Διαβήτης και αιμοπετάλια

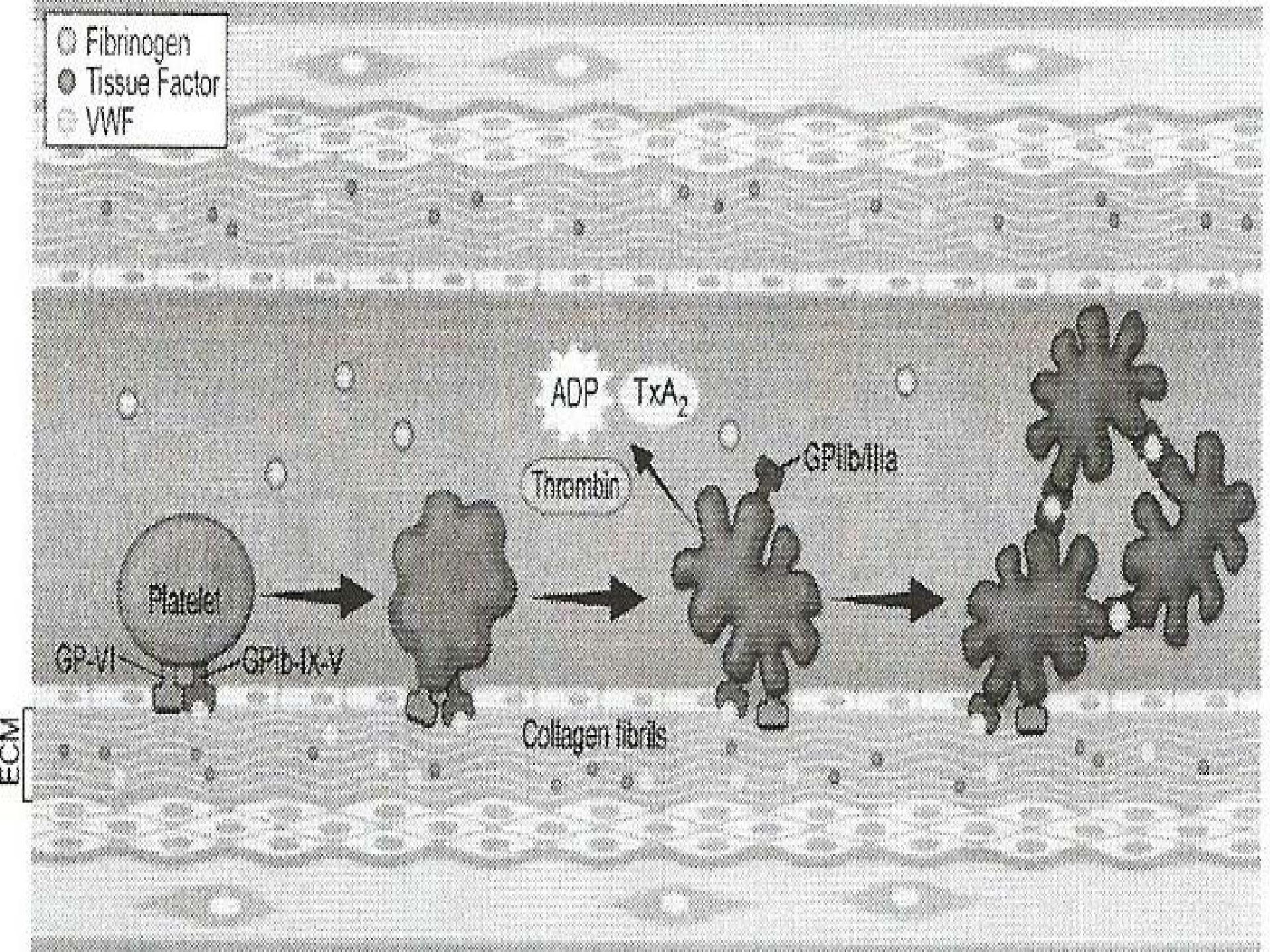
Ζαχαρίας Σινάκος
Ομ. Καθ. Ιατρικής Α.Π.Θ.

