Endothelium and Cancer
Mechanisms and Implications

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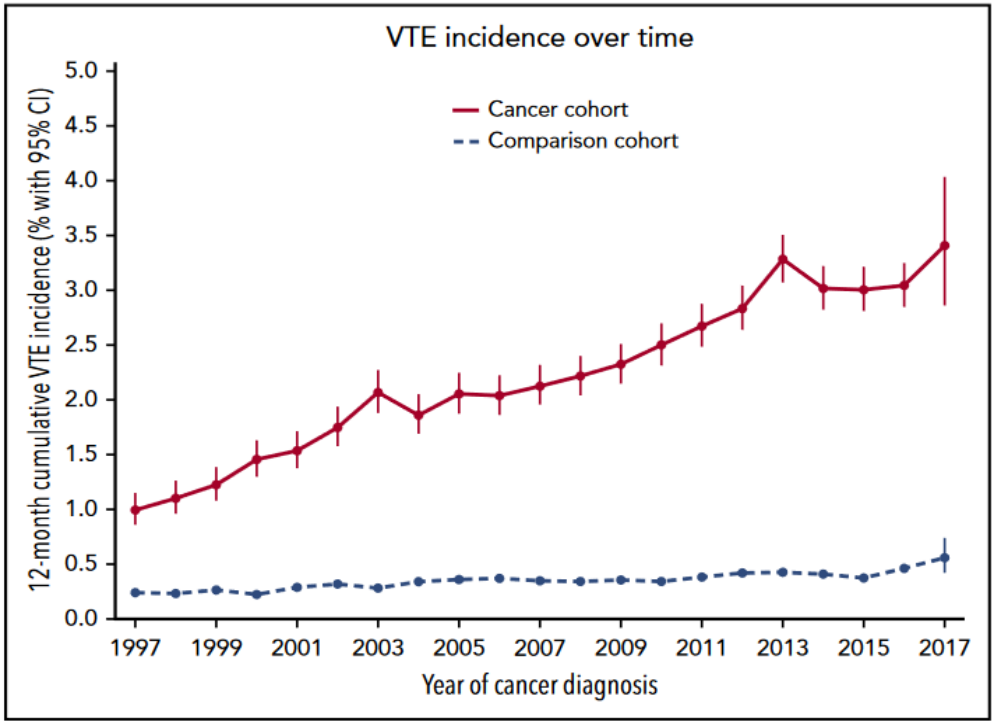
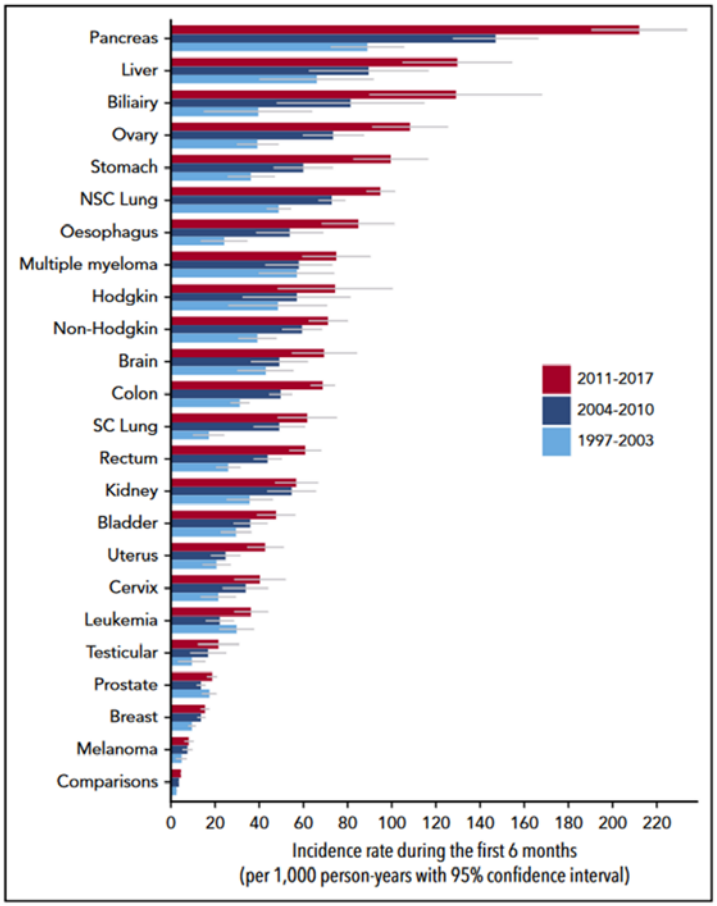
VTE Incidence over 20 years



Twelve months cumulative incidence of VTE in the cancer and comparison cohorts between 1997 and 2017



Danish medical registries were used to identify 499 092 patients with a first-time cancer diagnosis between 1997 and 2017, who were matched to 1 497 276 comparison individuals without cancer from the general population

Mulder Blood 2021

Risk of ATE in Cancer Patients

279,919 pairs of patients with cancer and matched controls

	Cancer	Controls
ATE (6m)	4.7%	2.2%
MI	2.0%	0.7%
Stroke	3.0%	1.6%

Excess risk correlated with cancer stage

Navi JACC 2017

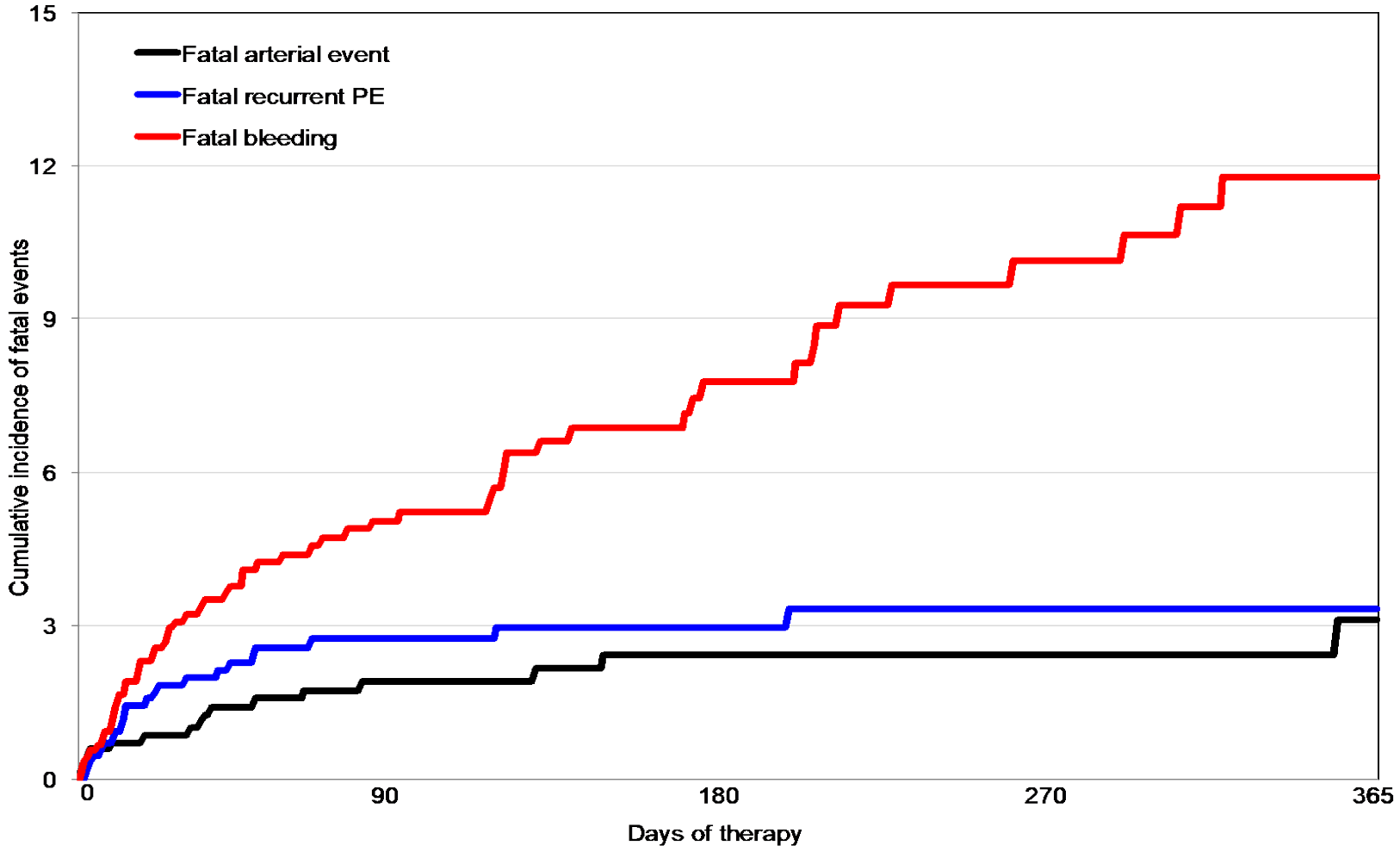
Hematological Cancers: Risk of TE and Bleeding Outcome

- Danish population- based cohort study (2000-2013) 32141 hematological cancers adult patients; each patient was matched with up to 5 controls.
- 10 years absolute risk for Thrombo-embolism or Bleeding complications – 19%
- VTE – 5.2%; MI – 3.3% ; Ischemic Stroke – 5.2%; Bleeding- 8.5%
- Hazard ratios compared to general population

MI-	1.36 (1.25-1.49)
Stroke –	1.22 (1.12-1.33)
VTE –	3.37 (3.13-3.64)
Bleeding –	2.39 (2.26-2.53)

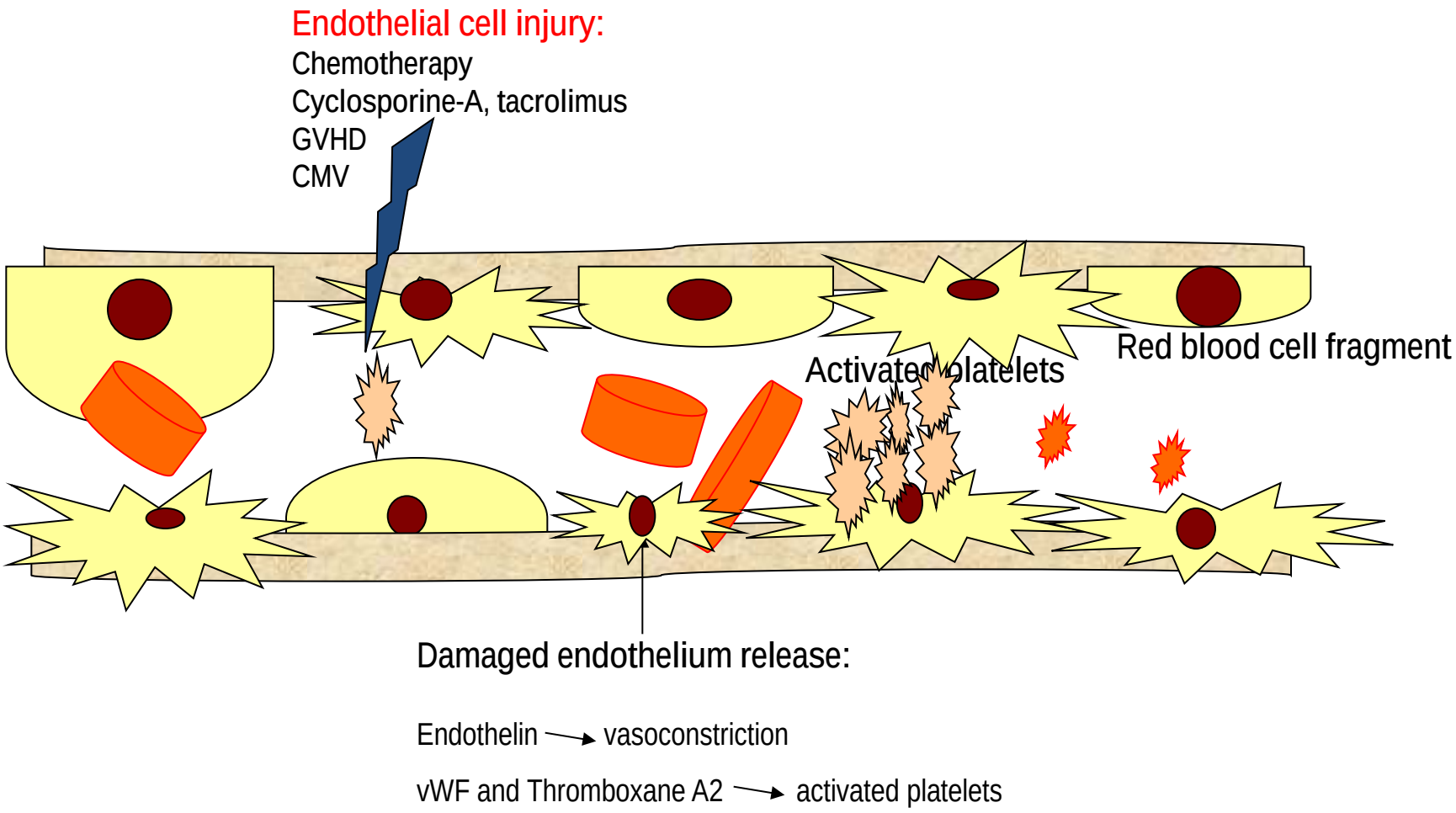
Adelborg JTH, 2019

Cumulative Mortality in Patients with VTE and Active Cancer (RIETE)



