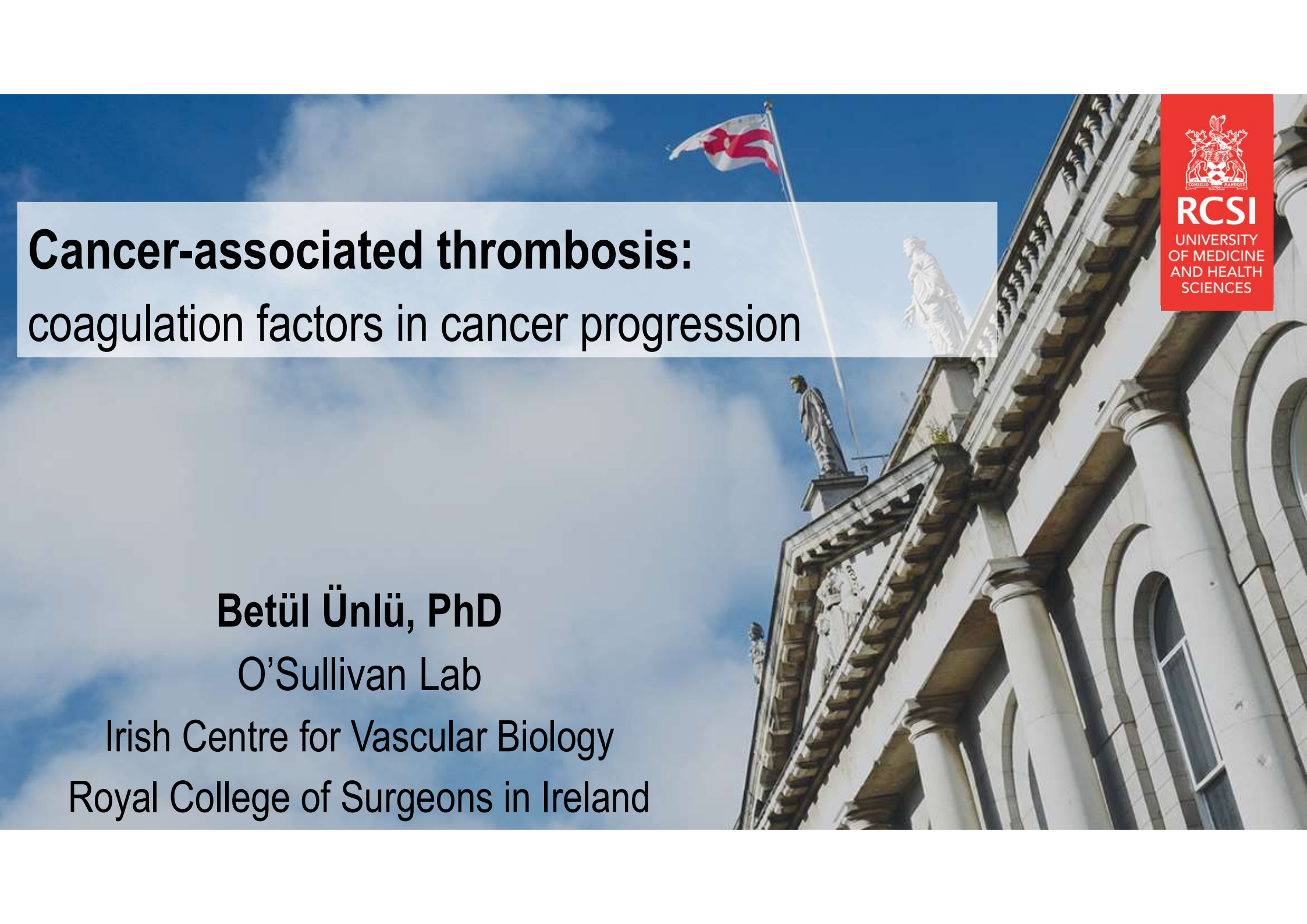




Cancer-associated thrombosis: coagulation factors in cancer progression

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Irish Centre for Vascular Biology

Royal College of Surgeons in Ireland



RCSI
UNIVERSITY
OF MEDICINE
AND HEALTH
SCIENCES

Conflict of interest

None

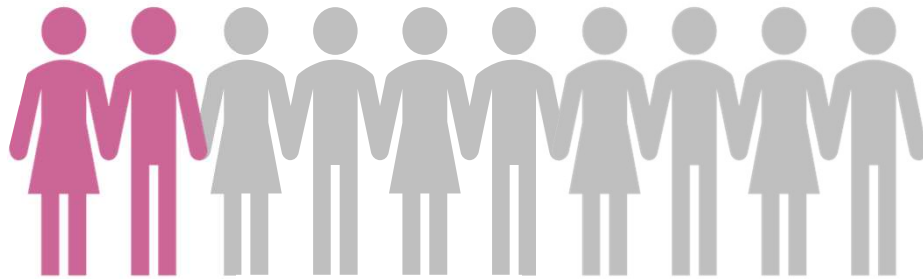
Trousseau's syndrome



Link between cancer and thrombosis

Cancer-associated thrombosis

- 20% of all venous thromboembolism (VTE) patients are diagnosed with cancer



- Cancer patients have ~9-fold increased risk of VTE
- High pancreas, brain
- Moderate lung, colon
- Low breast, prostate

Cancer-associated thrombosis decreases survival

Major morbidities

- Recurrent thrombosis
- Interruption of anti-cancer treatment
- Quality of life
- Increased risk of bleeding

Increased mortality

2nd leading cause of death

Exposure	HR
None	1.0 (reference)
Only VTE	2.6 (2.0-3.3)
Only cancer	7.4 (6.8-8.2)
Cancer-related VTE	31.2 (24.6-39.6)

Risk factors of cancer-associated thrombosis

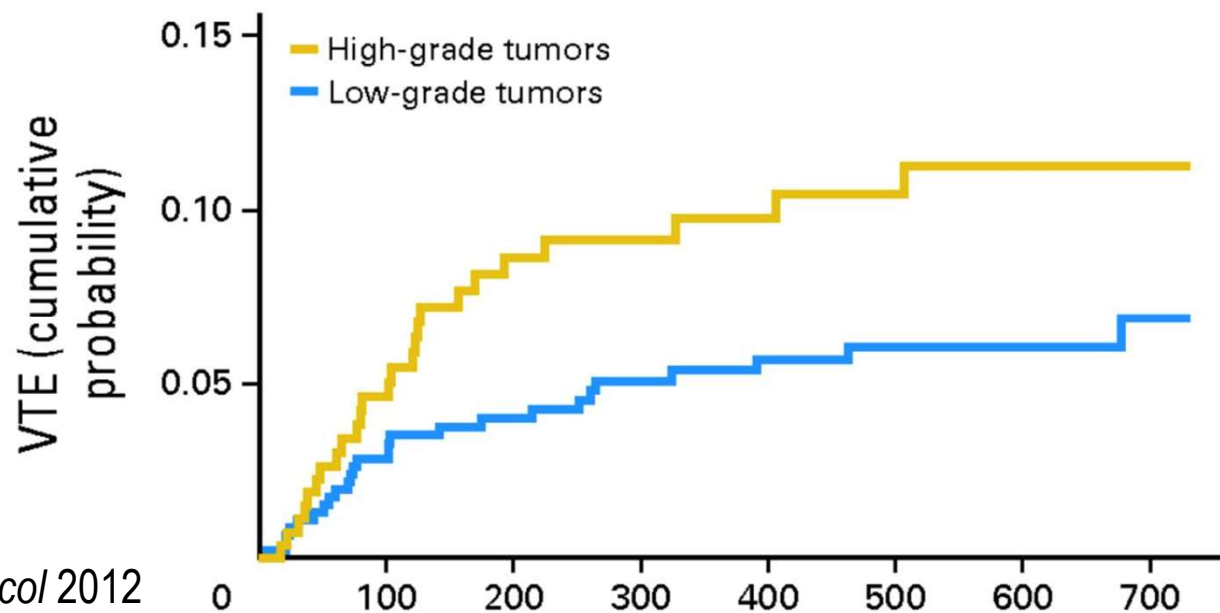
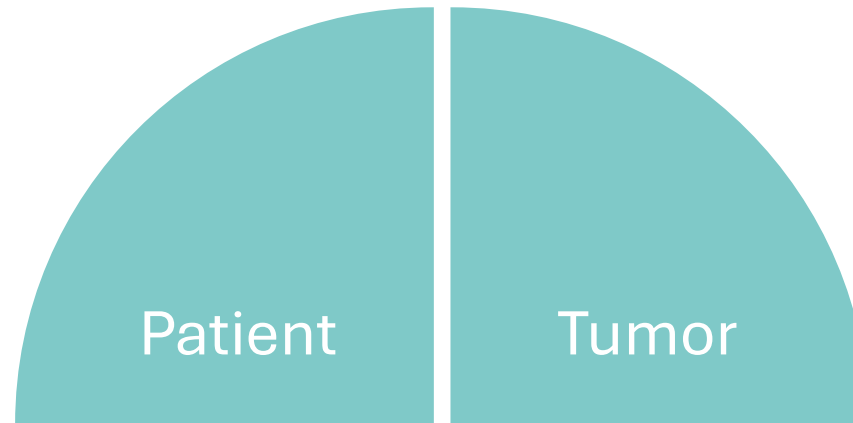
Age
Genetics
Ethnicity
History of VTE
Obesity