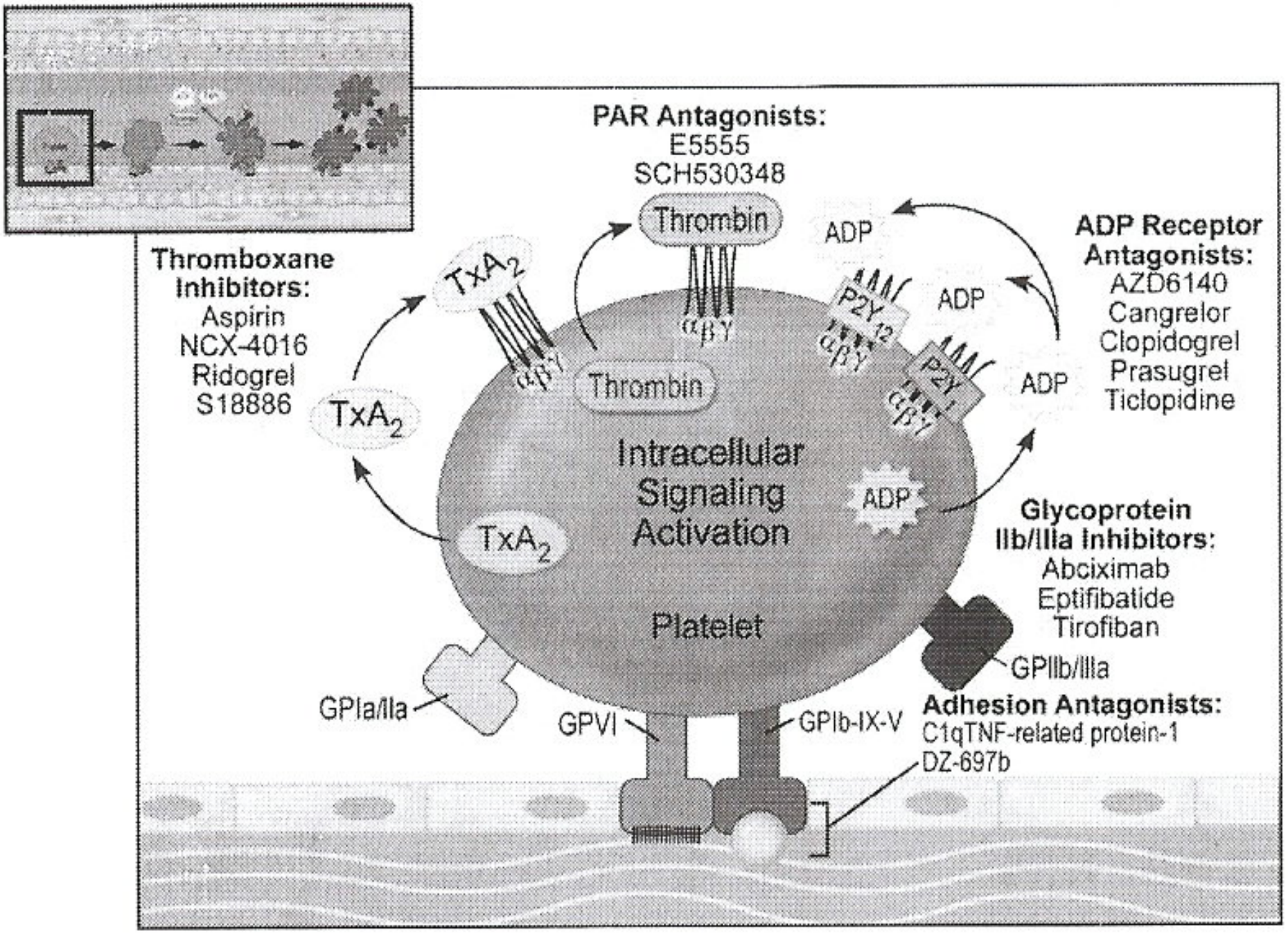
Diabetes is a strong risk factor for atherothrombotic complications.