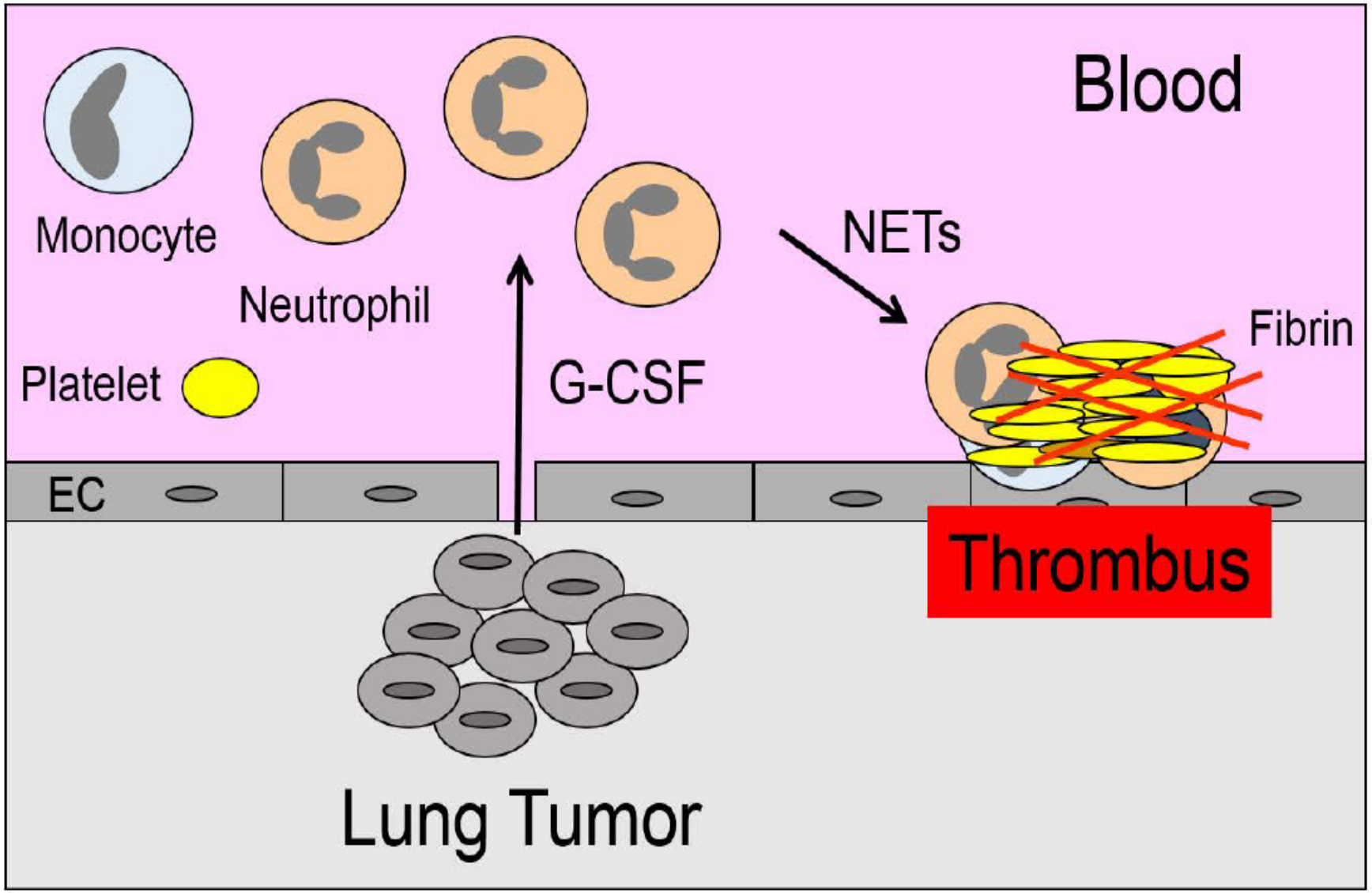
Brenner Am J Med 2018

Cancer Associated TMA



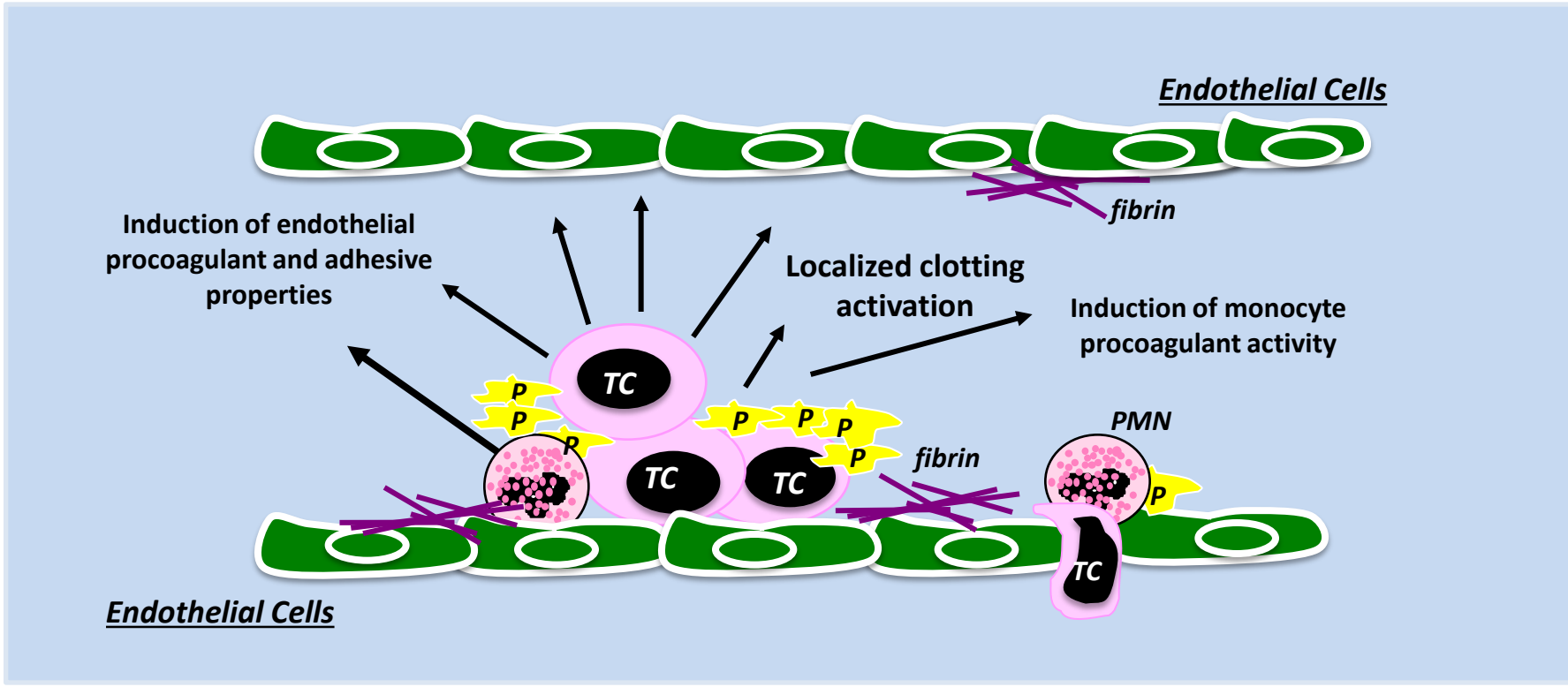
Virchow's Triad in Cancer Patients

- Endothelial damage
  - Shift to procoagulant endothelium
  - Invasion of cancer cells into vessel wall
- Stasis of blood
  - Frequent immobilization, surgery
  - Compression of blood vessels by tumour
- Changes in the blood constituents
  - Activation of clotting proteins and blood cells



Hisada Blood 2017

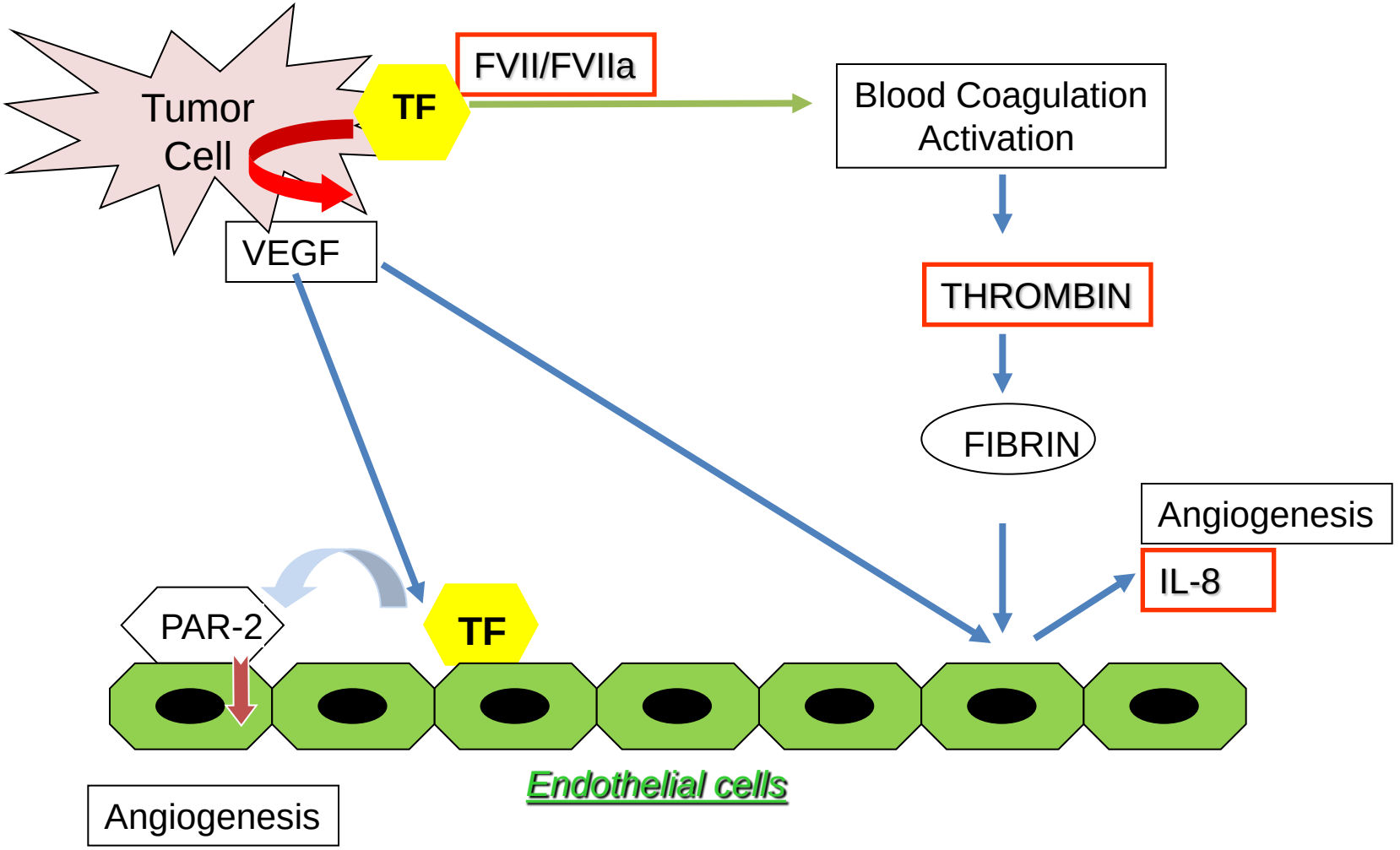
TUMOR CELLS-VASCULAR CELLS INTERACTION



TC = tumor cell
P = platelet
PMN = polymorphonuclear leukocyte

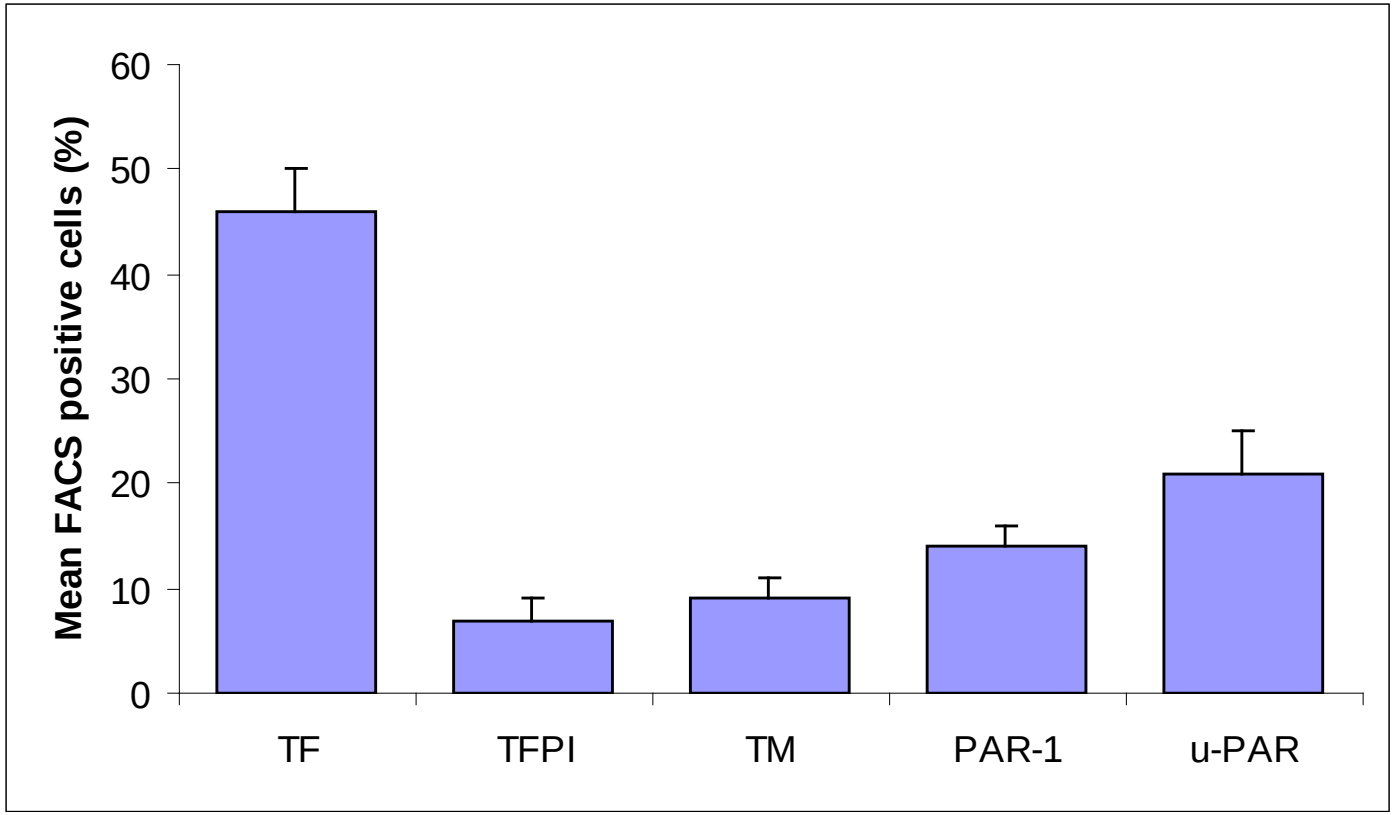
Prandoni, Falanga, Piccioli: Lancet Oncology, 2005

