Laboratory Tests of Hemostasis

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Disclosures

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- Research Support:
  - None
- Advisory Boards
  - None

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- Research Support:
  - Amgen
  - Janssen Scientific Affairs
  - Dova Pharmaceuticals
- Advisory Boards
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  - Dova Pharmaceuticals
  - Bristol-Myers Squibb, Pfizer

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Material To Cover

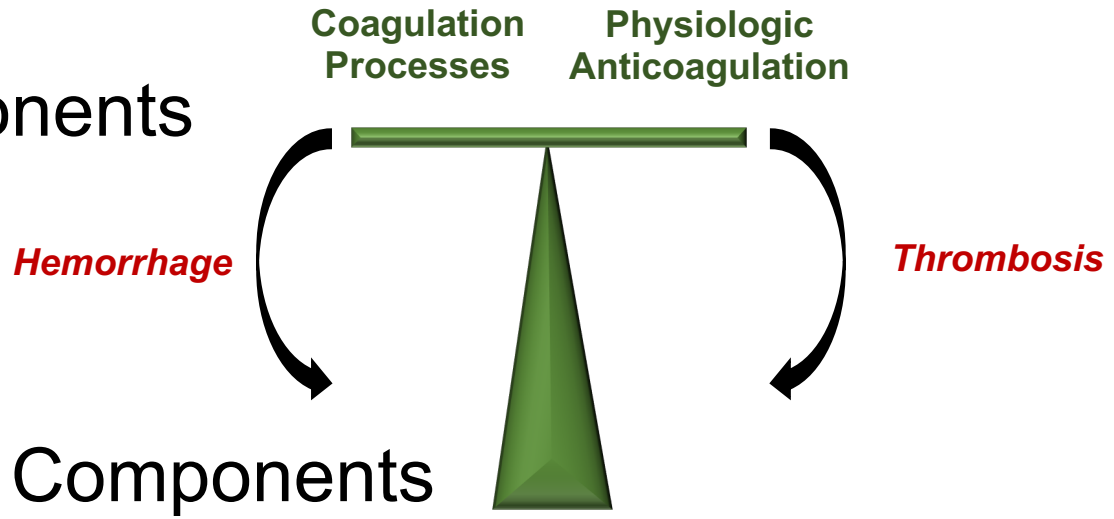
1. *The Hemostatic Balance*
2. *Overview of The Coagulation Cascade and Testing*
3. *Functional and Immuno Assays*
4. *The Prothrombin and Activated Partial Thromboplastin Times*
5. *Other Tests:*
   - *Anti-Xa Heparin Assay*
   - *Thrombin Time*
   - *Fibrinogen Assay*
   - *D-Dimer*
6. **Interpretation of Prolonged PT and/or aPTT Results**
7. *Tests Of Thrombotic Disease*
8. *Heparin Induced Thrombocytopenia/Thrombosis (HITT): Pathophysiology*
9. *Antiphospholipid Antibody Syndrome*
10. *Laboratory Testing for Thrombophilia (Hypercoagulable State)*
11. *APC-Resistance—Screening Assay For Factor V Leiden*
12. *Conditions That Impact Tests for Thrombotic Risk Factors.*
13. *If/When to Do Hypercoagulable Work-up*

The Hemostatic Balance

Module: 1

The Hemostatic Balance

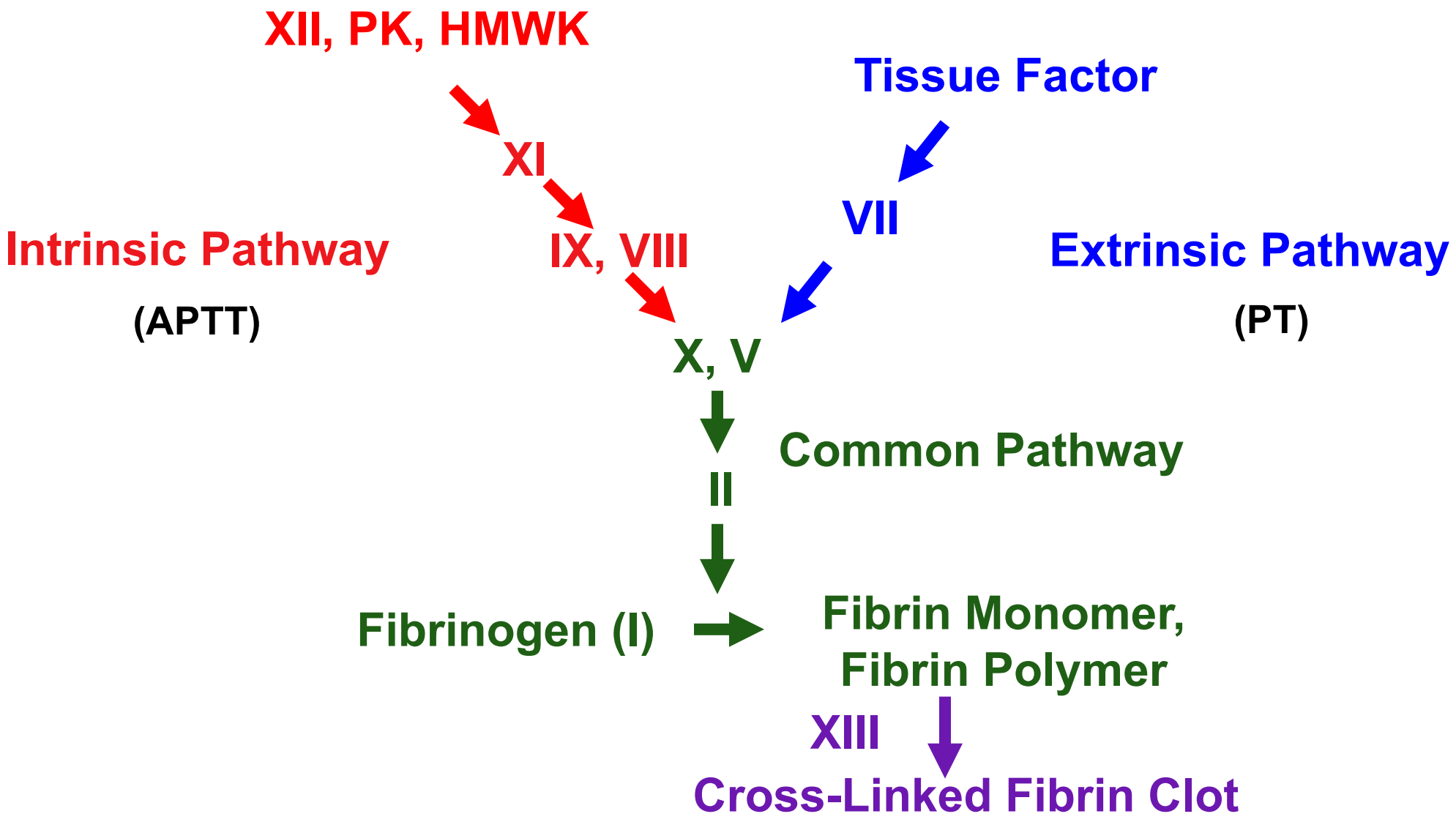
- Hemostasis is the balance between bleeding and clotting, and involves both cellular and soluble enzymatic components of the blood and vasculature.



- Primary Hemostasis/Cellular Components
  - Vascular endothelial cells
  - Platelets
- Secondary Hemostasis/Fluid Phase Components
  - Coagulation proteins:

Overview of The Coagulation Testing

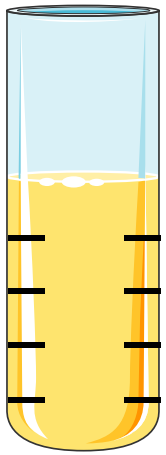
Module: 2


XII, PK, HMWK
Tissue Factor
XI
VII
Intrinsic Pathway
(APTT)
IX, VIII
Extrinsic Pathway
(PT)
X, V
Common Pathway
II
Fibrinogen (I)
Fibrin Monomer,
Fibrin Polymer
XIII
Cross-Linked Fibrin Clot

There Are Two Ways to Initiate Coagulation System *in Vitro*

Intrinsic Pathway:

Initiated by Negatively Charged Surface



XII, PK, HMWK

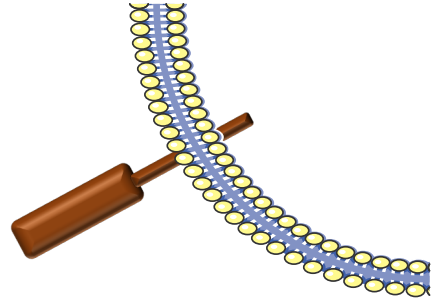
↓

XIIa

(APTT)

Extrinsic Pathway:

Initiated by addition of Tissue Thromboplastin (Tissue Factor and phospholipid)



TF bound to cell surface

TF:VII

Auto-Activation

↓

VIIa

(PT)

Preanalytical Considerations

- Specimen Collection
  - 3.2% sodium citrate
  - 9:1 volume of blood to anticoagulant
  - Hct <25% or >50% may affect results
- Specimen Stability
  - PT (stable up to 72 h, closed tube at RT)
  - APTT (stable up to 10 h, closed tube at RT)
  - APTT for heparin monitoring (stable for 4 h)
  - Special tests (must be performed within 4 h of collection)
    - If conditions cannot be met - plasma must be separated from cells and frozen at –80C

