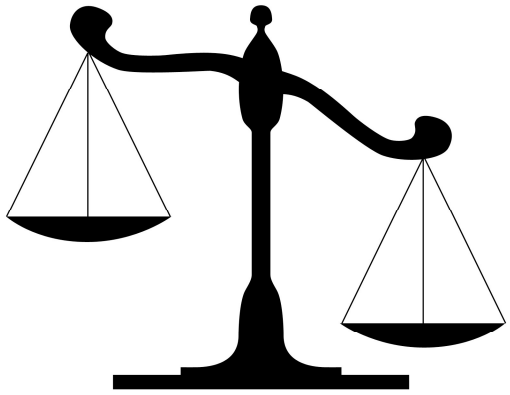
VWF-related pathologies

+

Thrombotic Thrombocytopenic Purpura (TTP)

VWF



-

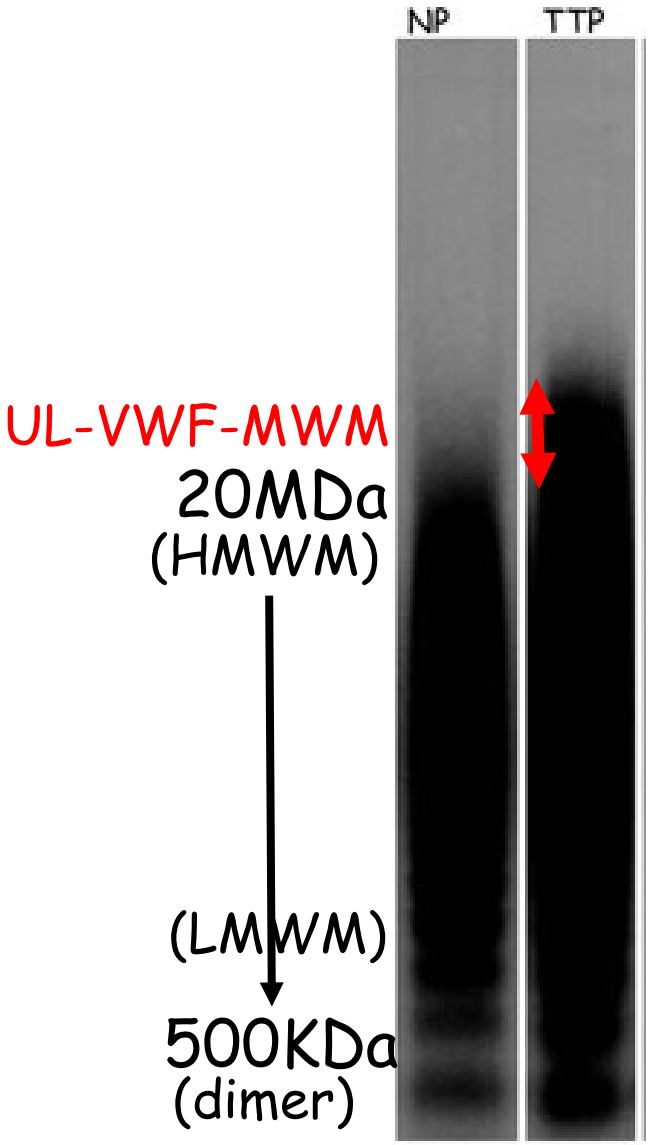
von Willebrand Disease (VWD)

Thrombosis **Haemostasis** **Bleeding**

TTP summary

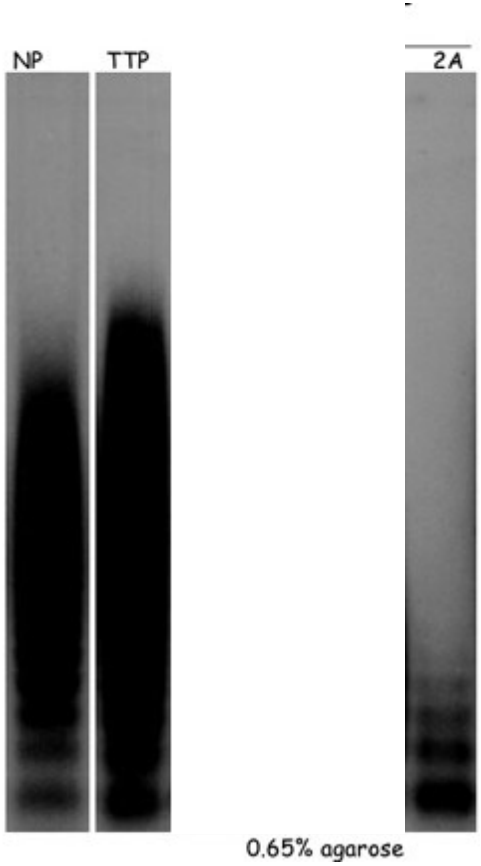
- Systemic disorder characterized by inappropriate deposition of VWF and platelet rich thrombi throughout the microvasculature, thrombocytopenia, microangiopathic hemolitic anemia, organ failure and death
- Presence of Ultra-large (UL)-VWF-MWMs in plasma
- TTP results from the deficiency of the metalloprotease ADMTS13 that cleaves circulating VWF
- **Rare inherited TTP**
- **More frequent acquired TTP** >
  inhibitory anti-ADMTS13 autoantibodies