Interface of Tumor Biology and Hemostasis → Tumor Growth and Angiogenesis



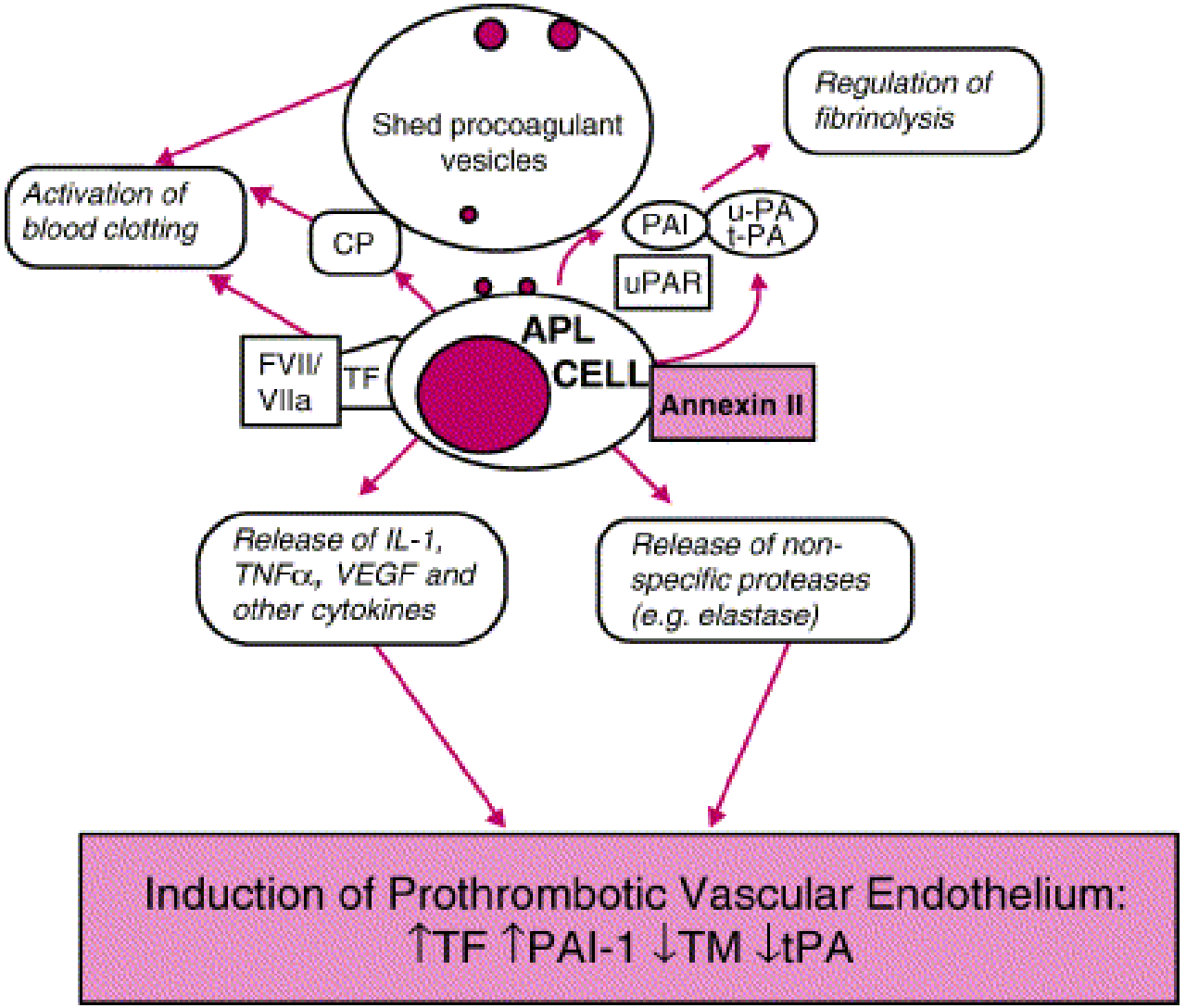
Falanga A & Rickles, FR, *New Oncology:Thrombosis*, 2005

Leukemic Cells Hemostatic Activity

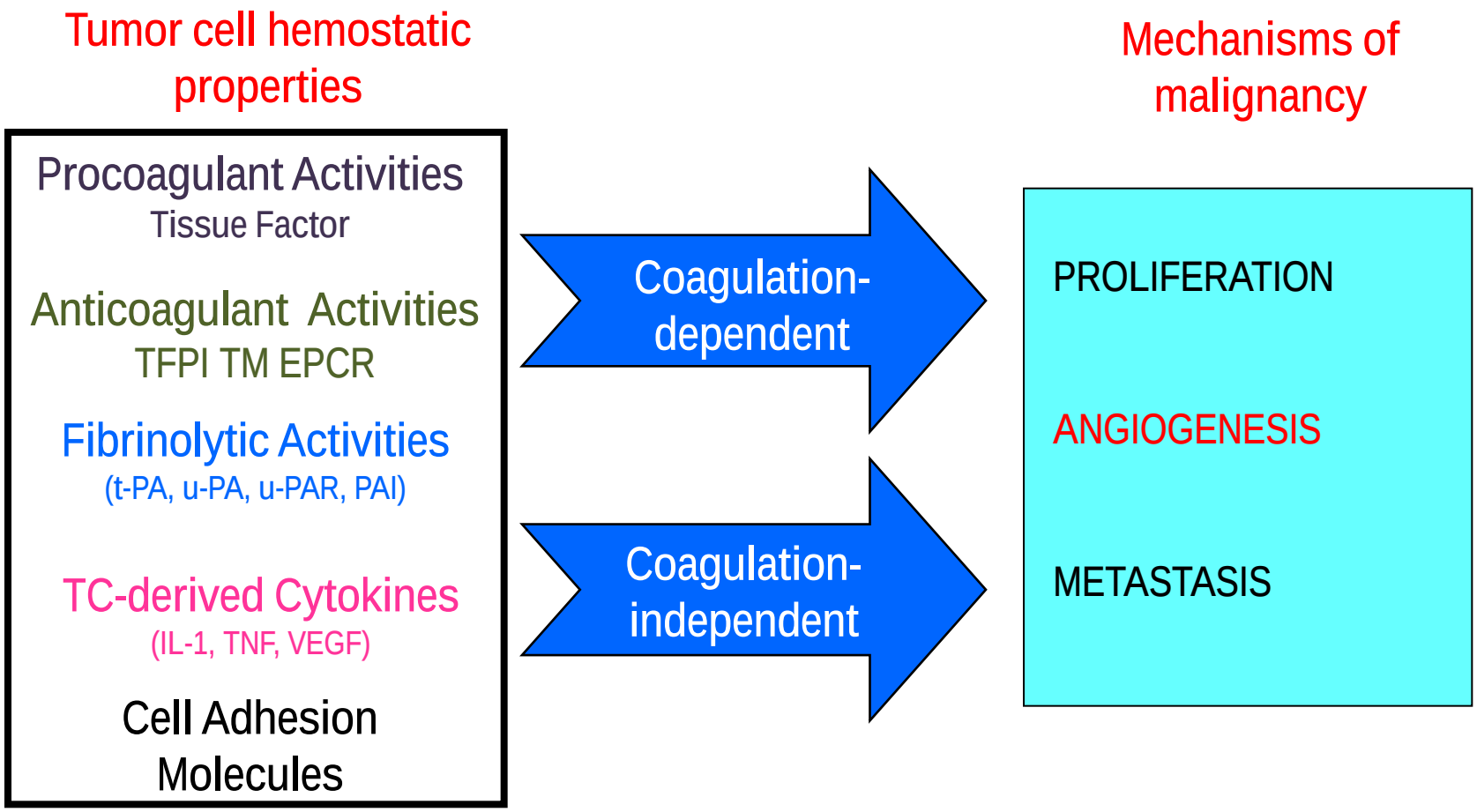


Nadir Haematologica, 2005

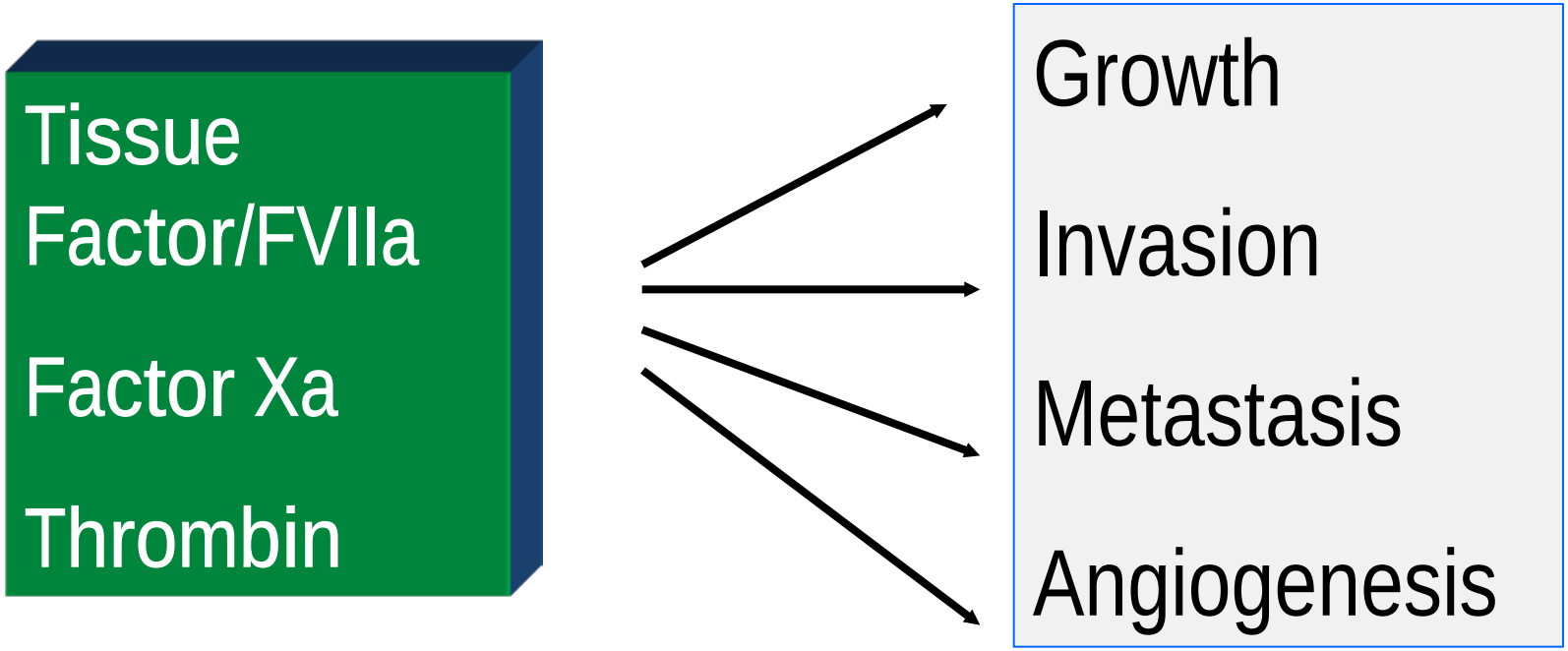
APL Coagulopathy



Tumor Cell Hemostatic Properties and Tumor Biology



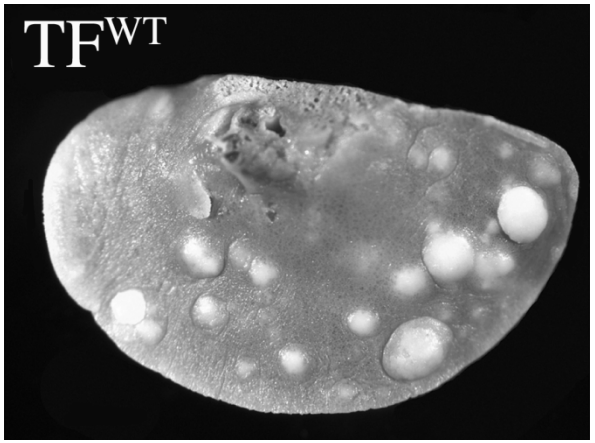
Coagulation Proteases in Tumour Biology

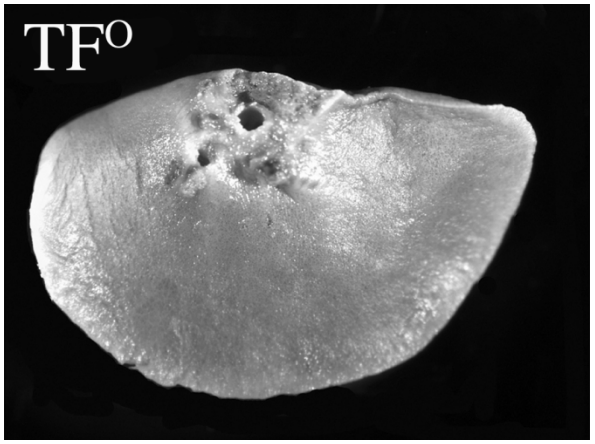


Fibrin generation plays additional roles in these processes

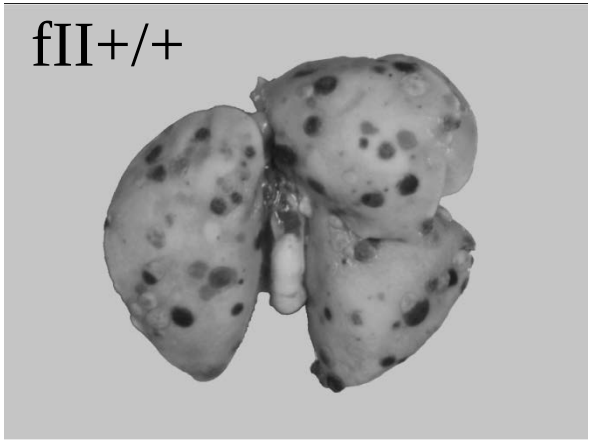
Hemostatic System Components Determine Metastasis