Risk factors of cancer-associated thrombosis

Age
Genetics
Ethnicity
History of VTE
Obesity

Primary tumor site
Histology
Metastasis



Ahlbrecht et al. *J Clin Oncol* 2012

Risk factors of cancer-associated thrombosis

Age
Genetics
Ethnicity
History of VTE
Obesity

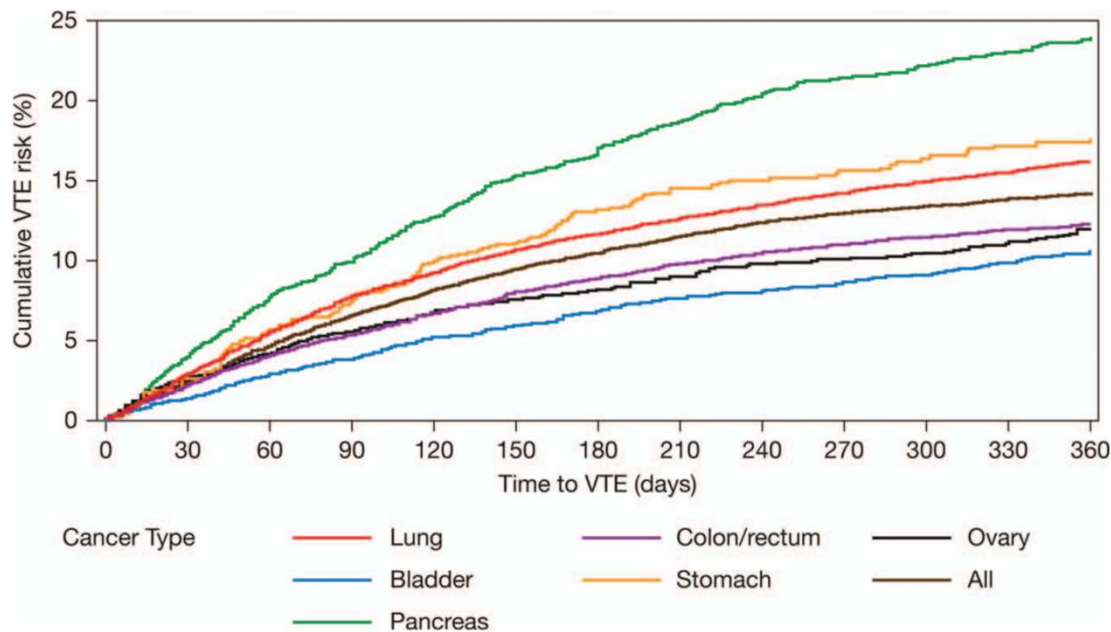
Patient

Primary tumor site
Histology
Metastasis

Tumor

Treatment

Surgery
Chemotherapy
Checkpoint inhibitors

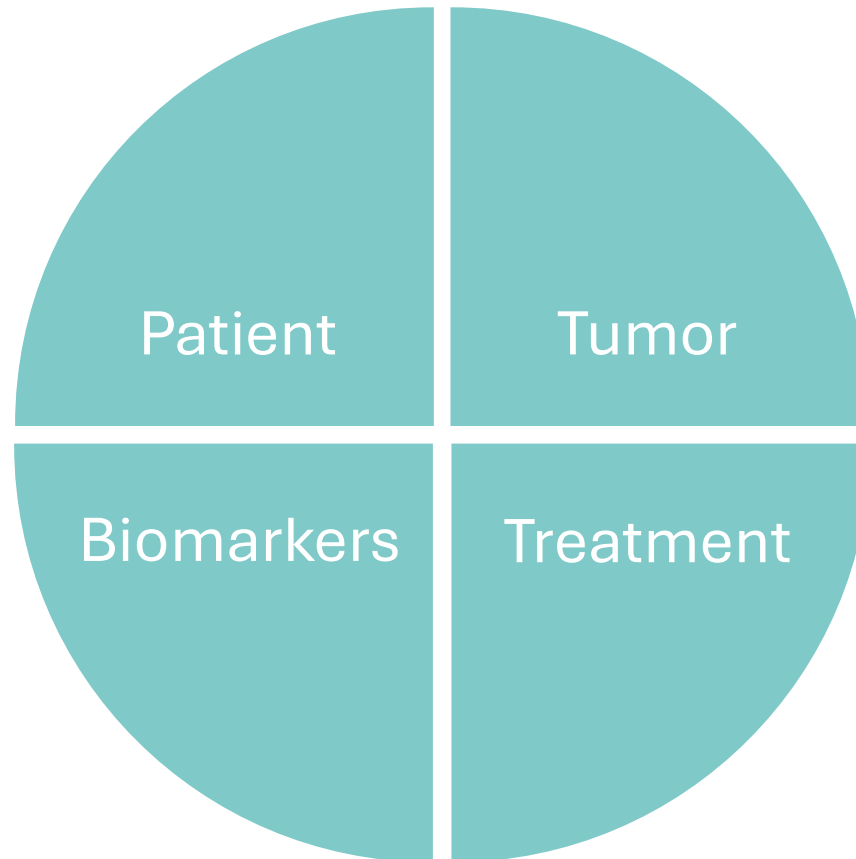


Risk factors of cancer-associated thrombosis

Age
Genetics
Ethnicity
History of VTE
Obesity

Up
D-dimer
Procoagulant factors
 TF, VWF, fibrinogen
Platelets

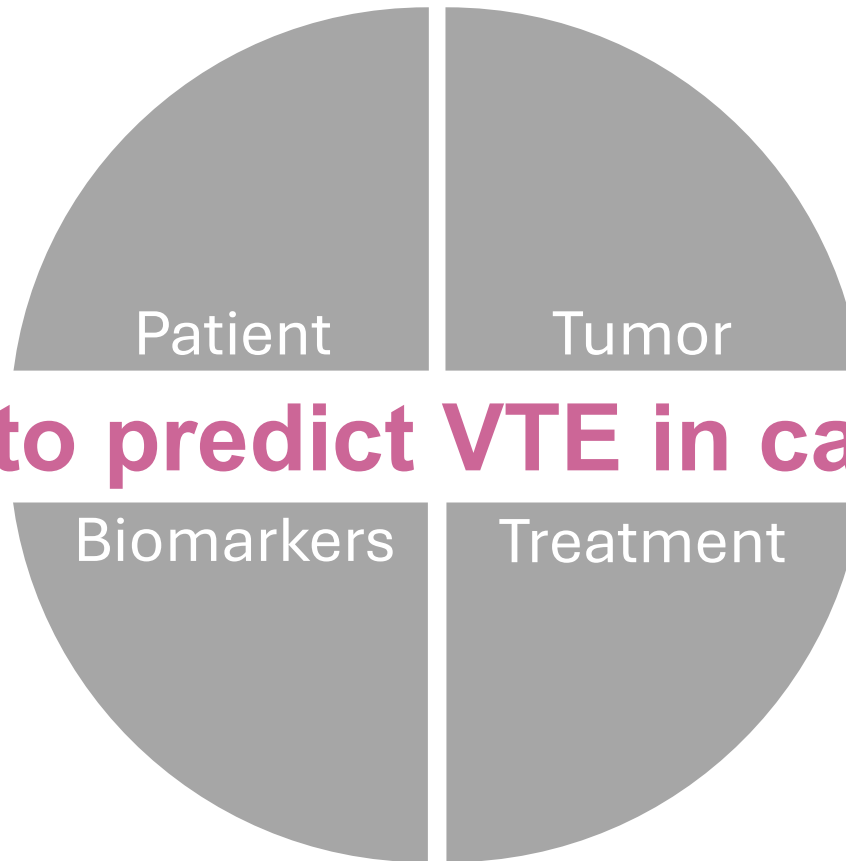
Down
APC activity
Fibrinolysis



Primary tumor site
Histology
Metastasis

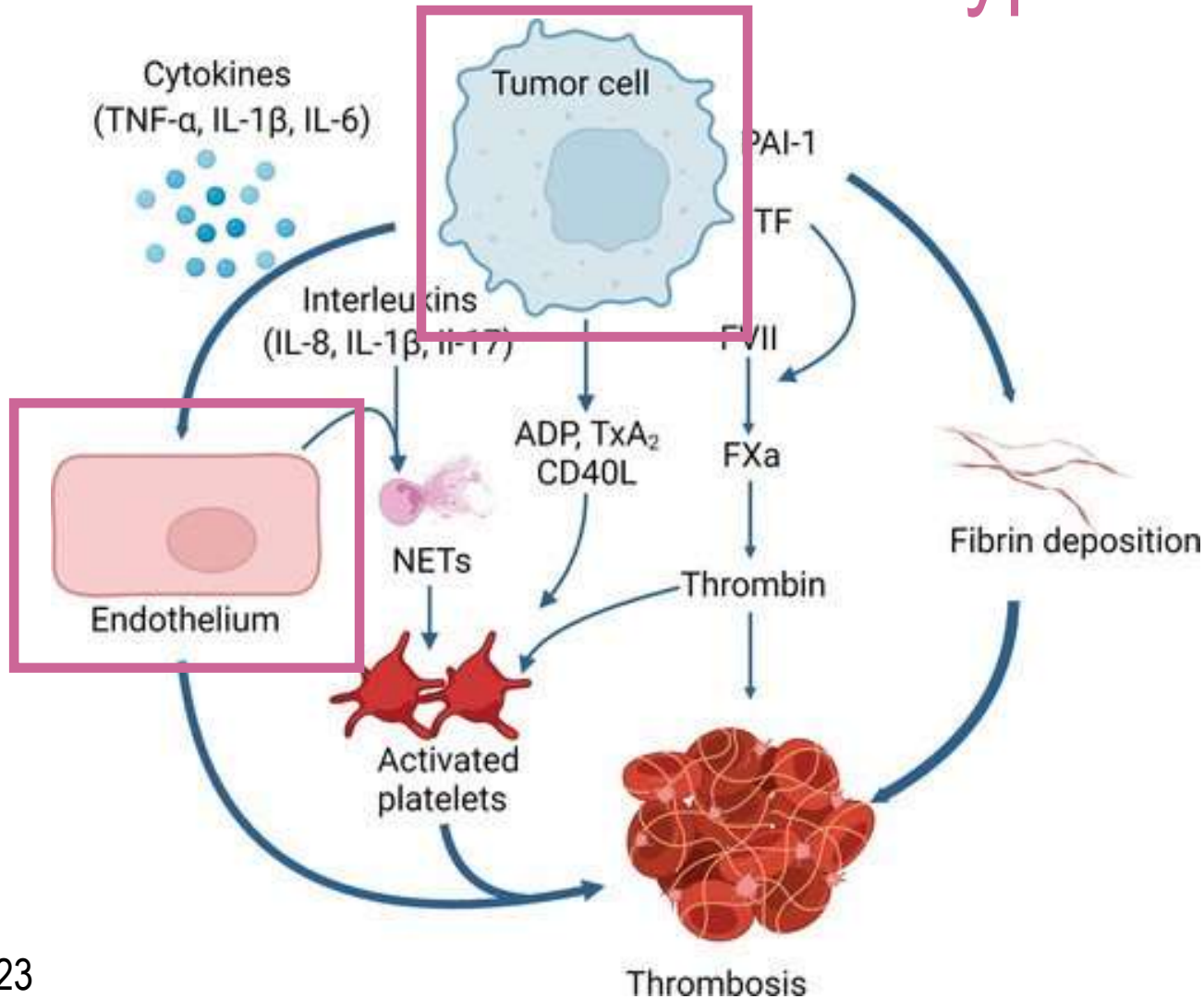
Surgery
Chemotherapy
Checkpoint inhibitors

