

VUmc



Cancer Center Amsterdam

Clinical Management of Antiangiogenic Drugs

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**Angiogenesis: a key
target in oncology**

VEGF is transported in the Platelet

Alpha granules

Proangiogenic factors

VEGF

PDGF

bFGF

LPA

HGF

TGF-beta

TPO

Anti-angiogenic factors

Thrombospondin

Platelet factor-4

Endostatin

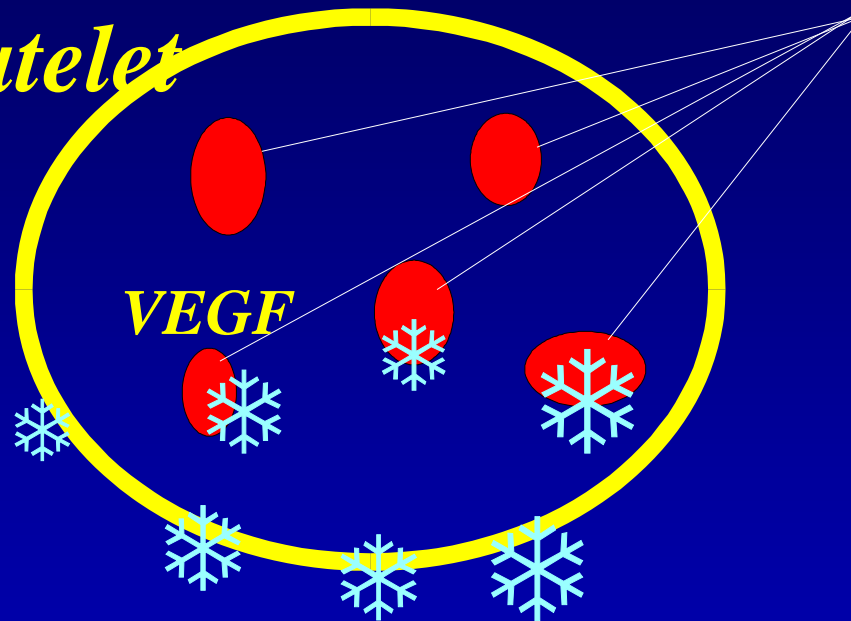
Other proteins:

Fibrinogen

Vitronectin

Von Willebrand factor

Platelet



VEGF

Adhesion proteins

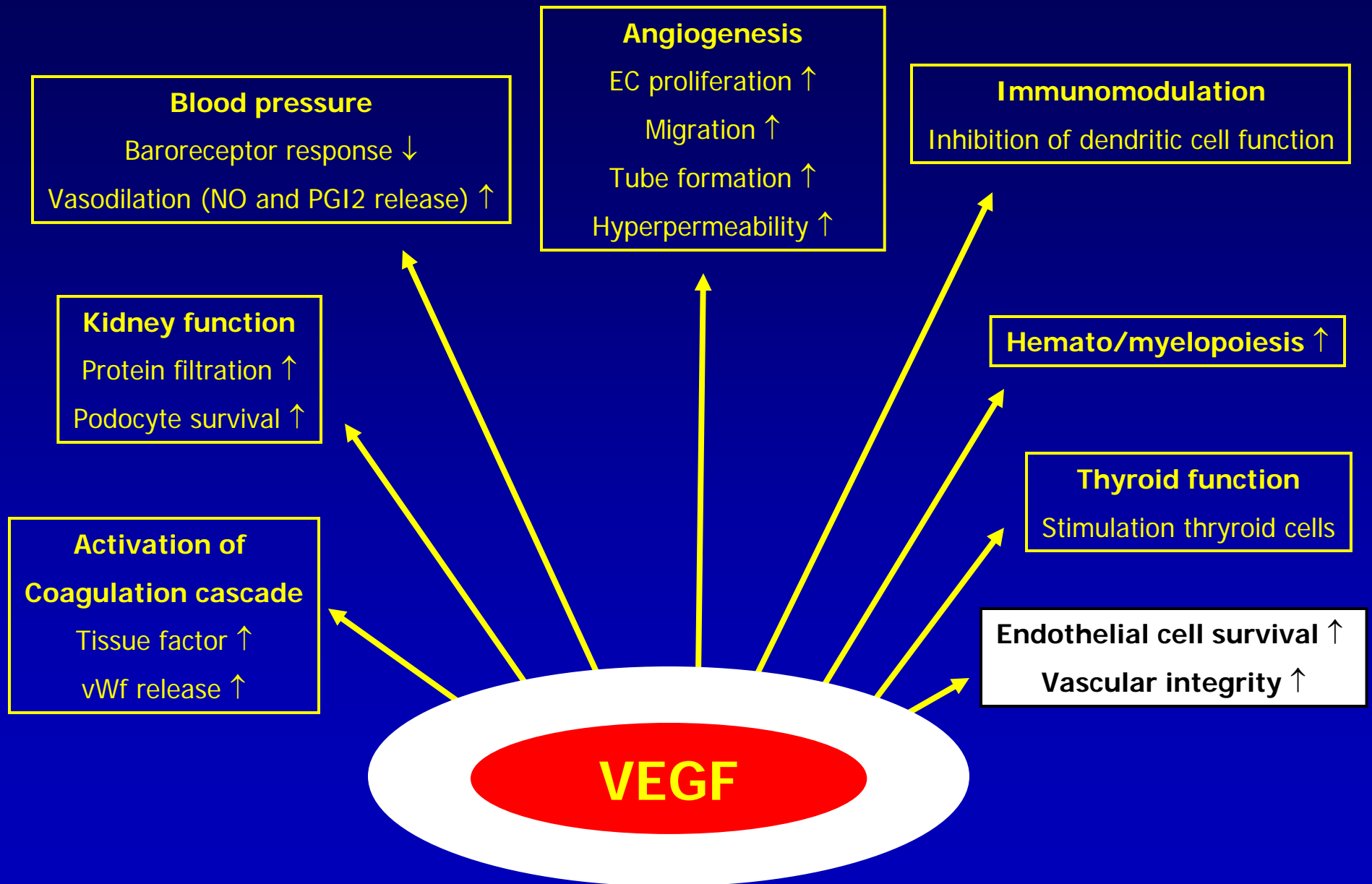


Secreted platelet α -granule proteins

Protein	Amount in 10^9 platelets (ug)	Index of relative concentration of proteins in platelets vs plasma
PF ₄	11.2-12.4	20000
Thrombospondin	30-50	20000
PDGF	0.03-0.1	450
VEGF	0.5-1.5	350
VWf	0.34	4
Fibrinogen	140	3
Fibronectin	3.5	0.5

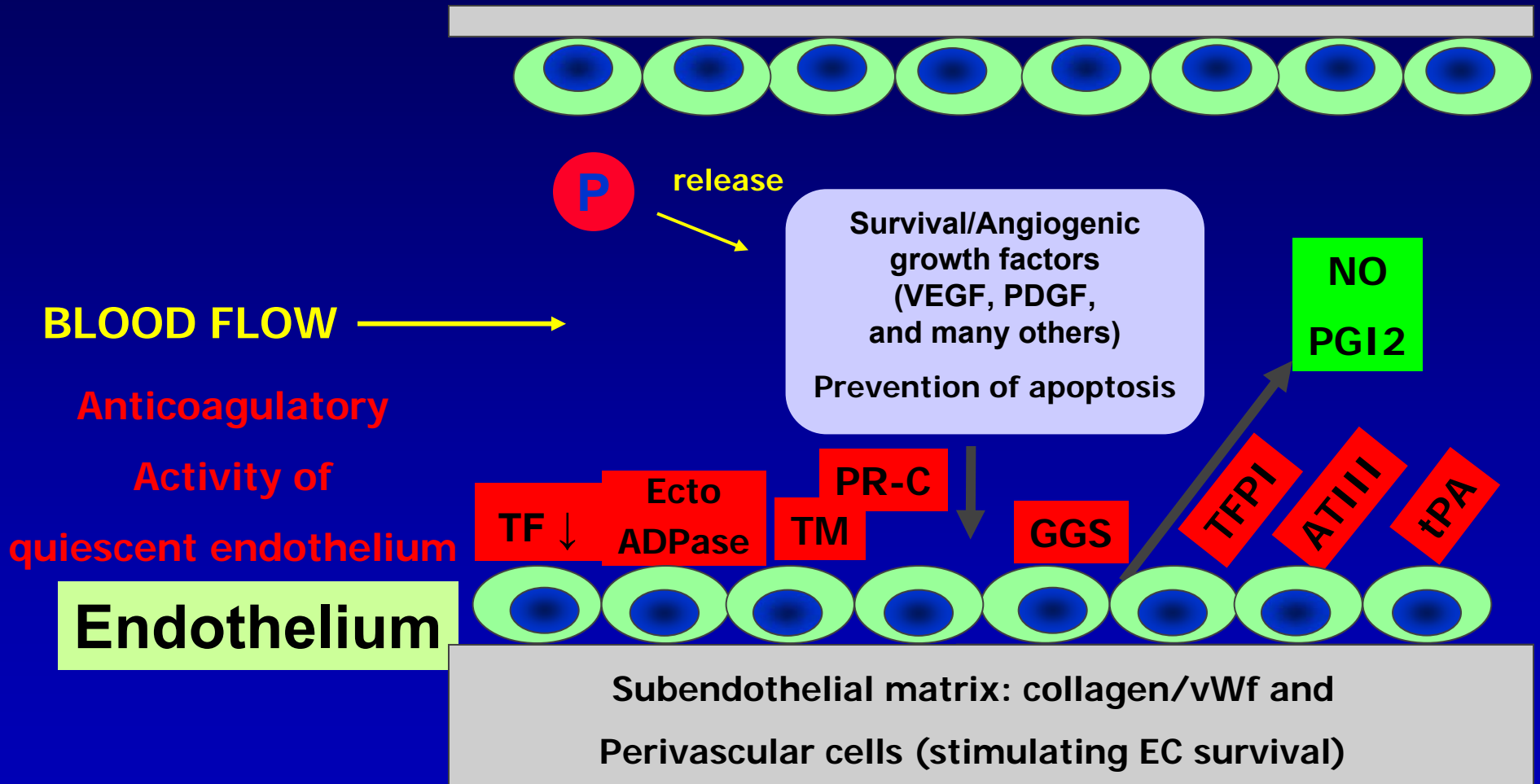
Modified from Niewiarowski, S. et al. In: Ch. 25 Hemostasis and Thrombosis: basic principles and clinical practice; Ed. Colman, R. et al., 1994