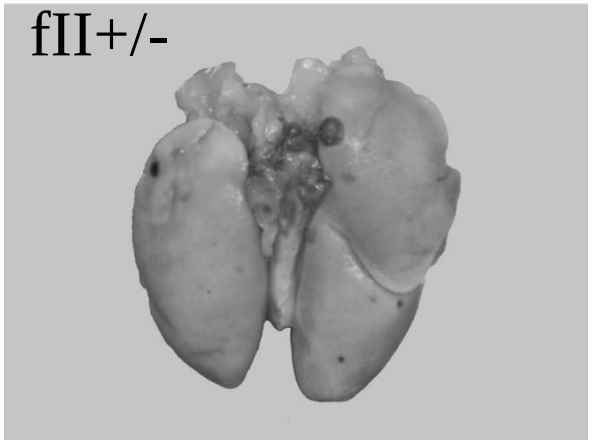
Tumor Cell-Associated Tissue Factor



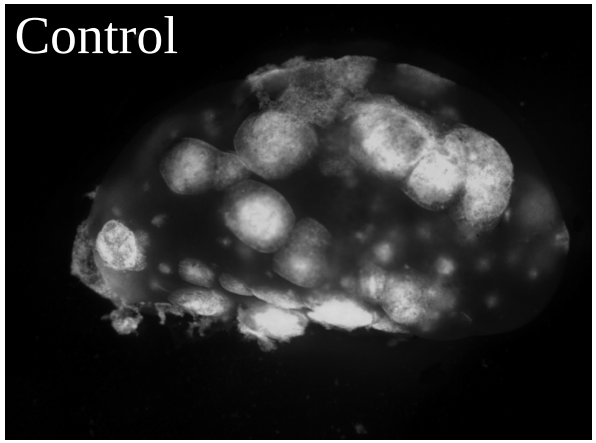


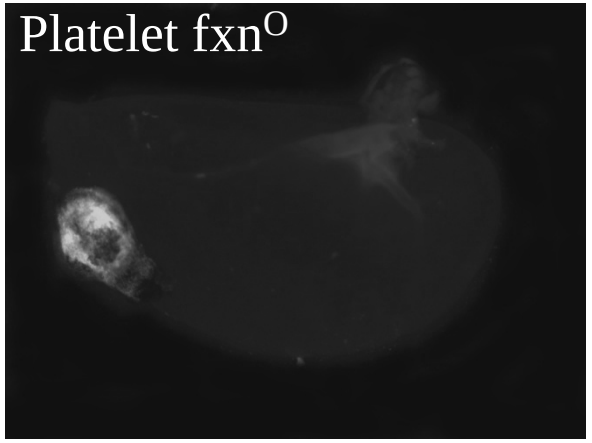
Prothrombin



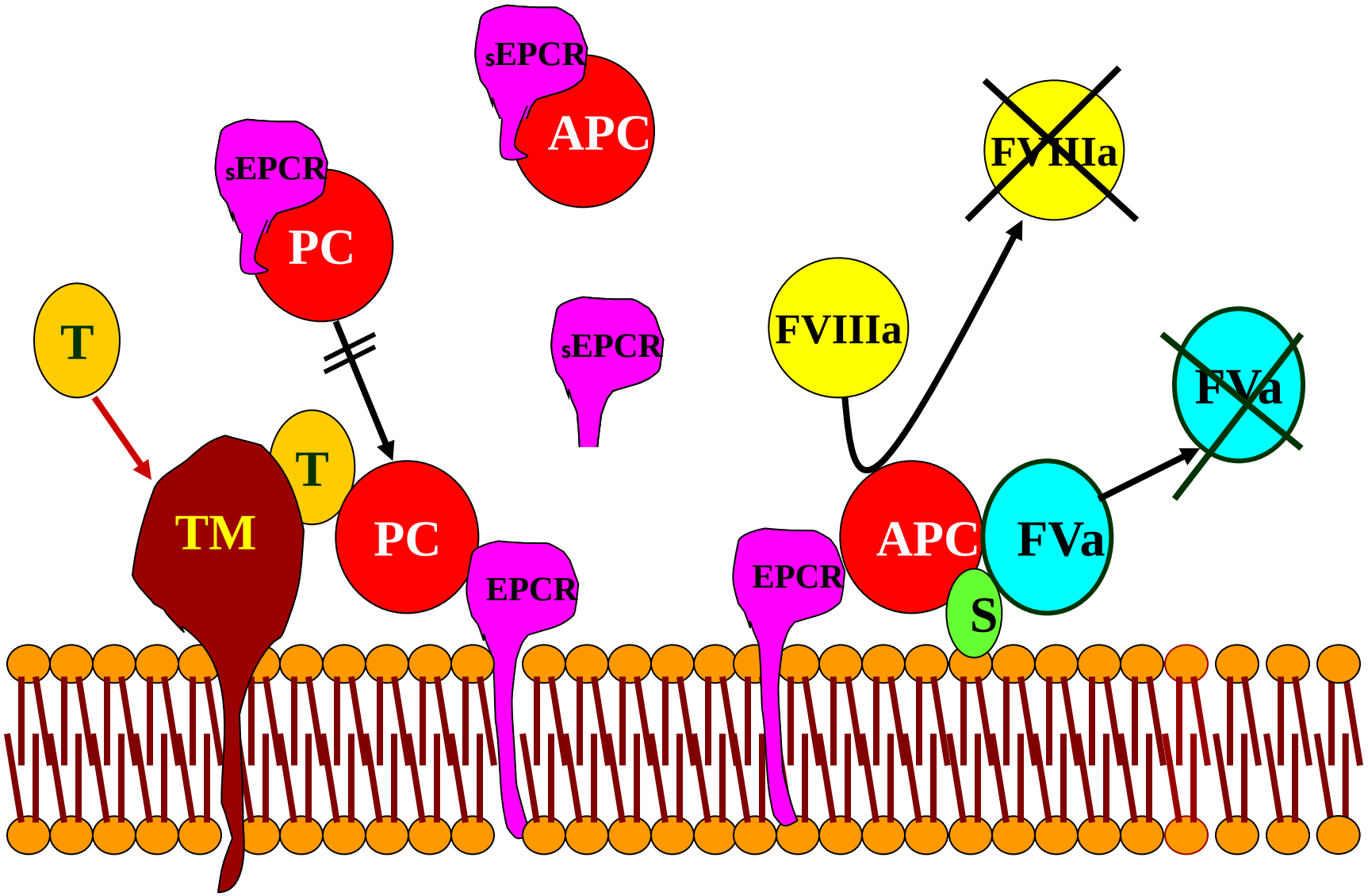


Platelet Function





Protein C Pathway



Hypothesis: Thrombomodulin (TM)-mediated regulation of thrombin function is a key factor in suppressing metastatic potential

Approach: Mice homozygous for a Glu^{387} to Pro mutation (TM^{Pro}) exhibit an ~1000-fold decrease in protein C activation.

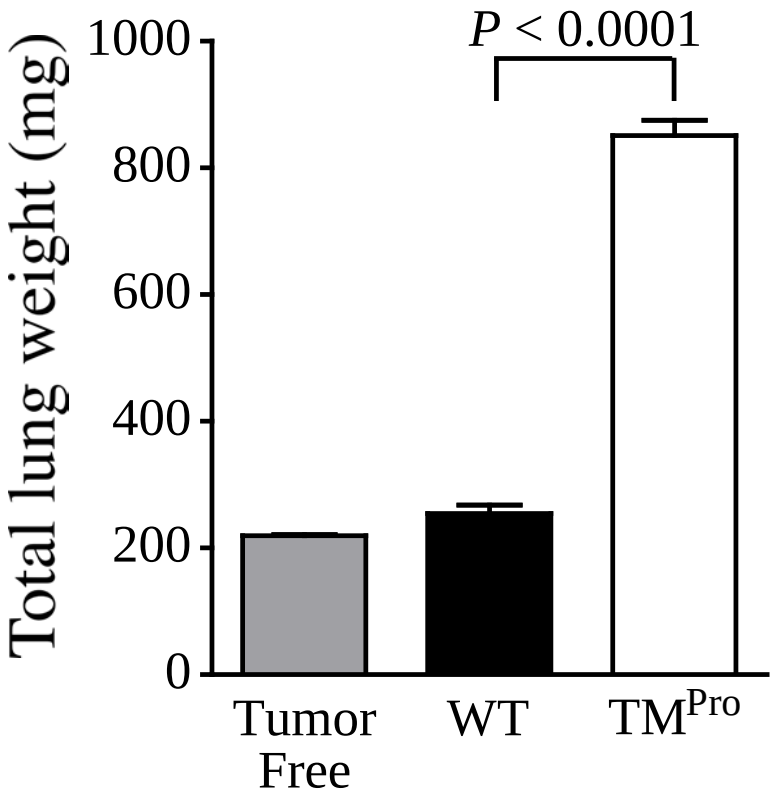
Weiler et al. JCI. 1998

Hypothesis Prediction:

Wildtype TM: ↓ thrombin procoagulant function, ↓ metastasis

TM^{Pro} : ↑ thrombin procoagulant function, ↑ metastasis

TM^{Pro} mice develop profoundly more metastases after injection with LLC cells.



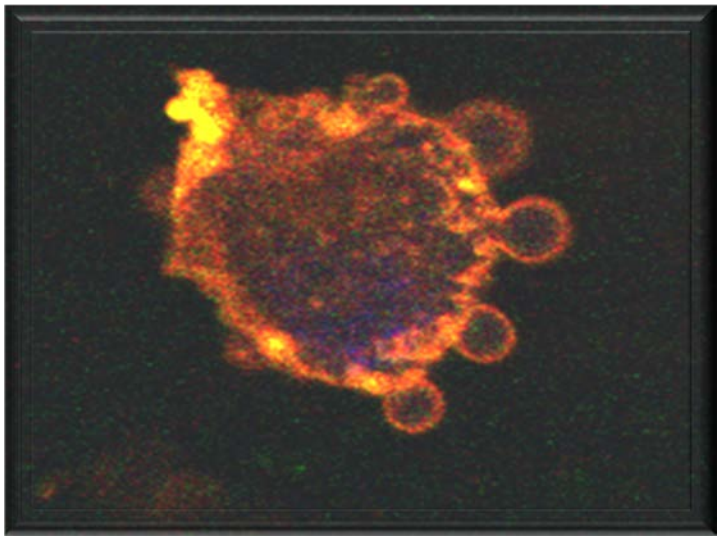
3 X 10^5 LLC cells/mouse

Findings Summary Horowitz Blood 2011

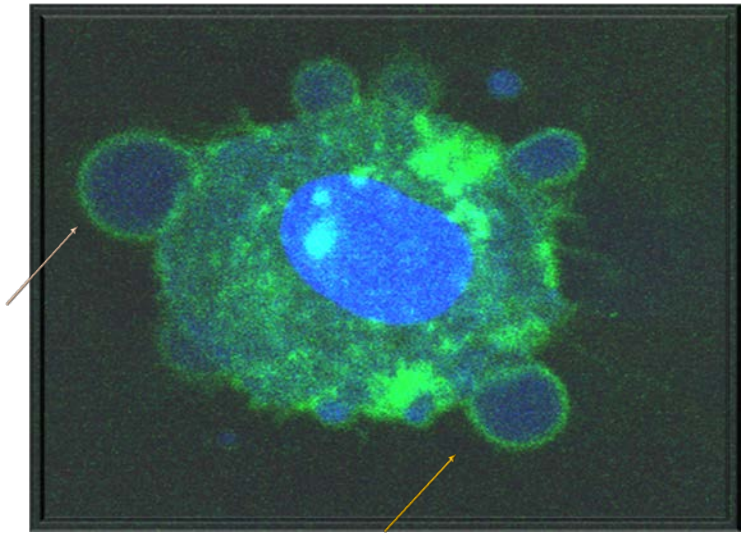
- A thrombomodulin mutation favoring procoagulant function (TM^{Pro}) profoundly increases metastatic potential in various tumor models.
- TM^{Pro} promotes metastasis by supporting the sustained adhesion/early survival of newly established micrometastases.
- The prometastatic phenotype conferred by TM^{Pro} is crucially dependent on tumor cell-associated tissue factor, circulating prothrombin and platelets.
- Endothelial modulators of thrombin activity are powerful determinants of metastatic potential.