Risk factors of cancer-associated thrombosis



Challenging to predict VTE in cancer patients

Multifactorial mechanism to drive hypercoagulant state



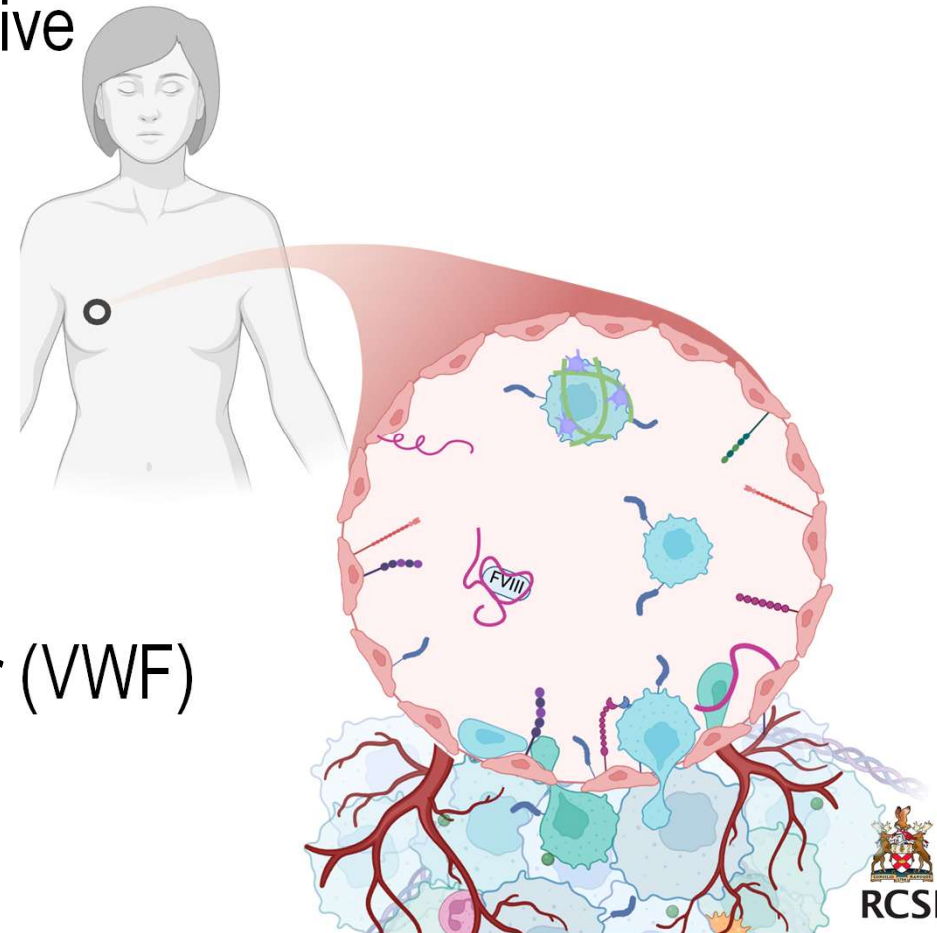
Aim

Coagulation factors to promote cancer progression

Triple-negative breast cancer is highly aggressive and metastatic

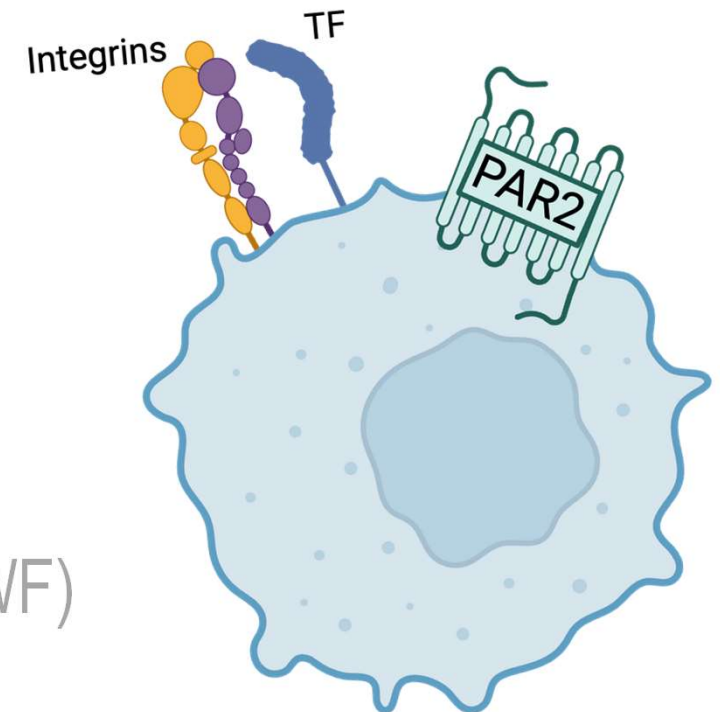
MDA-MB-231

1. Tumor-expressed Tissue Factor (TF)
2. Endothelium-derived von Willebrand Factor (VWF)



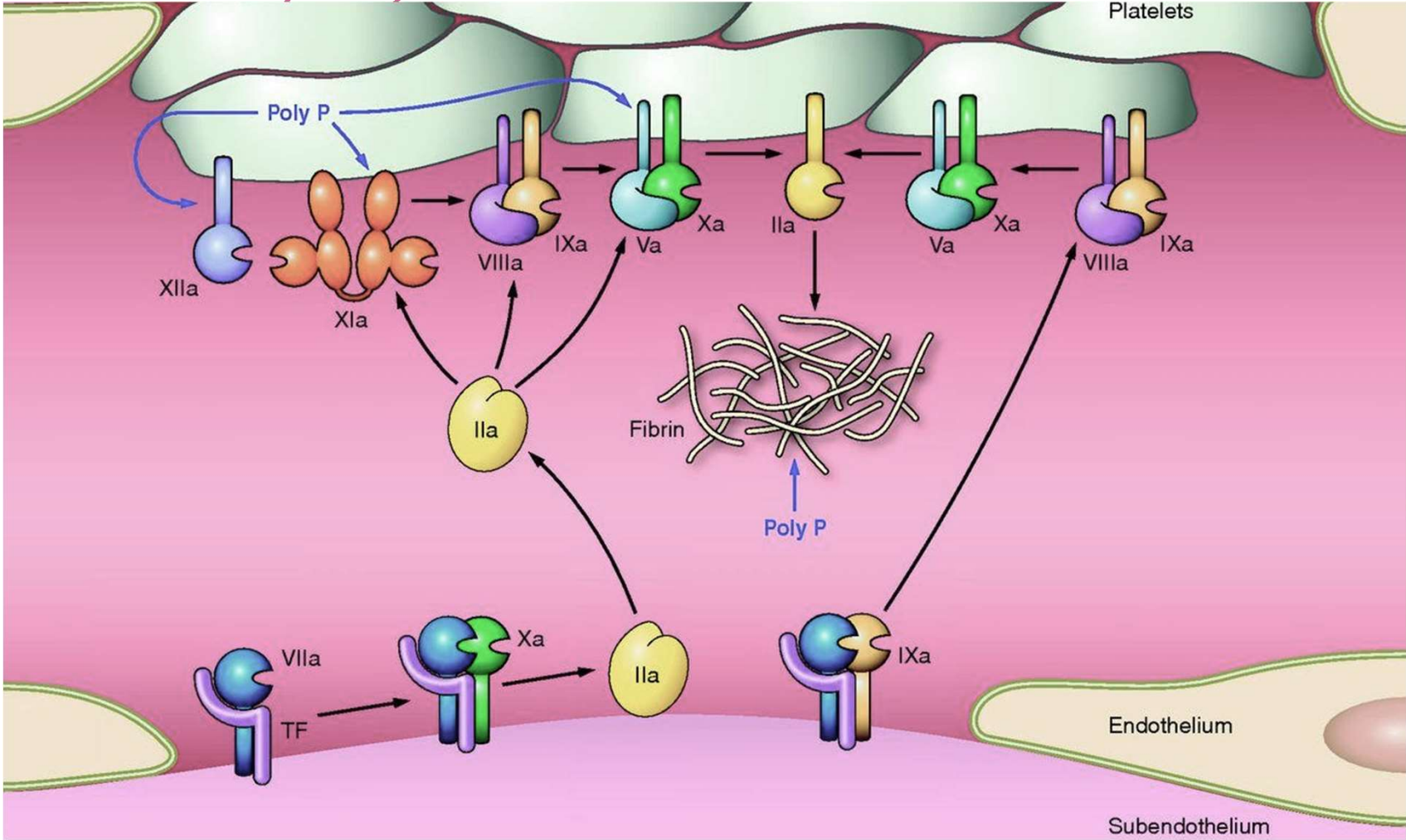
Aim

Coagulation factors to promote cancer progression



1. Tumor-expressed Tissue Factor (TF)
2. Endothelium-derived von Willebrand Factor (VWF)

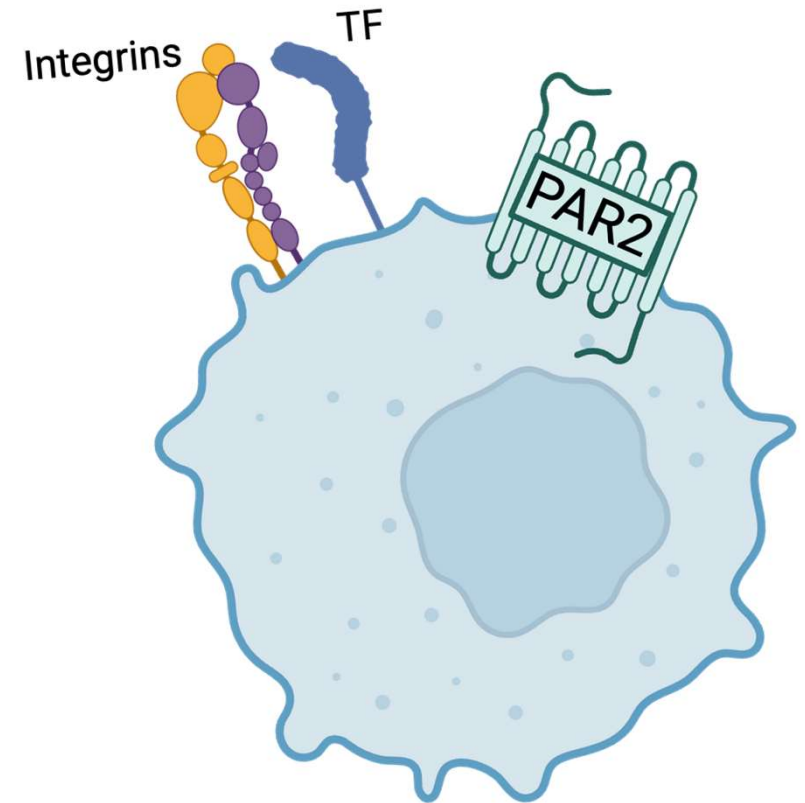
Tissue Factor (TF) in hemostasis



Tissue Factor in cancer progression

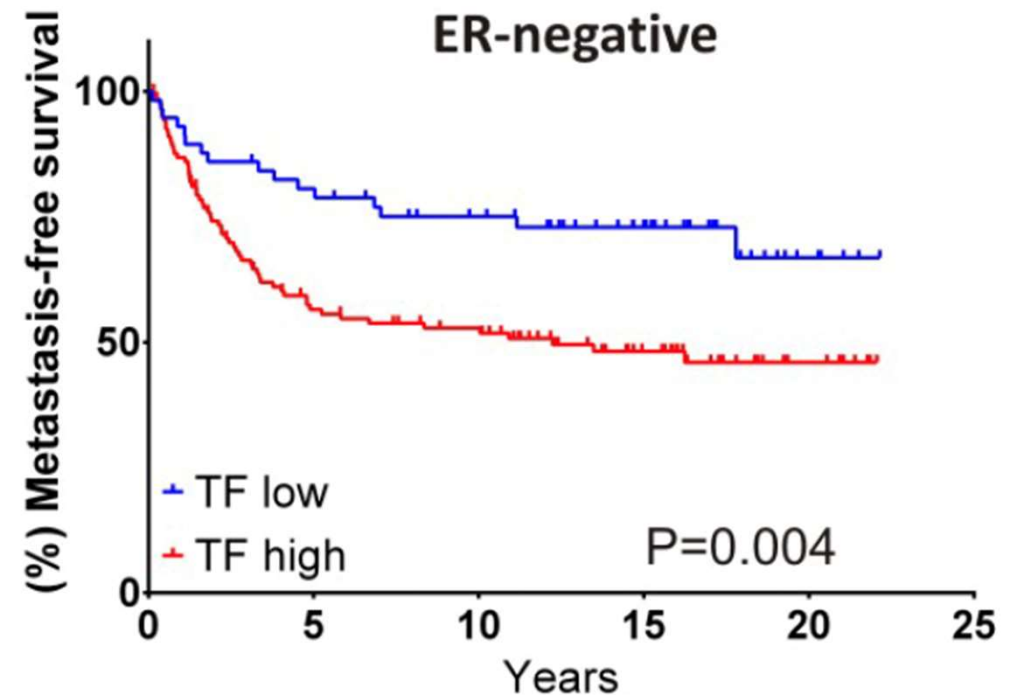
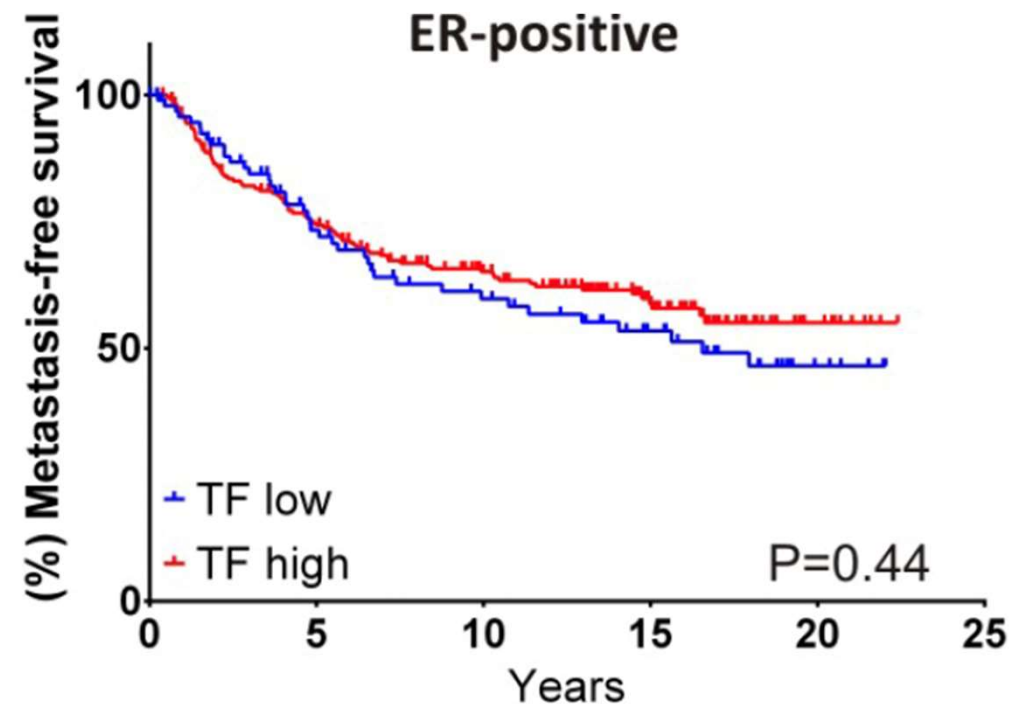
Elevated TF expression in cancer cells

- Higher tumor grade
- Increased angiogenesis
- Increased invasive and metastatic behavior



Metastasis associates with TF in ER-negative tumors

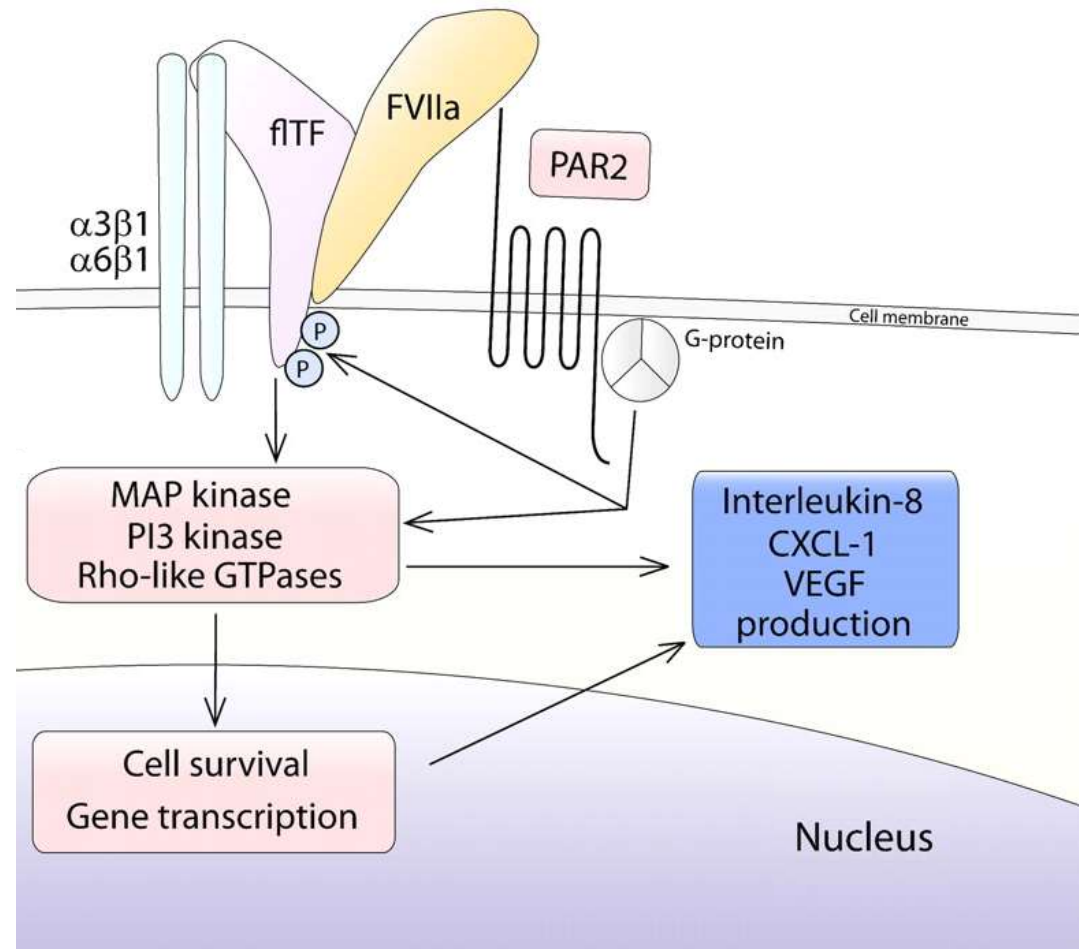
574 breast cancer specimens



TF-mediated cancer progression

Two functional roles

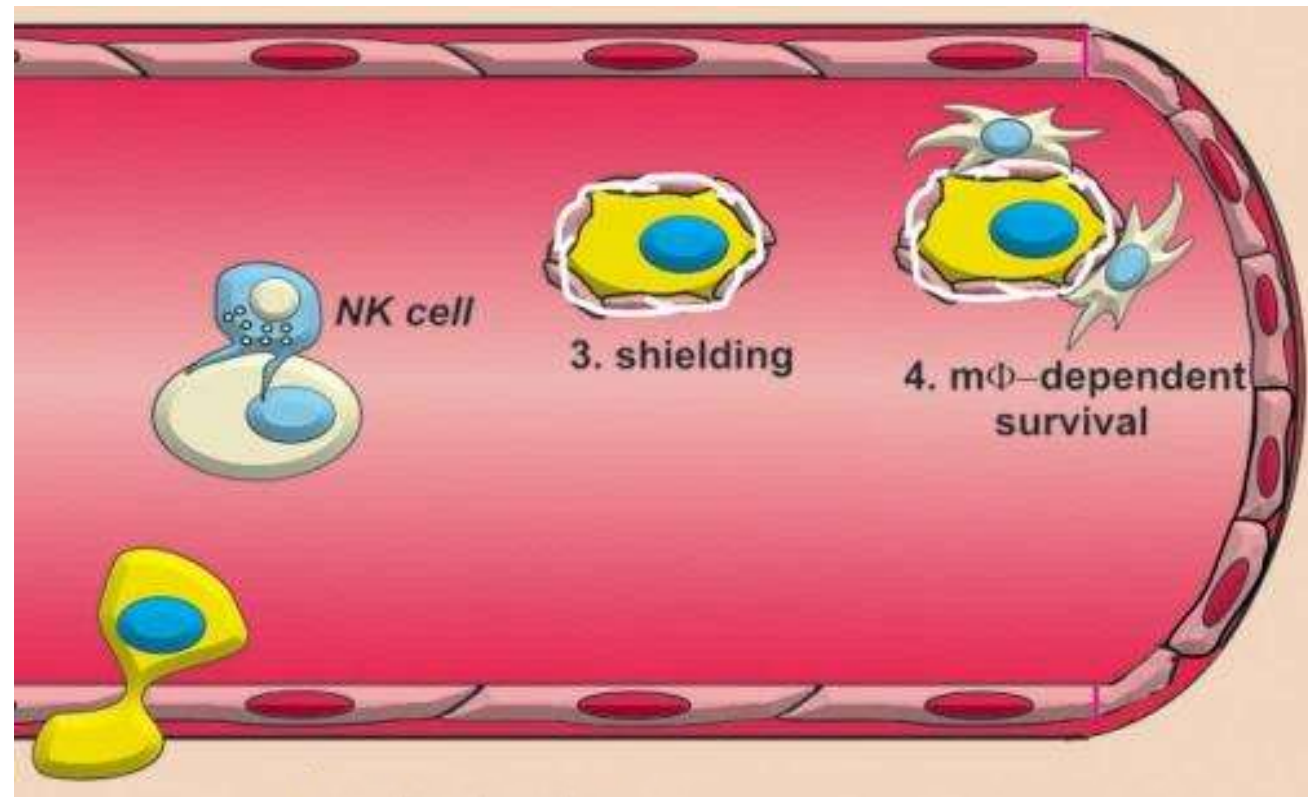
1. **Signaling** to promote tumor growth



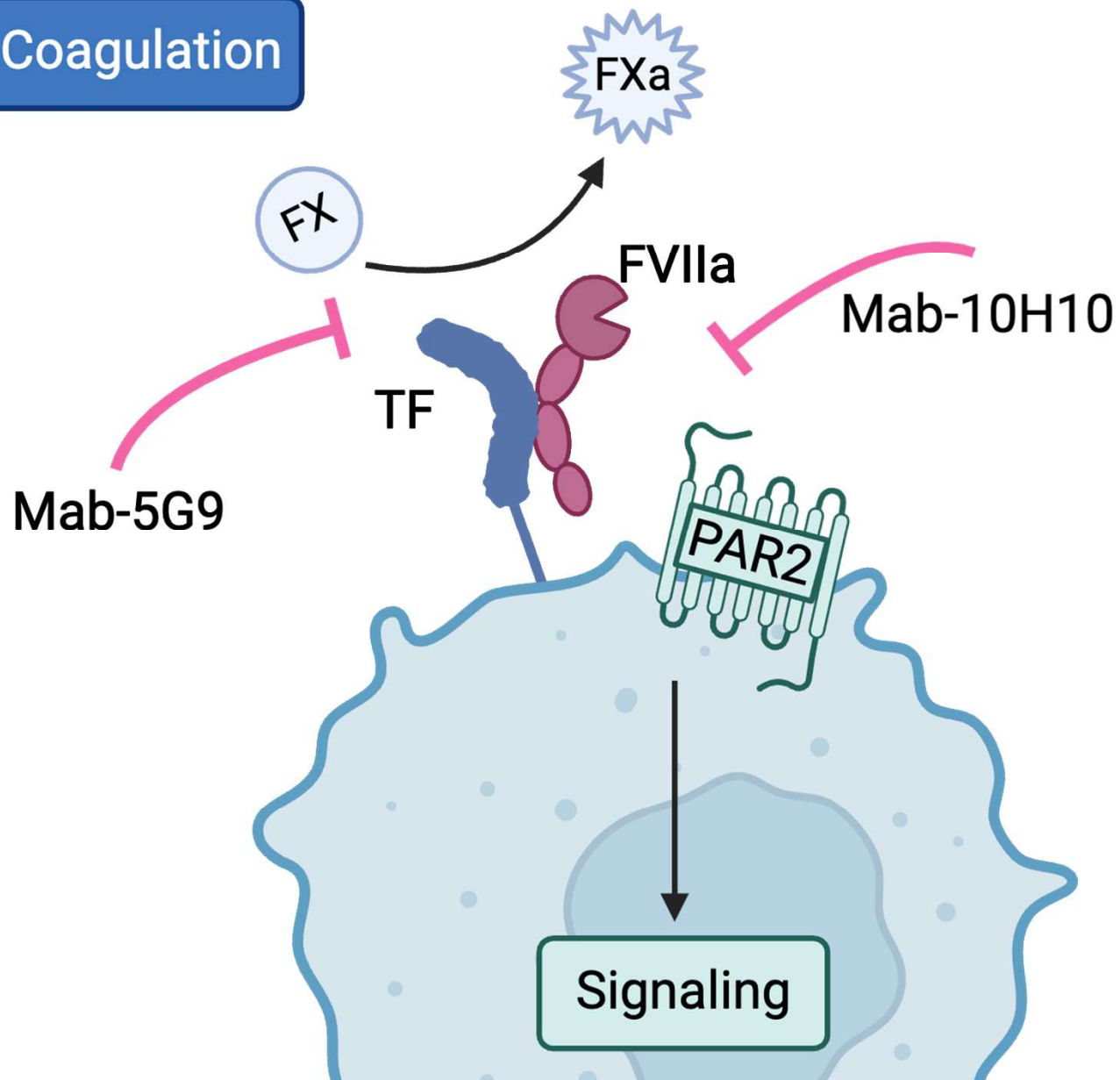
TF-mediated cancer progression

Two functional roles

1. **Signaling** to promote tumor growth
2. **Hemostasis** to promote survival of metastatic cells