Biological activities of VEGF stimulation (Verheul & Pinedo, Nature Reviews Cancer)

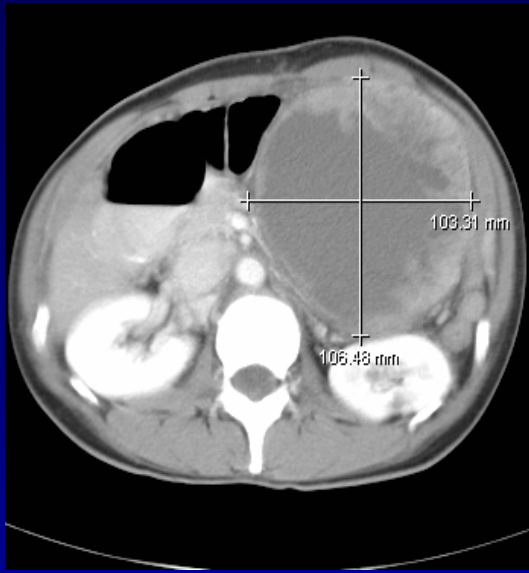


Vascular integrity maintained by platelet-endothelial cell homeostasis
(Verheul & Pinedo, Nature Reviews Cancer)

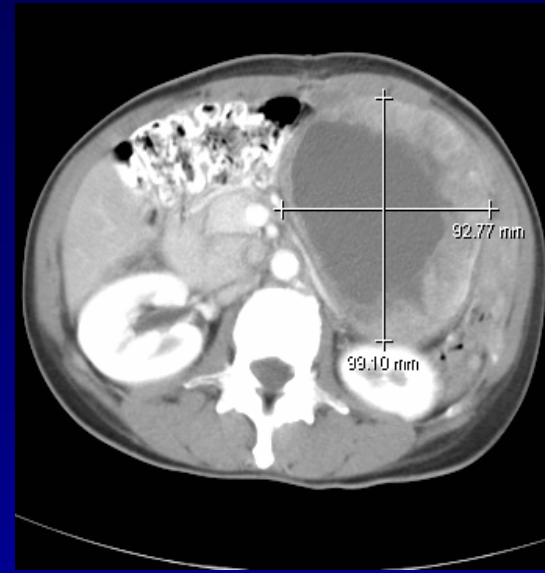
BLOOD VESSEL



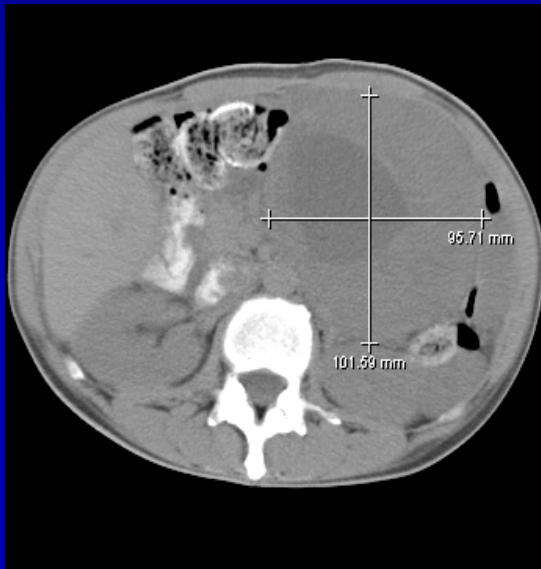