Yuen M., Diabetologica 2007

Major cardiovascular events cause about 80% of the total mortality in diabetic patients.

Coccheri S., Drugs 2007


Fibrinogen
Tissue Factor
VWF
ADP
TxA_2
Thrombin
GPIIb/IIIa
Platelet
GP-VI
GPIb-IX-V
Collagen fibrils
ECM


PAR Antagonists:
E5555
SCH530348
Thrombin
ADP
ADP Receptor Antagonists:
AZD6140
Cangrelor
Clopidogrel
Prasugrel
Ticlopidine
Thromboxane Inhibitors:
Aspirin
NCX-4016
Ridogrel
S18886
TxA2
TxA2
Thrombin
ADP
ADP
ADP
Intracellular Signaling Activation
TxA2
Platelet
Glycoprotein IIb/IIIa Inhibitors:
Abciximab
Eptifibatide
Tirofiban
GPIIb/IIIa
GPIa/IIa
GPVI
GPIb-IX-V
Adhesion Antagonists:
C1qTNF-related protein-1
DZ-697b

Metaanalysis of 287 studies of antiplatelet therapy in high risk patients with vascular disease established that antiplatelet therapy reduces the incidence of death, MI or stroke by 25%

Coccheri S., Drugs 2007

Will there is no doubt that
the concept of inhibiting platelets is
vital for the treatment of
vascular disease ,
the optimal degree of such inhibition
remain an unsolved mystery.

Eur. Heart J, 2007

Patients in whom inhibition of platelets activation is inadequate experience recurrent MI and bleeding occurs in patients given excessive doses.
These observations underscore the potential value of individualization of dosage.

J. Schneider, Circulation 2007

Thrombotic vascular events in DM may result from endothelial dysfunction, platelet hyperactivity and impaired fibrinolysis.