Microvesicles

Endothelial Cells MVs



Trophoblasts MVs TF



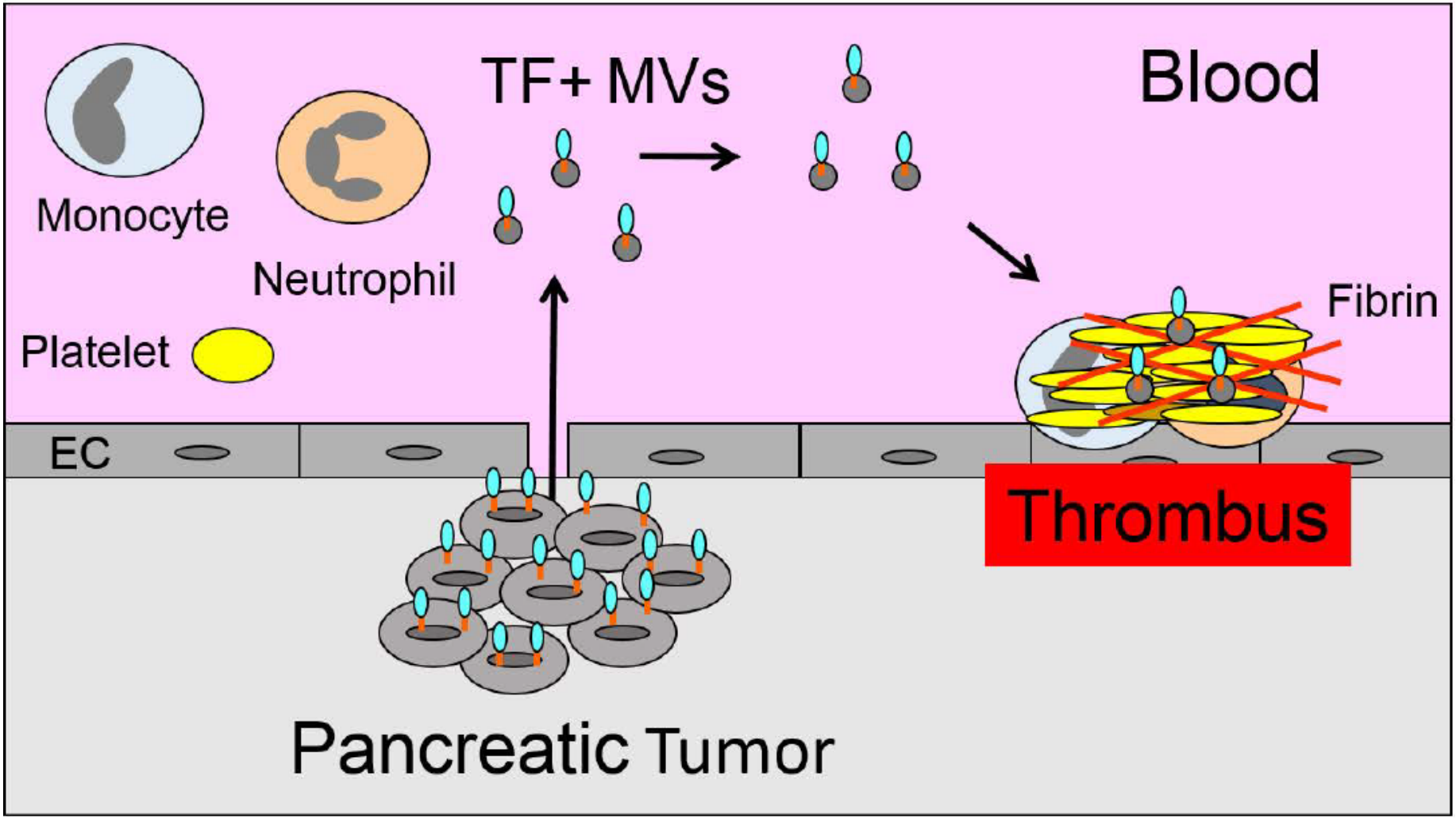
Aharon Thromb Haemost, 2008
Shomer Hypertension, 2013

MVs and cancer

- **MV cargo include growth factors, cytokines, enzymes, chemokines and genetic material.**

- **MVs transfer surface receptors, mRNA, microRNA and lipids to the cells.**

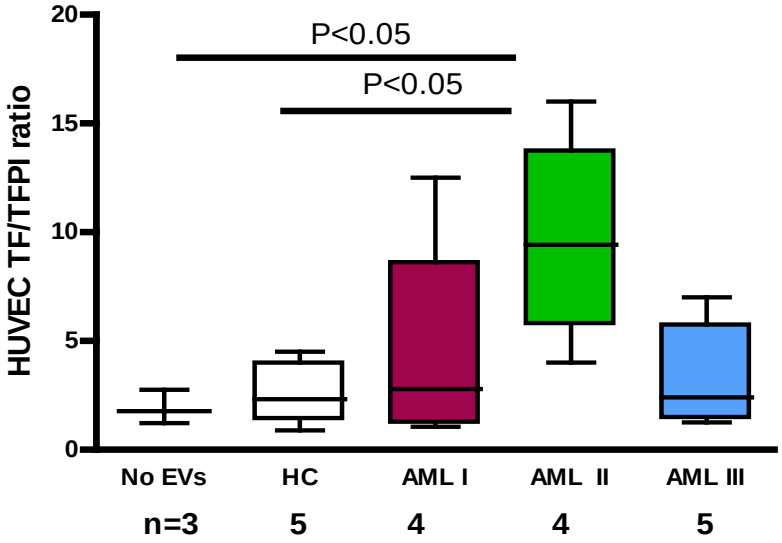
- **MVs affect cancer progression by promoting drug resistance, immuno-escape, angiogenesis and coagulation.**



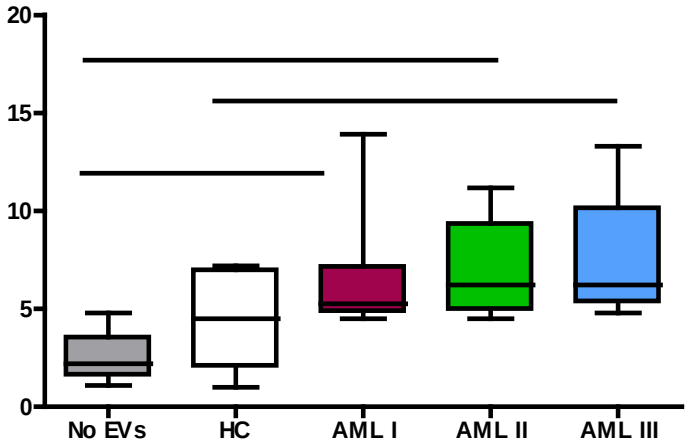
Hisada Blood 2017

AML Patients' MVs Pro-thrombotic Effects on Endothelial Cells

Pro- and anti-coagulant antigens ratio (FACS analysis)

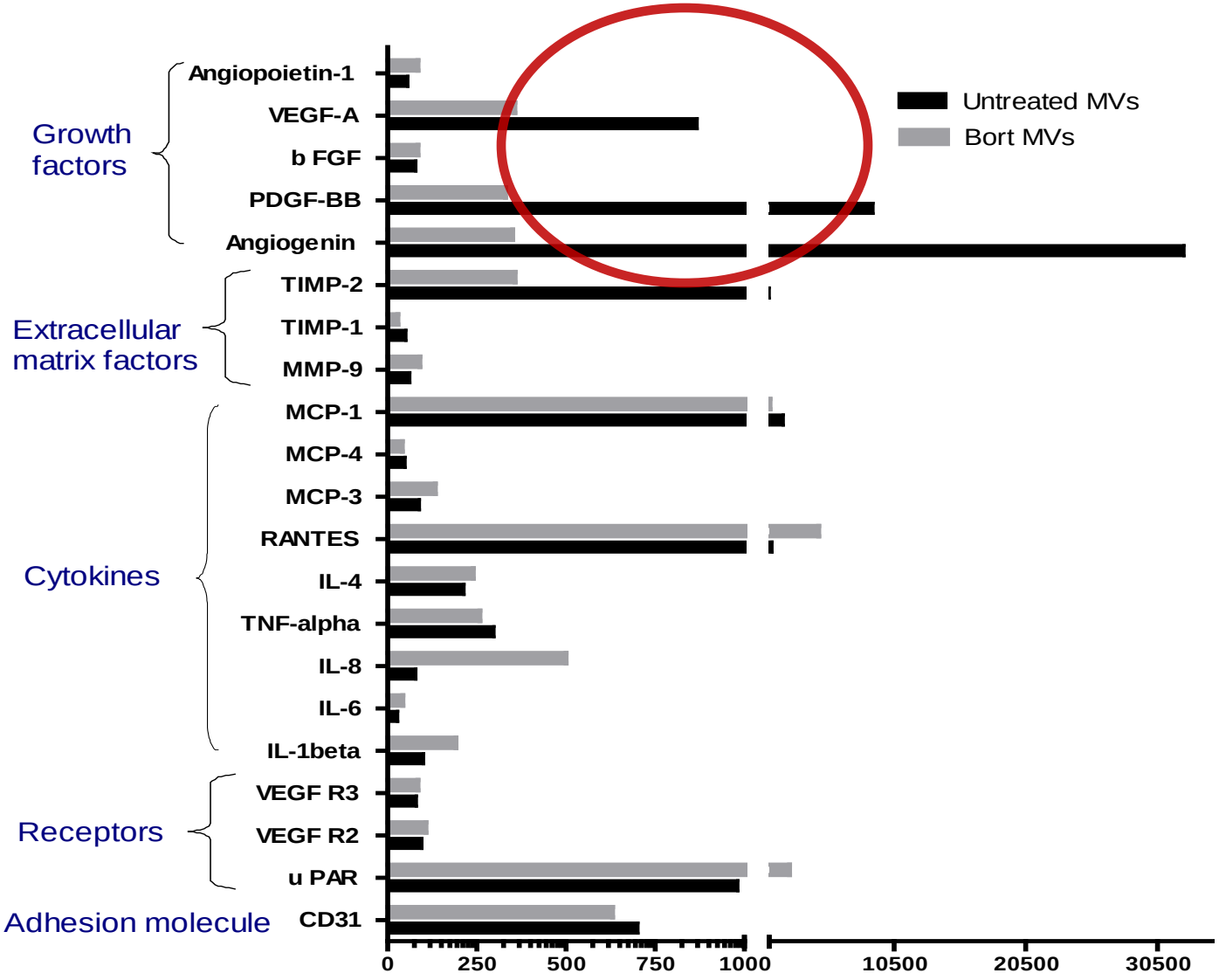


Pro-coagulant activity FXa chromogenic



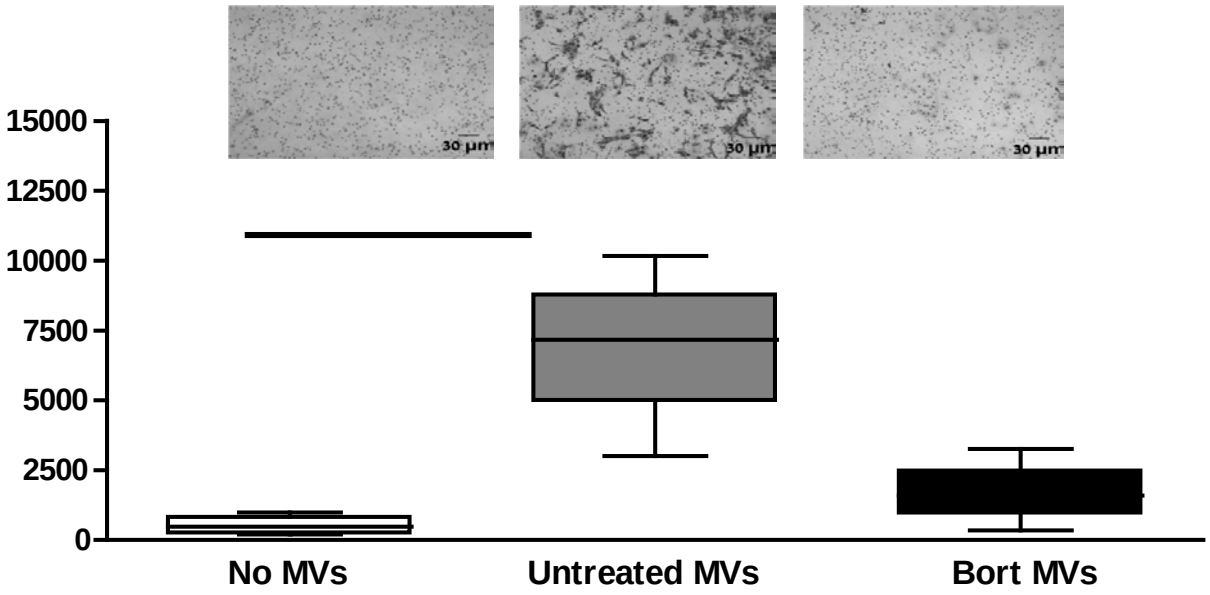
Tzoran Exp Hematol, 2015

MM MVs Contain Angiogenic Factors



Zarfati Angiogenesis 2019

MV Effect on EC Migration

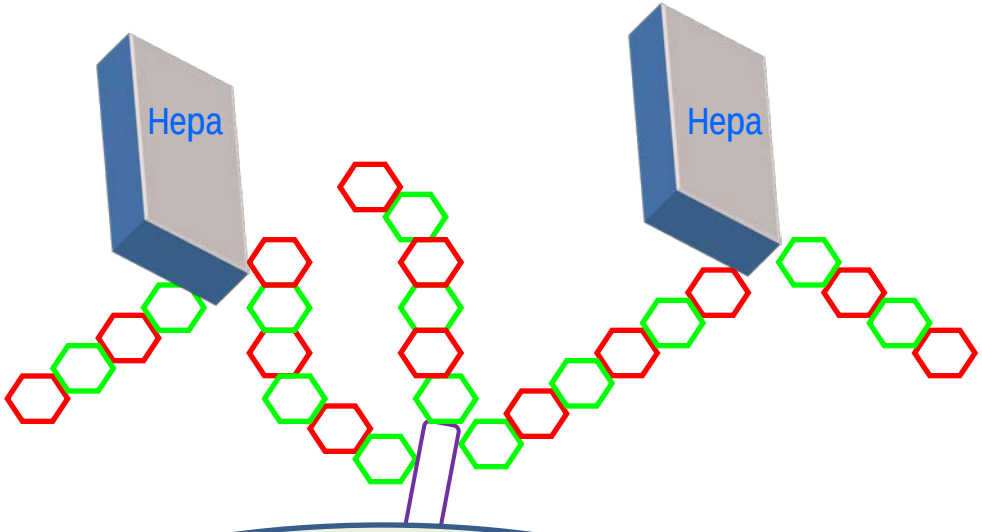


- MVs from myeloma patients triggered HUVEC migration
- Bortezomib treated MVs suppressed HUVEC migration