Patient with sarcoma treated with VEGF-R inhibitor



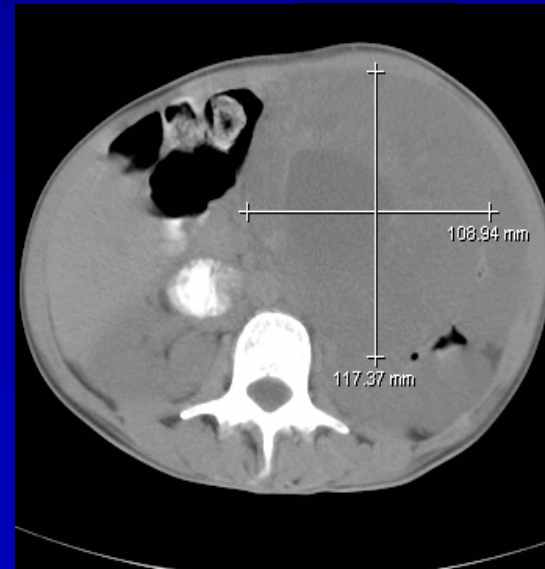
Pre-treatment



4 weeks on treatment



8 weeks on treatment



12 weeks on treatment

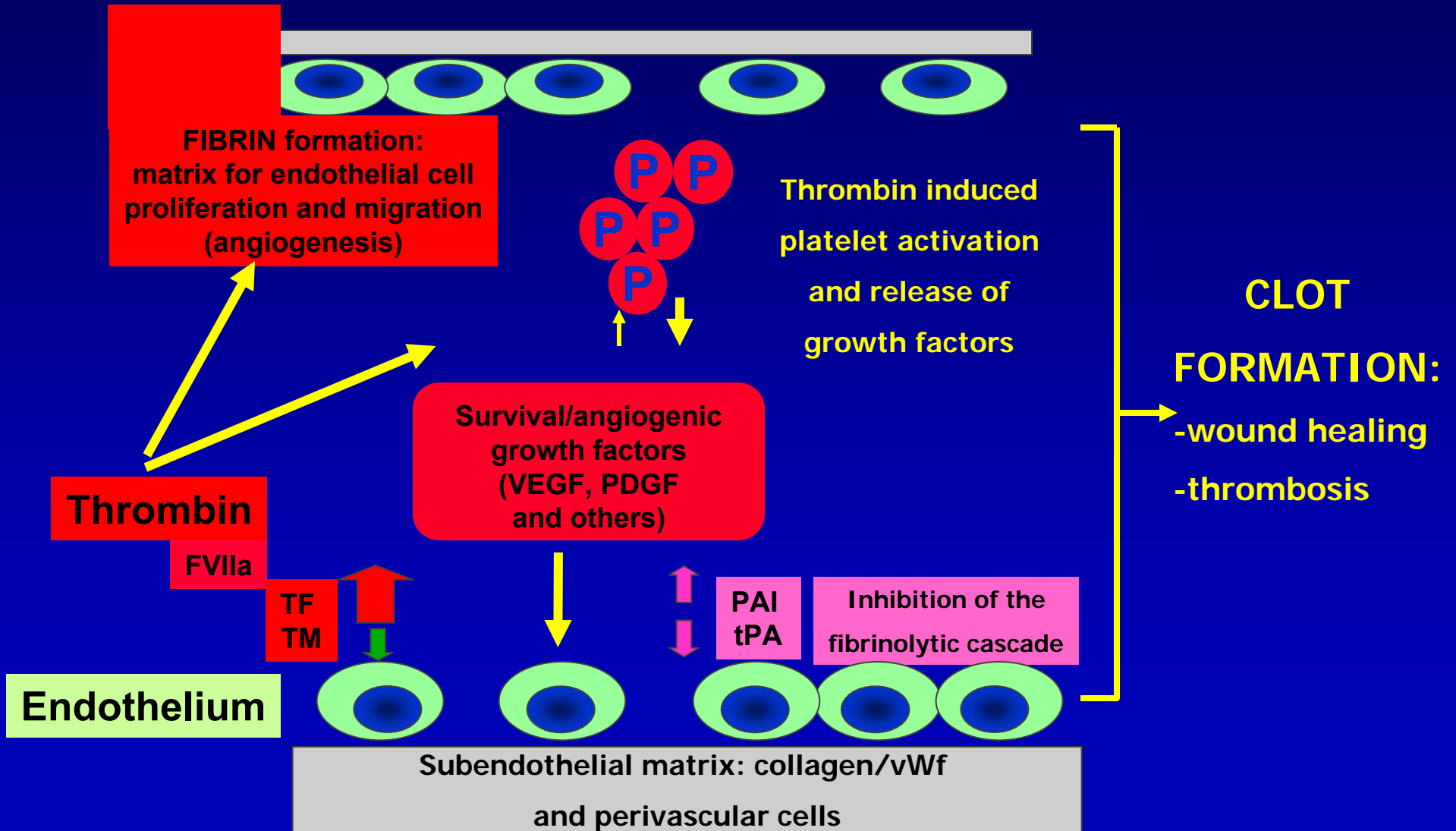
There is an urgent need to redefine the response criteria in cancer patients