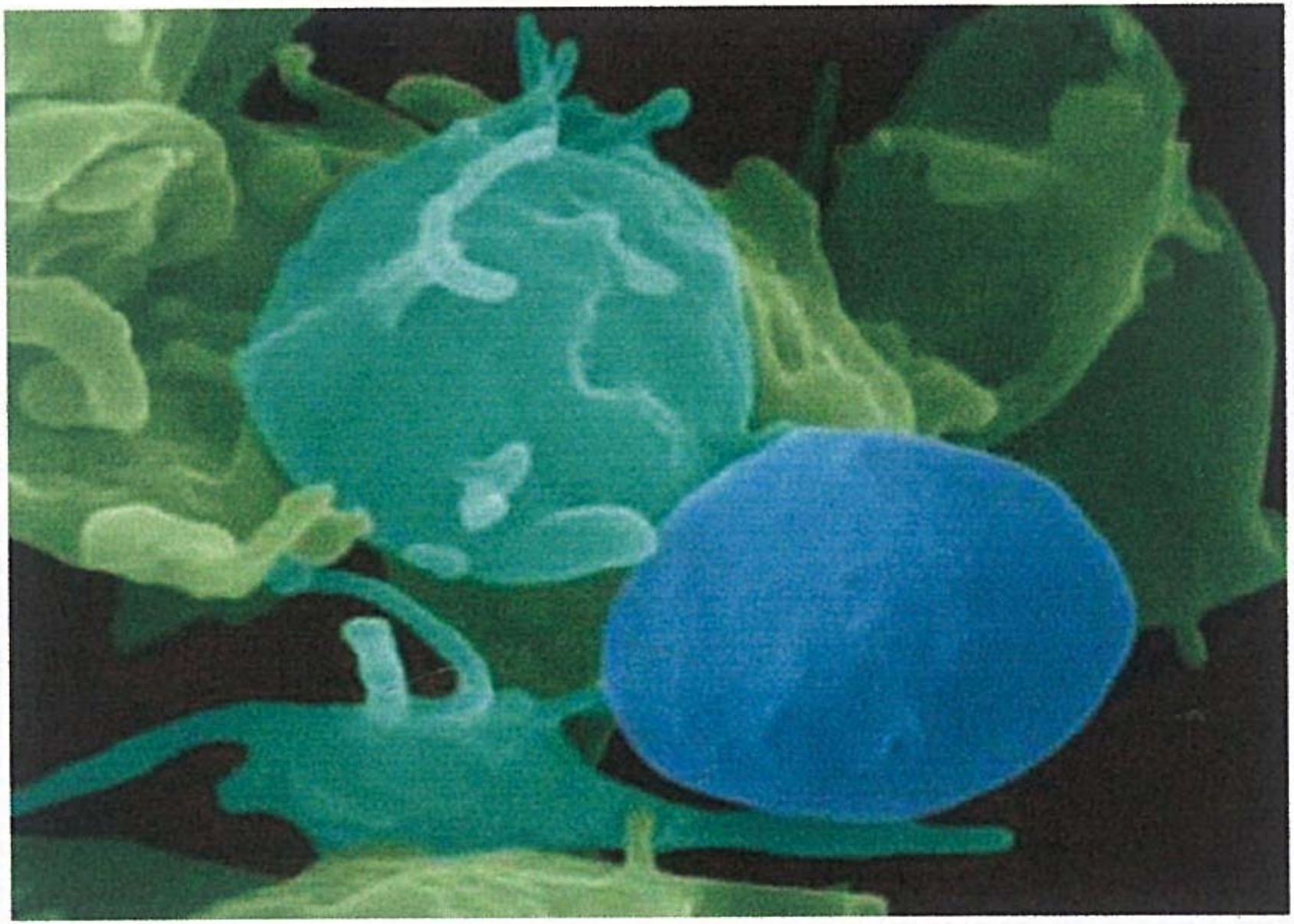
Colwell J., Diabetes Care 2003.

Platelets in diabetic patients are found in permanent prethrombotic state.
Platelets "priming" to more spontaneous activation and aggregation are considered central mechanisms in the pathophysiology of acute atherothrombotic events in DM