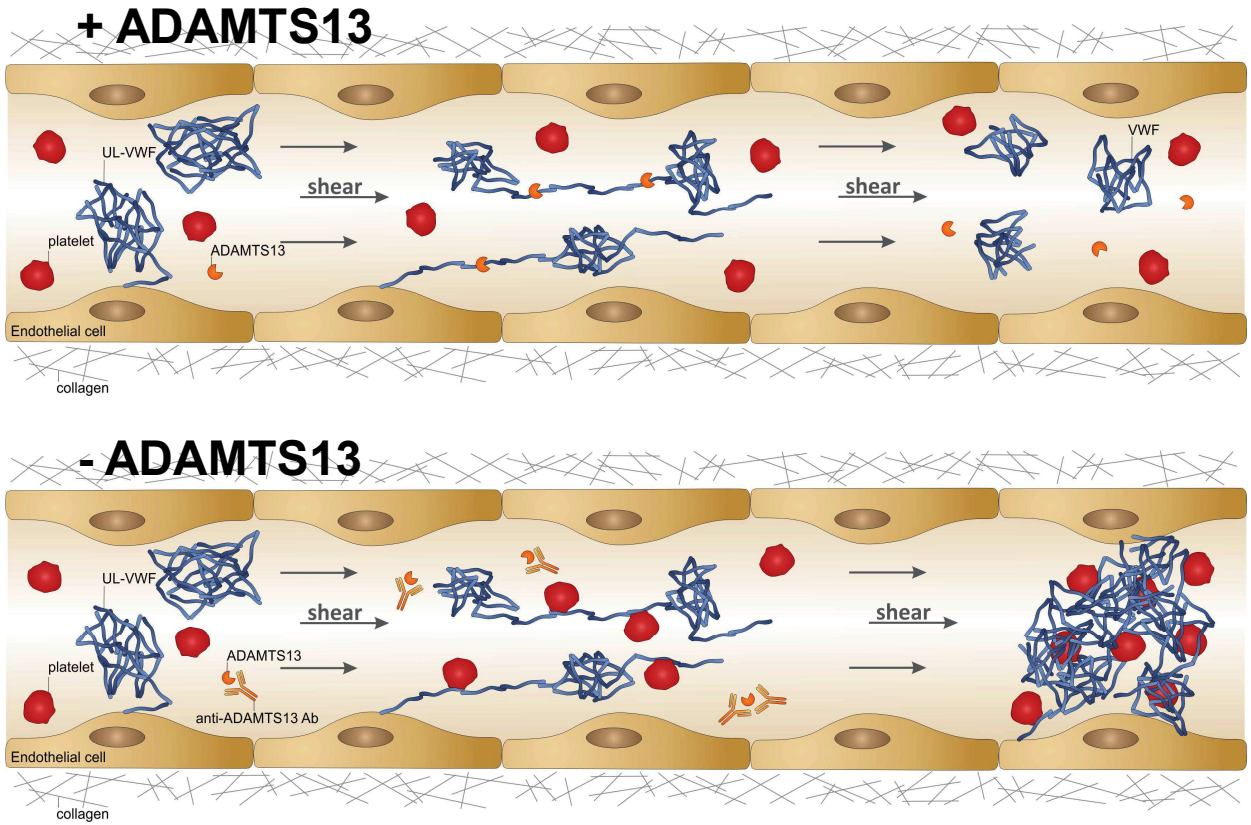
- Presence of Ultra-large (UL)-VWF-MWMs in plasma