VEGF and Coagulation factors in tumor fluid vs plasma levels

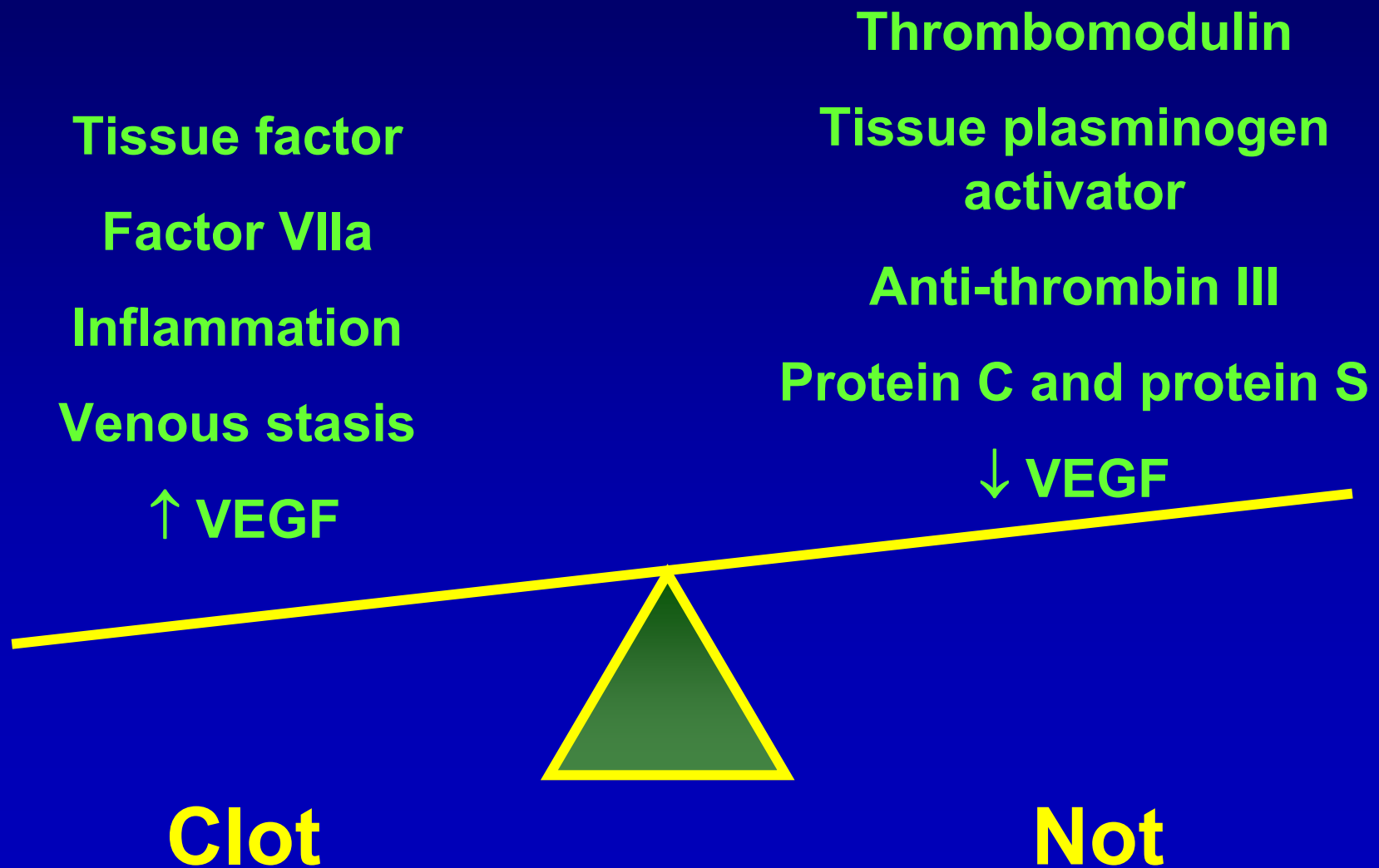
Coag.factor	Normal plasma Median (range)	Tumor fluid (n=12)	Ratio
Total protein (g/l)	60-80	52 (33-74)	
VEGF (ng/ml)	0.04	18 (0.3-345)	450
TF (pg/ml)	349 (296-469)	723 (400-4998)	2
TAT complex (ug/l)	2 (2-3.5)	126 (33-184)	63
Thrombomodulin (ug/l)	44 (35-55)	181 (39-700)	4