Analytical Considerations

- Types of Assays
  - Functional
    - Enzymatic activity
    - Cofactor activity
  - Immunologic
    - Protein antigen content

Functional and Immuno Assays

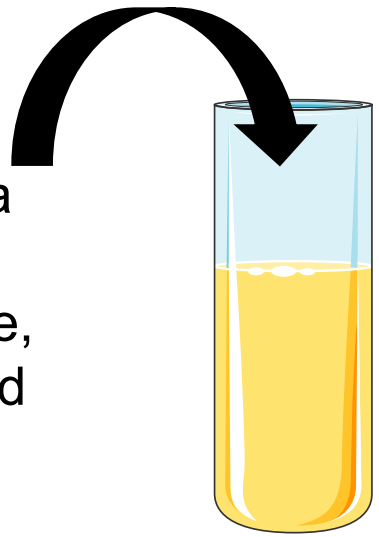
Module: 3

Functional Assays: Clot-Based Assays

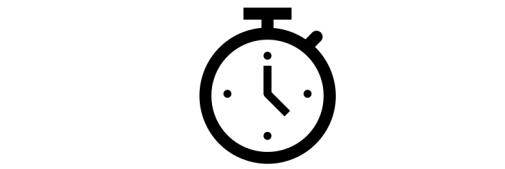
- Good screening assays
- Based on a **functioning coagulation** cascade
- Subject to exogenous and intrinsic interferences

Activated Partial Thromboplastin Time [aPTT]

Platelet Poor Plasma (PPP)
+ Activator (i.e. Celite, Silica) + Phospholipid
+ Incubate



Add Calcium

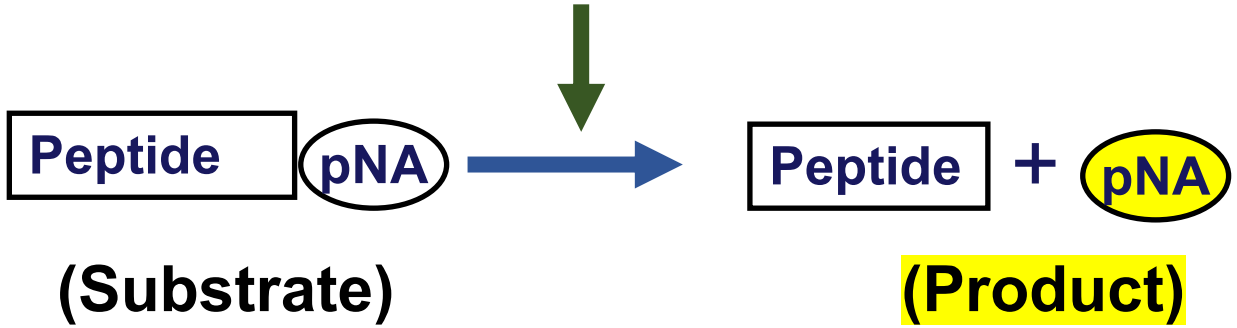


Record Clotting Time

Functional Assays: Chromogenic Assays

Discreet measure of the activity of a **specific enzyme**
Affected by *fewer* preanalytical variables.

Enzyme of interest cleaves substrate



(Substrate)

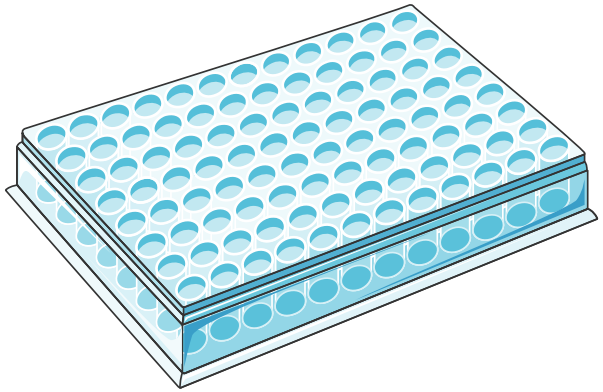
(Product)

Color develops.
Quantify spectrophotometrically
Absorbance correlates with activity

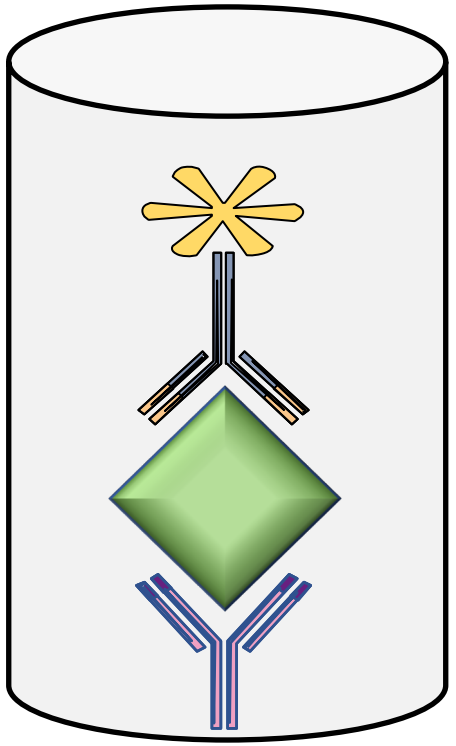
Immunologic Assays

- Latex Induced Agglutination Assays (LIA)
- Enzyme-Linked Immunosorbent Assay (ELISA)
- Measures the amount of protein antigen present rather than function.

Sandwich ELISA



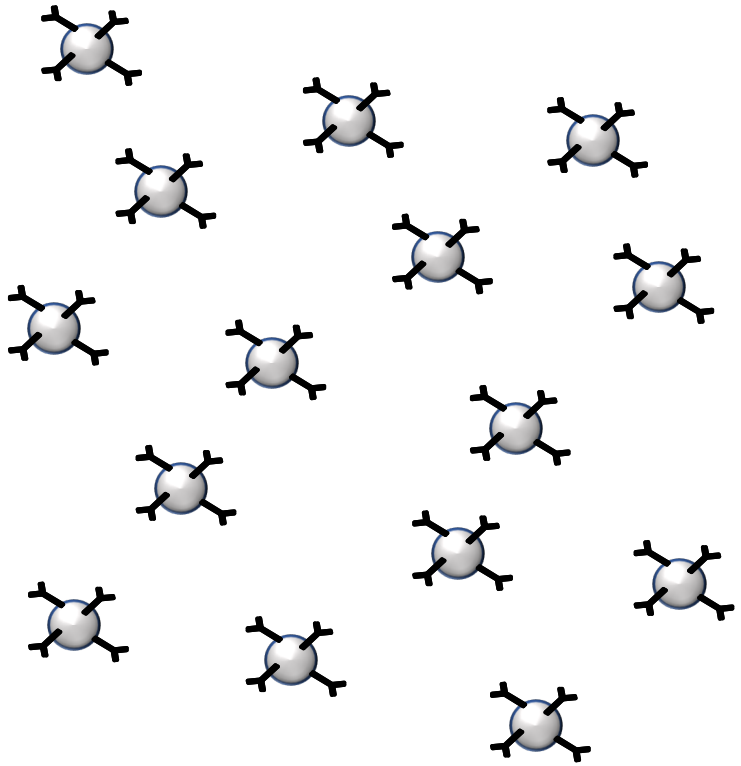
- First antibody captures antigen to surface.
- Second antibody, labelled with enzyme, binds to immobilized antigen.
- Substrate cleaved by conjugated enzyme
- Color development
- Spectrophotometric quantification



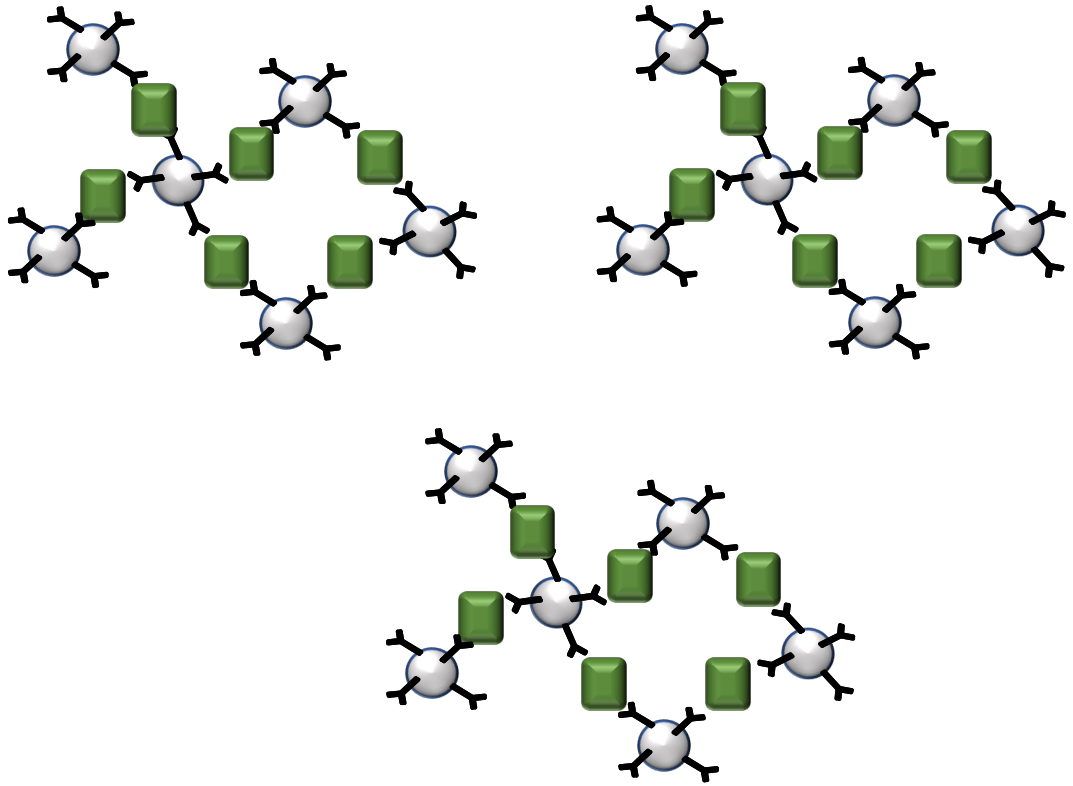
Latex Agglutination

- Antibody coated latex beads
- Agglutination in presence of antigen
- Agglutination is measured optically