ADAMTS13

- ADAMTS13 deficiency > TTP > UL-VWF-MWMs
- ADAMTS13 hyper-activicty (mutations in VWF that result in increased susceptibility to ADAMTS13 cleavage) > VWD-type 2A > absence of HMWMs and increased satellite bands





VWF-related pathologies
Thrombotic Thrombocytopenic Purpura (TTP)

- Systemic disorder characterized by inappropriate deposition of VWF and platelet rich thrombi throughout the microvasculature, thrombocytopenia, organ failure and death
- Presence of Ultra-large (UL)-VWF-MWMs in plasma

VWF-related pathologies
von Willebrand Disease (VWD)

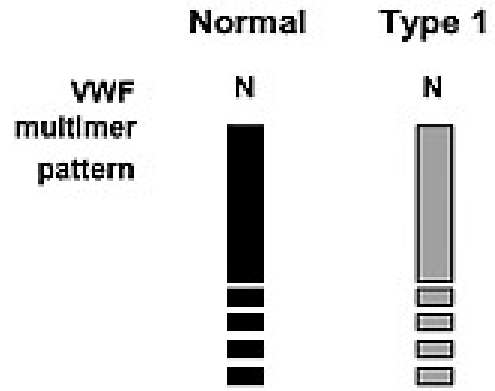
- One of the most frequent inherited bleeding disorder (prevalence of patients with clinically significant bleeding 1:10.000)
- More than 300 mutations
- Extremely heterogeneous > many different **types** have been described based on specific phenotypes
- VWD-type 1 > Quantitative deficiency
- VWD-type 2 > Qualitative deficiency
- VWD-type 3 > Absence of VWF

VWF-related pathologies
von Willebrand Disease (VWD)

- Type 1 & 2 generally inherited in an autosomal-dominant pattern
- Type 3 inherited in an autosomal-recessive pattern

von Willebrand Disease type 1

- VWD type 1 is the most common form of VWD. It affects 80% of all individuals diagnosed with VWD and is traditionally characterized by reduction of functionally normal VWF in the presence of mucocutaneous bleeding.
- Several mechanisms have been shown to cause low VWF levels mostly related to decreased cellular secretion of VWF, including mutations that affect gene expression, protein trafficking, or mild increases in VWF clearance.
- Low amount of circulating VWF but normal multimer distribution



von Willebrand Disease type 1

- The ability to identify a causative mutation in patients with VWD, particularly with type 1, is sometimes difficult:
  - Because mild bleeding is common in the general population
  - And many individuals will have low to borderline levels

- To increase the complexity there are many patients, particularly with VWD type 1, for whom there is no causative mutation identified and **genetic modifiers** outside of the *VWF* gene may play significant roles in the modulation of VWF quantity, function, and multimer status.

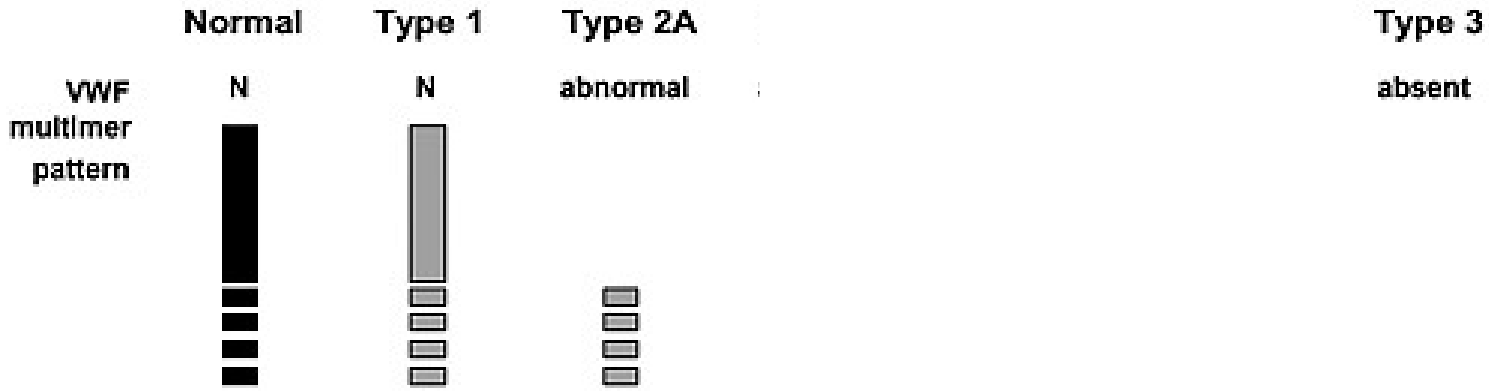
  > Therefore, a significant number of patients diagnosed with VWD type 1 may have a complex genetic disorder in which 1 gene coupled with environmental stressors is responsible for the phenotype

von Willebrand Disease type 3

- VWD type 3 is a severe deficiency of VWF and leads to low FVIII levels.
- The bleeding pattern of these patients is severe and can mimic hemophilia