Angiogenic growth factors (e.g. VEGF) stimulation of the endothelium cause activation of the coagulation cascade and angiogenesis (Verheul & Pinedo, Nature Reviews Cancer)

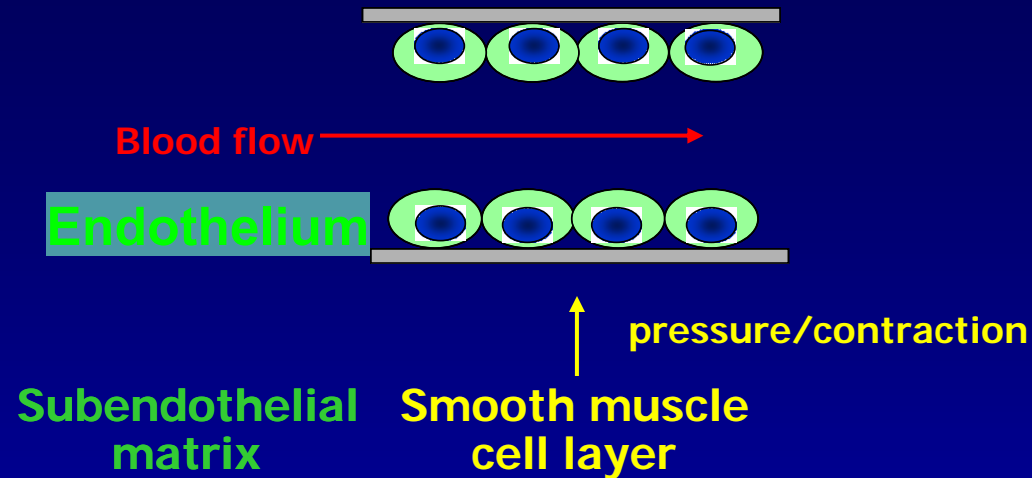
BLOOD VESSEL



The balance between pro-coagulant forces and anti-coagulation in cancer patients



Blood pressure regulation by the vascular system (Verheul & Pinedo, Nature Reviews Cancer)



Decrease blood pressure:

relaxation smooth muscle cells

- NO/PGI₂ release by ECs/platelets ↑
- Baroreceptor response ↓
- Sympathicus ↓
- ATP/shear stress ↓
- Blood volume ↓

Increase blood pressure:

contraction smooth muscle cells

- Baroreceptor response ↑
- Sympathicus ↑
- ATP/shear stress ↑
- Blood volume ↑
- Endothelin to endothelin receptor A

Possible effect of angiogenesis

Inhibitor on blood pressure

- Baroreceptor response disturbance
- Reduced NO/PGI₂
- Increased activity of endothelin
- Inappropriate density of vessels/
vascular stiffness

Dosing in relation to Toxicity

- Optimal effective dose is difficult to determine
- So far, it has been hard to find biological markers
- The old concept of more is better is being applied
- Body weight is used to determine the dose of antibodies, while fixed dose is used for TK inhibitors
- “Off target” toxicity is likely to occur
- Tumor related toxicity is being observed
- Damaged epithelial and mucosal lining may be the origin of toxicity
- High doses cause edema, hypertension and fatigue