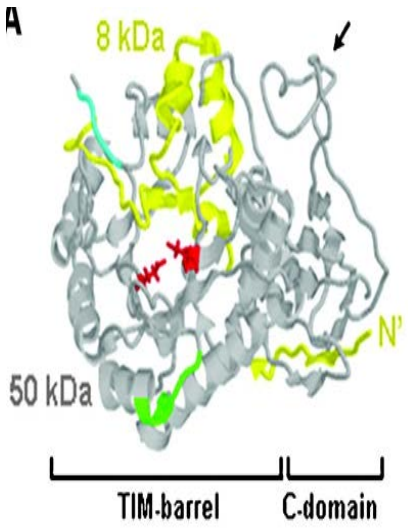
Zarfati Angiogenesis 2019

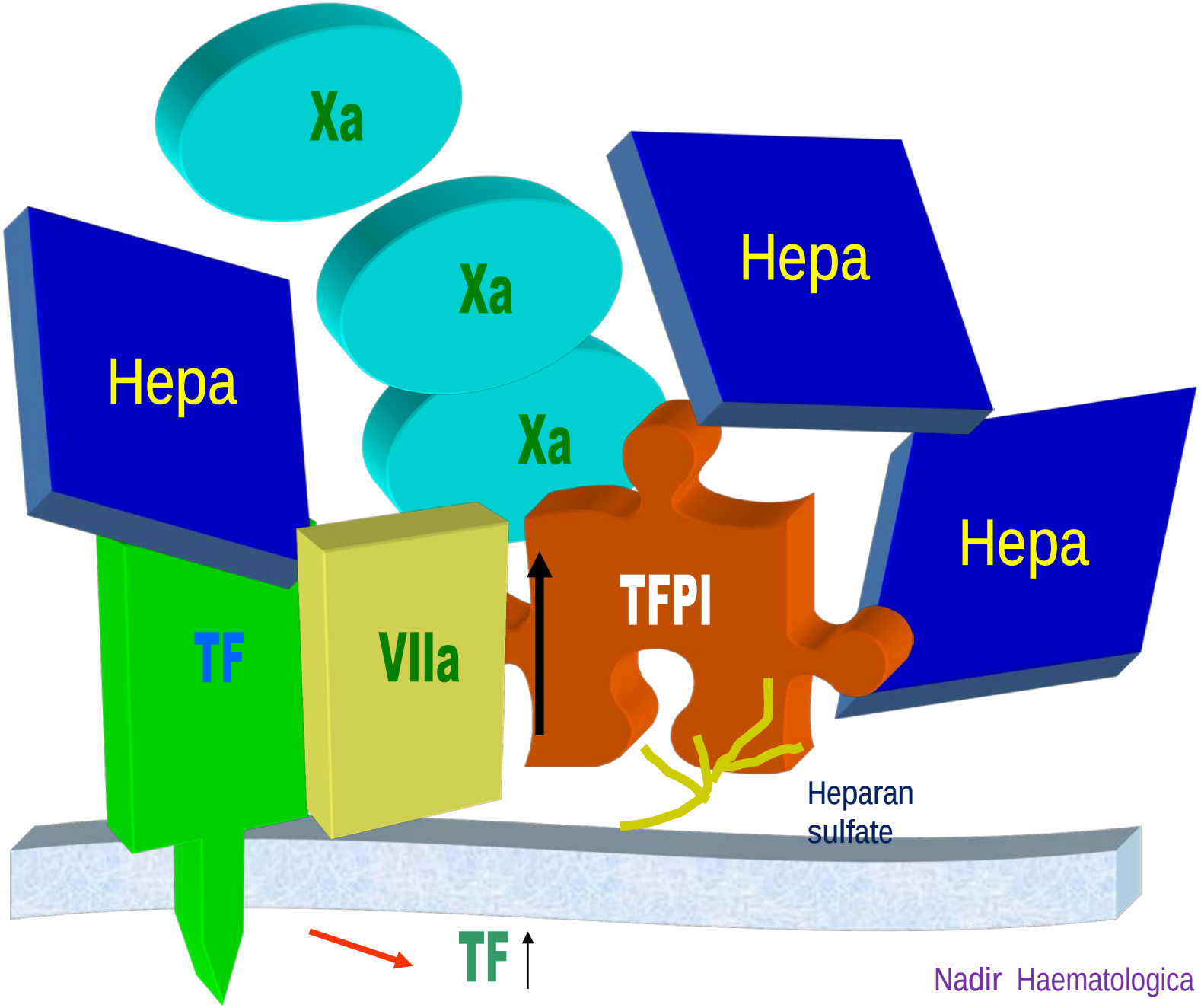
Heparanase

Heparanase is an endo-β-D-glucuronidase which cleaves heparan sulfate chains on cell surfaces and in the extra-cellular matrix.



Heparanase enhances angiogenesis inflammation and cancer progression





Nadir Haematologica 2010

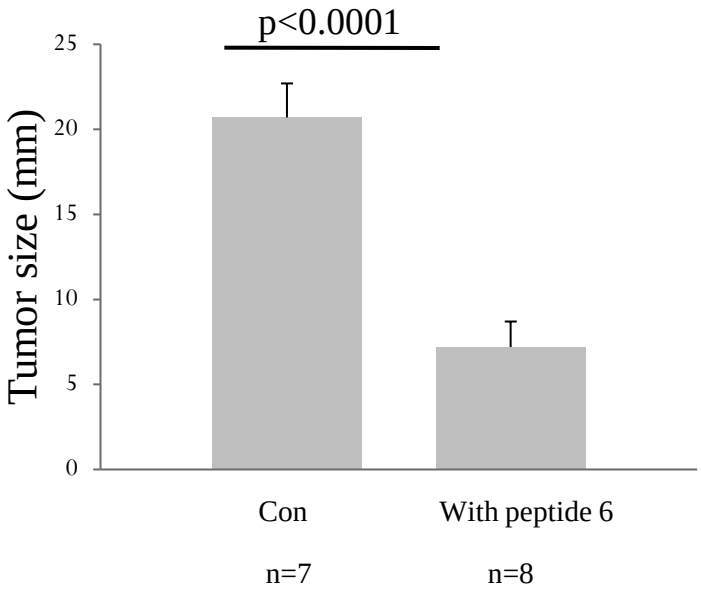
Heparanase Procoagulant-activity Inhibitory Peptides

Control →

With peptide 6 →

B16 melanoma
Peptides 5,6,7
3 mg/kg

C57BL/6 mice

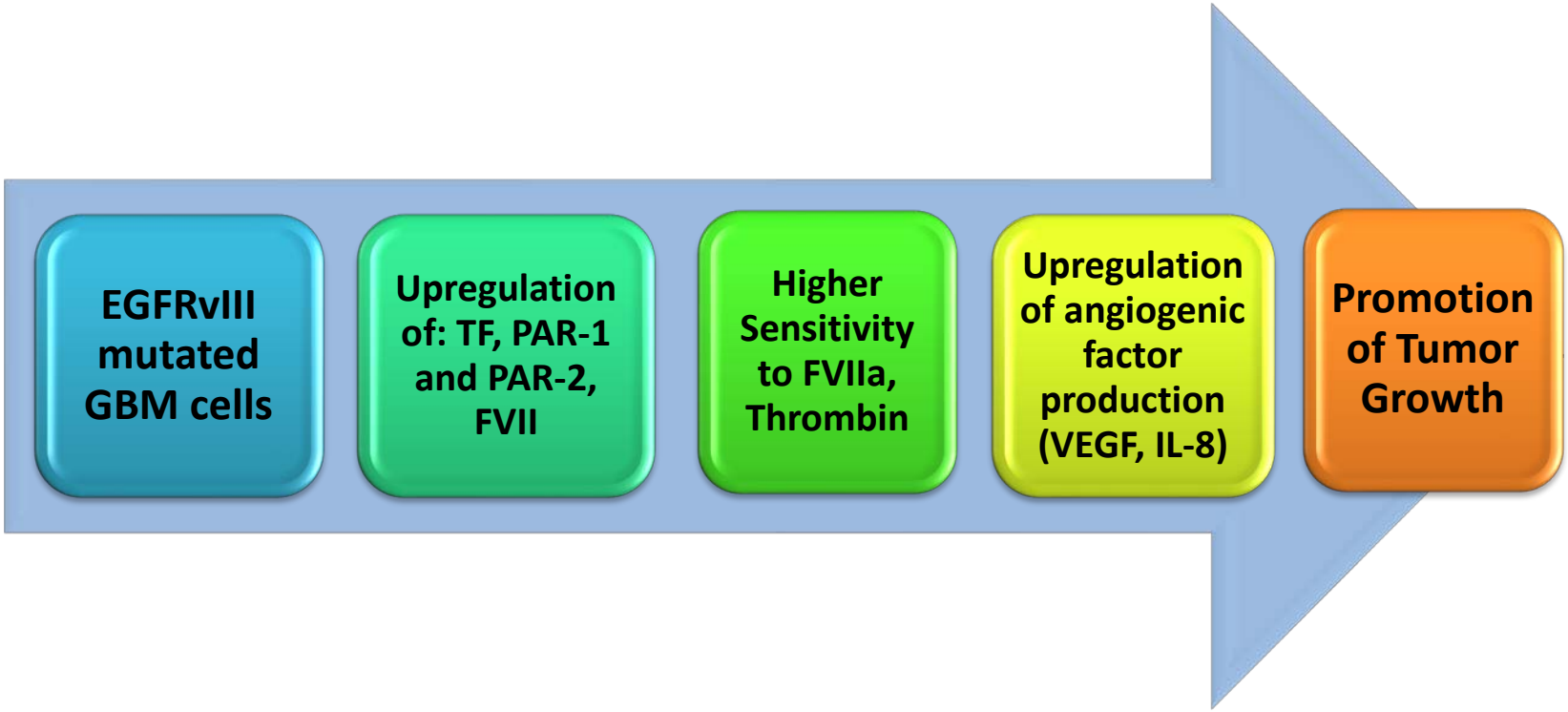


Crispel Thromb Haemost 2016

Biology of Tumor Cell/Blood Coagulation Interaction

“ Activation of Clotting Proteins is driven by Tumor Genetic Programs”

EGFRvIII mutant in Glioblastoma multiforme (GBM) cells



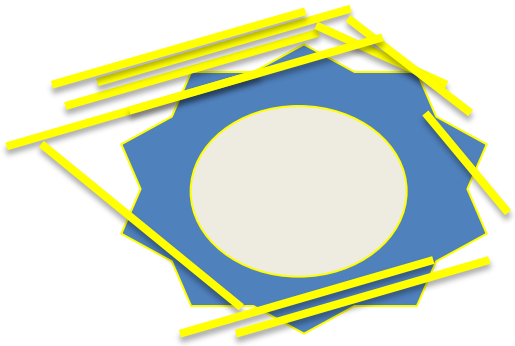
Oncogenic epidermal growth factor receptor upregulates multiple elements of the tissue factor signalling pathway in human glioma cells

