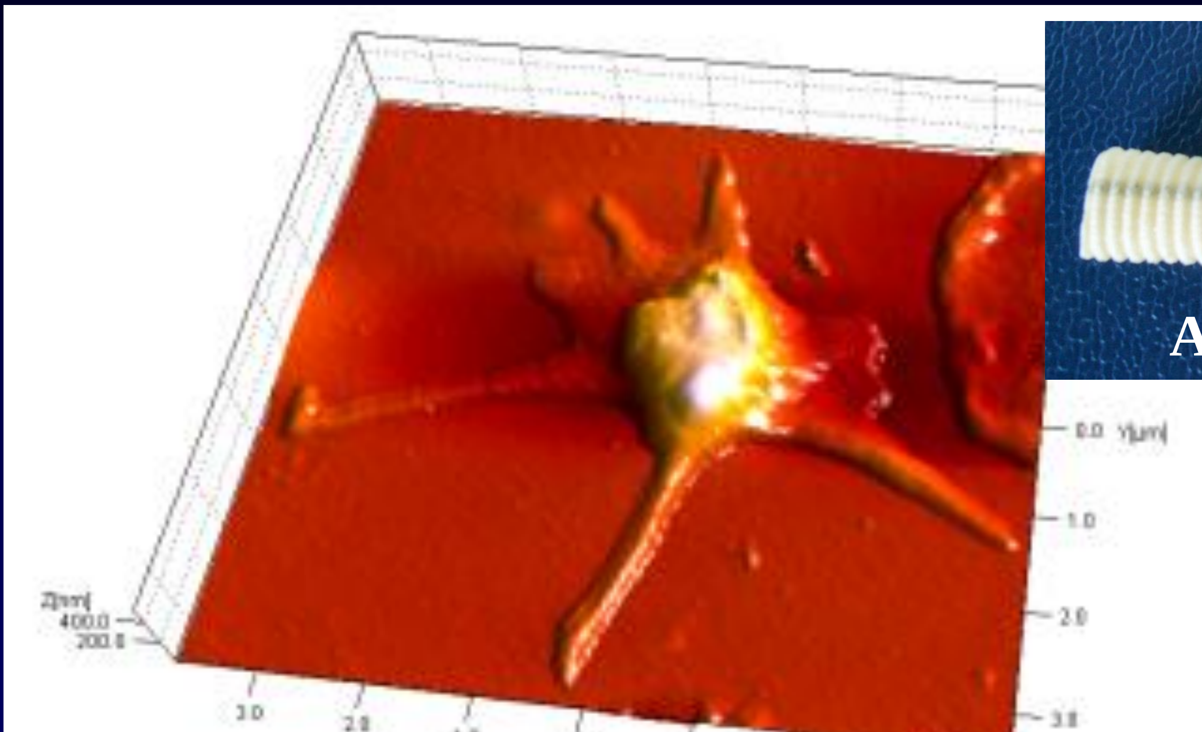
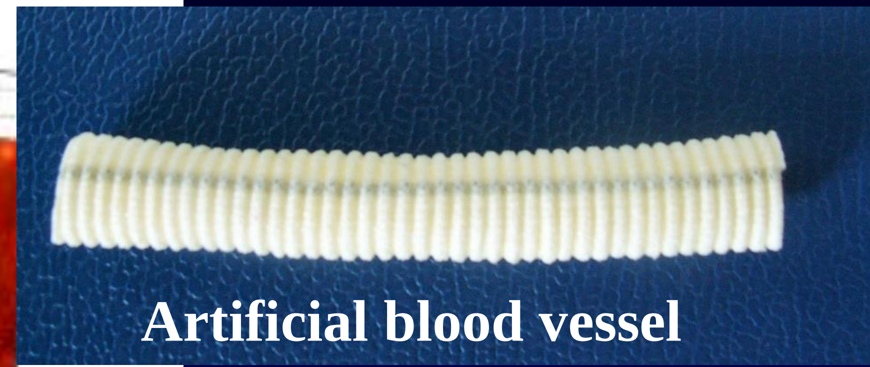
Plasma Nanotechnologies for Cardiovascular Implants