Absence/Low Level of Antigen



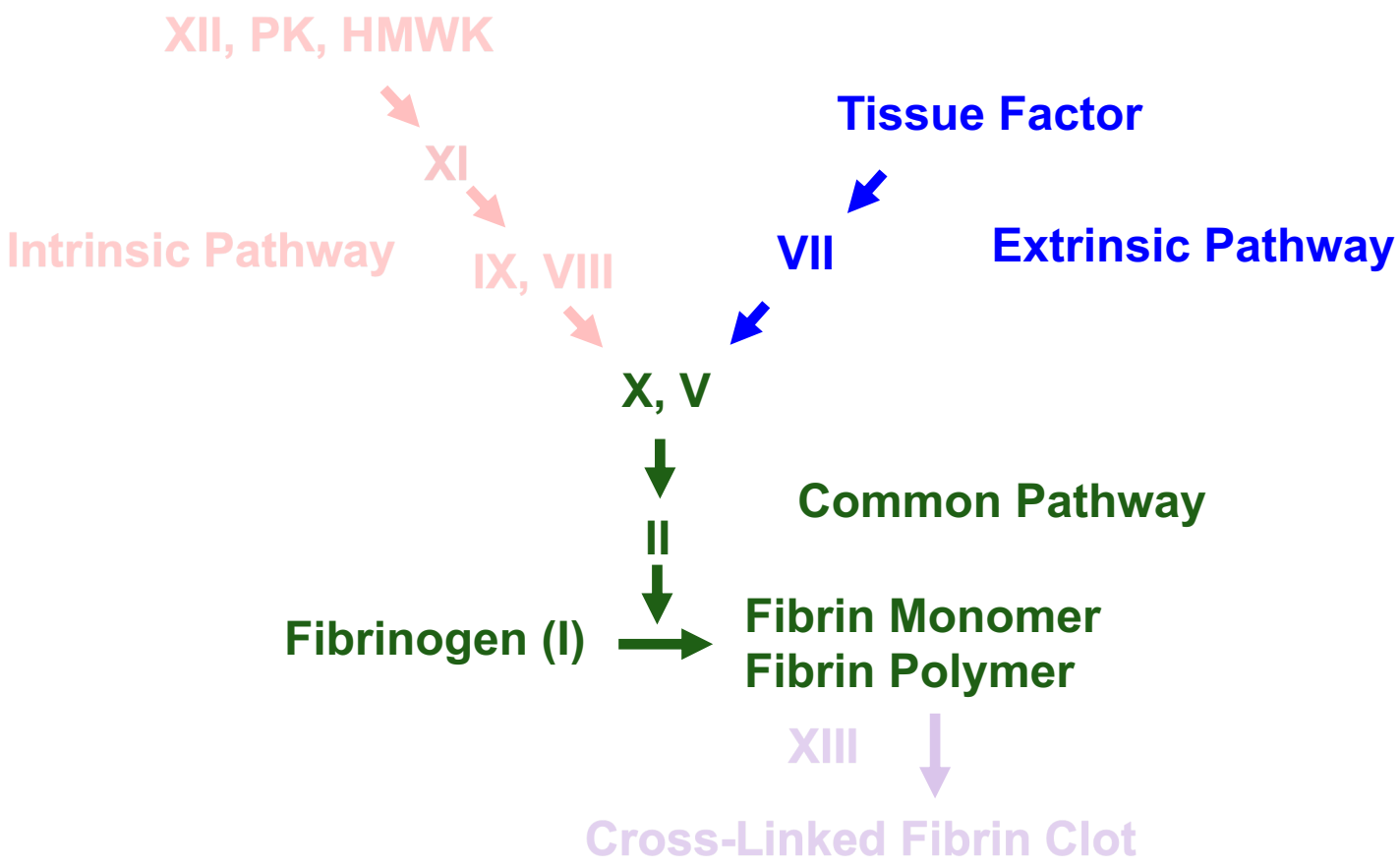
High Level of Antigen



The Prothrombin and Activated Partial Thromboplastin Times

Module: 4

Prothrombin Time

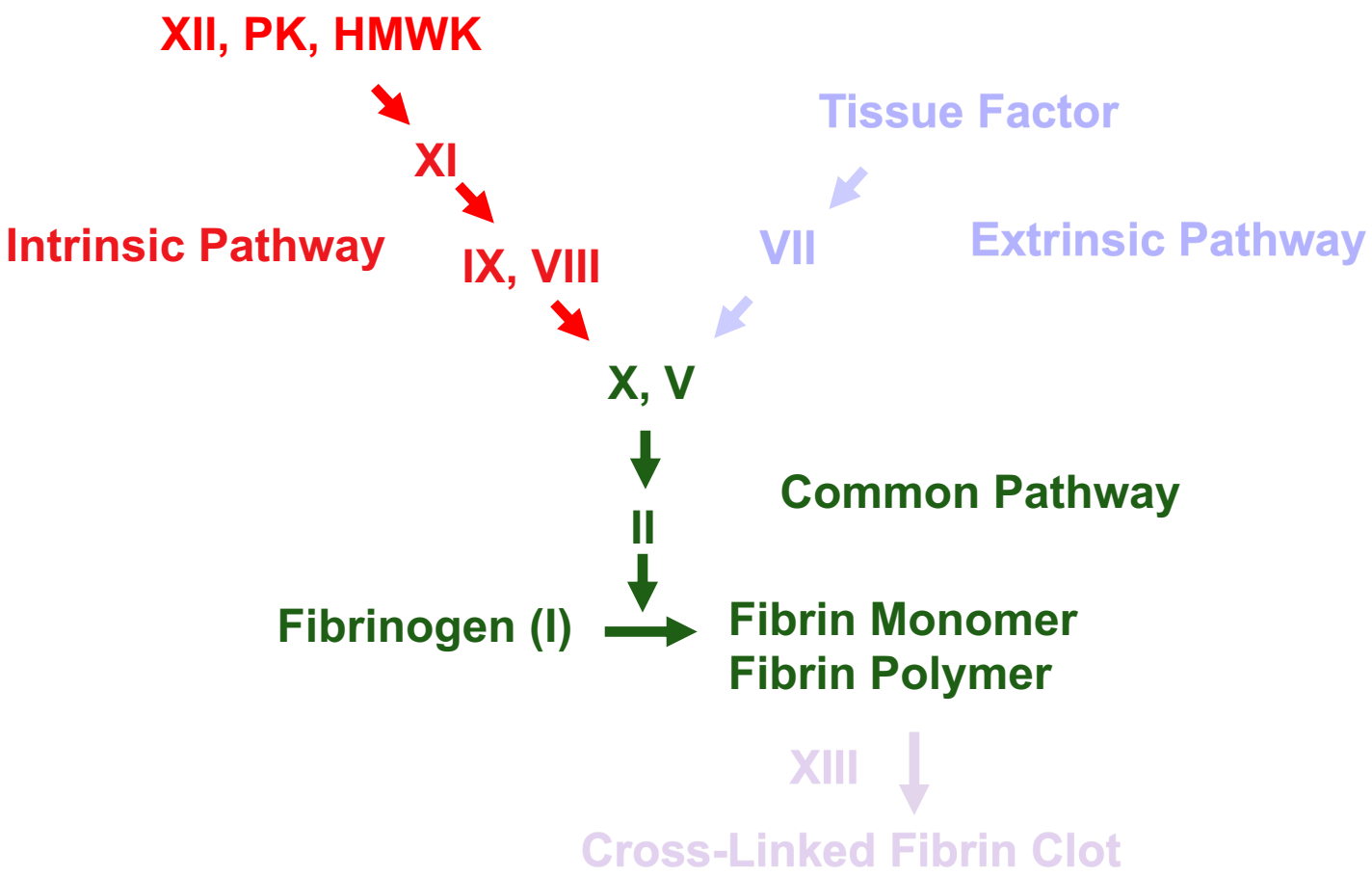


- **Measures:**
  - Factors of the Extrinsic Pathway (VII) and Common Pathway (I, II, V, X)
- **Major Uses:**
  - Hemostasis Screening
  - Monitoring Warfarin Anticoagulation
- **Results:**
  - Reported in Seconds and INR.

INR (International Normalized Ratio)

- INR= International Normalized Ratio
  - (patient PT/mean normal PT)^{ISI}
  - ISI= International Sensitivity Index
- Developed to standardize result reporting, accounting for variation in thromboplastin reagents.
- INR validated for warfarin titration, but practically used in other settings.