N Magnus, D Garnier , J Rak. BLOOD 2010

Involvement of Fibrin in Tumor Progression

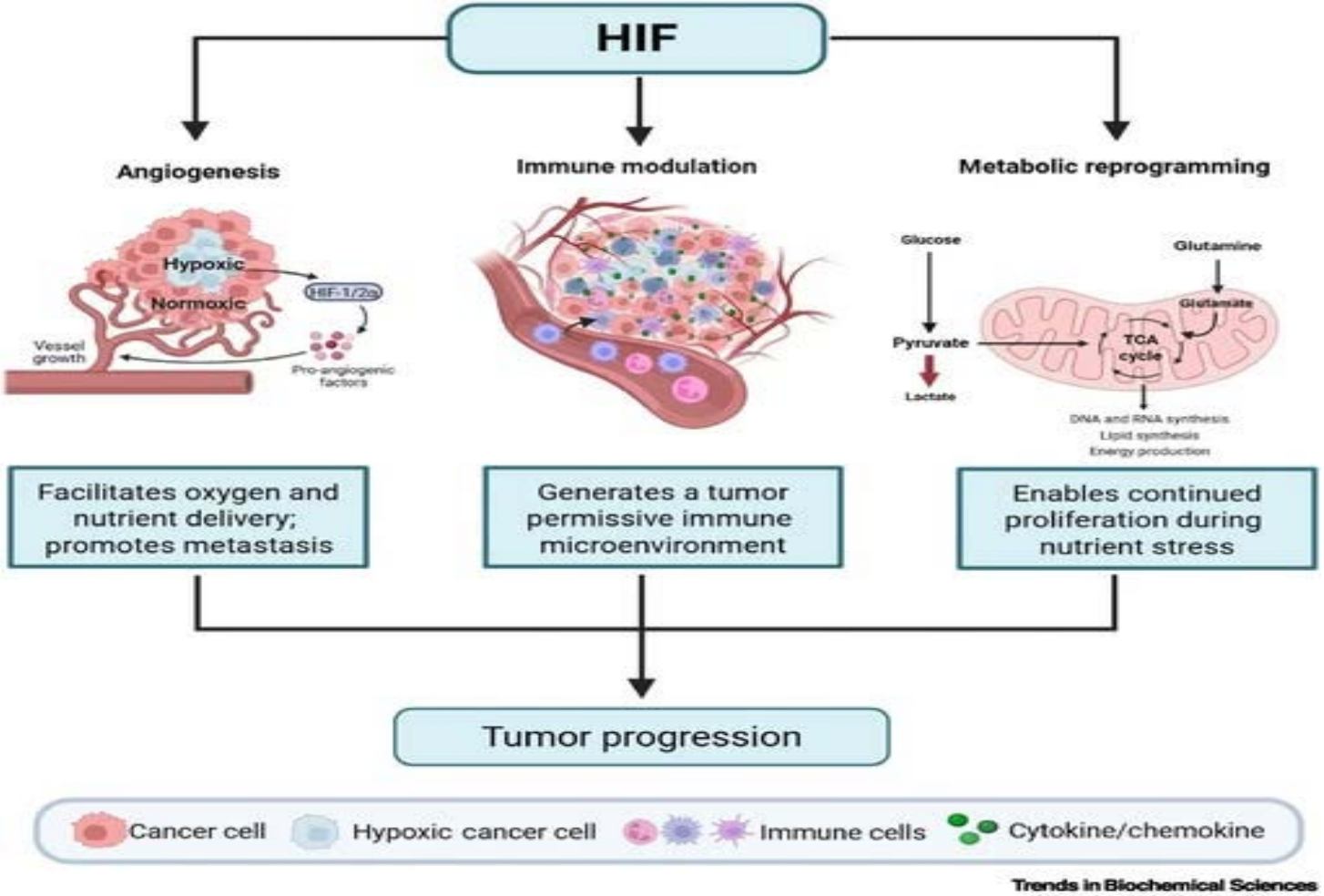
Activation of blood coagulation

FIBRIN



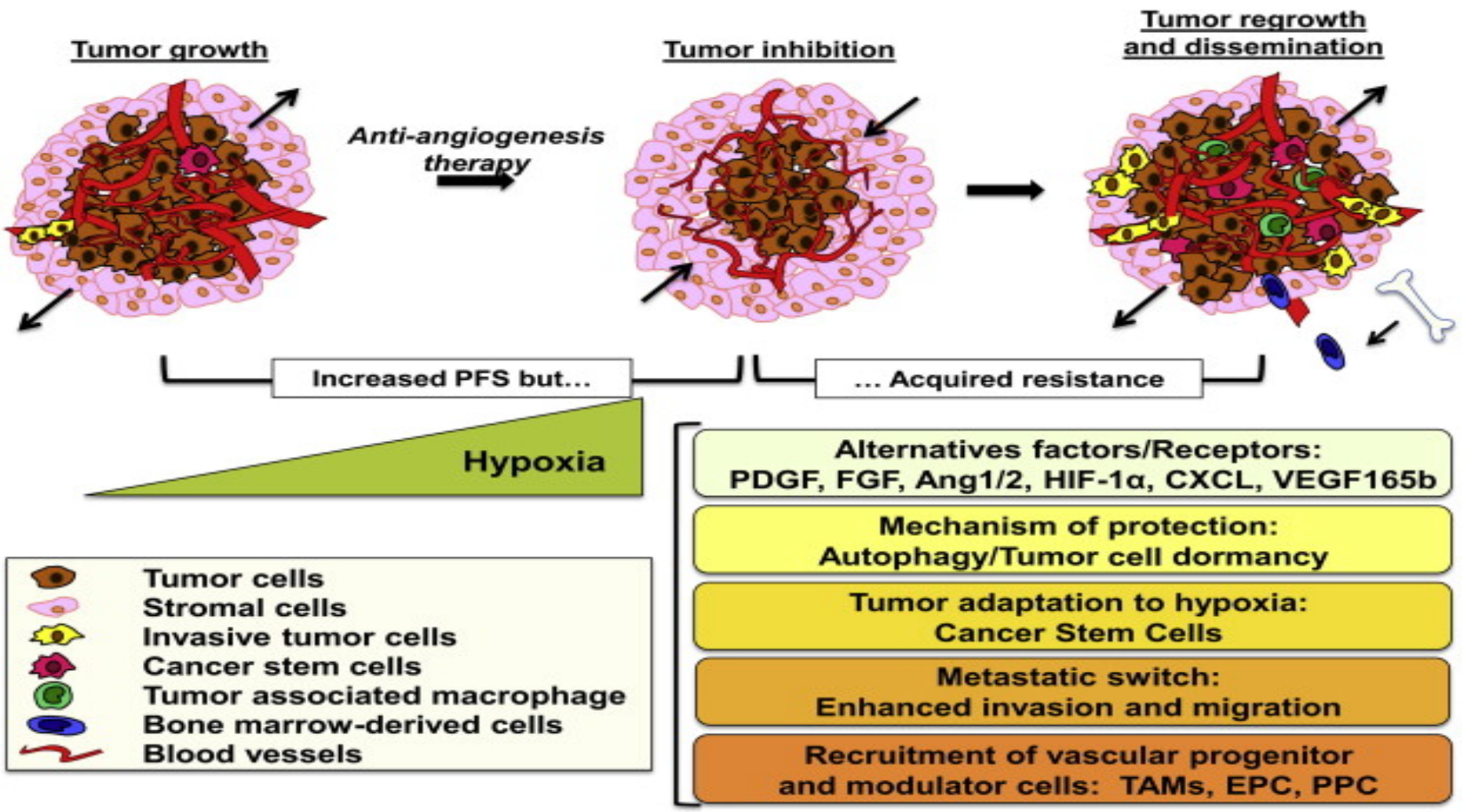
Tumor cell

- Fibrin matrix provides the proper scaffold to the formation of new vessels
- Fibrin coat protects cancer cells from immune system attack
- Fibrin deposits on malignant cells mediate the attachment of these cells to endothelial cells
- Fibrin products induce TF and IL-8 expression by endothelial cells

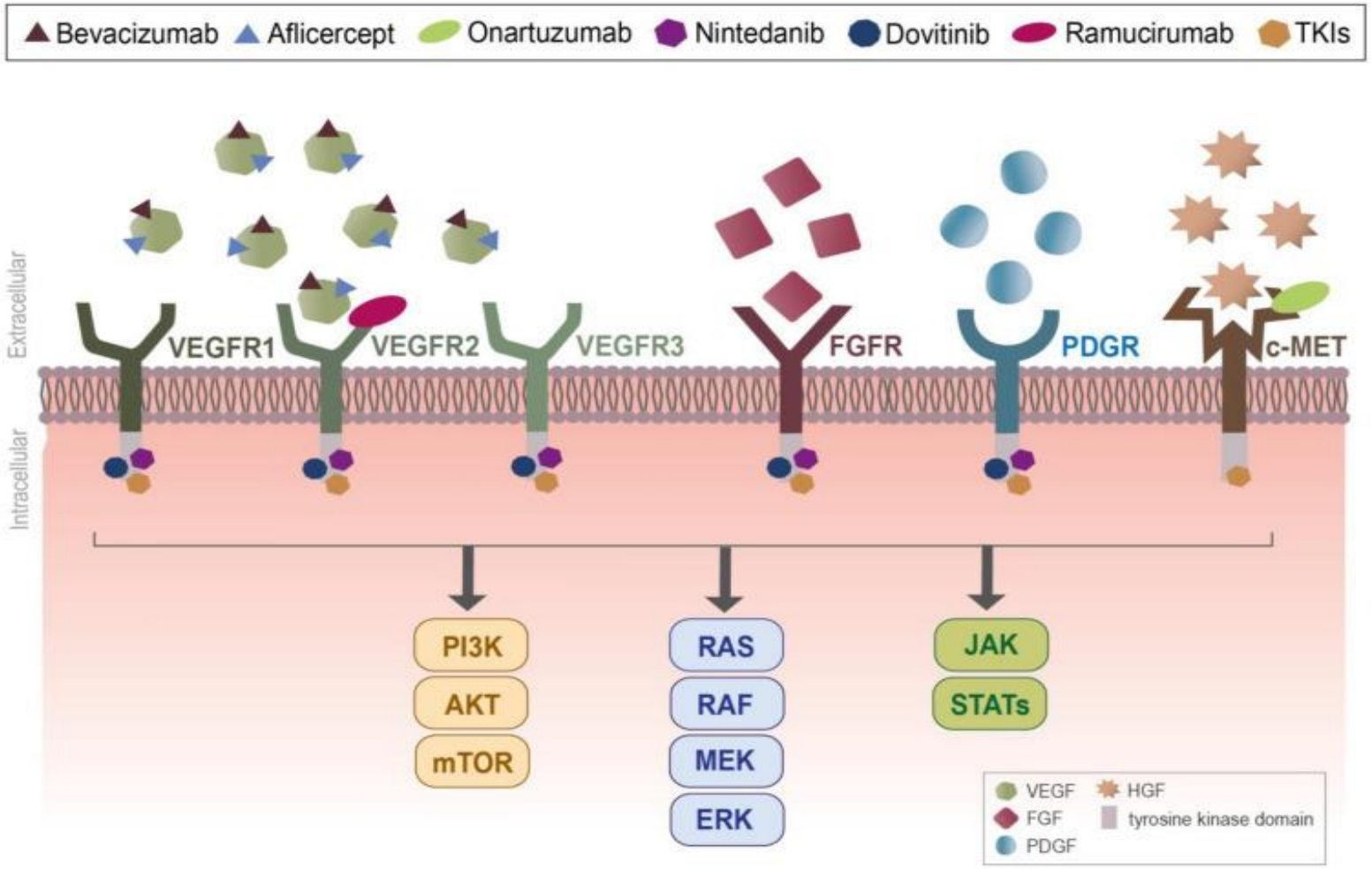


HIF activation drives key axes that contribute to cancer progression: angiogenesis, immune modulation, and metabolic reprogramming.

Anti-angiogenic drugs - Premise and Challenges



Anti-angiogenic drugs-receptors and pathways



Lopes-Coelho, Molecular Science, 2021

Anti-angiogenic Agents Types

Types	Agents
Anti-VEGF mAb	Bevacizumab
Anti-VEGFR mAb	Ramucirumab
VEGF-trap receptor	Aflibercept
TKIs	Nintedanib, Axitinib, Sorafenib, Sunitinib, Vatalanib, Cediranib, Pazopanib, Vandetanib, Cediranib, Pazopanib, Vandetanib, Regorafenib, Cabozantinib, Anlotinib, Motesanib, Apatinib, Lenvatinib

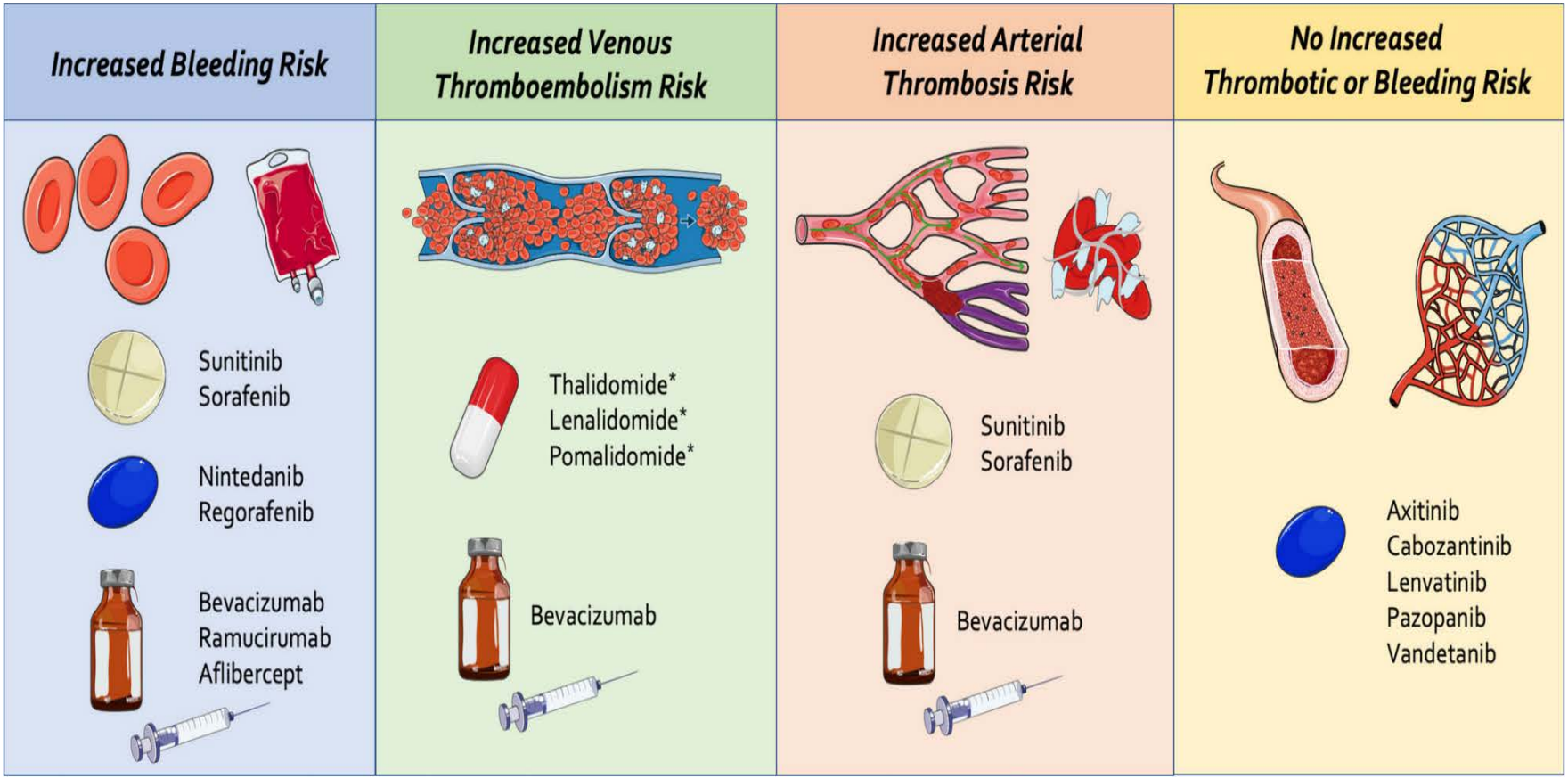
Abbreviations: TKI, tyrosine kinase inhibitor; mAb, monoclonal antibody.

Anti-angiogenic Agents
Arterial Thrombosis

	MI	AT
➢ VEGF receptor inhibitor	3.5	2
➢ Oral TKI of VEGF		
Sunitinib, Sorafenib		3

Faruque Plos One 2014
Choueiri JCO 2010

Anti-angiogenic drugs- Thrombo-hemmorrhagic Risks



Watson, JTH, 2021

TKIs and Thrombosis

- Dasatinib is known to cause a reversible form of pre-capillary pulmonary arterial hypertension, but does not seem to increase risk for ATEs.

