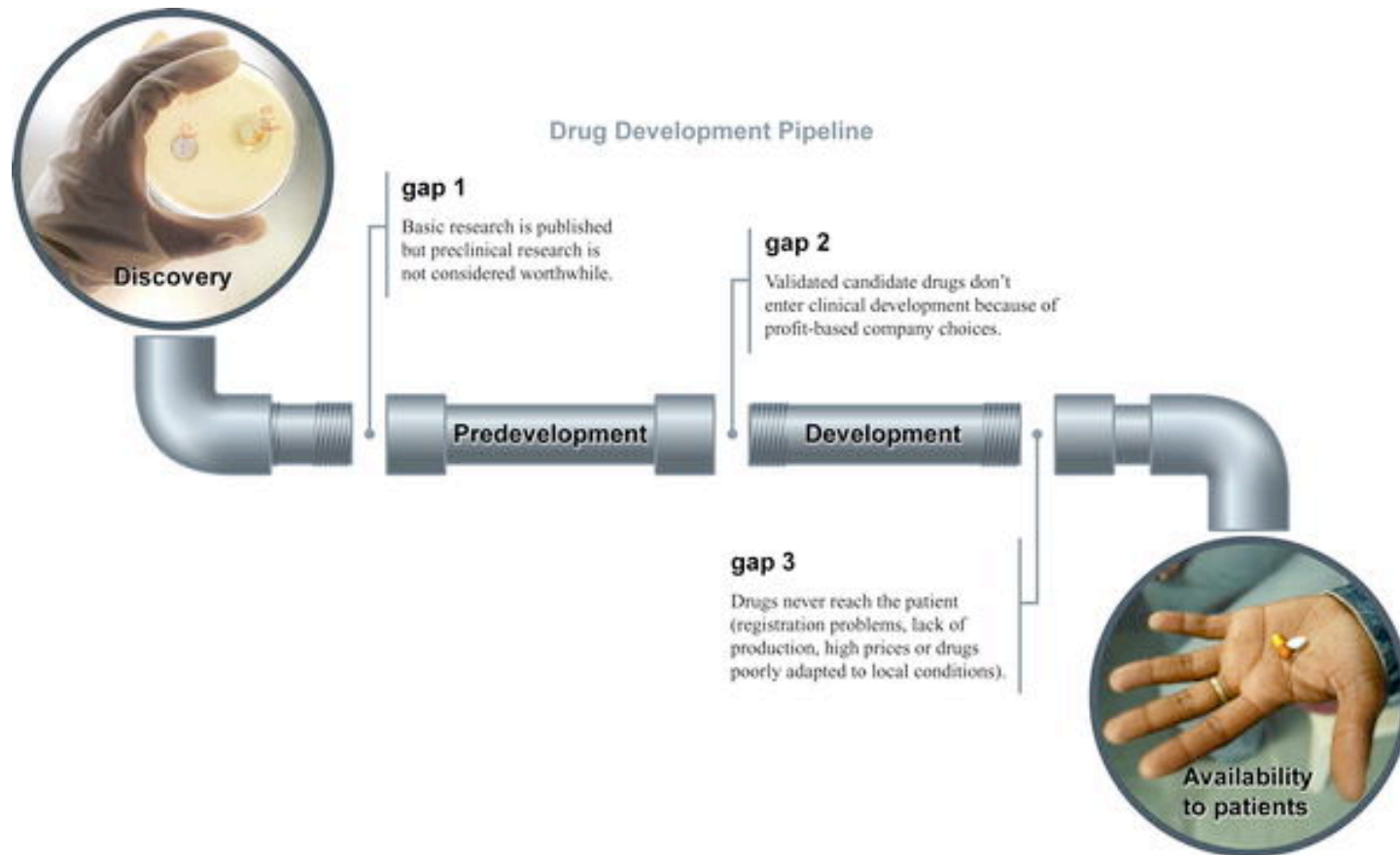
## Apixaban:

- good bioavailability; Half-life: ~ 12 hours
- Twice daily dosing
- phase III trial for VTE prevention in hospitalized medical patients planned

## REG1 anticoagulant system

- The first drug-antidote pair
- Given intravenously
- It is composed of RB006, a specific aptamer based inhibitor of coagulation factor IXa and RB007, an antidote designed to neutralize the pharmacological activity of RB006
- A phase I trial in healthy volunteers was successful

# And the research continues.....



.....Until next year