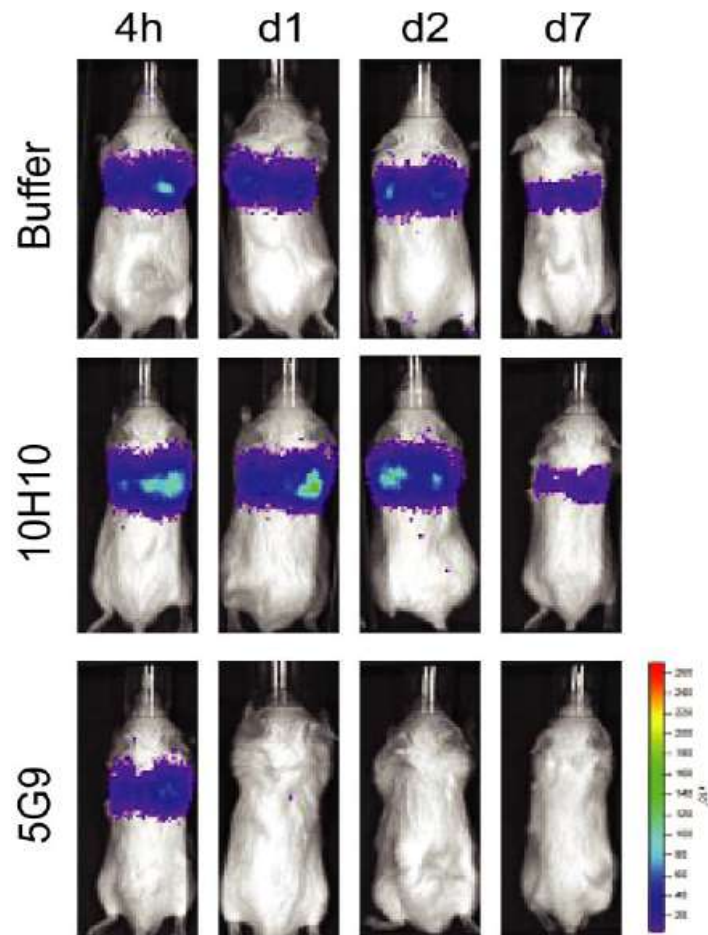


Coagulation



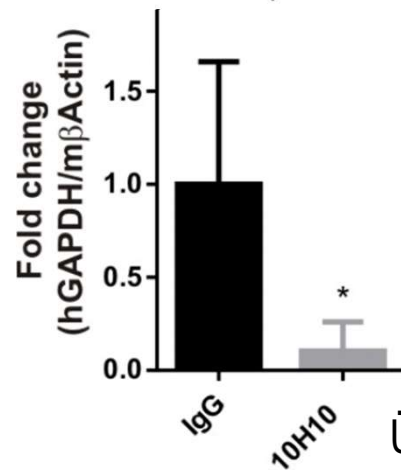
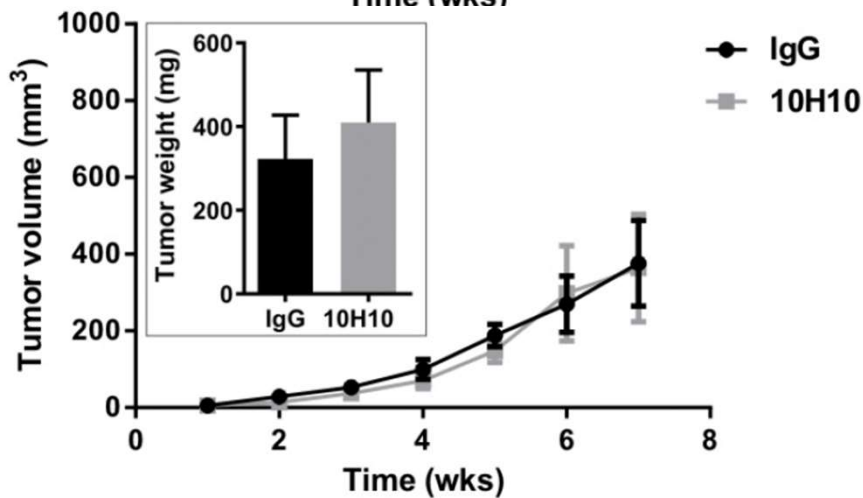
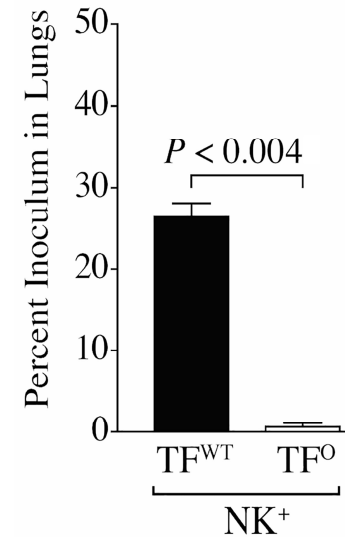
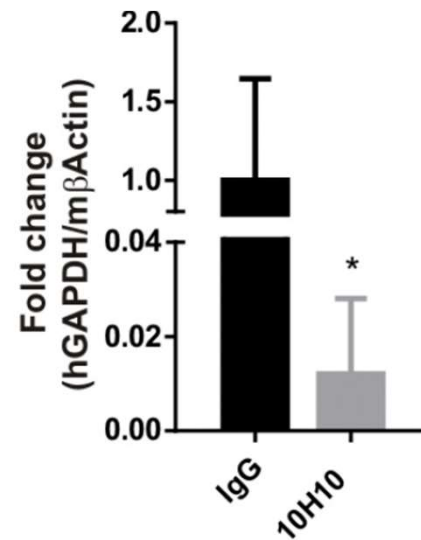
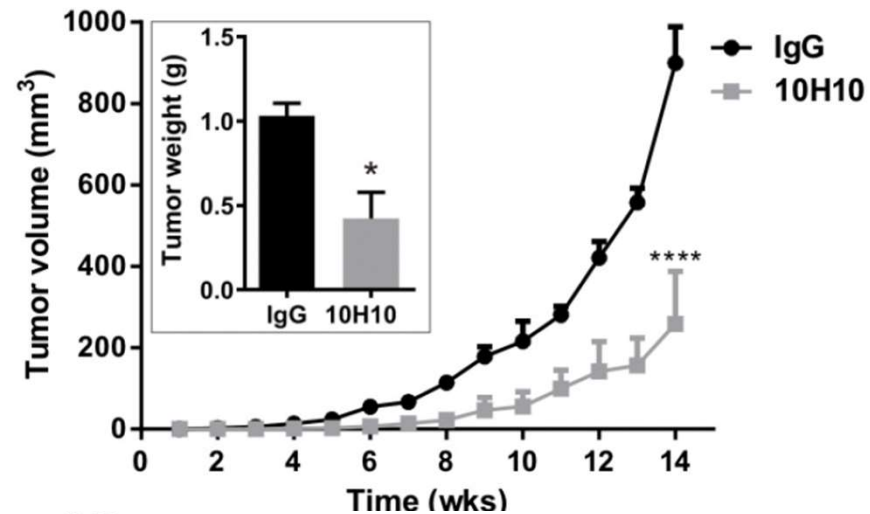
Targeting specific TF functions reduces cancer progression *in vivo*

5G9 — Coagulation
10H10 — Signaling



Versteeg et al. *Blood* 2008

Blockade of TF signaling reduces metastasis *in vivo*; independent of NK cells



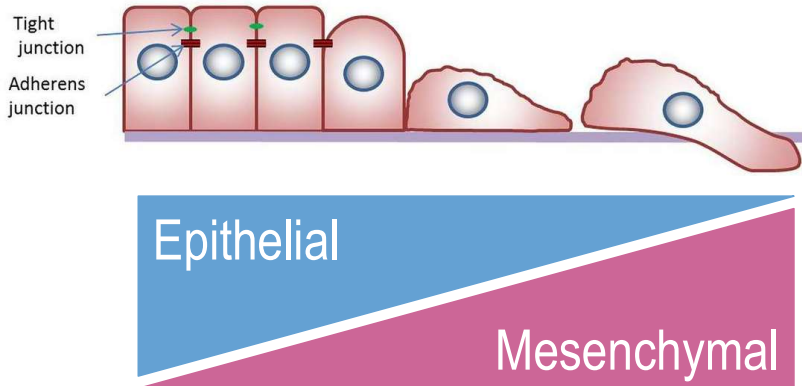
10H10 —| Signaling

Ünlü et al. *Oncogene* 2022

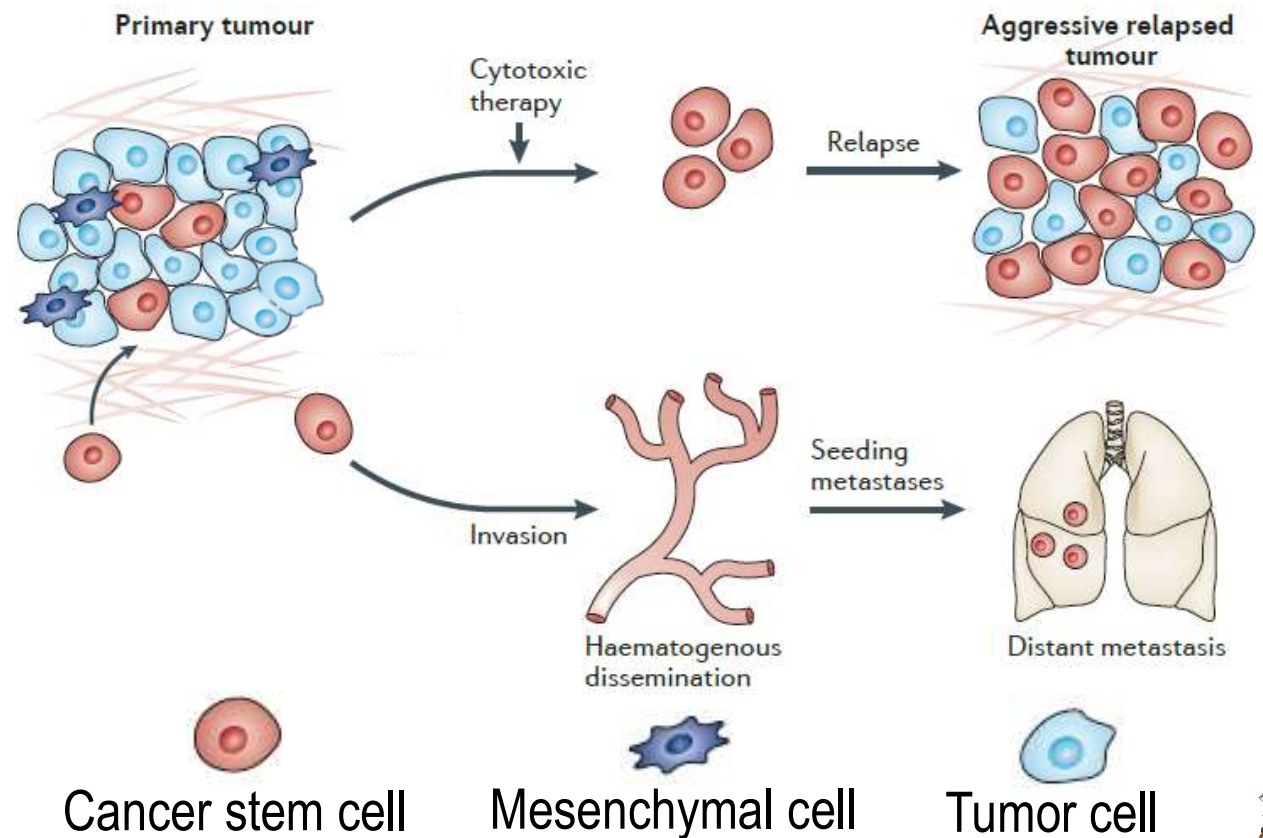


Molecular mechanism of metastasis

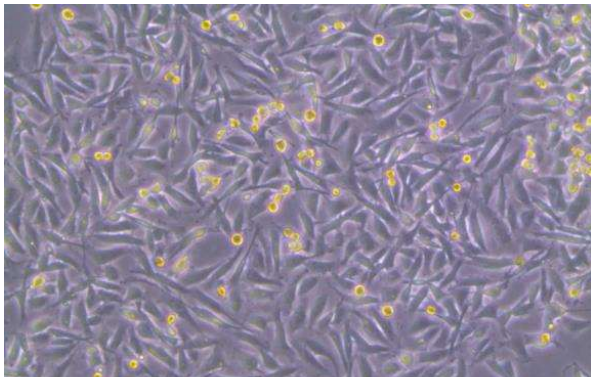
Epithelial to Mesenchymal Transition (EMT)



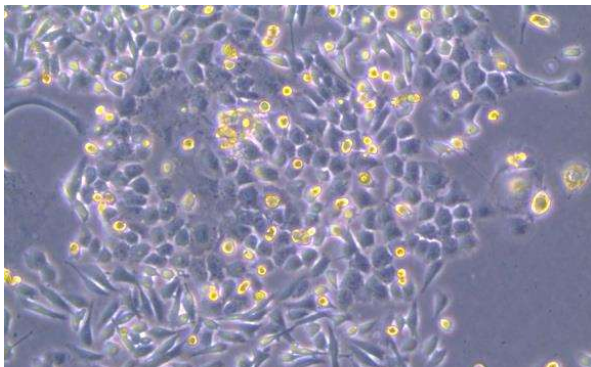
Cancer stem cells (CSCs)



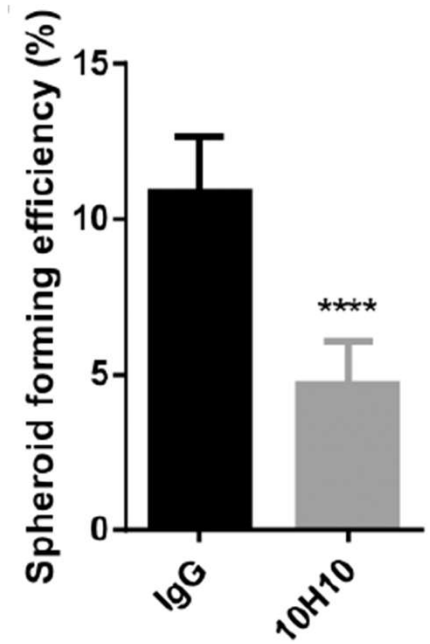
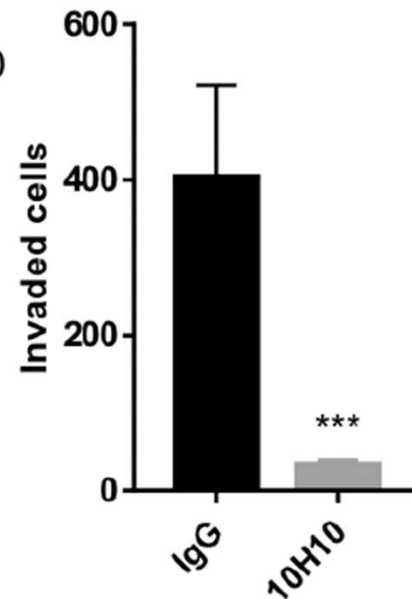
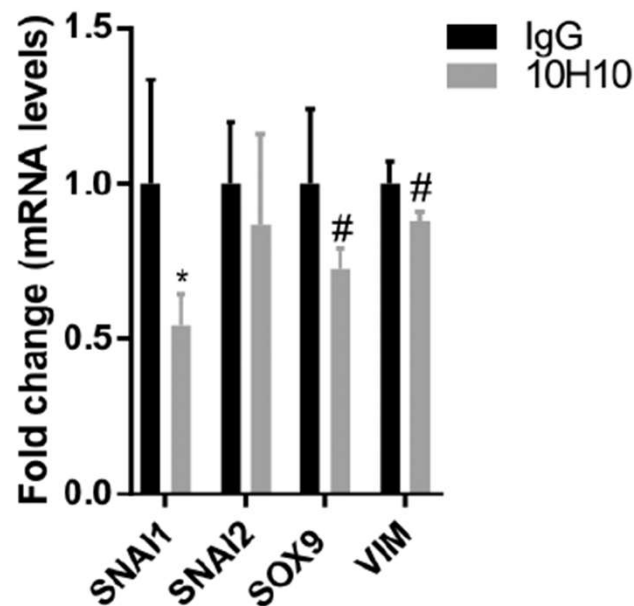
Inhibition of TF signaling reduces cancer cell aggressiveness