Activated Partial Thromboplastin Time (aPTT)



- **Measures:**
  - Factors of the Intrinsic Pathway (XII, PK, HMWK, XI, IX, VIII) and Common Pathway (I, II, V, X)
- **Major Uses:**
  - Hemostasis Screening
  - Monitoring unfractionated heparin therapy.
- **Results:**
  - Reported in Seconds

APTT: Monitoring UFH Therapy

- **APTT reagents are variably sensitive to UFH**
  - Laboratories establish reagent specific therapeutic range
  - Reagent standardization has not been successful
- **APTT response to heparin may be exaggerated by**
  - **Conditions that elevate the APTT:**
    - Concomitant warfarin therapy
    - Lupus anticoagulant
    - Liver disease
- **APTT response to heparin may be blunted by**
  - **Conditions that shorten the APTT:**
    - Cause of *in vitro* drug "resistance"
    - Elevated Factor VIII
    - Antithrombin deficiency
- **Alternative: chromogenic anti Xa assay**

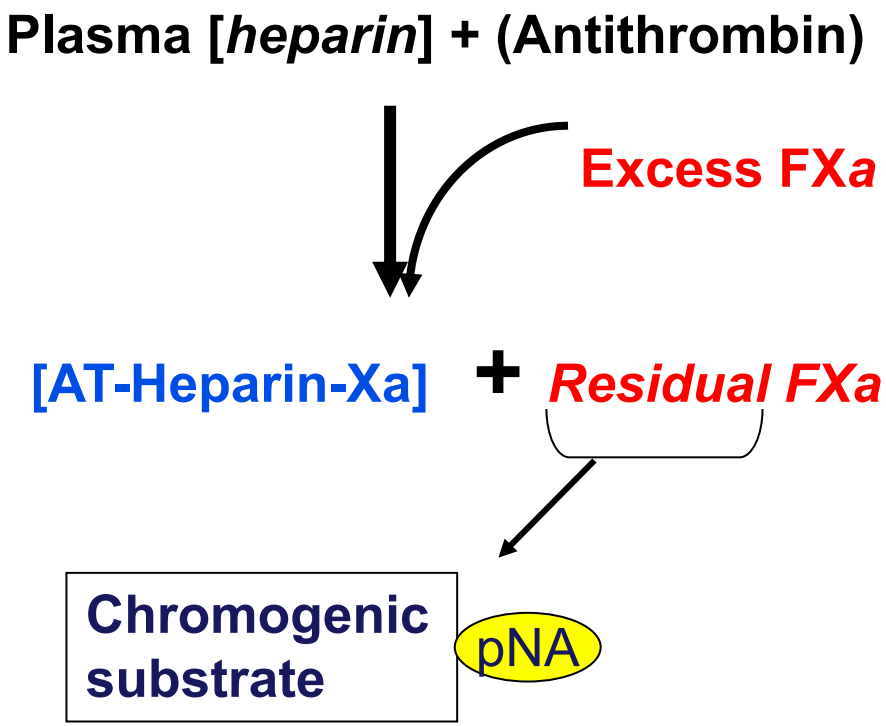
Other Tests:

- Anti-Xa Heparin Assay
- Thrombin Time
- Fibrinogen Assay
- D-Dimer

Module: 5

Anti-Xa Heparin Assay: Monitoring UFH & LMWH

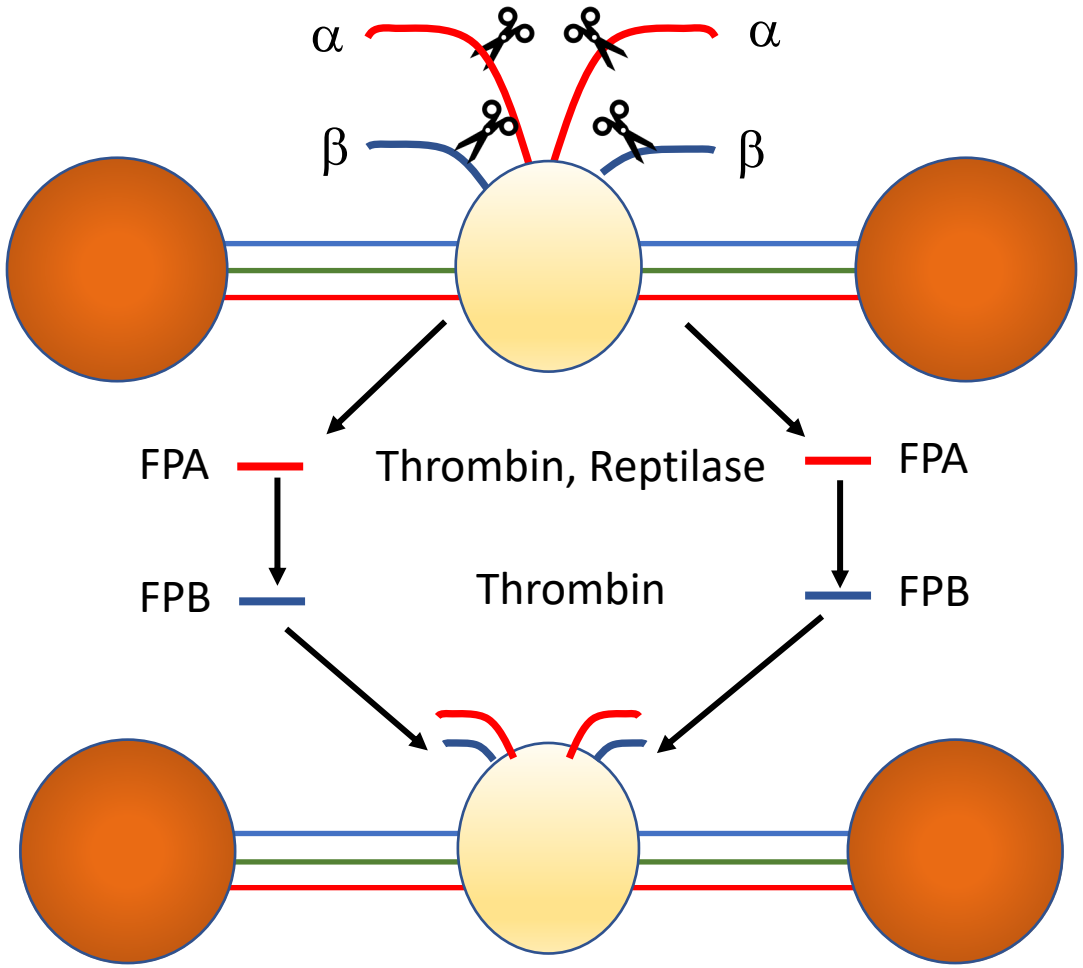
- Specifically determines *anticoagulant activity* of LMWH and UFH by measuring ability of heparin-bound antithrombin to inhibit F Xa
- More specific than aPTT since it measures inhibition of a **single enzyme**
- Major advantage is **lack** of biologic interference
  - Eikelboom JW. Thromb Haemost 2006;96:547-52.
  - Francis JL. Pharmacotherapy 2004;24:108S-19S.



*Color development is **Inversely** proportional to the anticoagulant concentration in the plasma sample*

Thrombin Time:
Evaluates the Conversion of Fibrinogen to Fibrin

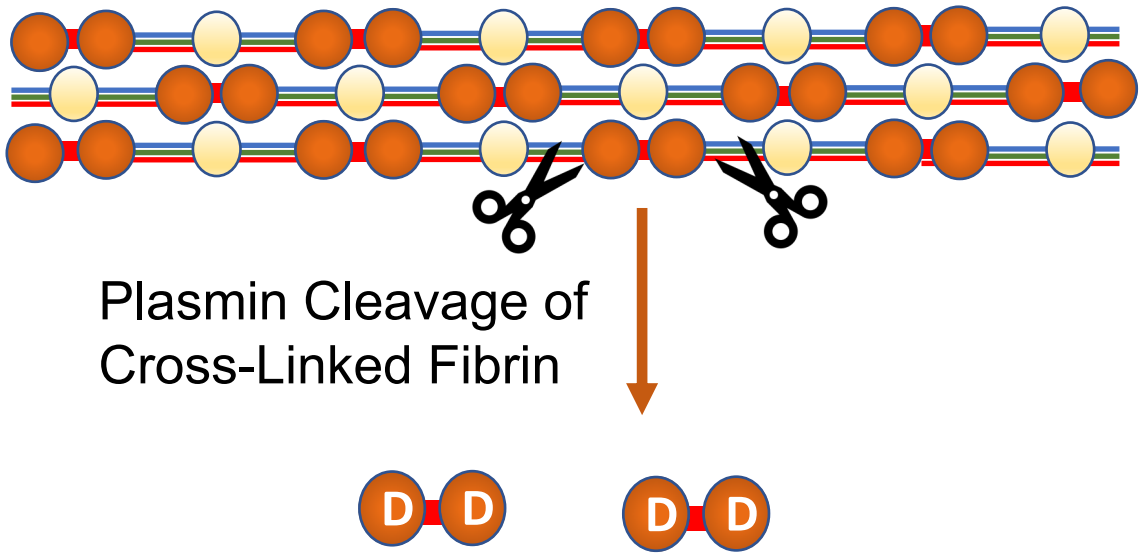
- Dysfibrinogenemia (follow with Reptilase Time)
  - Thrombin: FPA & FPB
  - Reptilase: FPA
  - Need fibrinogen result for interpretation
- Hypo/Dysfibrinogenemia
  - Compare functional fibrinogen with fibrinogen antigen
- Effect of Heparin:
  - Thrombin Time prolonged
  - Reptilase Time not prolonged



Comparison of Thrombin Time with Fibrinogen Assay

- Similar assay conditions and reaction
  - Fibrinogen + thrombin
    - Cleavage of FPA, FPB
  - Fibrin monomers
  - Fibrin monomer polymerization **CLOT**
- Fibrinogen Assay
  - **Diluted Patient plasma** + excess thrombin
- Thrombin Time
  - Patient plasma+ **diluted thrombin** (~1 U/ml)
  - Highly sensitive to UFH and direct thrombin inhibitors (dabigatran, argatroban, bivalirudin)

D-Dimer:
Degradation Product of Crosslinked Fibrin



Quantitation

LIA TEST

- MoAb to D-dimers linked to microbeads
- Agglutination of beads occurs in the presence of D-dimers
- Agglutination is measured optically

Presence indicates activation of both coagulation (thrombin) and fibrinolysis (plasmin).