Blood plattelet in dendritic form



Artificial blood vessel

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Classical technologies for materials processing run close to thermal equilibrium

Rather high temperature is required for chemical reactions

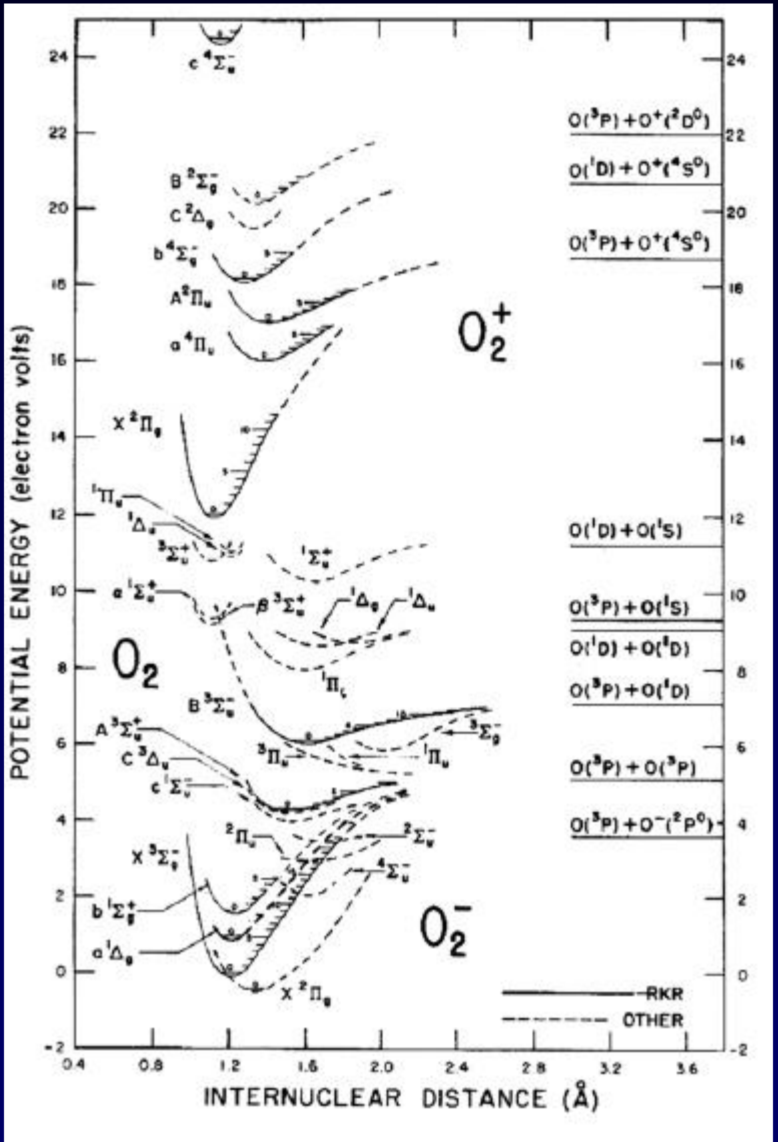
Materials can be damaged before achiving certain effects

Q: Is it possible to avoid high temperature?

Heating of materials by gas depends on the gas temperature

Chemical reactivity of oxygen depends on the concentration of molecules in excited states