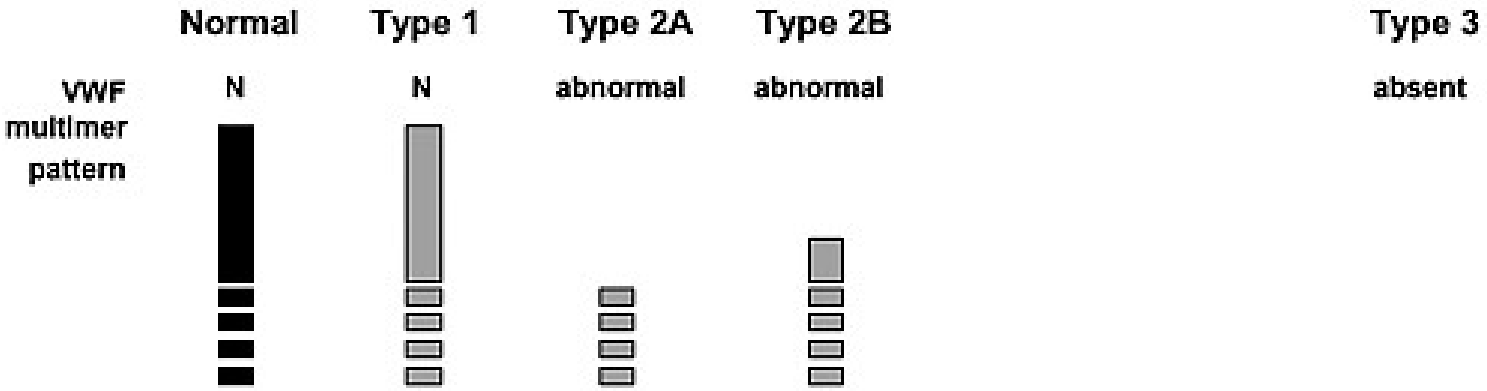
von Willebrand Disease type 2

- VWD type 2 is characterized by qualitative defect in VWF
- The specific subtypes are due to mutations in VWF gene that cause abnormalities in the interaction of VWF with its ligands leading to functional defects.
- VWD type 2A is the most common form of type 2. Loss of intermediate and high molecular weight VWF multimers. Due to abnormal synthesis or packaging of VWF or increased susceptibility to ADAMTS13.



von Willebrand Disease type 2

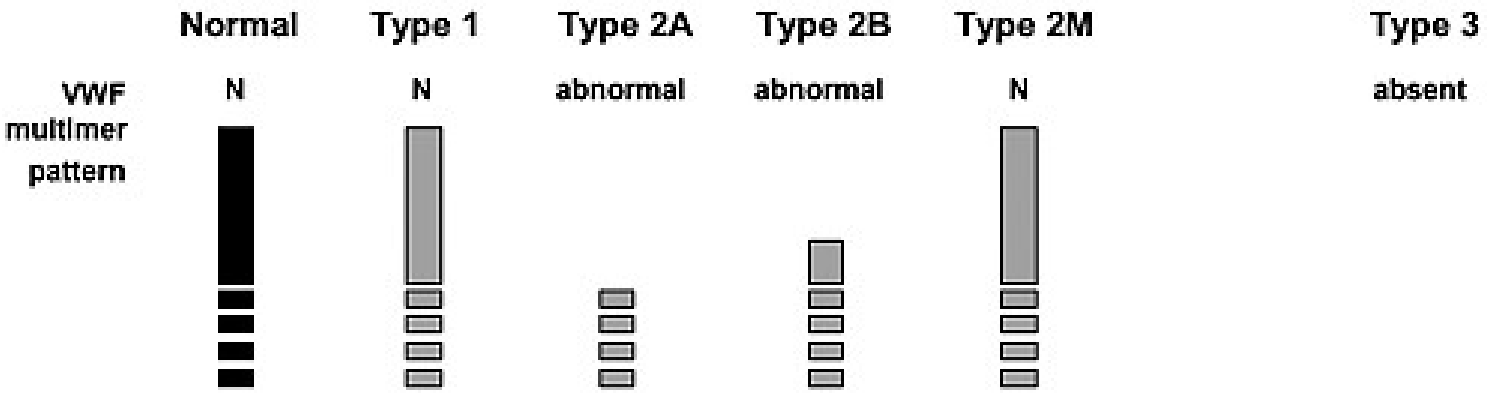
- VWD type 2B is due to increased VWF-platelet GPIb binding because of gain-of-function mutations in *VWF* gene. Platelets aggregates form in circulation and are rapidly cleared. Decreased VWF levels, Loss of HMWM and often but not always thrombocytopenia.