Utilization of D-Dimer Testing

- DIC
  - Reference Range: <243 ng/ml
- Evaluate for DVT/PE
  - Rule out thrombosis in the outpatient setting in individuals with low suspicion for thrombosis
    - Cut off: <230 ng/ml
      - NPV 100%
      - Specificity 49%
        - Cancer
        - Inflammatory conditions
- Reporting Units:
  - D-Dimer Units (DDU)
  - Fibrinogen Equivalent Units (FEU):
  - Conversion: 1 FEU = 0.5 DDU

Interpretation of Prolonged PT and/or aPTT Results

Module: 6

Interpretation of Prolonged PT and/or aPTT Results

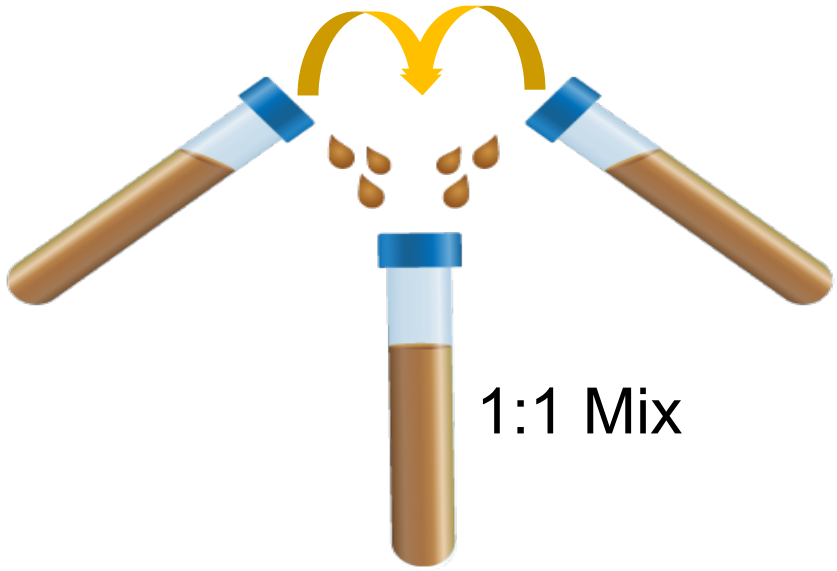
- Factor Deficiency
  - Single vs multiple deficiencies.
  - In general, factor levels must be under 40-50% of normal to prolong the test.
  - Factor XIII deficiency does not prolong PT or aPTT
- Acquired Inhibitors
  - Specific factor inhibitor (i.e. F VIII)
- Global Anticoagulant
  - Lupus Anticoagulant
  - Paraproteins
  - Therapeutic Anticoagulants: UFH, LMWH, Direct Oral Anticoagulants

Sensitivity of PT/aPTT to Factor Deficiencies

Factor	PT	aPTT
I (Fibrinogen)	Yes	Yes
II (Prothrombin)	Yes	Yes
V	Yes	Yes
VII	Yes	No
VIII	No	Yes
IX	No	Yes
X	Yes	Yes
XI	No	Yes
XII	No	Yes
XIII	No	No
Prekallikrein (PK)	No	Yes
High Molecular Weight Kininogen HMWK)	No	Yes

Prolonged PT/APTT Work-Up: Mixing Studies

- Mix patient and normal plasma 1:1
- Perform aPTT and/or PT immediately and after 1-hour incubation at 37°C
- In presence of an inhibitor, the 1:1 mix "fails to correct".
- Specific antibodies require time to bind to the antigen target.
- Common inhibitors: heparin, Lupus Anticoagulant, dysproteins, paraproteins, Fibrin Split Products (DIC), factor-specific antibodies.



Mixing Studies

Factor Deficiency

aPTT	Patient	Normal	1:1
Immediate	51”	29”	33”
1 Hour Incubation @ 37°C	52”	29”	32”

Lupus Anticoagulant: Antiphospholipid Antibody

aPTT	Patient	Normal	1:1
Immediate	51”	29”	48”
1 Hour Incubation @ 37°C	52”	29”	50”

Anti-Factor VIII Antibody

aPTT	Patient	Normal	1:1
Immediate	51”	29”	33”
1 Hour Incubation @ 37°C	52”	29”	50”

Case Study:

- **84 y.o. female with history of atrial fibrillation considered for cardiac ablation**
- Currently on Apixaban
- Known Hemophilia A Carrier
  - F VIII: 47%
  - F IX: 110%
  - F XI: 105%

- Abnormal Coagulation Screening Test Result:
  - **APTT – 110 sec**

Mixing study

aPTT	Patient	Normal (22.5-36.5”)	50/50 mix
Immediate	92.6”	29.4”	60.7”
1 Hour Incubation @ 37°C	104.1”	29.3”	67.5”

Additional Studies:

Thrombin Time: 13.8 sec. (NI: 13-18 sec.)

Apixaban level (Peak): 39 ng/ml. (Peak, therapeutic level, 91-321 ng/mL)

What is the most likely cause of the prolonged APTT

- 1. Apixaban
- 2. Low F VIII
- 3. Lupus anticoagulant

Questions

CME Credit Instructions

Check In to Claim Credit

Option 1: Texting

- Add & save your mobile cell phone # to your **MyCME** Profile
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If you have successfully checked in, you will receive the following message:

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*Claim credits within 90 minutes of scheduled meeting time

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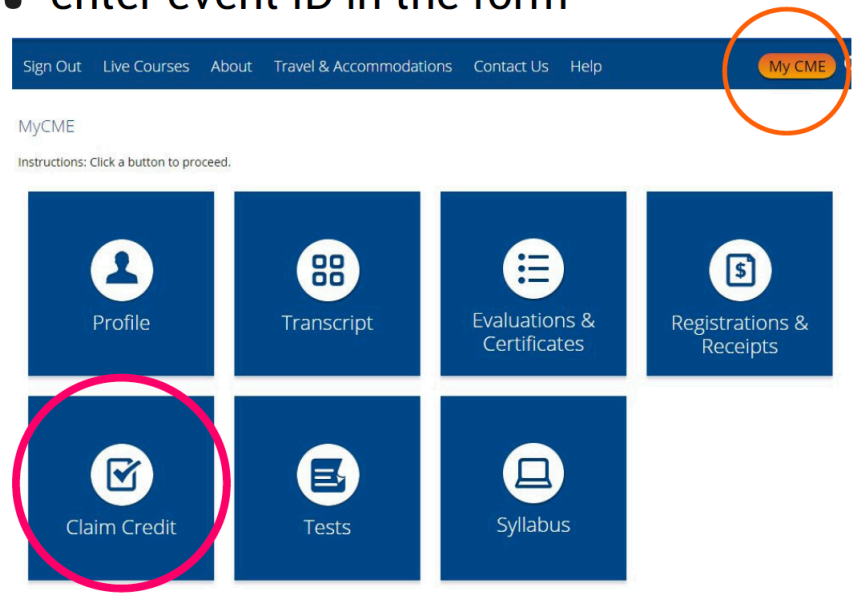

Email cme@mskcc.org for EVENTIDNUMBER

Tests Of Thrombotic Disease

Module: 7

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  - None

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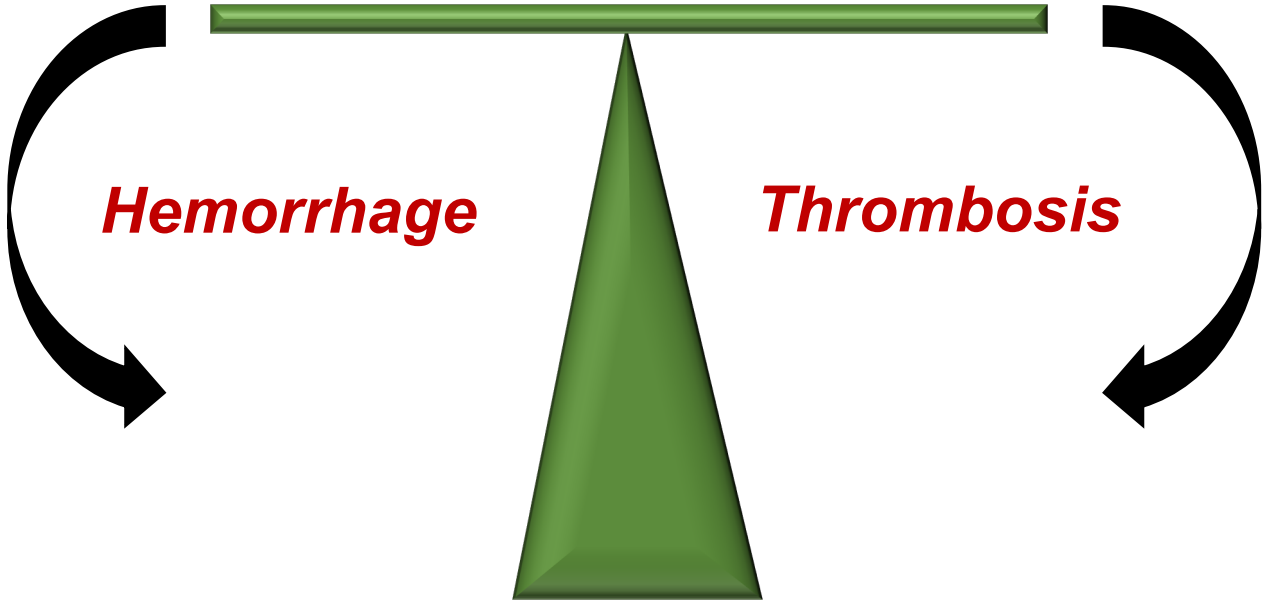
Thrombotic Disease