$$\frac{N_a}{N} = e^{-W_a / kT}$$

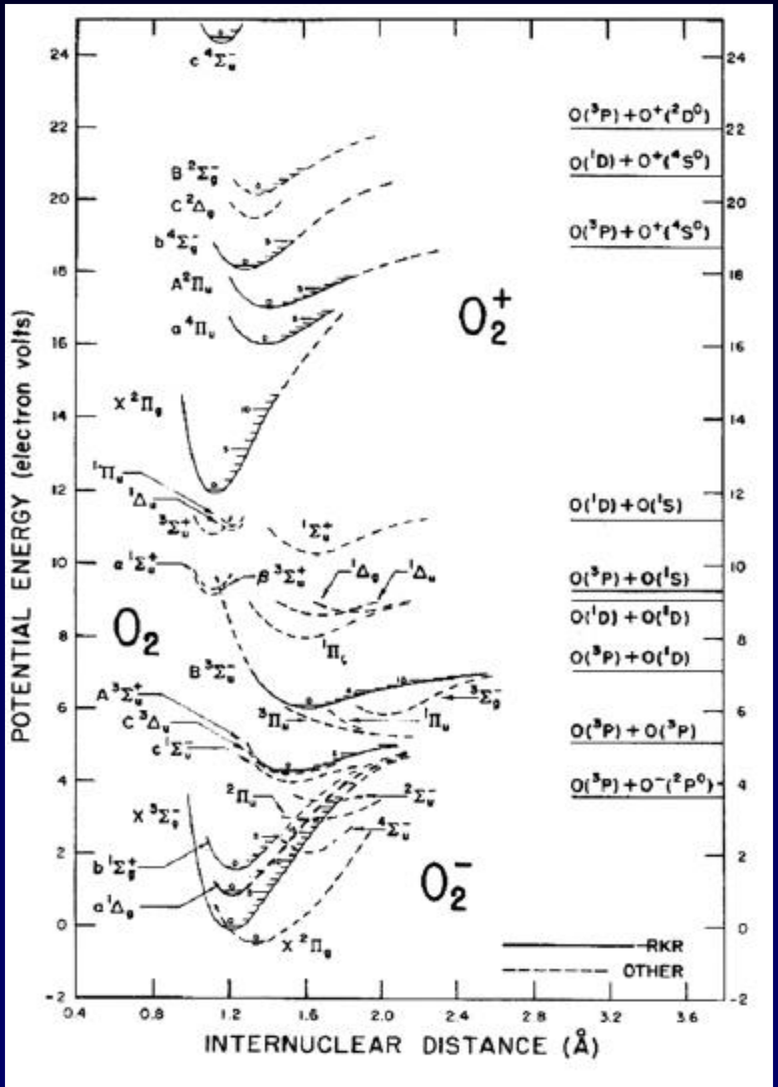


Jozef Stefan Institute,
Department of Surface Engineering and Optoelectronics

Nature does not allow high density of excited states at low gas temperature

Avoid the basic law of thermodynamics!