- Nilotinib can cause severe peripheral arterial occlusive disease that may be rapidly progressive, even in the absence of risk factors for PAOD, MI and IS

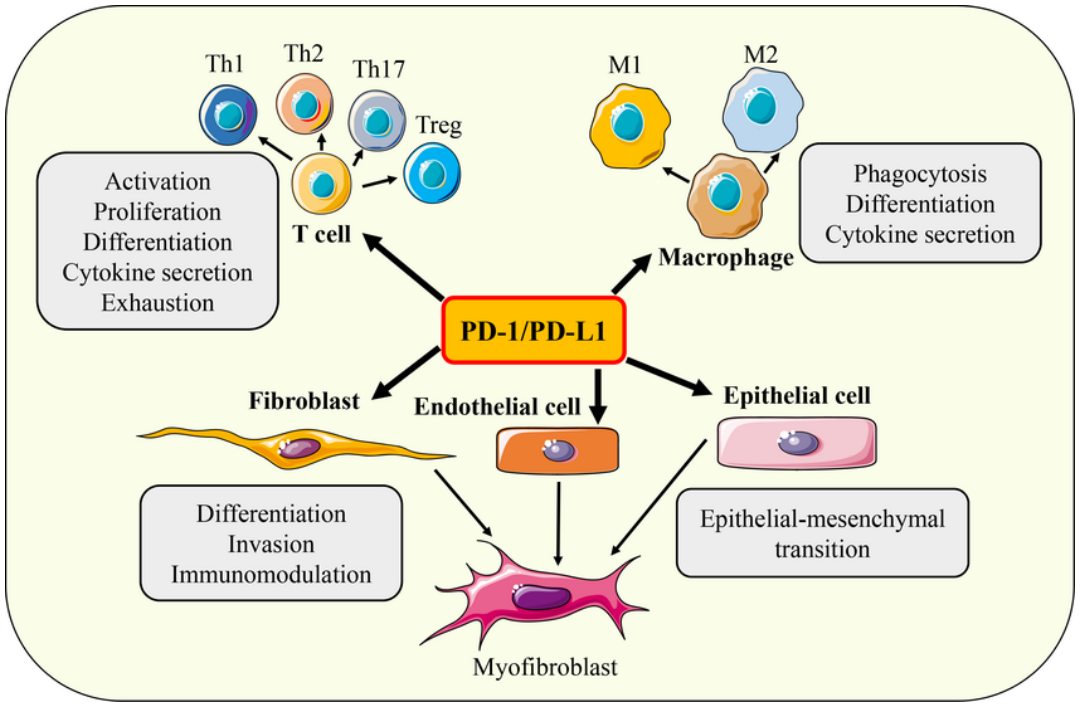
Saglio Annals of Hematology 2017
Valent Blood 2015
Mirault Eur J Haematol 2015

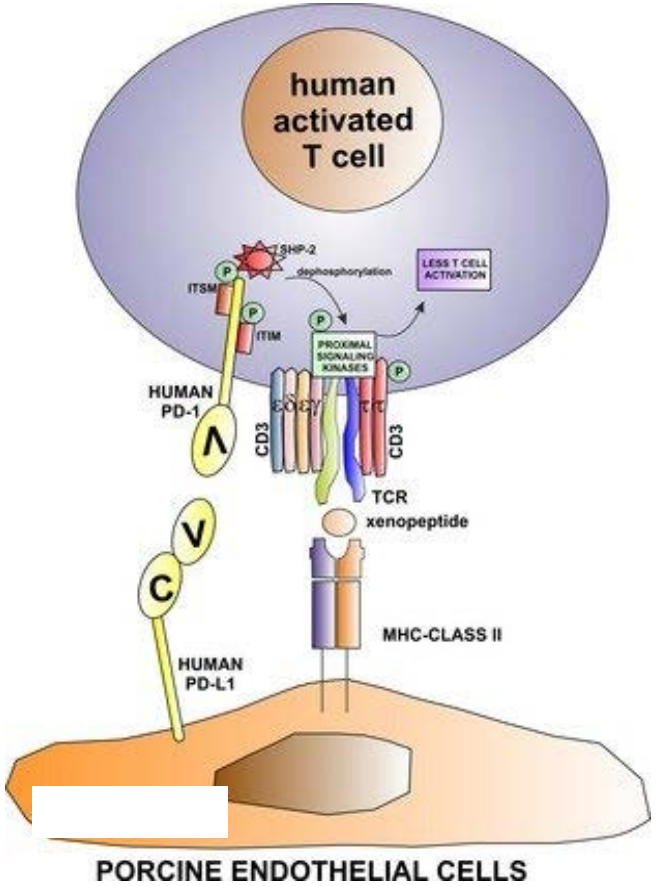
TKIs and Thrombosis [2]

- **Ponatinib** was withdrawn from the US market in 2014 due to high rates of serious ATEs (11.8% of patients over 24 months).
- ATEs events have been described in patients receiving **bosutinib**, but with a lower frequency compared with patients receiving nilotinib or ponatinib.

Cortes N Engl J Med , 2013
Groarke N Engl J Med, 2013
Tefferi Leukemia, 2013

Immune Checkpoint Inhibitors



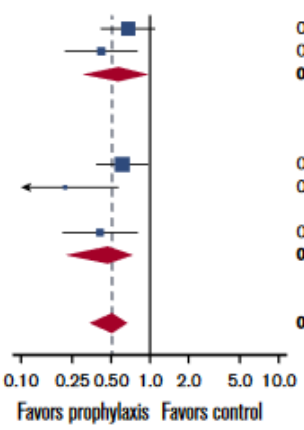


Primary Prophylaxis in Ambulatory Cancer Patients with a Khorana Score of ≥ 2: Venous Thromboembolism

Forest plot for study outcomes in cancer patients with an intermediate to high risk of VTE (Khorana score ≥2).

A Venous thromboembolism

Study	Agent	Prophylaxis Events	Patients	Control Events	Patients	RR	95%-CI
DOAC							
CASSINI (2019)	Rivaroxaban	25	420	37	421	0.68	[0.42-1.10]
AVERT (2019)	Apixaban	12	291	28	283	0.42	[0.22-0.80]
Random effects model		**37**	**711**	**65**	**704**	**0.57**	**[0.30-0.98]**
Heterogeneity: tau^2<0.0001, chi^2=1.35, df=1 (P=0.24), I^2=26%							
LMWH							
FRAGMATIC (2016)	Dalteparin	26	654	45	689	0.61	[0.38-0.97]
CONKO-004 (2015)	Enoxaparin	5	154	21	144	0.22	[0.09-0.57]
ABEL (2013)	Bemiparin	0	11	0	8		
SAVE-ONCO (2012)	Semuloparin	12	764	30	787	0.41	[0.21-0.80]
Random effects model		**43**	**1583**	**96**	**1628**	**0.47**	**[0.22-0.74]**
Heterogeneity: tau^2=0.0038, chi^2=3.69, df=2 (P=0.16), I^2=46%							
Random effects model		**80**	**2294**	**161**	**2332**	**0.51**	**[0.34-0.67]**
Heterogeneity: tau^2<0.0001, chi^2=5.53, df=4 (P=0.24), I^2=28%							
Test for subgroup differences: chi^2=0.50, df=1 (P=0.48)							

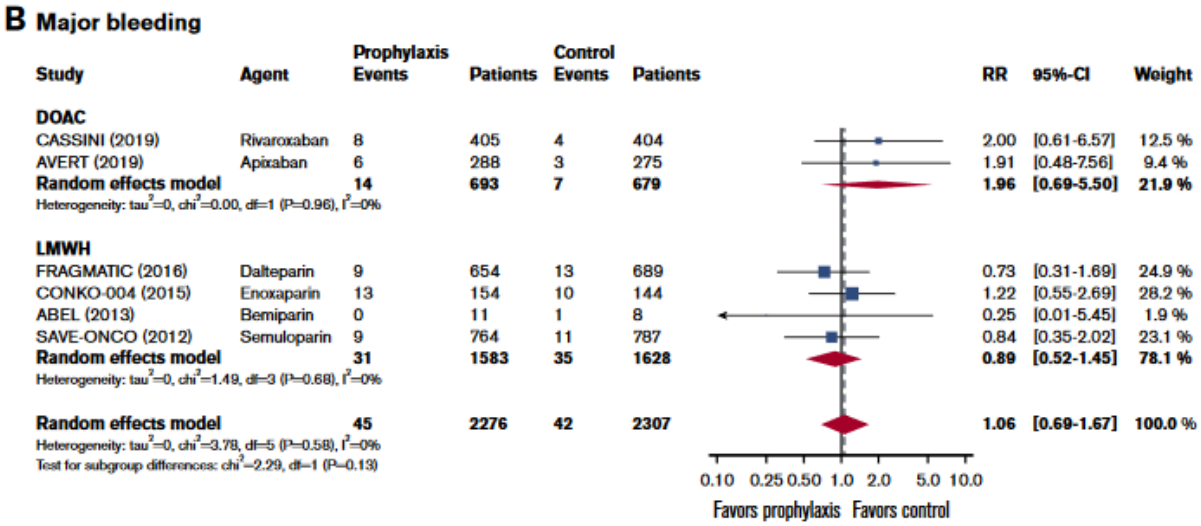


p = 0.48

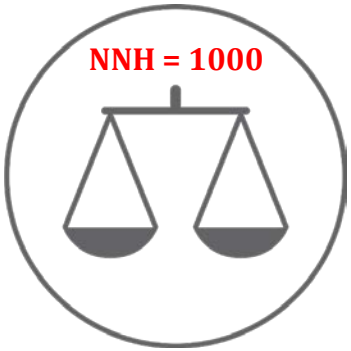
Bosch, Blood Adv 2020

Primary Prophylaxis in Ambulatory Cancer Patients with a Khorana Score of ≥ 2: Major Bleeding

Forest plot for study outcomes in cancer patients with an intermediate to high risk of VTE (Khorana score ≥2).



$p = 0.13$



Bosch, Blood Adv 2020

Guidelines: Prevention of VTE in Ambulatory Cancer Patients Receiving Systemic Therapy

ASH

Low risk: **no** thromboprophylaxis

Intermediate risk: either thromboprophylaxis with a DOAC (apixaban or rivaroxaban) OR no prophylaxis

High risk: thromboprophylaxis with a DOAC (apixaban or rivaroxaban) OR parenteral thromboprophylaxis (LMWH)

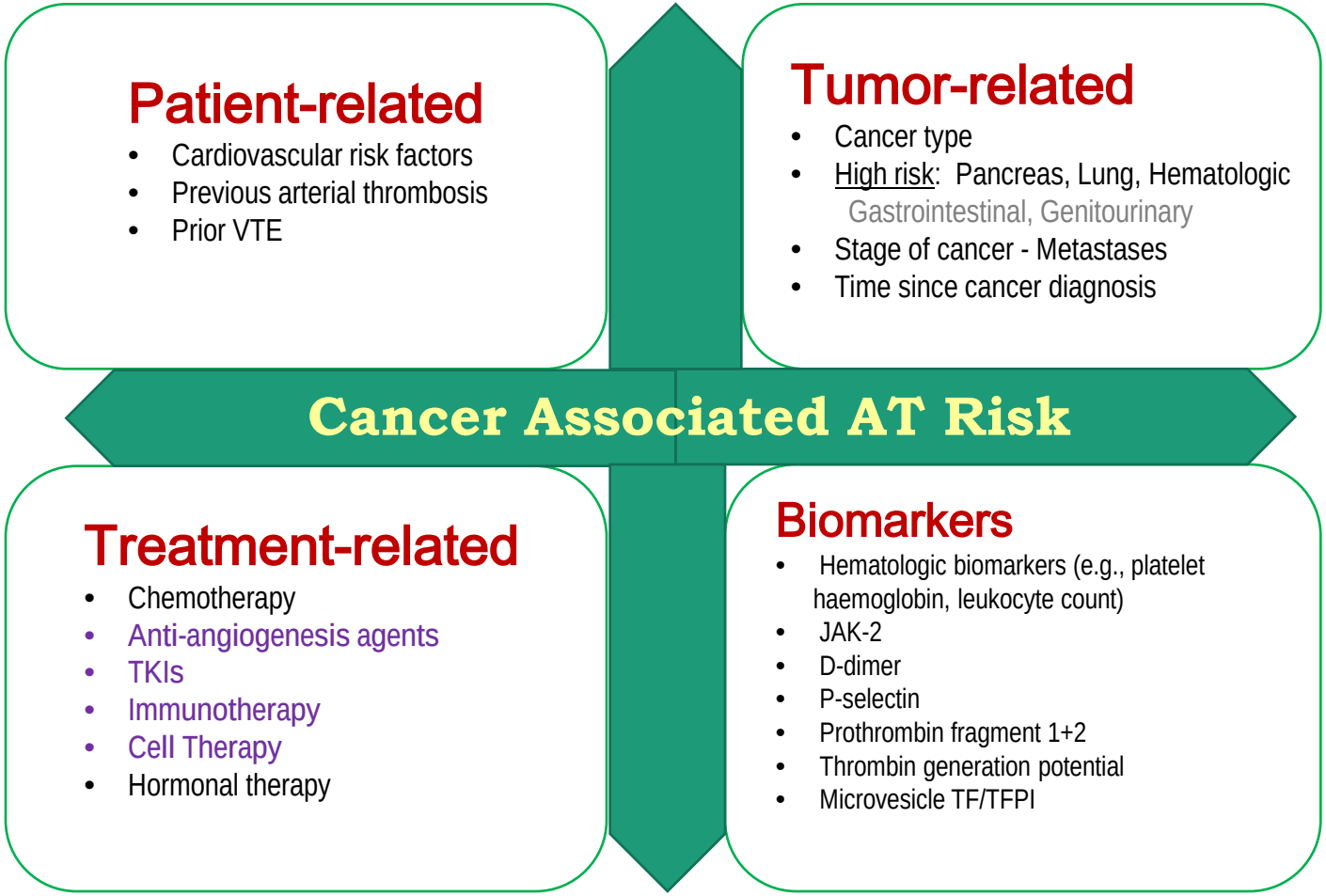
Multiple myeloma treated with thalidomide-, lenalidomide- or pomalidomide-based regimens: thromboprophylaxis with low-dose aspirin, fixed-dose VKA or LMWH

ASCO

Khorana Score 2 or greater: either thromboprophylaxis with a DOAC (apixaban or rivaroxaban) OR parenteral thromboprophylaxis (LMWH)

Multiple myeloma treated with thalidomide-, lenalidomide-based regimens with chemotherapy and/or dexamethasone: thromboprophylaxis with low-dose aspirin or LMWH for low risk and LMWH for high risk patients

Lyman Blood Adv 2021
Key J Clin Oncol 2019


Patient-related
Cardiovascular risk factors
Previous arterial thrombosis
Prior VTE
Tumor-related
Cancer type
High risk: Pancreas, Lung, Hematologic
Gastrointestinal, Genitourinary
Stage of cancer - Metastases
Time since cancer diagnosis
Cancer Associated AT Risk
Treatment-related
Chemotherapy
Anti-angiogenesis agents
TKIs
Immunotherapy
Cell Therapy
Hormonal therapy
Biomarkers
Hematologic biomarkers (e.g., platelet haemoglobin, leukocyte count)
JAK-2
D-dimer
P-selectin
Prothrombin fragment 1+2
Thrombin generation potential
Microvesicle TF/TFPI

Conclusions

- Patients with solid tumours and haematological malignancies are at high risk of thrombosis and bleeding.
- Mechanisms of Endothelium–Cancer interactions are complex and affect tumour progression and vascular events.
- While anti-angiogenic ,immunomodulatory and cellular therapy are increasingly used in cancer patients, thrombo-hemmorrhagic events remain a limitation.
- Role of thromboprophylaxis needs to be evaluated.

Thank you !