- Arterial vs venous thrombosis
  - Arterial thrombosis
    - Vascular Damage
    - Platelets
    - No/Limited laboratory tests
  - Venous Thrombosis
    - Stasis
    - Decreased regulation of coagulation
    - Increased procoagulant activity
    - Decreased fibrinolytic activity
    - Laboratory testing available

The Hemostatic Balance

Coagulation Processes

Physiologic Anticoagulation



PT
APTT
Fibrinogen
Thrombin Time
D-dimer
Factor Assays

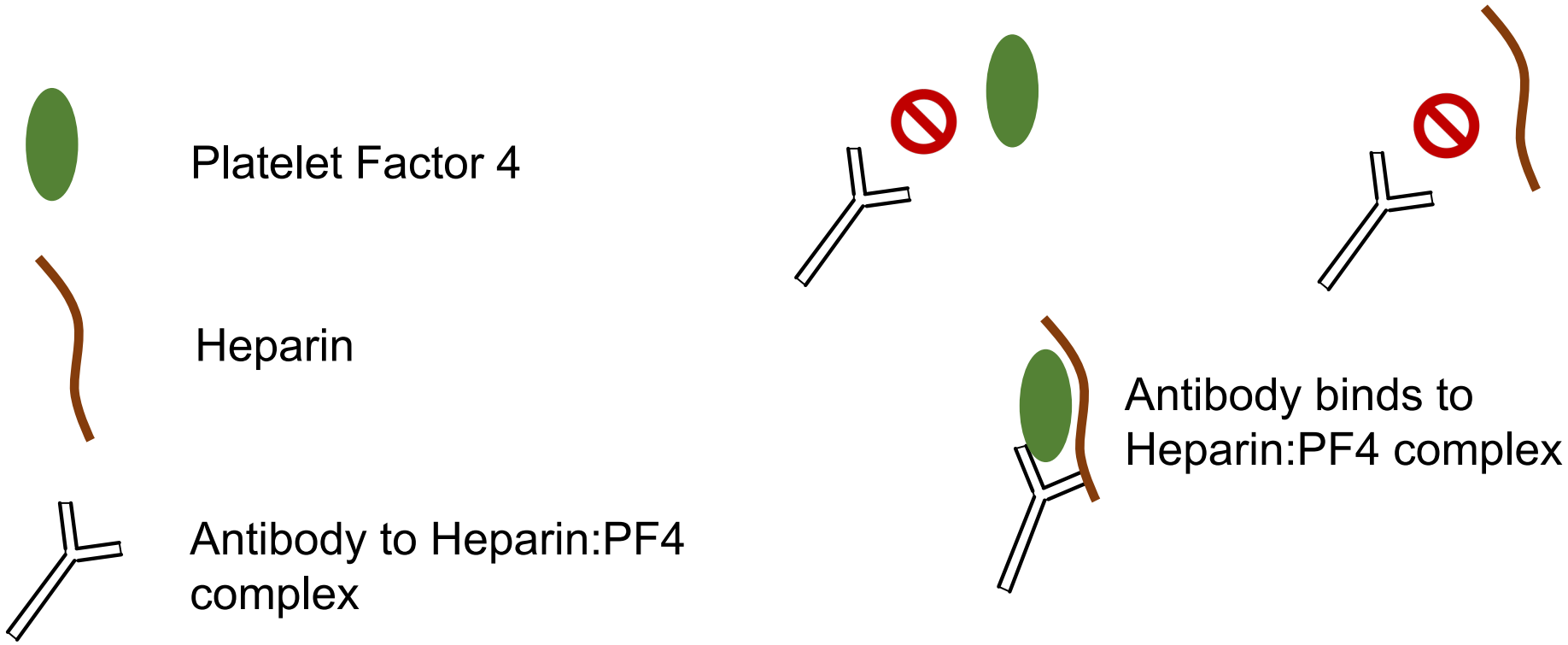
VWD testing

HIT
LA
Protein C
Protein S
AT
FV Leiden
PT G20210A

Heparin Induced Thrombocytopenia/Thrombosis (HITT): Pathophysiology

Module: 8

Heparin Induced Thrombocytopenia/Thrombosis (HITT): Pathophysiology



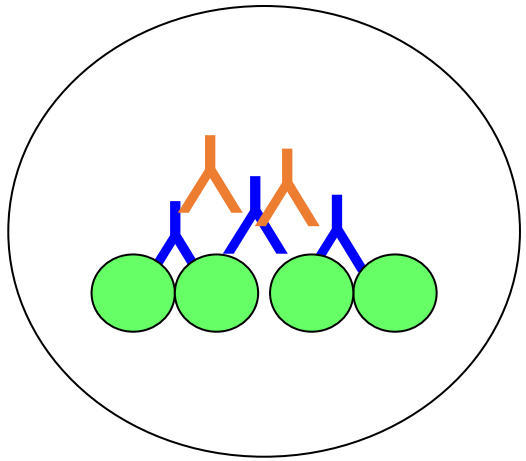
HITT: Antibody:Heparin:PF4 complex associated with arterial, venous, and microvascular thrombosis.

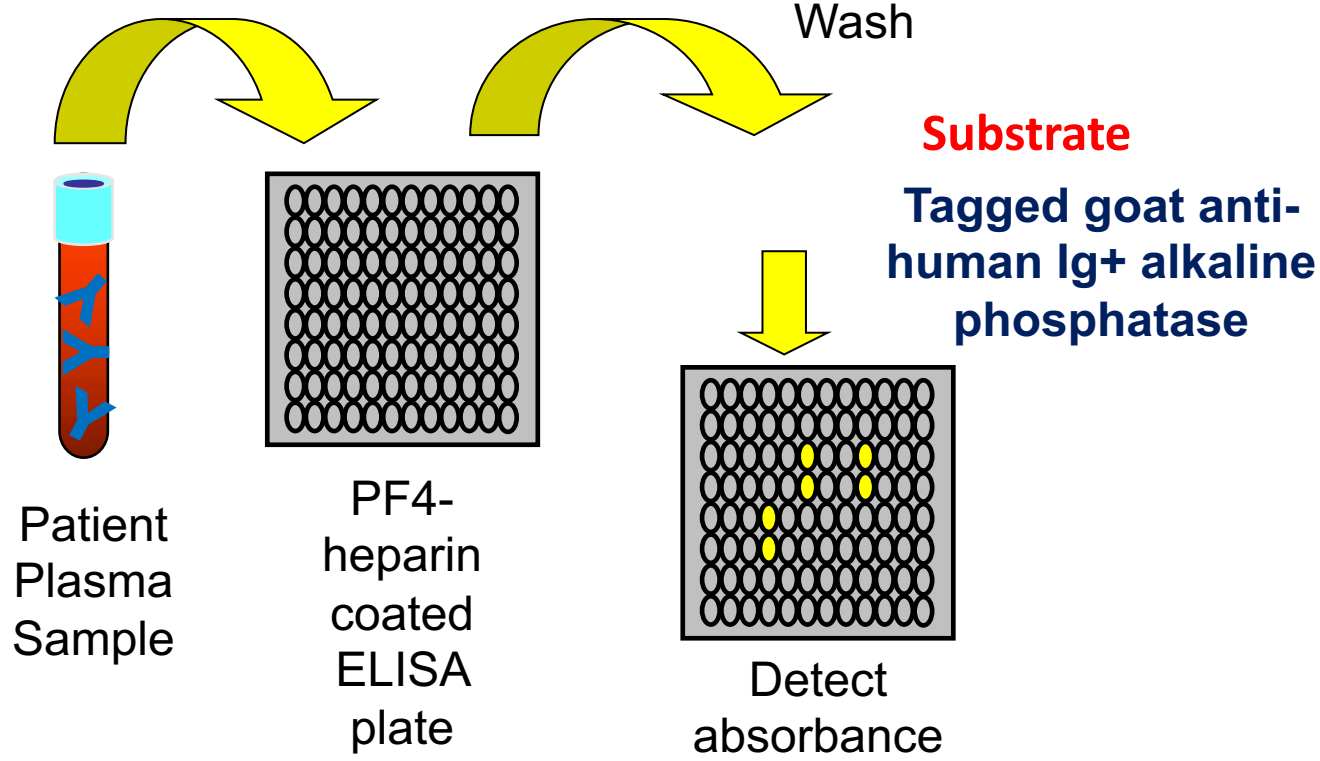
HIT Testing: Screening ELISA

- Antibodies to heparin-PF4 complexes
  - Combined IgG, IgA, IgM titers
  - IgG titer (OD) more specific
- High Negative Predictive Value

ELISA-Based Assay

- Anti-human IgG + AP
- Patient Antibody
- Heparin:PF4 complex





4T Scoring System for Pretest Probability

Points	2	1	0
Thrombocytopenia	>50% fall in PLT or PLT nadir of 20K-100K	30-50% fall in PLT or PLT nadir 10K-19K	<30% fall in PLT or PLT nadir of <10K
Timing	5-10 d post heparin [<1 day if previous heparin within 100 days]	unclear or PLT fall after 10 days	PLT fall <5 days and without recent heparin
Thrombosis	New thrombosis, skin necrosis	Progressive or recurrent thrombosis, some skin lesions e.g. erythema	None
Other causes of Thrombocytopenia	None	Possible	Other causes clearly identified

Score ≤3: < 5% chance of HIT
Score 4-5: Intermediate risk
Score ≥ 6: Very high risk of HIT

Cuker, A. et al Blood 2012, 120(20): 4160–4167.