Drug resistance in relation to toxicity

- Underlying mechanisms of resistance have not been determined yet preclinical data offer some indications
- Tumors may use alternative pathways to promote angiogenesis
- Mutations in the target receptors or increased expression of either the Growth Factor or the Receptor
- Classical resistance mechanisms may as well play a role
- Termination of treatment may induce new side effects

TK inhibitor and Bevacuzimab related toxicities

- Related to the combination of TKs (VEGF, PDGF, c-KIT and EGF family) being inhibited
- Combination with chemotherapy will result in alternative toxicities to single agent chemotherapy
- Toxicity to Bevacuzimab is solely related to VEGF binding
- Duration of toxicity is related to the pharmacology of the antiangiogenic drug

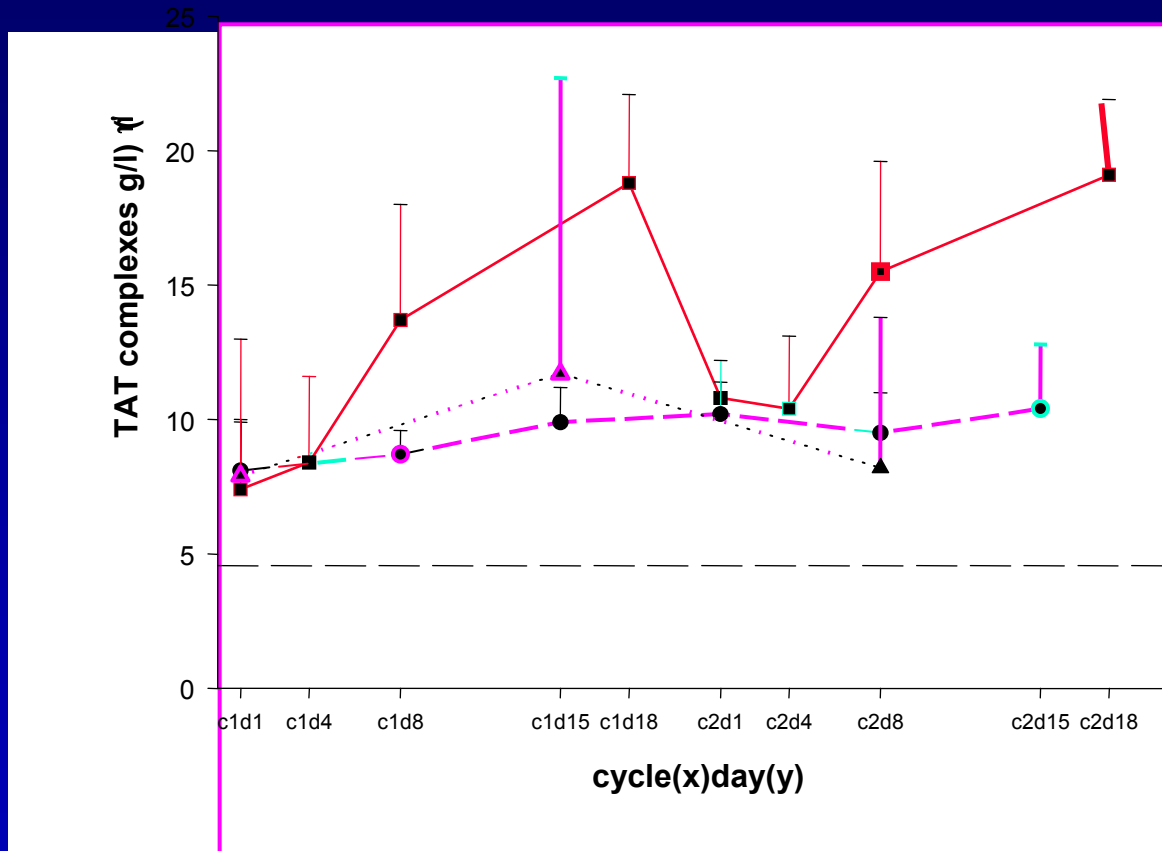
Toxicities of antiangiogenic agents inhibiting at least VEGF that have reached phase 2 trials (1)

- Hypertension
- Decreased cardiac ejection fraction
- Fatigue
- Hypothyroidism
- Reversible Posterior Leukoencephalopathy Syndrome
- Bleeding
- Thrombotic events