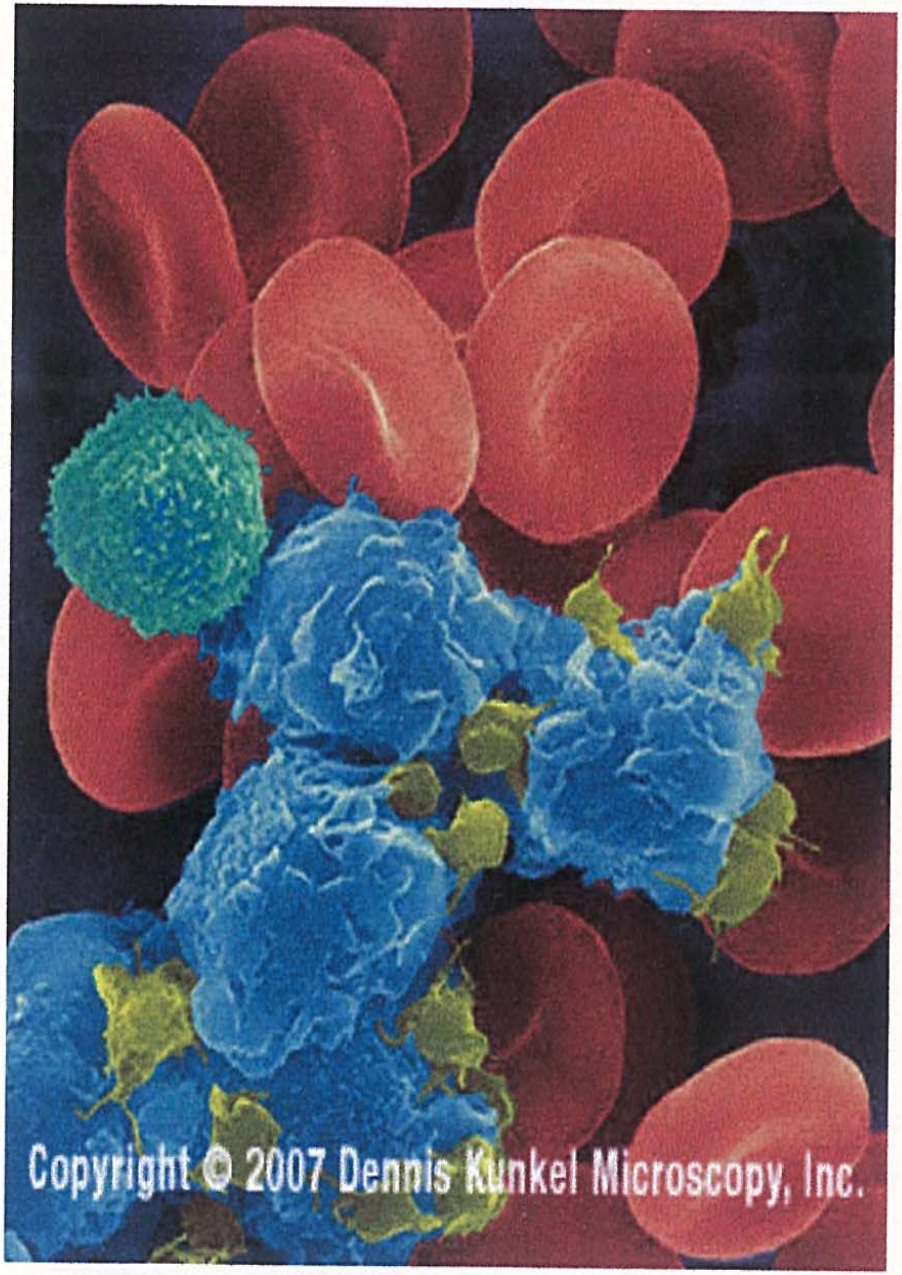
Watala C., Pharmacol. Rep. 2008.

Diabetes is associated with platelet hyperactivity, increase in circulating activated platelets and platelet-leucocyte aggregates.