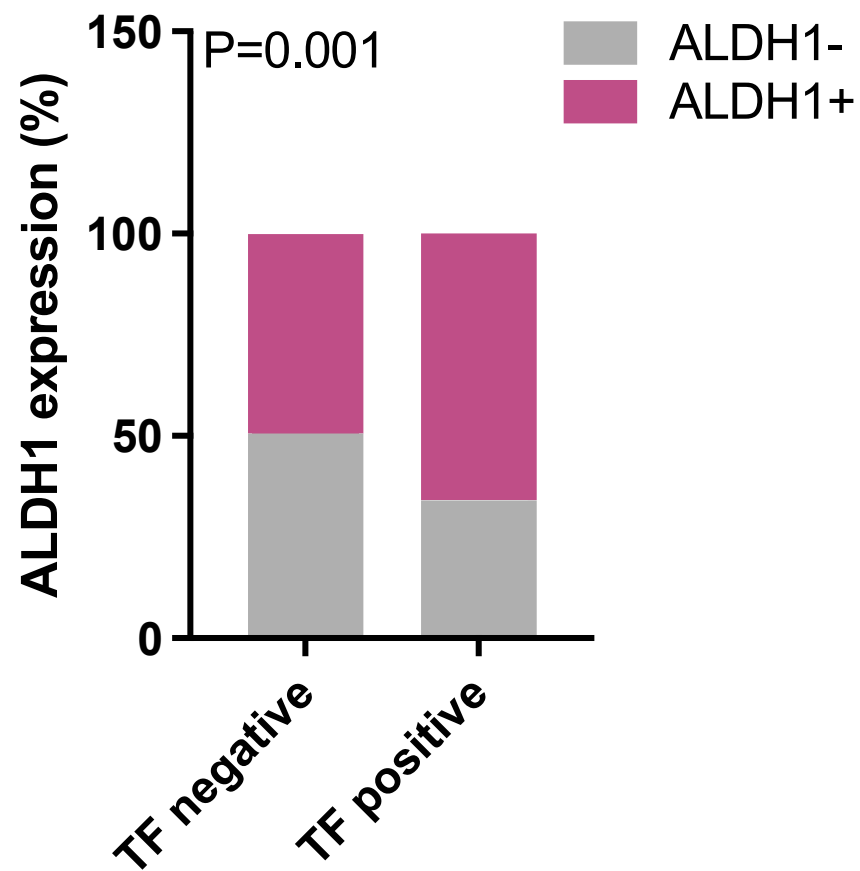
IgG: mesenchymal



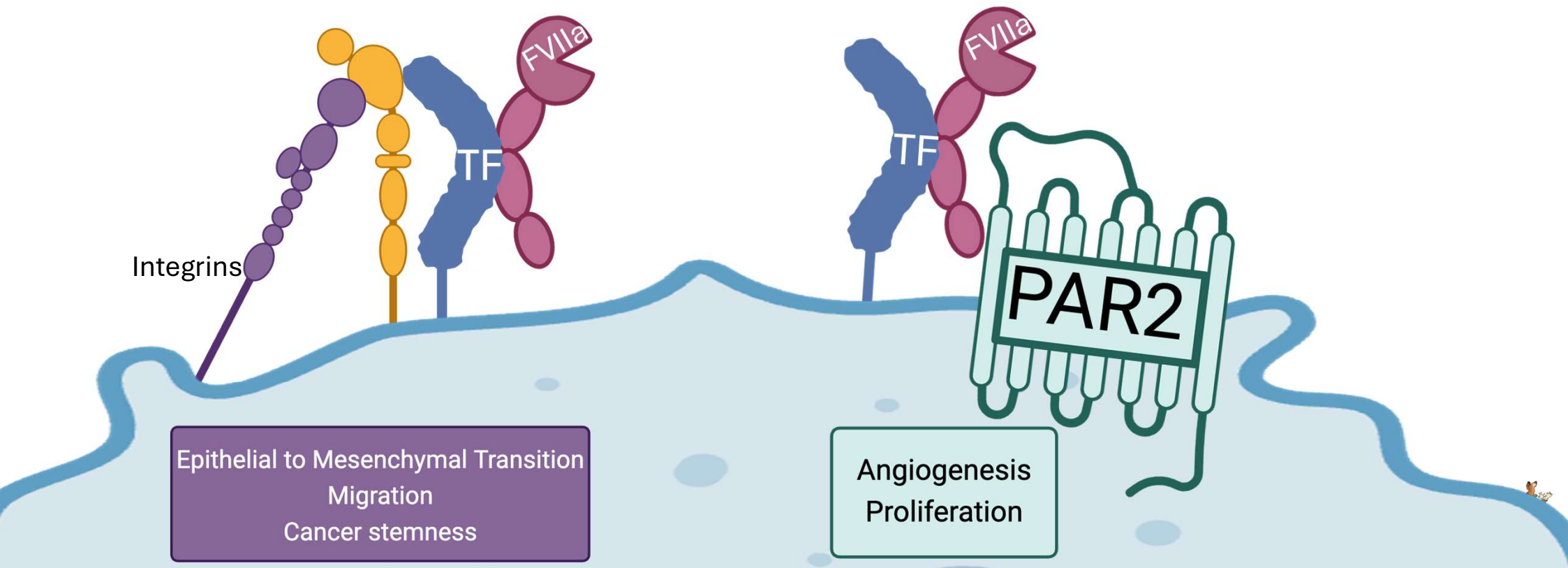
10H10: epithelial



TF expression associates with breast cancer stem cell marker ALDH1 in patients



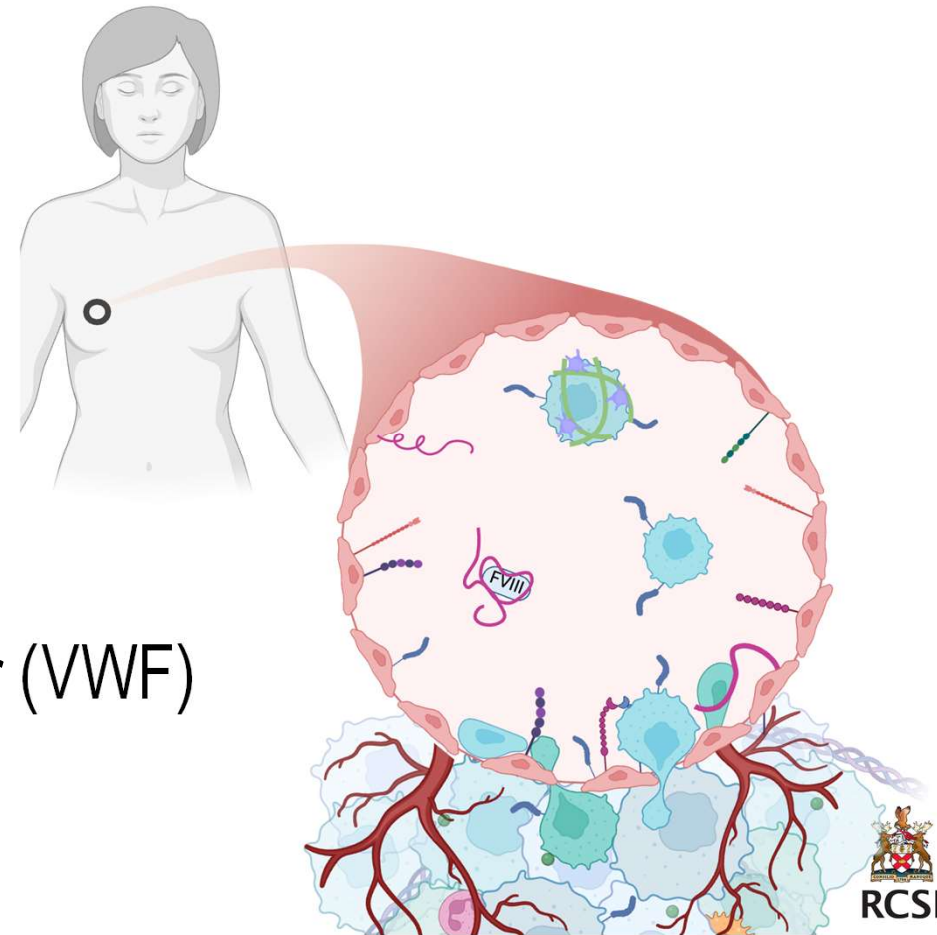
Integrin dependent TF signaling



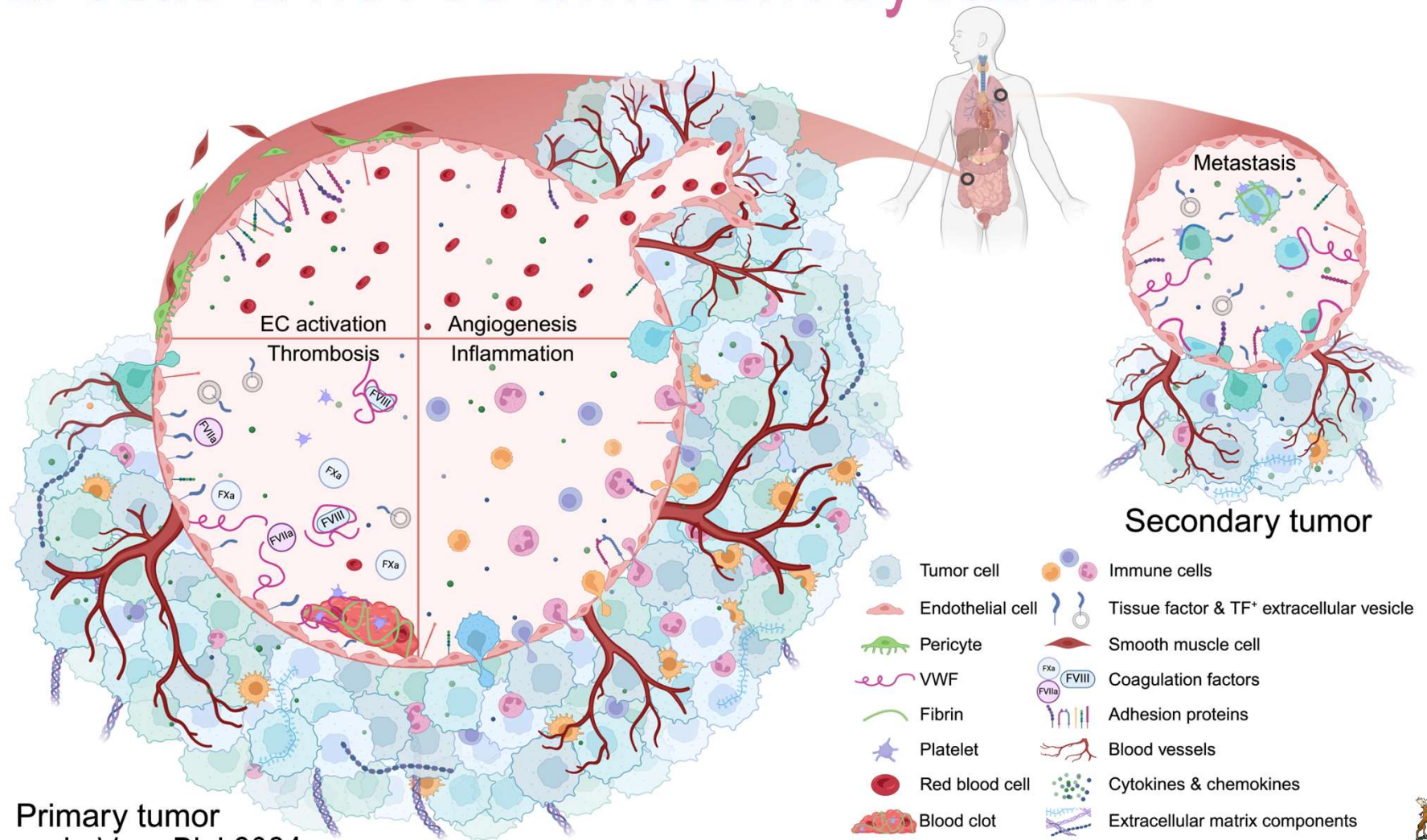
Aim

Coagulation factors to promote cancer progression

1. Tumor-expressed Tissue Factor (TF)
2. Endothelium-derived von Willebrand Factor (VWF)



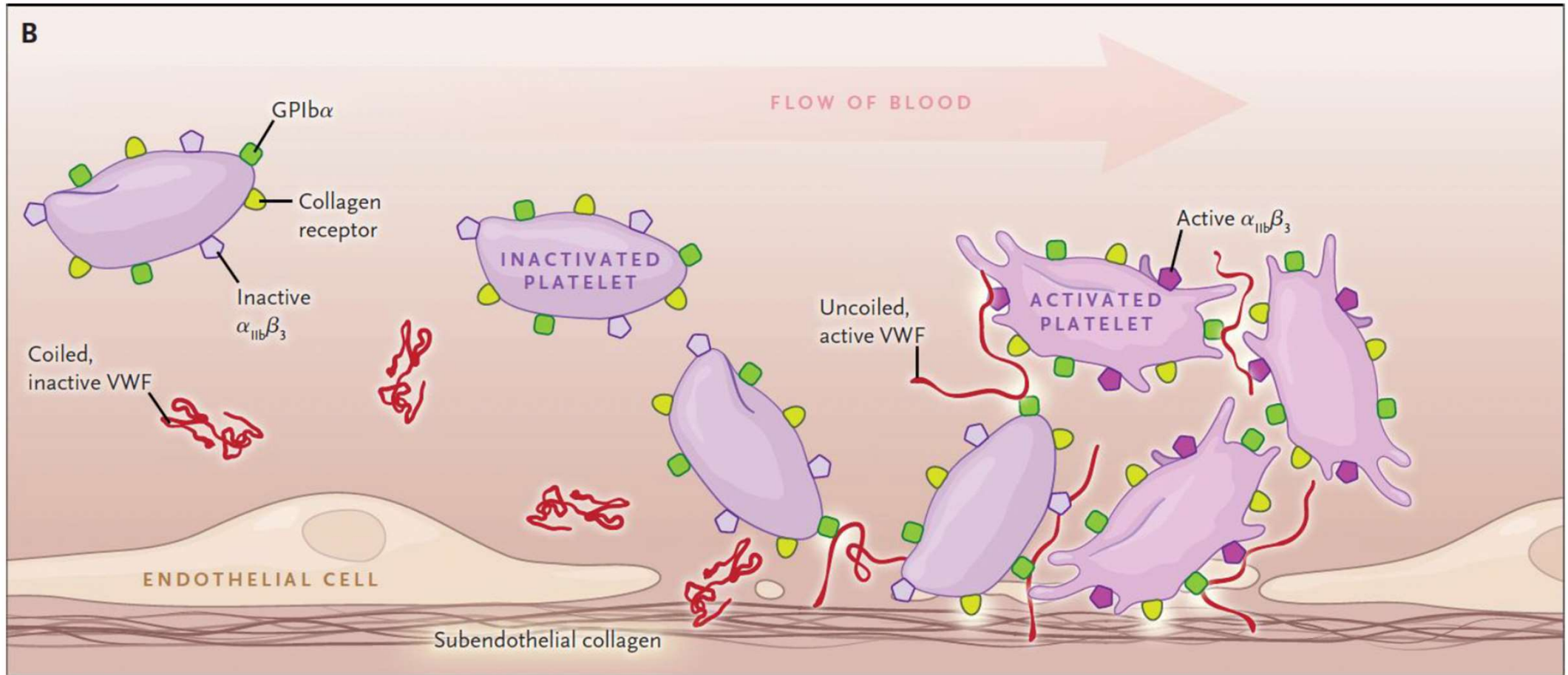
Endothelial cells a not-so-innocent bystander