HIT/T RESULTS

- Negative ELISA screen– HIT unlikely
- Positive ELISA screen- consistent with HIT/T **in the appropriate clinical setting**

Interpretation of HIT Titers In View of Serotonin Assay Confirmatory Results

HIT Titer (OD)	Probability of Serotonin Assay POSITIVITY
< 0.4	0%
0.4 - < 1.00	< 5%
1.00 - < 1.40	~ 20%
1.40 - < 2.00	~50%
>2.00	>90%

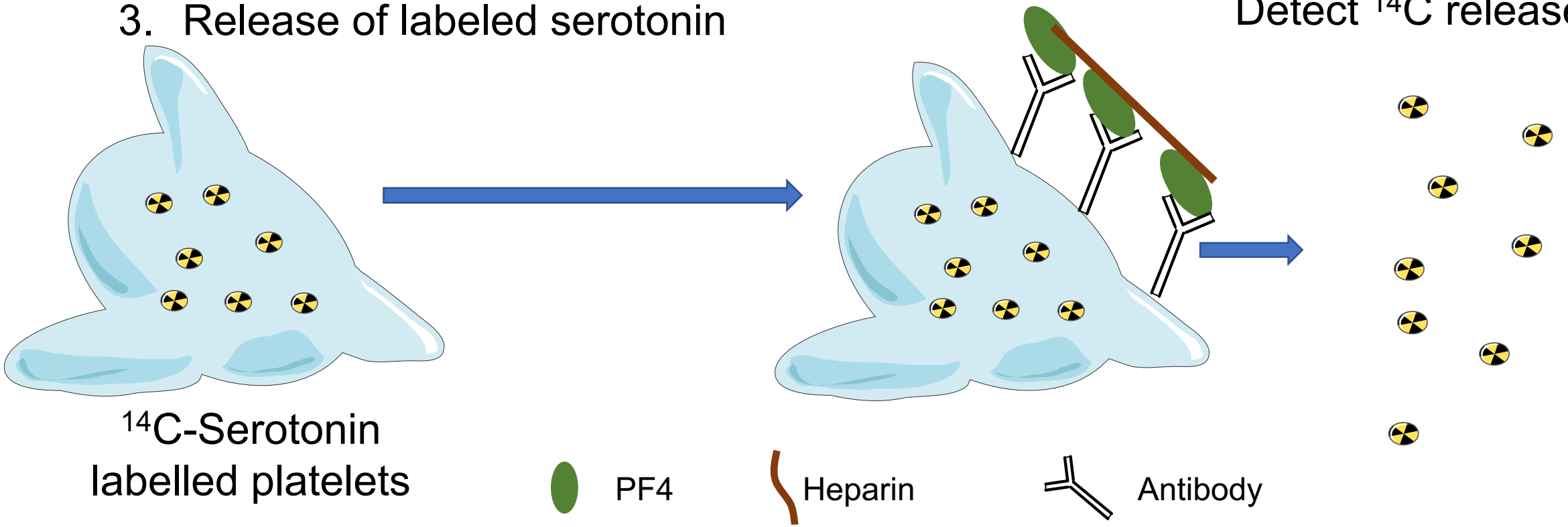
Low titer positive screening test results may not require further work-up

HIT/T Testing: Serotonin Release Assay

Uses fresh platelets, "loaded with ^{14}C-Serotonin" in dense granules.

1. Exposure to Antibody:Heparin:PF 4 Complex.
2. Activation of platelets
3. Release of labeled serotonin

Detect ^{14}C release



Antiphospholipid Antibody Syndrome

Module: 9

Lupus Anticoagulant

- Prevalence of 1-4% in the general population
- A key component of the Antiphospholipid Antibody Syndrome.
- Heterogeneous antibodies against phospholipids and phospholipid binding proteins
- Not usually associated with bleeding
  - Arterial/venous thrombosis
  - Rarely patients may also have antibodies against F II
    - Check PT for prolongation
- **Prolongs Screening APTT**
  - Clinical APTT reagents are variably sensitive to LA
  - Normal APTT does not rule out a LA

Lupus Anticoagulant Insensitive aPTT Reagents

- Used to rule out significant coagulation factor deficiencies
- Used to overcome inhibitory effect of LA on clot-based factor assays
- Normal APTT Actin FS results rule out a significant factor deficiency.

84 y.o. Patient

aPTT	Patient	Normal (22.5-36.5”)	50/50 mix
Immediate	92.6”	29.4”	60.7”
1 Hour Incubation @ 37°C	104.1”	29.3”	67.5”

Additional Studies:

APTT- Actin FS: 32.1 sec

ISTH Guidelines for Lupus Anticoagulant Testing
(Pengo V, et al. J Thromb Haemost 2009; 7: 1737–40)

- Specialized testing is required
- Two tests based on *different principles*
  - dRVVT (activates common pathway)
  - *sensitive* aPTT (low phospholipid and **silica** as activator)
  - A single test will detect only 60 -80% of cases
  - Both tests used together have a 20% false negative rate for low and intermediate titer lupus anticoagulants
- *LA should be considered **positive** if **one** of the two tests gives a positive result*
- False positive rate: ~10%
  - (Dembitzer et al, Am J Clin Pathol 2010; 134:764-773)

Lupus Anticoagulant Testing: dRVVT

- Dilute Russel's Viper Venom enzyme is a phospholipid-dependent procoagulant.
  - Thiagarajan P et al, Blood 1986
- DRVVT TEST RESULT:
  - Ratio SCREEN/CONFIRM
  - Positive: ratio >1.2

Interpretation of Lupus Anticoagulant Testing

- **Interferences**

- DOACs (dabigatran, rivaroxaban, apixaban) even at trough levels produce false positive results in 20-40% of patients.
  - (Ratzinger F, et al. Thromb. & Haemost. 2016; 116:235-240)
- Warfarin may produce false positive DRVVT test results
  - Ortel T. Am J Hematol. 2012 May; 87(Suppl 1): S75–S81.
- Heparin may produce false positive aPTT based test results
  - Ortel T. Am J Hematol. 2012 May; 87(Suppl 1): S75–S81.

Laboratory Testing for Thrombophilia (Hypercoagulable State)

Module: 10

Laboratory Testing for Thrombophilia (Hypercoagulable State)

- No Screening test exists
- Requires a panel of tests
- Diagnosis of an abnormality can be made in ~50% of patients.

1. Antiphospholipid Antibody Syndrome.
    1. Lupus anticoagulant
    2. Anti cardiolipin antibodies
    3. Beta 2 glycoprotein I antibodies
2. Antithrombin (AT)
3. Protein C
4. Protein S
5. F V Leiden
6. Prothrombin G20210A
7. Homocysteine
   (Controversial if should be tested)

Physiologic Anticoagulants

Antithrombin (AT)

- As there is no Antithrombin I or II, it is now commonly referred to as Antithrombin.
- With heparin/heparan as a cofactor, AT inactivates the activated serine protease enzymes of the coagulation system.
- Factors Xa, IXa, XIa, IIa (thrombin), VIIa.

Protein C/Protein S

- Inactivates the activated cofactors of the coagulation system.
- Factors Va, VIIIa
- Activate Protein C also has anti-inflammatory activity.

Antithrombin Assay (Functional)

The assay measures functional AT activity in patient plasma.

AT + Heparin ⟶ **[AT:Heparin] Complex**

[AT:Heparin] + FXa or F IIa (*excess*) ⟶ **[AT-FXa- Heparin] + *FXa or F IIa (residual)***

Chromogenic substrate —*FXa/IIa (residual)*→ **Peptide + *pNA***

Result is inversely proportional to the AT activity in the plasma sample.