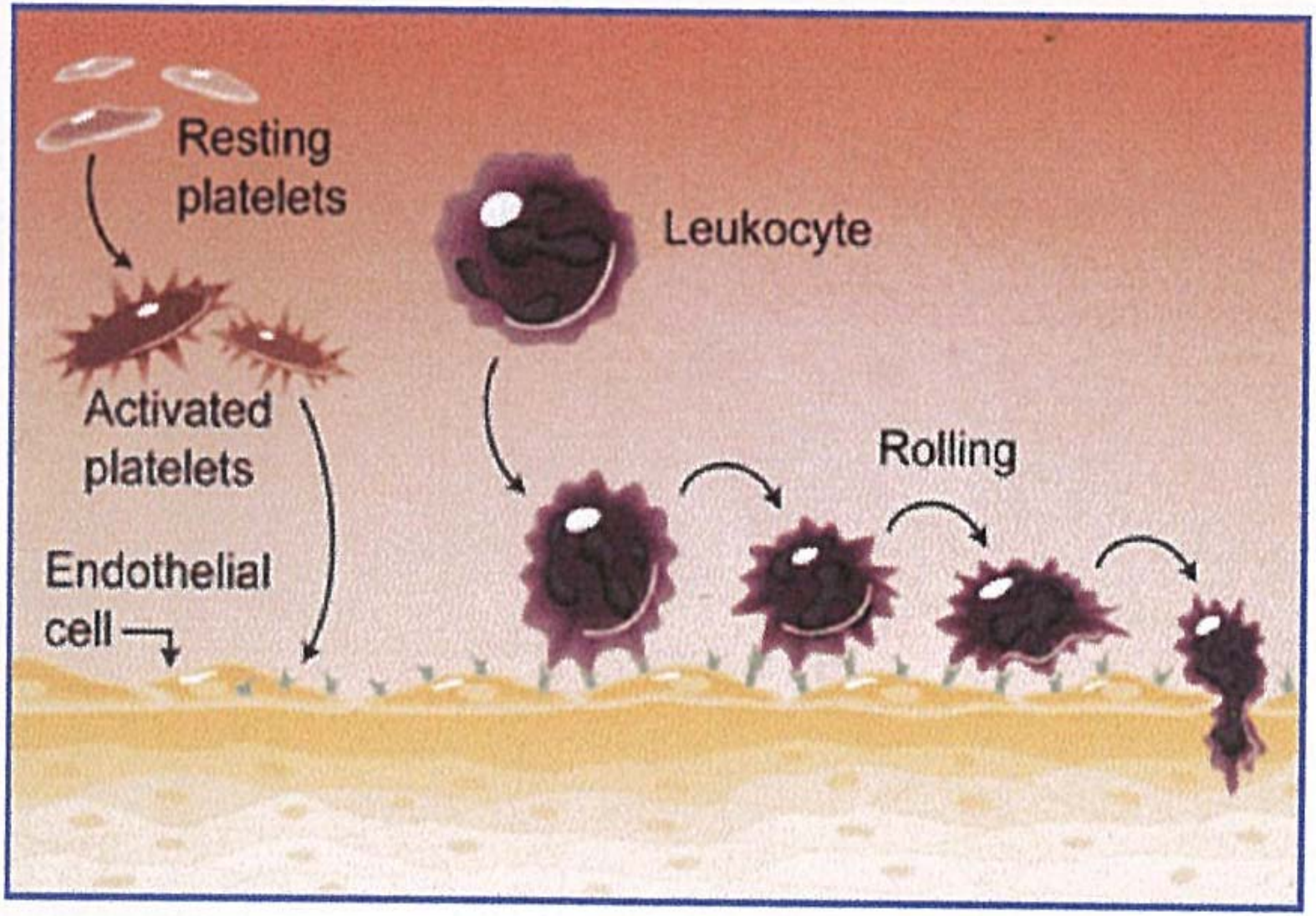
Rasmara M., Diabetes Care 2007



Inactivated (smooth) platelet (stained blue) among spiky, activated platelets as seen through a scanning electron



Human red blood cells, activated platelets and white blood cells



Activated platelets trigger endothelial exocytosis, externalizing P-selectin, whi rolling. Illustration by A. Y. Chen.

In DM a disturbed carbohydrate and lipid metabolism may lead to altered physico- chemical properties of cell membrane…….
result in altered exposure of surface membrane receptors.

Watala C., Eur J Hematol. 1998.

Acute short-term hyperglycemia (14 mmol \ L) enhances platelet activation in patients with DM.

Gregele P. J., Amer. Col. Card . 2003

High glucose levels enhanced platelet reactivity to agonists stimulation through elevated osmolality.

Sudic D., Br. J. Hematol. 2006

Hyperglycemia in healthy individuals induced platelet activation and monocyte TF expression promoting a procoagulant state.

Vaidyula VP., Platelets. 2006

High glucose attenuated activation endothelial nitric oxide synthase [Enos] and NO production.

Meng L., Arch. Pharm. Res. 2008

The loss of responsiveness to insulin might explain the hyperactivity of platelets in patients with DM 2.

Ferreira I., Art. Thromb. Vasc. Biol. 2007

Effect of insulin treatment on postprandial platelet activation in patients with NIDDM.

Karolinska, Oct . 2008

Prior to development of a thrombotic state,
a prothrombotic state
may exist in which only a small number
of platelets is activated.
Identification of a prothrombotic state
by use of activated platelets
may help direct medical intervention to
prevent a thrombotic episode.

Wills W., Amer. J. Vet. Res. 2006

Measurement of soluble pSel. may be helpful marker of impending coronary artery insult in diabetic patients.