Primary tumor

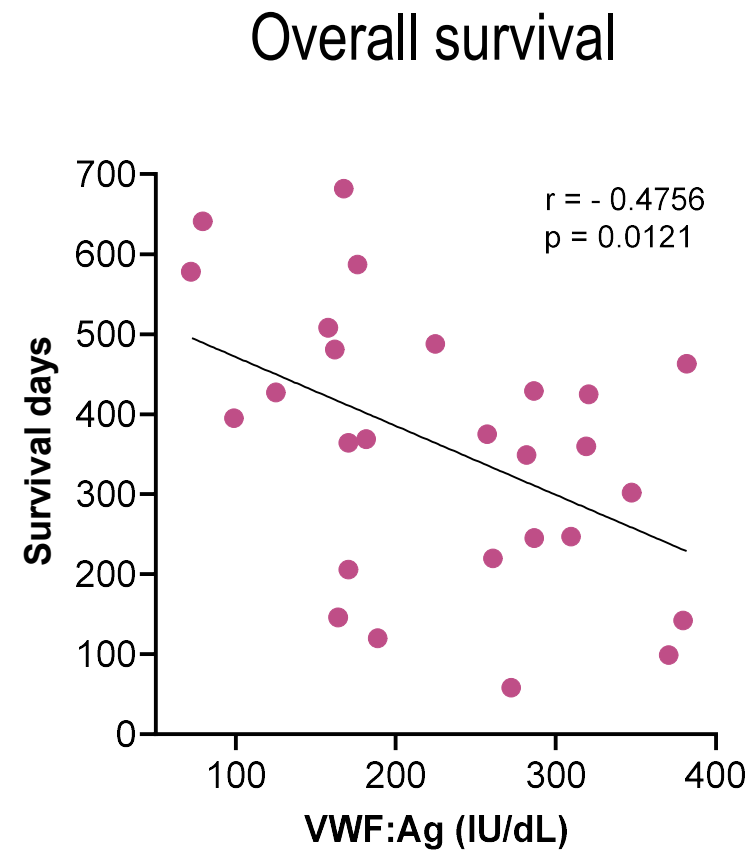
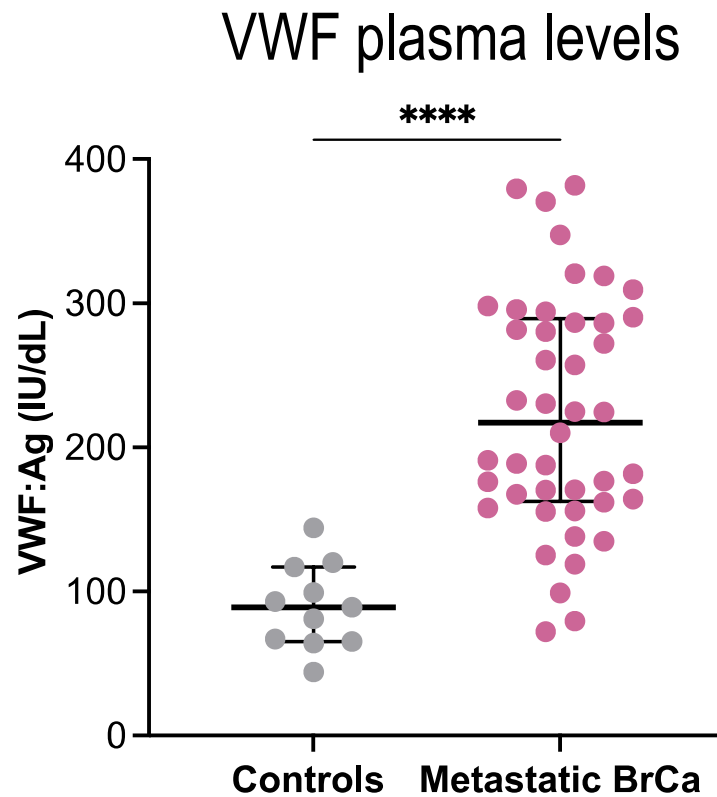
Secondary tumor

Von Willebrand Factor in primary haemostasis



Eikenboom & Leebeek, NEJM 2016

Elevated levels of von Willebrand Factor in breast cancer



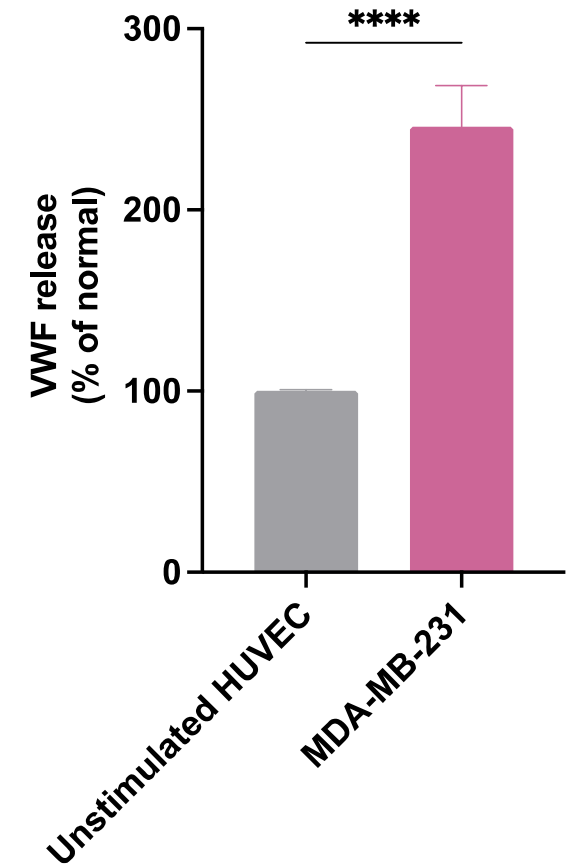
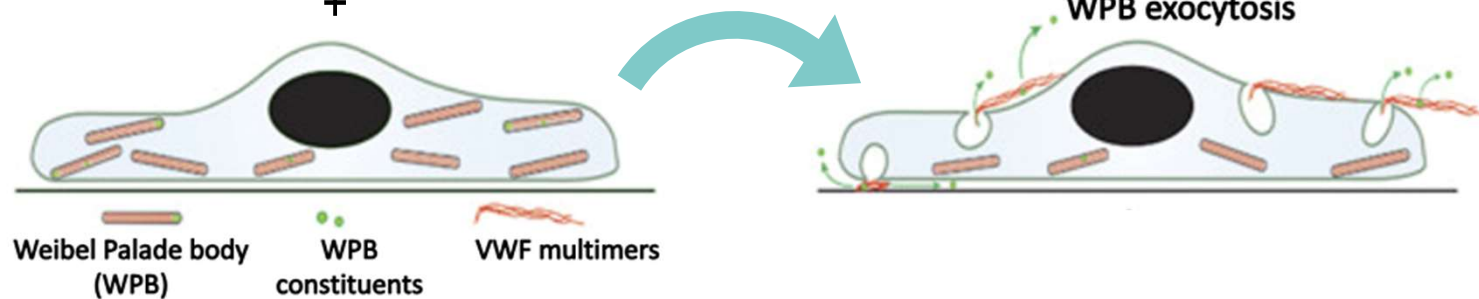
Adapted from Dhimi et al. JTH 2022

Breast cancer cells induce VWF secretion

Supernatant from MDA-MB-231
tumour cells

+

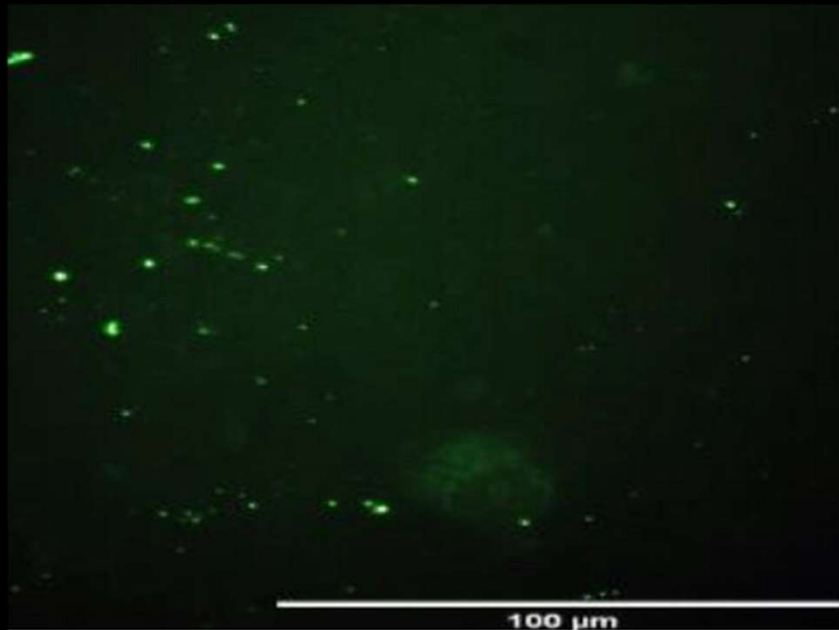
EC activation



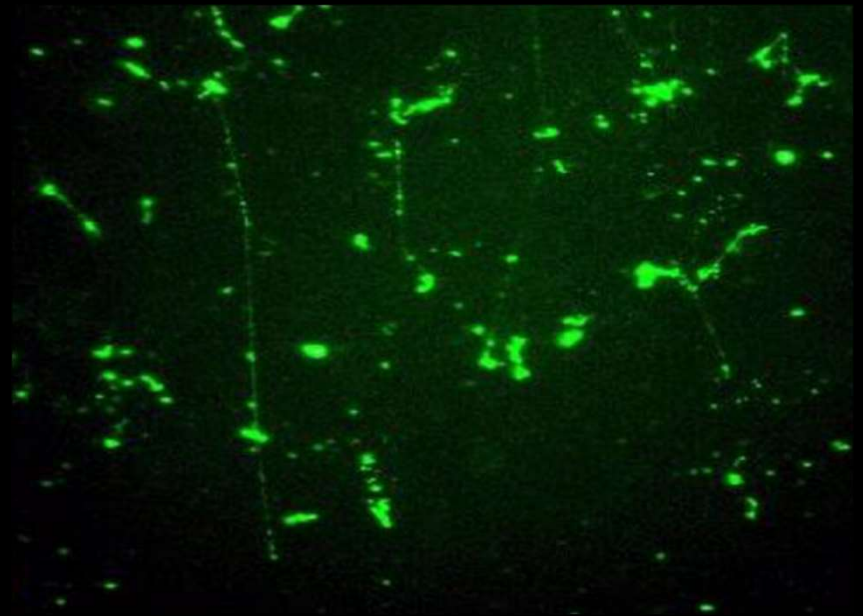
Adapted from Dhimi et al. JTH 2022

Breast cancer cells induce VWF secretion

Unstimulated ECs

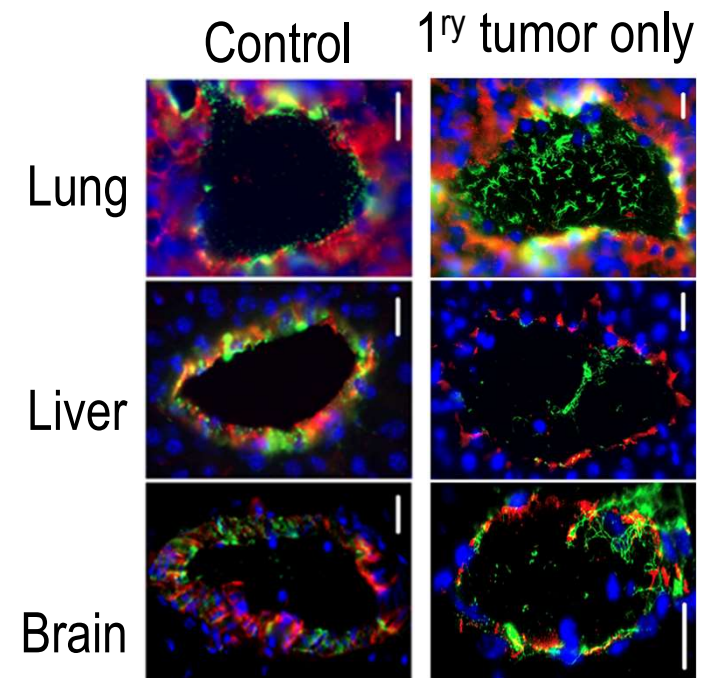
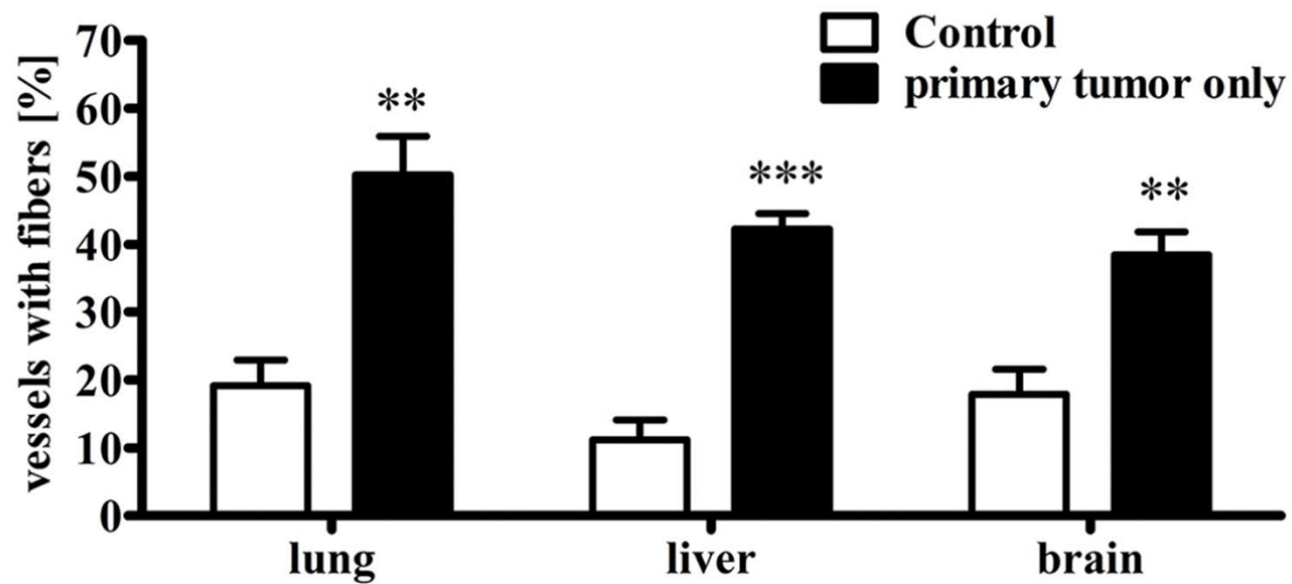