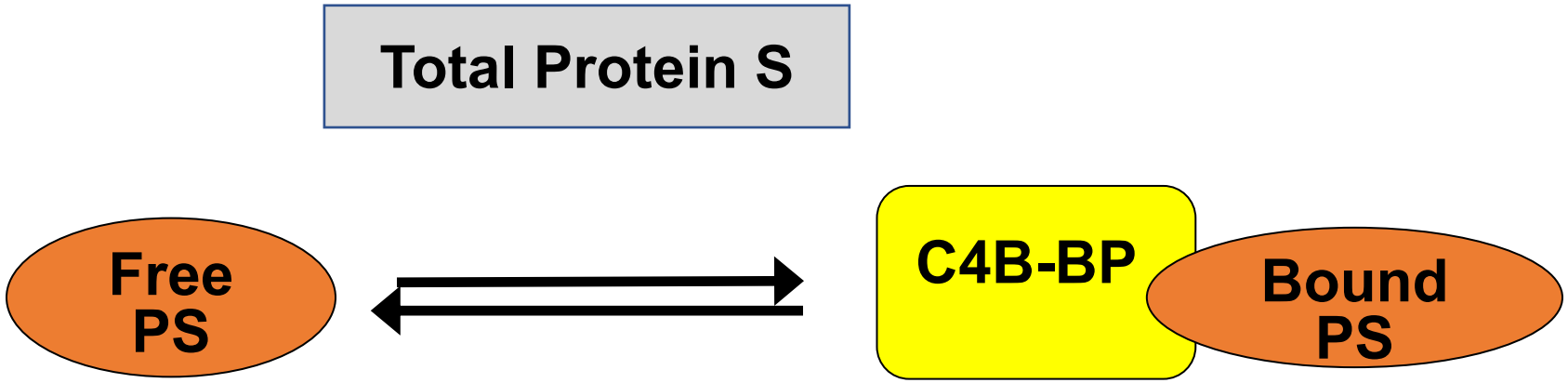
Protein C Assays

Clot-Based Assay (functional)	Chromogenic Assay (functional)
1. Dilute patient's plasma (*1:10*) in PC-deficient plasma 2. Incubate; Add $CaCl_2$ 3. Record time to Clot formation (sec) 4. Prolonged clotting time correlates with PC activity	1. Test Plasma + Venom to activate Protein C Incubate 2. APC + substrate-pNA → release of pNA 3. Hydrolysis of the specific chromogenic substrate correlates with PC activity
Subject to a number of preanalytical variables ➢ FVIII ➢ FVL ➢ Hyperlipidemia → ***Falsely low levels*** ➢ DOAC ➢ Heparin ➢ Lupus Anticoagulant → ***Falsely normal or high results***	➢ Subject to **fewer** preanalytical variables ➢ Detects **most** functional defects but not all

Protein S Circulates in Two Forms

Free Protein S: Active

Protein S to C4b Binding Protein (C4b-BP): Inactive



- Equilibrium between bound and free Protein S.
- Normally, ~60% of total Protein S is bound.
- Increase in C4B-BP reduces levels of free Protein S.

Three Types Protein S Assays

1. **Clot-based functional PS assay—"activity" assay**
    1. Based on APC inactivation of FVa and FVIIIa
2. **Antigenic - Free PS assay (represents functional PS)**
    1. Free PS is adsorbed on the C4BP latex particle → triggers an agglutination reaction with the second latex reagent which is sensitized with a monoclonal antibody directed against human Protein S
    2. The degree of agglutination is directly proportional to the free PS concentration
3. **Antigenic - Total PS assay**
    1. Immunologic assay that measures PS bound to C4BBP + free PS

Three Types of Protein S Deficiencies

Type	PS (Activity)	PS (Free)	PS Total	C4B-BP
I	*Decreased*	*Decreased*	*Decreased*	*Normal*
II	*Decreased*	*Normal*	*Normal*	*Normal*
III	*Decreased*	*Decreased*	*Normal*	*Elevated*

- Type 1 is most common hereditary pattern.
  - (Although hereditary protein S deficiency is rare).
- Type 3 is usually an acquired state.
  - Observed in some inflammatory or reactive states, due to elevated C4B-BP Levels.
  - This contributes to the hypercoagulable state of pregnancy and with use of estrogen containing oral contraceptives.
  - Malm, J et al. British J. Haemat. 1988.

APC-Resistance/Factor V Leiden

Module: 11

APC-Resistance—Screening Assay For Factor V Leiden

- Ratio of aPTTs (**+/-** APC)

$$\frac{\textbf{(aPTT with APC)}}{\textbf{(aPTT without APC)}}$$

- Normal Ratio >2.0

- 90% of APC Resistance is caused by a defect in the Factor V molecule
- **"Screening assay"** for FVL mutation
- Sensitivity and specificity approach 100% with **modified** assay
  - Uses FV-deficient normal plasma + patient plasma

a. Screening assay is affected by
   - Lupus anticoagulant
   - DOAC
b. High FVIII levels may lower APC ratio *(pregnancy/inflammatory states)*
c. Decreased II and X (<50%) may produce higher APC ratios
d. DNA-based assay confirms FVL

Molecular Assays: PCR Assays

Factor V Leiden

- Caused by single point mutation in the FV gene
- Substitution of adenine for guanine at 1691 – G1691A
- Changes arginine to glutamine at 506 – R506Q
- Molecular mechanism of most cases of APC Resistance

F II Polymorphism

- Single nucleotide substitution G20210A in the 3' UT regions of the prothrombin gene
- G → A substitution at nucleotide 20210 in prothrombin gene
- Results in elevated levels of prothrombin (~30% increase)
- No screening test available

Conditions That Impact Tests for Thrombotic Risk Factors

Module: 12

Conditions That Impact Tests for Thrombotic Risk Factors.

- Accelerated Factor Consumption
  - Recent/Acute thrombosis
  - DIC, surgery, trauma
- Reduced Synthesis
  - Liver disease, Vitamin K deficiency
  - Estrogen

- Interference by Anticoagulant Therapy
  - Warfarin
    - Decreased Protein C and S
  - Heparin
    - Decreased AT
  - DOAC
    - False positive lupus anticoagulant
    - False increase in clot-based PC, PS, AT assays
    - False negative APC Resistance ratio

Effects of Anticoagulants on Laboratory Testing

- **Functional Assays**
  - Clot-based assays
    - Dose dependent inhibition/prolongation of coagulation
  - Chromogenic assays
    - Variable effect depending on reaction and substrate
  - **Antigenic assays**
    - ELISA or LIA technologies
    - Not affected
- **DNA-based assays**
  - Not affected by anticoagulant therapy

If/When to Do Hypercoagulable Work-up

Module: 13

Hypercoagulable Work-up

- Why work-up?
  - Avoidance of oral contraceptives
  - Family knowledge
- Growing Consensus in Hematologic Community is to not routinely do hypercoagulable workup.
- Studies fail to show recurrent VTE rates associated with thrombophilia.

Routine Testing for Hereditary Thrombophilias in Patients With a First VTE ?

- "Routine testing for hereditary thrombophilias in patients with a first VTE is not helpful in predicting risk of recurrence or altering initial therapy."

  - Galioto et al, Am Fam Physician. 2011 Feb 1;83(3):293-300
  - Christiansen et al . JAMA. 2005;293(19):2352–2361.
  - Kearon et al. Chest. 2008;134(4):892]. Chest. 2008;133(6 suppl):454S–545S.
  - Baglin T et al Lancet. 2003;362(9383):523–526.
  - Ho et al. Arch Intern Med. 2006;166(7):729–736.
  - Segal JB et al. Evid Rep Technol Assess. 2009(180):1–162.

Questions?

CME Credit Instructions

Check In to Claim Credit

Option 1: Texting

- Add & save your mobile cell phone # to your **MyCME** Profile
- **Text EVENTIDNUMBER to 646-681-7499**

If you have successfully checked in, you will receive the following message:

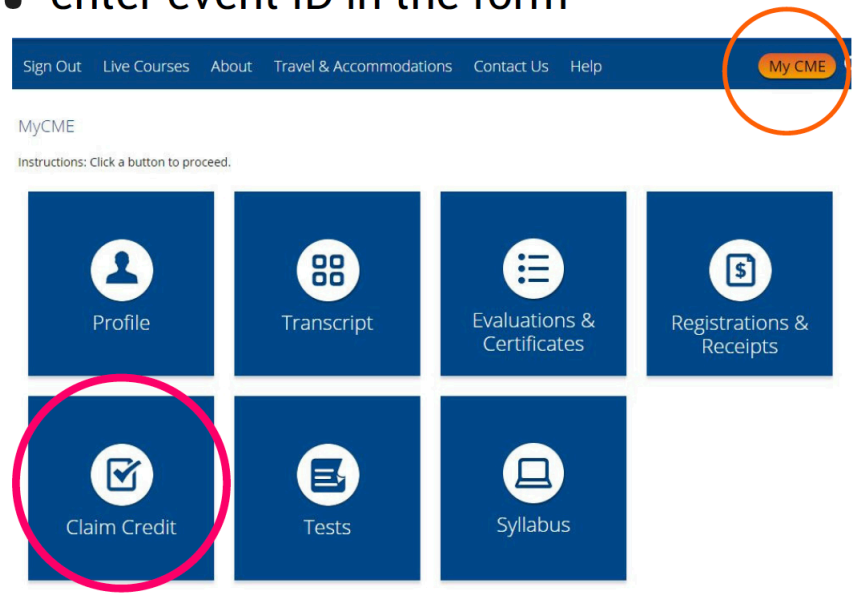
Thank you, we have recorded your attendance.

Option 2: Claim Credit on the Portal

*Claim credits within 90 minutes of scheduled meeting time

or

- Sign in to your account at **www.mskcc.org/cmeportal**
- Click **My CME**
- then click **Claim Credit**
- enter event ID in the form



Email cme@mskcc.org for EVENTIDNUMBER