Salah A., Hematology 2005.

High levels of
solCD40 and solP-sel.
have been shown in patients
with DM
and may be associated with
adverse cardiovascular outcome.

Lim H., Circulation 2004

Soluble CD40L induces dysfunction in human coronary endothelial cells

-Result : **reduction of eNOS**

Cheng C., Blood 2008

PMN integrins [CD18] and activated platelets are involved in the presence of diabetic vascular complications and may be potential targets for pharmacological interventions.

Cihan T., Int. J. Endocrin. 2008

Therapeutic targeting of P-selectin in atherosclerosis.

Woollard K., Inflam, Allergy Drugs Targets 2007

Diabetic patients exhibit high platelet activity and do not respond well to the available antiplatelet regimens. Clinical trials in DM are urgently need in order to define the optimal degree of platelet inhibition.

Serebruany V., Thromb.Hemost. 2008.

Aspirin 100 mg\d does not inhibit platelet function adequately in a significant number of patients with DM and CAD.

Dugerly M., Amer. J Card, 2008

Diabetic patients with CAD during therapy with 81 mg have prevalence of aspirin resistance than nondiabetic patients.

Di Chiara, J. Diabetes 2008

Aspirin resistence: Fact and Fiction

Peterson P., Amer. J . Clin. Path. 2005

Aspirin resistence was present in almost 20% of diabetic patients.

Evangelista V., Thromb. Hemost. 2005

Patients who are resistant to aspirin are at a greater risk [fourfold] of clinically important CAD, than… Aspirin resistant patients did not benefit from other antiplatelet treatment.

St. Krassopoulos, G. B. M. J. 2008

There is no evidence that changing therapy in response to a finding of “aspirine resistance”change clinical outcomes.

Storey R., Eur. Heart J. 2007

The field of aspirin resistance remain an important area for future research.

Meadows S., Circ. Res. 2007.

…clopidogrel resistance may be a marker for increased risk of recurrent cardiovascular events.

Wiviott S., Circulation 2004

Aspirin 300 mg\d or 100 mg plus 75mg\d clopidogrel

…adequate inhibition in a significant number of patients with impaired response.

Dujenly M., Amer. J. Card. 2008

Standard dosage of 75mg\d of clopidogrel resulted in a suboptimal response in subjects with T2DM.

A 150mg dosage was shown to enhance platelet inhibition in high risk group.

A need for more clinical studies: higher doses ,stronger antiplatelet drugs and individualized treatment….

Soemaher S ., CAD|Diabetes 2008.

Intensive antiplatelet therapy with prasugrel resulted in fewer ischaemic outcome than with clopidogrel.

Wiviott SD., Lancet 2008

…. overall mortality did not differ.

N. Engl. J. Med. 2007

Meeting ACA 2007:

Nilsen S : the drug is approvable

Wikeman R : we don’t like bleeding

Stone G : patient selection will be an issue..

TRITON –TIMI 38 showed that diabetic patients responded particularly well to prasugrel. [14% vs 22 & p 0,009]

Circulation 2008

Third optimizing antiplatelet therapy in DM (OPTIMUS 3) : Prasugrel vs clopidogrel.

- *EI. Lilly, April 2008.*

A sensitive and specific yet rapid and inexpensive screening test that detects predisposition to thrombosis or bleeding , be it sensitive to aspirin, thienopyridine or GPIIb- IIIa antagonists may prove clinically useful.

A. Maree , Circulation 2007

Patients on aspirin who have evidence of higher levels of urinary TX metabolites had twice the risk of Myoc.Inf.

Eur. Heart Journal , 2007

The gold standard to monitor clopidogrel is the vasodilator stimulated phosphoprotein [VASP] assay, due to its P2Y12 selectivity.

Chr. Gachet, Eur. Heart J. 2007

Physicians and clinics specializing in anticoagulation can offer support and should be consulted to assist with therapeutic decisions and management, particularly during periods of anticipated high risk.

F. Spenser, Amer. Heart J. 2007