+ MDA-MB-231 media

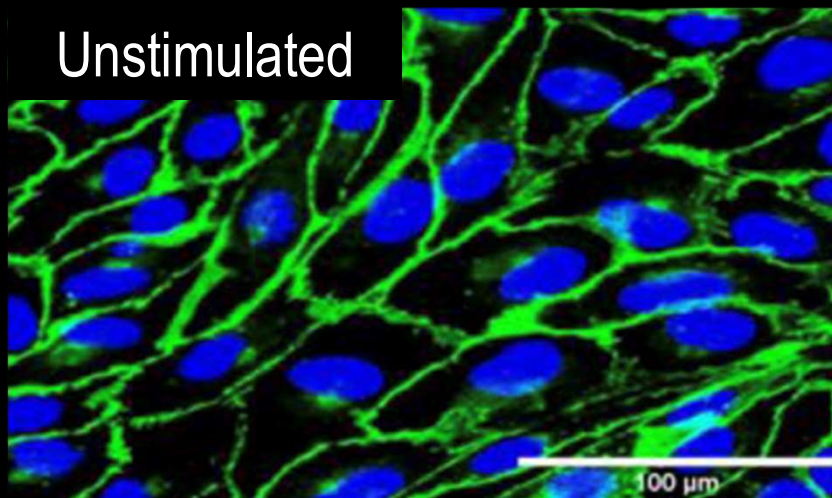


VWF

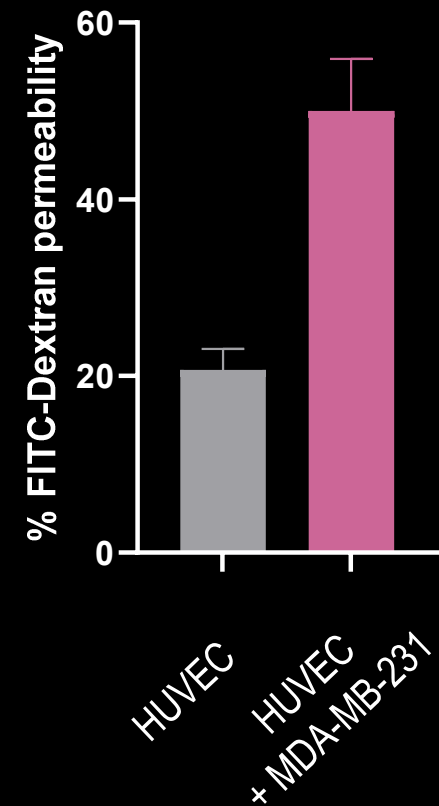
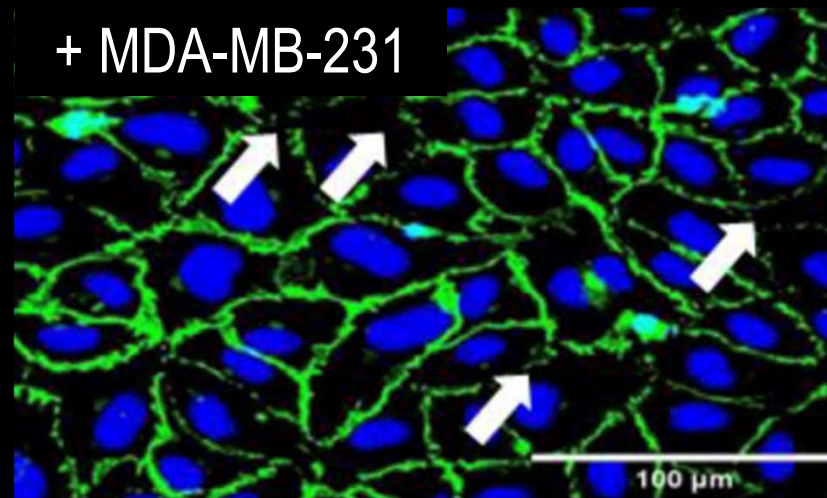
Cancers can induce VWF secretion at distant organs



Breast cancer cells increase endothelial cell permeability

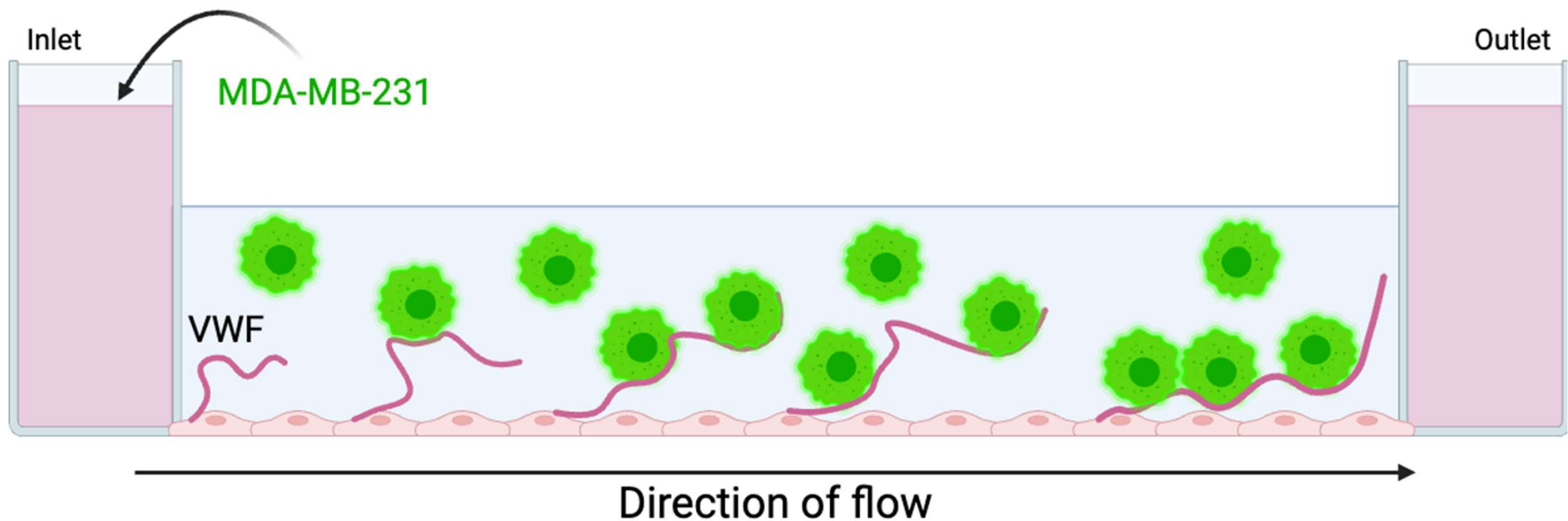


VE-cadherin
Nuclei



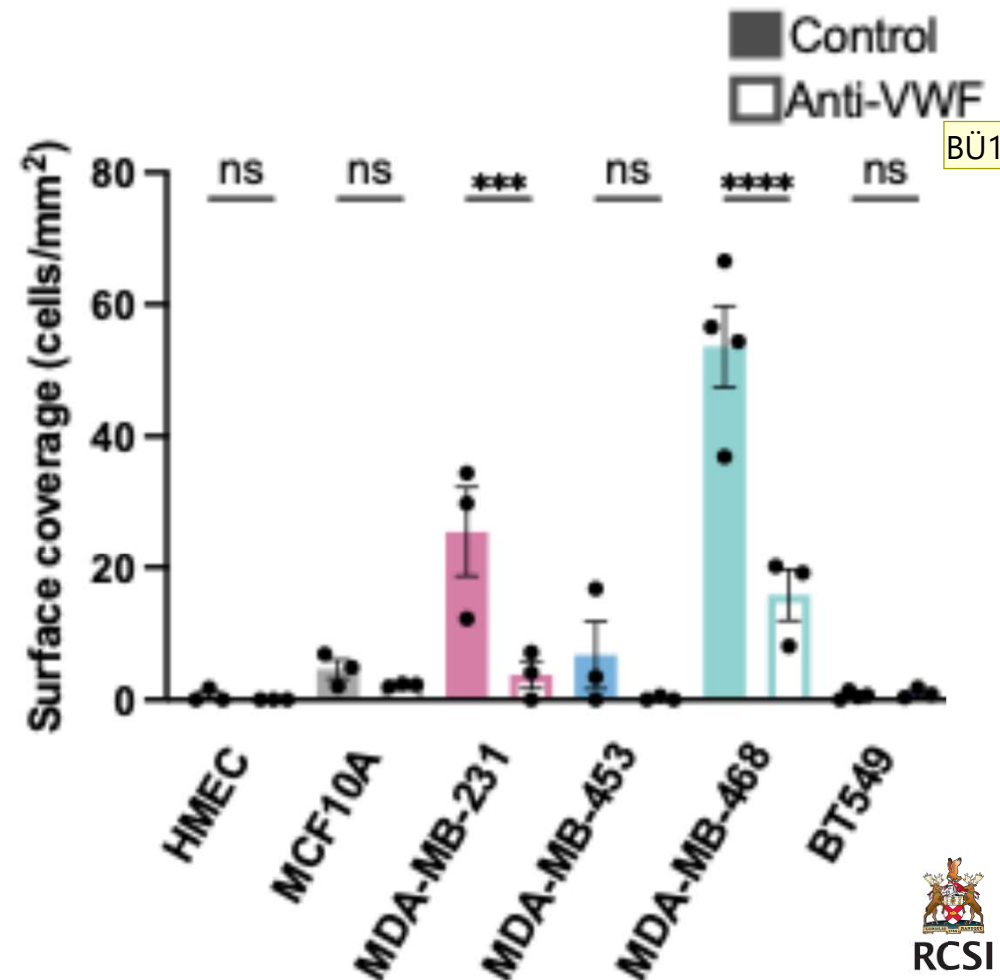
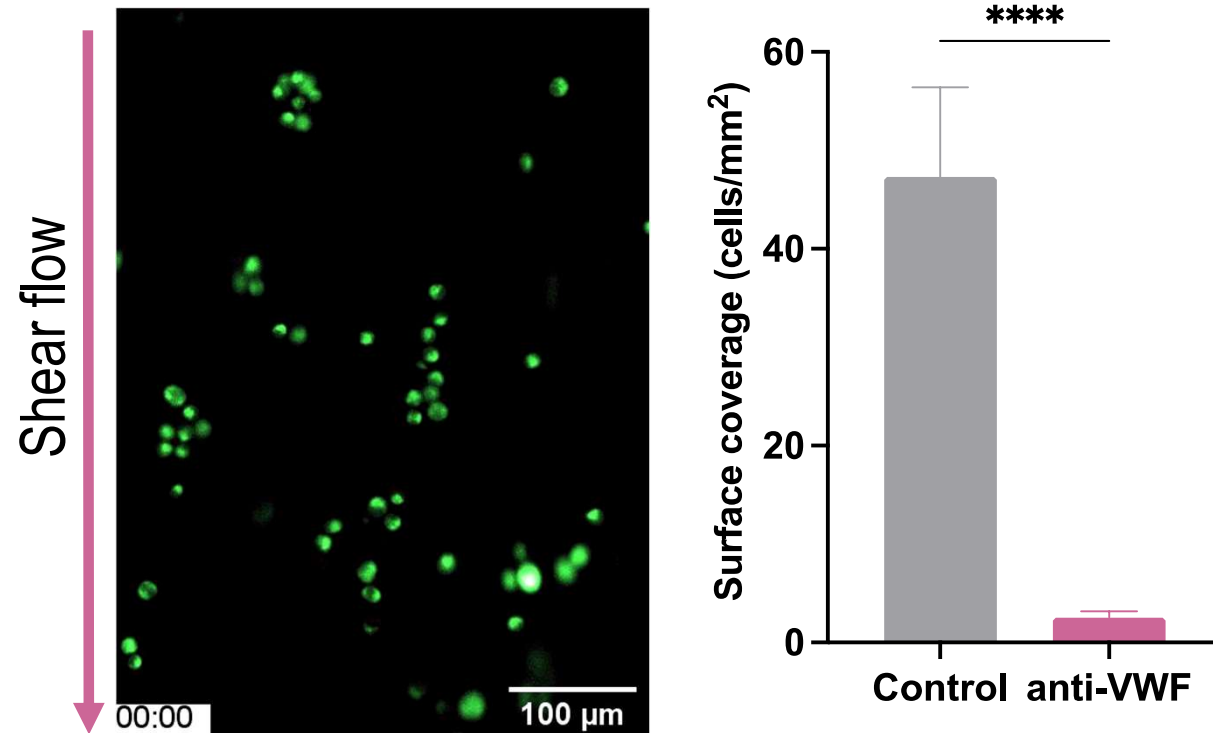
Adapted from Dhimi et al. JTH 2022

Circulating breast cancer cells directly bind VWF under venous shear stress



Circulating breast cancer cells directly bind VWF under venous shear stress

Perfusion of MDA-MB-231 over ECs



BÜ1

Adapted from Dhimi et al. JTH 2022; unpublished data

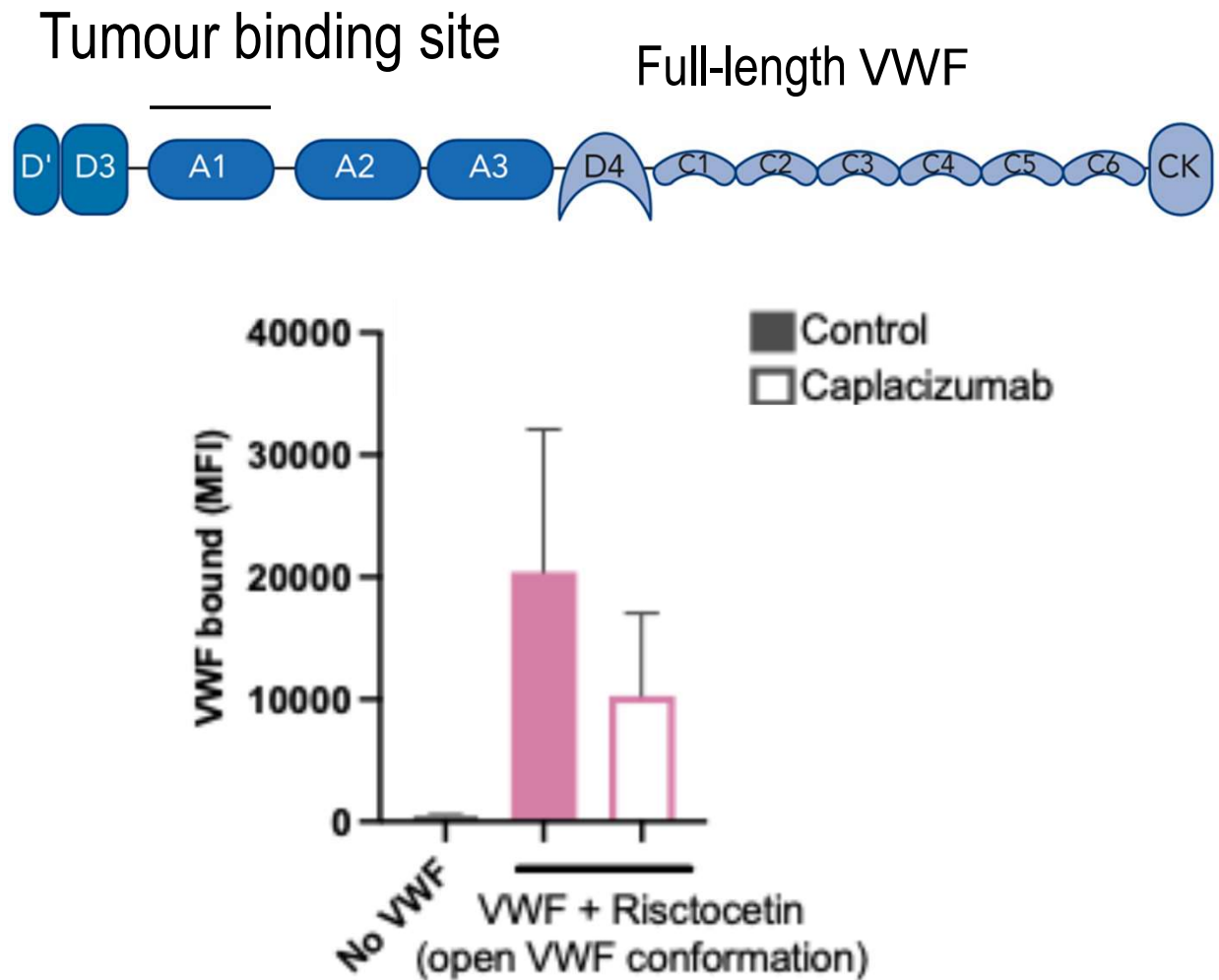
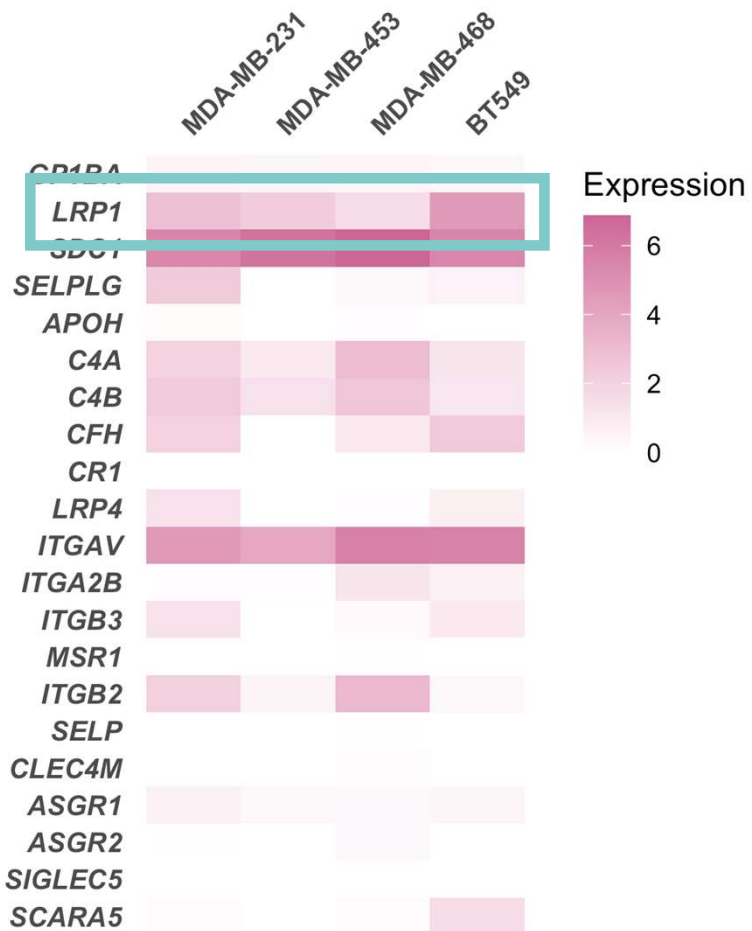
Diapositiva 35