von Willebrand Disease type 2

- VWD type 2B is due to increased VWF-platelet GPIb binding because of gain-of-function mutations in *VWF* gene. Platelets aggregates form in circulation and are rapidly cleared. Decreased VWF levels, Loss of HMWM and often but not always thrombocytopenia.

- VWD type 2M is due to mutations that cause decreased interaction between VWF and platelet GPIb. Multimer distribution is normal but they are dysfunctional because they cannot bind platelet properly.

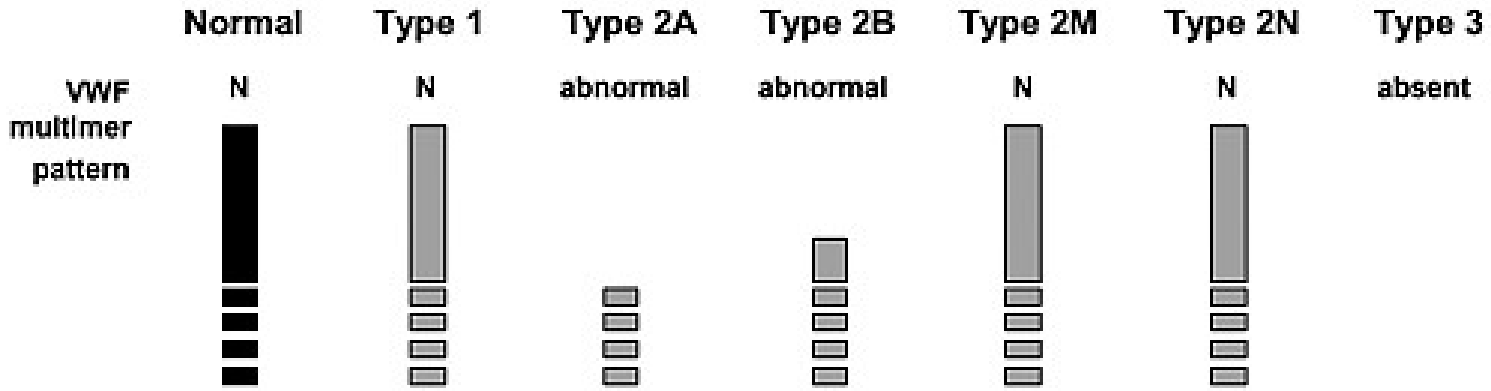


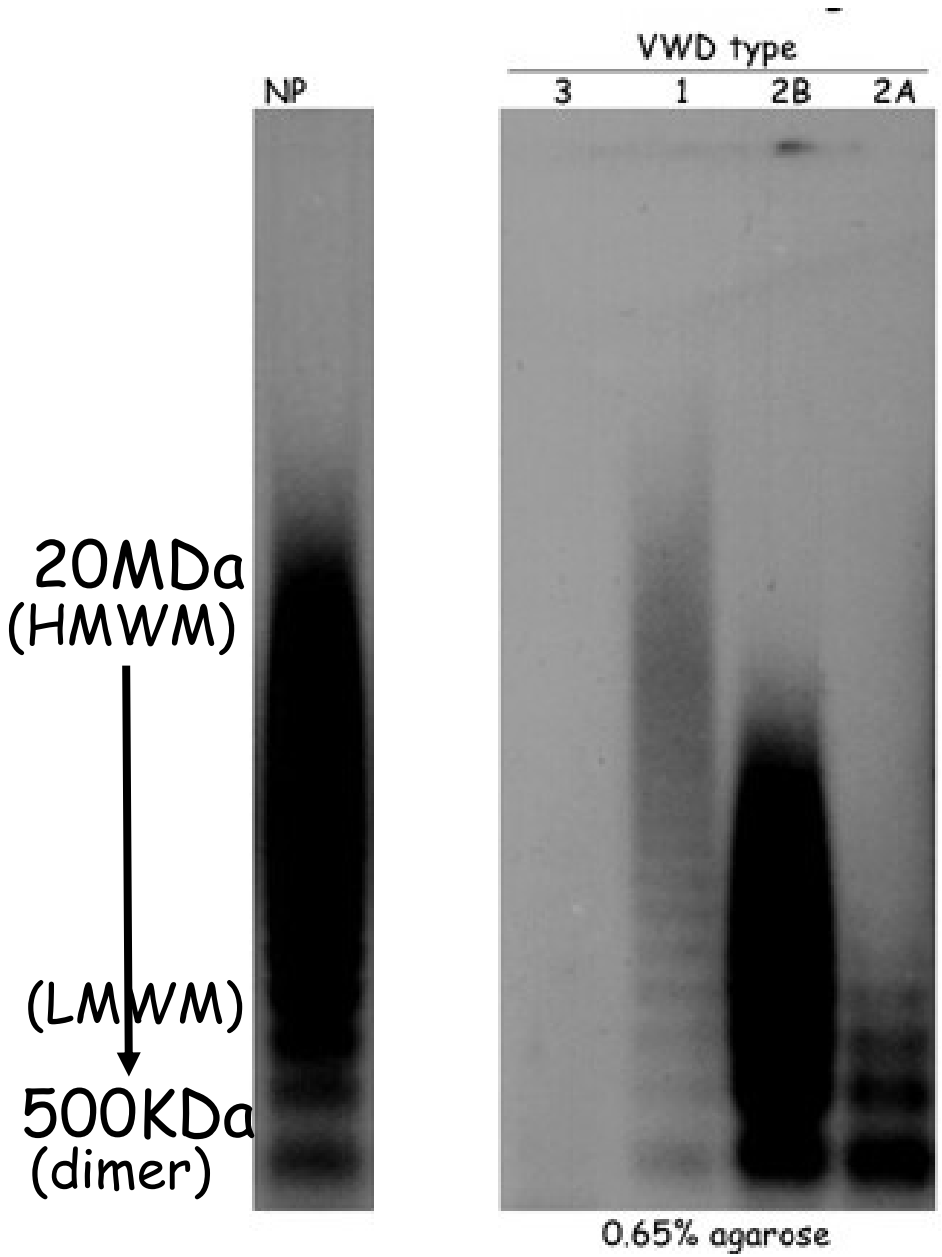
von Willebrand Disease type 2

- VWD type 2B is due to increased VWF-platelet GPIb binding because of gain-of-function mutations in *VWF* gene. Platelets aggregates form in circulation and are rapidly cleared. Decreased VWF levels, Loss of HMWM and often but not always thrombocytopenia.

- VWD type 2M is due to mutations that cause decreased interaction between VWF and platelet GPIb. Multimer distribution is normal but they are dysfunctional because they cannot bind platelet properly.

- VWD type 2N is a rare disorder and result from the inability of VWF to bind FVIII leading to accelerated FVIII clearance. Normally due to mutations in the D'D3 domains (FVIII binding region)




VWD type
NP
3
1
2B
2A
20MDa
(HMWM)
(LMWM)
500KDa
(dimer)
0.65% agarose

The acquired von Willebrand syndrome (AVWS)

- Bleeding disorder misdiagnosed as von Willebrand disease.
- AVWS is characterized by structural or functional defects of von Willebrand factor (VWF)
- Secondary to autoimmune, lymphoproliferative or myeloproliferative, malignant, cardiovascular, or other disorders
- VWF abnormalities in these disorders can result from antibody-mediated clearance

1. functional interference,
2. adsorption to surfaces of transformed cells or platelets
3. increased shear stress and subsequent proteolysis.

"Basi molecolari delle alterazioni del fattore di von Willebrand nelle neoplasie mieloproliferative

- SEMINARIO
- RELATORE:
-
- **Prof. Raimondo De Cristofaro**
- Università Cattolica S. Cuore - Roma
-
-
- **Martedì 7 Maggio 2019 – ore 9.30**
- AULA C3, Palazzo Manfredini