Phase 1 trial of SU5416 plus cisplatin/gemcitabin

- Cisplatin 80 mg/m² day 1
- Gemcitabine 1250 mg/m² day 1 and 8
- SU5416 85 and 145 mg/m² twice weekly
→ day 4, 8, 11, 15, 18
- every 3 weeks

Anti-VEGF and coagulation TAT complexes



- = cisplatin-gemcitabine plus SU5416 (3 pts)
- = cisplatin-gemcitabine alone (6 pts)
- ▲ = SU5416 alone (16 pts)

Toxicities of antiangiogenic agents inhibiting at least VEGF that have reached phase 2 trials (2)

- Proteinuria and edema
- Leukopenia, lymphopenia
- Biochemical abnormalities
- Immune modulating effects
- Disturbed wound healing and GI perforations
- Skin toxicity: rash, hand-foot syndrome and hair discoloration

Bevacizumab toxicity

	IFL + placebo (n=397)	IFL + Avastin™ (n=393)
Bleeding (%)		
Grade 3	2.5	2.3
Grade 4	0	0.8
Any thromboembolic event (%)	16.1	19.3
Deep vein thrombosis	6	9
Pulmonary embolism	5	4
Myocardial infarction	0.8	1.5
Any hypertension (%)	8.3	22.4*
Grade 3	2.3	10.9*
Grade 4	0	0
Any proteinuria (%)	21.7	26.7
Grade 3	0.8	0.8
Grade 4	0	0

*p<0.01

NB: not adjusted for differential time on therapy

Bevacizumab in NSCLC: safety

- **Six (9%) life-threatening pulmonary haemorrhages (four fatal) in patients who received CP plus Avastin**
- **Centrally located lesions (cavitary/necrotic)**
- **In a multivariate analysis, apart from Avastin treatment, only squamous cell histology was identified as an independent risk factor**
 - **4/6 bleeds (19% of enrolled subjects)**
- **Similar bleeds not seen in other trials**

Bevacizumab activity

- Colorectal cancer: in combination with irinotecan, 5FU-LV
- Renal cell cancer
- Non-small cell lung cancer
- Pancreatic cancer?
- Breast cancer

Sunitinib Safety Profile

- Dose limiting toxicity
 - Fatigue/Asthenia
- Other adverse events
 - Thrombocytopenia
 - Neutropenia
 - Nausea and vomiting
 - Diarrhea
 - Skin toxicity
 - Hypertension
 - Yellow skin & urine
 - Hair discoloration
 - Sore mouth

Adverse Events Are Reversible and Manageable

Sunitinib in Gist: response

Type of response	SUTENT (N=207)	Placebo (N=105)
Partial response	7.7%	0%
Stable <6 months	47%	49%
Stable >6 months	19%	1%

Sunitinib RR (%) in NET's

	Carcinoid (N=41)	Islet cell (N=61)	All patients (N=102)
Partial remission (95% CI)	1 (2) (0.1–12.9)	8 (13) (5.8–24.2)	9 (9) (4.1–16.1)
Stable disease	38 (93)	46 (75)	84 (82)
Progressive disease	0	4 (7)	4 (4)
Not evaluable	2 (5)	3 (5)	5 (5)

Response based on baseline and at least 1 subsequent imaging assessment using RECIST (ITT population).

Kulke et al.

Grade 3/4 Hematological and Biochemical Abnormalities ($\geq 5\%$ of Patients)

	Nexavar	Placebo
Blood cells		
Lymphopenia	55/434 (13%)	31/424 (7%)
Coagulation		
Prolonged INR	23/435 (5%)	28/425 (7%)
Metabolic/laboratory		
Hypophosphatemia	58/436 (13%)	11/427 (3%)
Elevated lipase	54/436 (12%)	30/427 (7%)
Hyponatremia	28/436 (6%)	20/427 (5%)
Hyperglycemia	15/436 (3%)	23/427 (5%)
Hyperkalemia	22/436 (5%)	14/427 (3%)

Nexavar in Hepatocellular Cancer

Randomized Study discontinued

Anti-angiogenic agents

- Anti-VEGF agents
- *Thalidomide*
- Combrestatin (tubulin inhibitor)
- Endostatin/angiostatin (inhibit endothelial cells)
- Squalamin (chemically synthesized aminosterol)
- Thrombospondin
- Matrix metalloproteinases
- Conventional cytotoxic agents (metronomic therapy)
- Cytolytic virus therapy