- BÜ1

Replace with TNBC panel +/- dako
Betül Ünlü; 2025-06-11T11:53:49.995
- 1 0

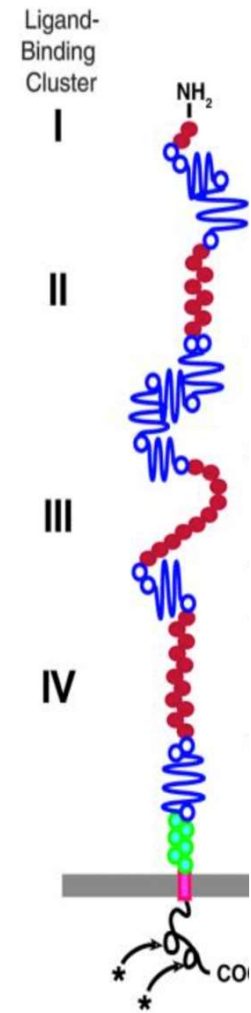
Not enough datapoints
Betül Ünlü; 2025-06-12T09:57:09.504

A-domain of VWF binds to breast cancer cells



Unpublished data; Adapted from Chion et al. Blood 2024

LRP1 expression on triple-negative breast cancer cells



Multi-ligand binding protein

Proteinase metabolism

Modulates inflammation

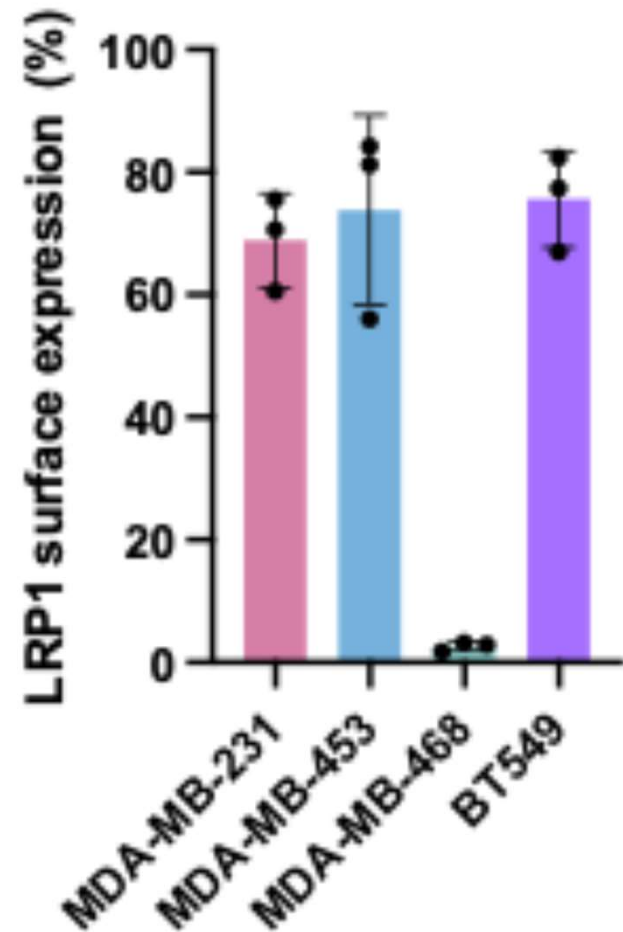
Cancer progression

Proliferation

Migration & invasion

Chemoresistance

Poor survival



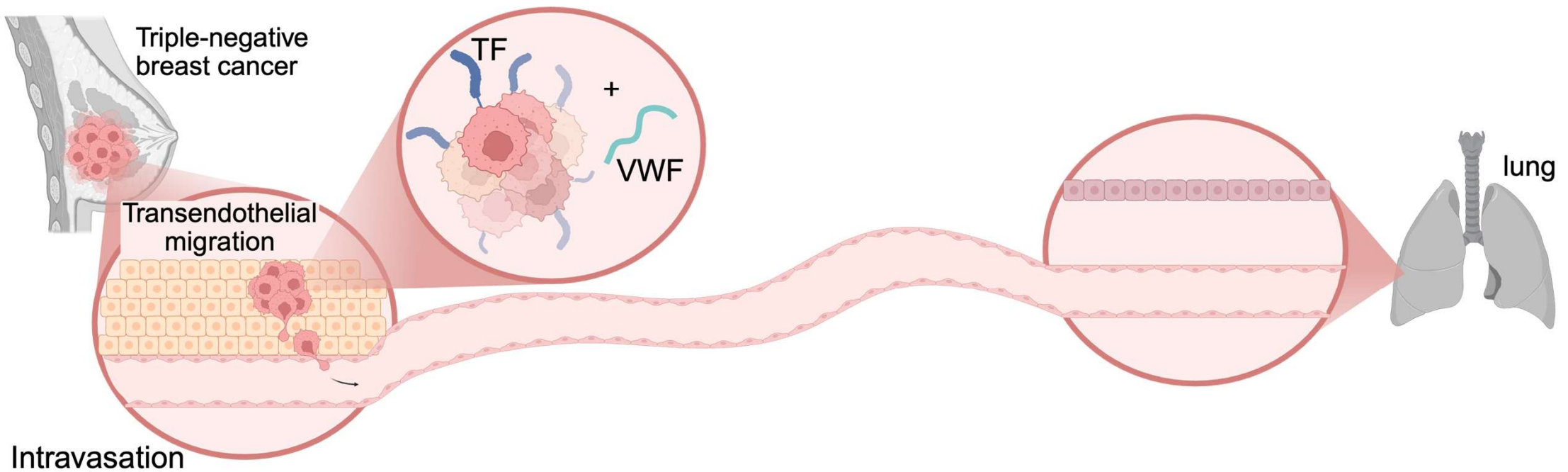
Unpublished data, Hertz, JCI 2001

Conclusion

Cancer-associated thrombosis
complicates treatment
increases mortality

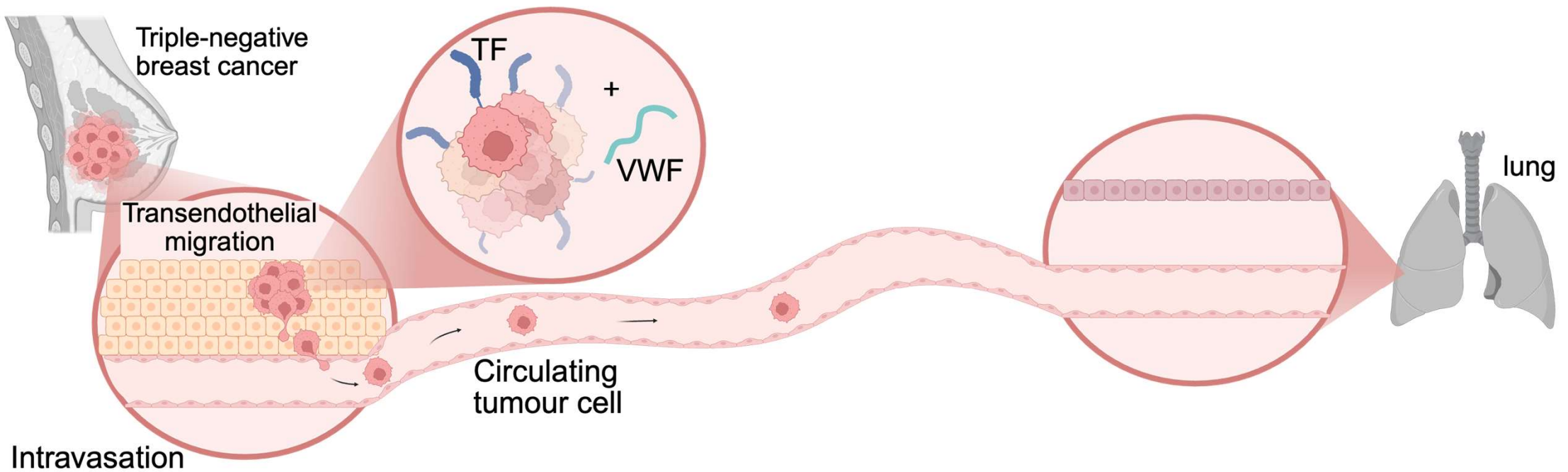
Challenging to predict those at risk

Conclusion



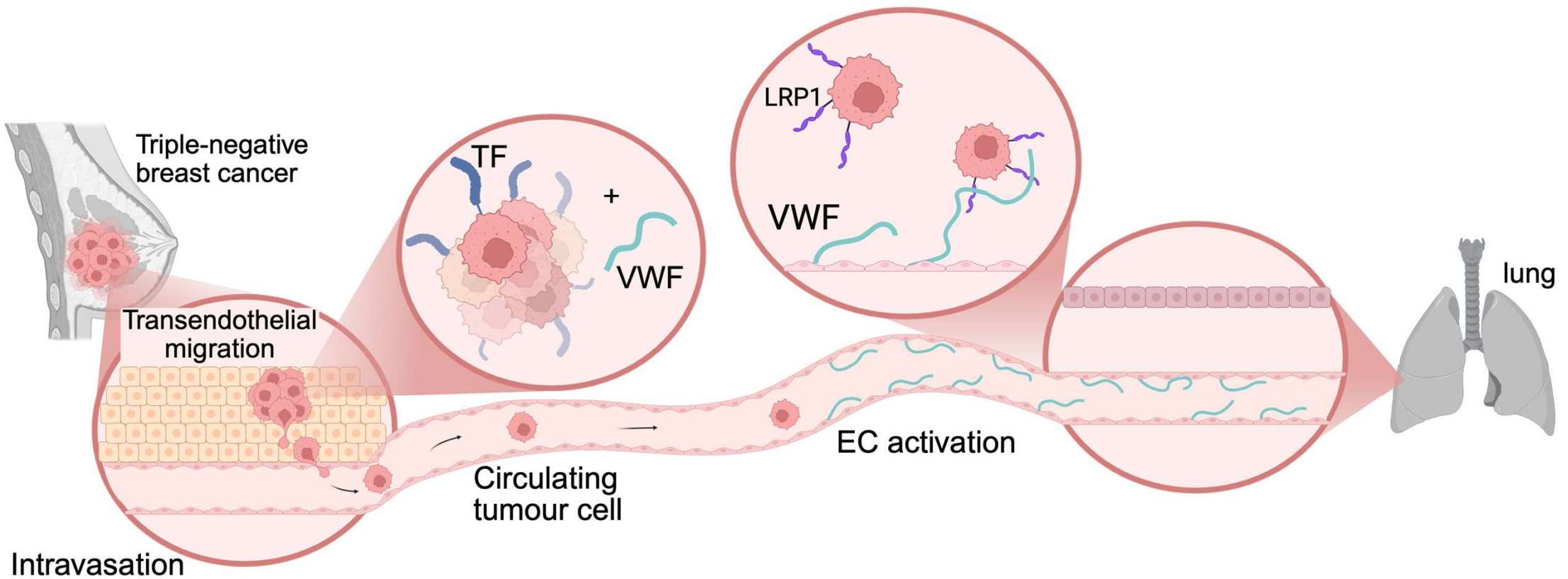
Tumor- and host-expressed coagulation factors promote metastasis

Conclusion



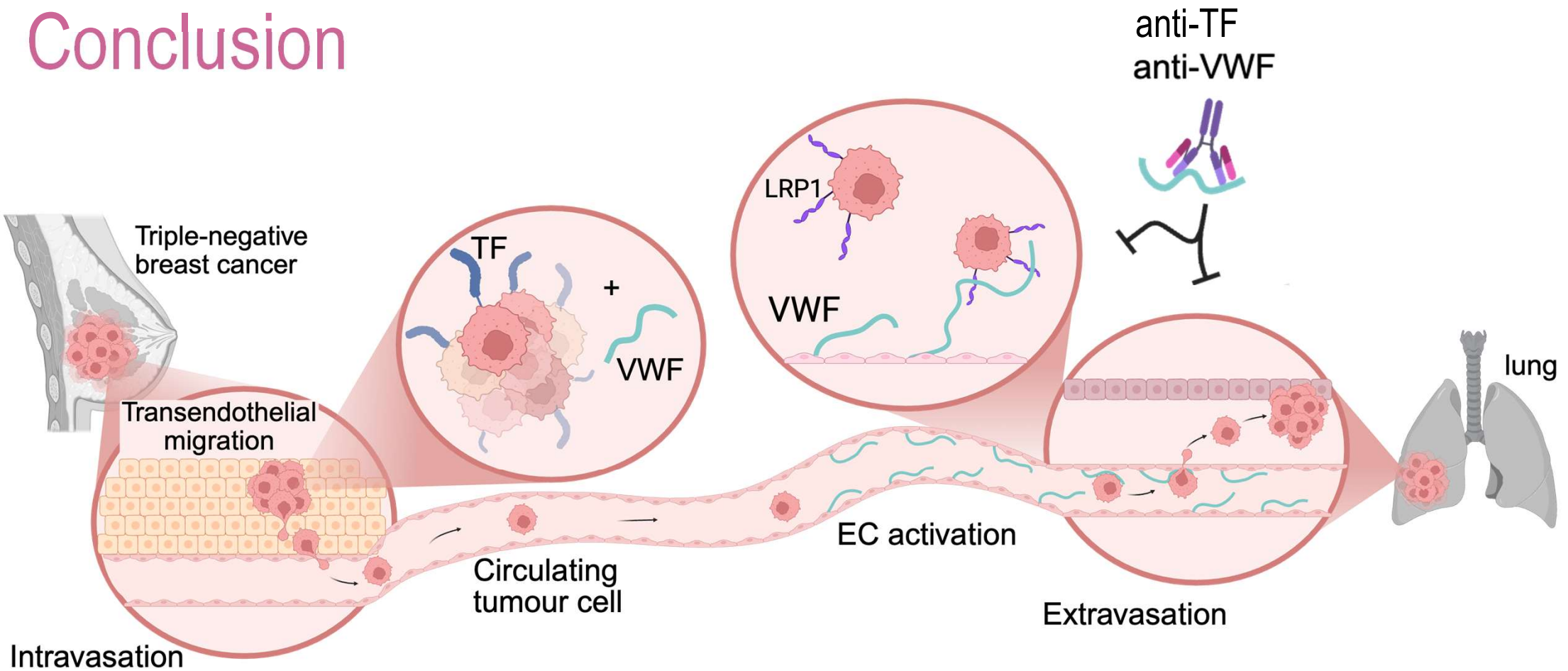
Tumor- and host-expressed coagulation factors promote metastasis

Conclusion



Tumor- and host-expressed coagulation factors promote metastasis

Conclusion



Tumor- and host-expressed coagulation factors promote metastasis

Acknowledgements

Versteeg Lab

B. Kocatürk
A.M.R. Rondon
N. Swier
R.F.P. van den Akker
J.T. Buijs
E.H. Laghmani
M.Y. Kapteijn

Henri H. Versteeg

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