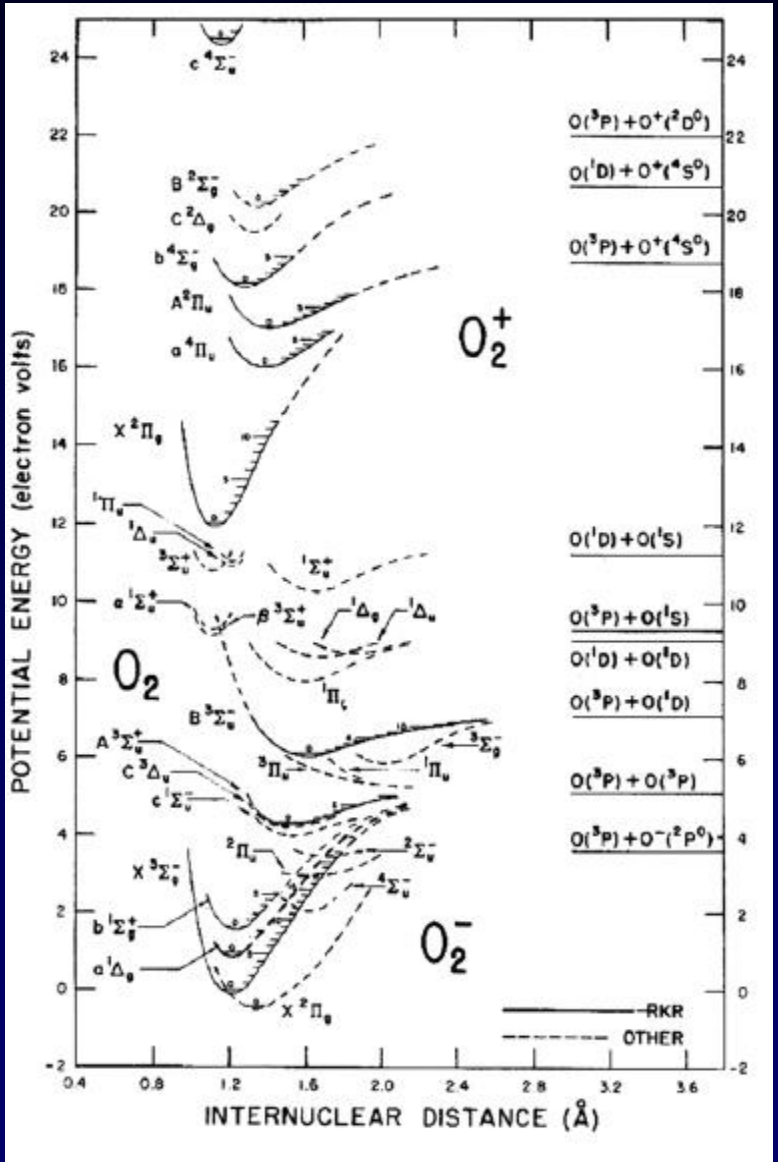
$$\frac{N_a}{N} = e^{-W_a/kT}$$



Q: How do we avoid thermodynamics?

A: Do not create highly excited states by heating of gas.

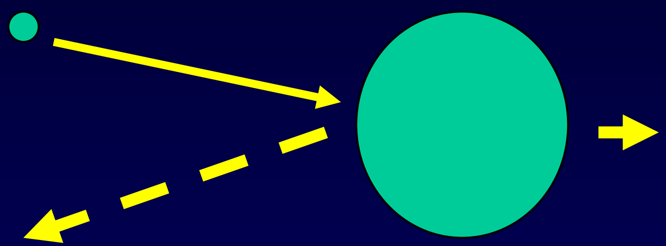
Use free electrons instead

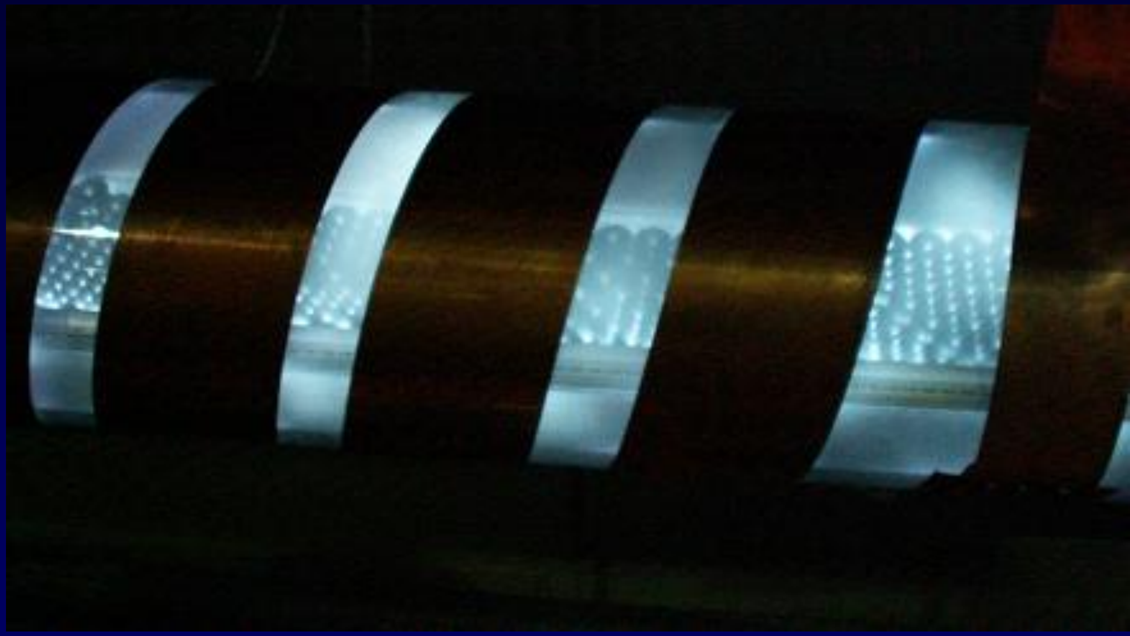


Free electrons are capable to excite molecules without heating them!

Electrons cannot heat gas (transfer kinetic energy to a molecule) due to the small mass

Elastic collision



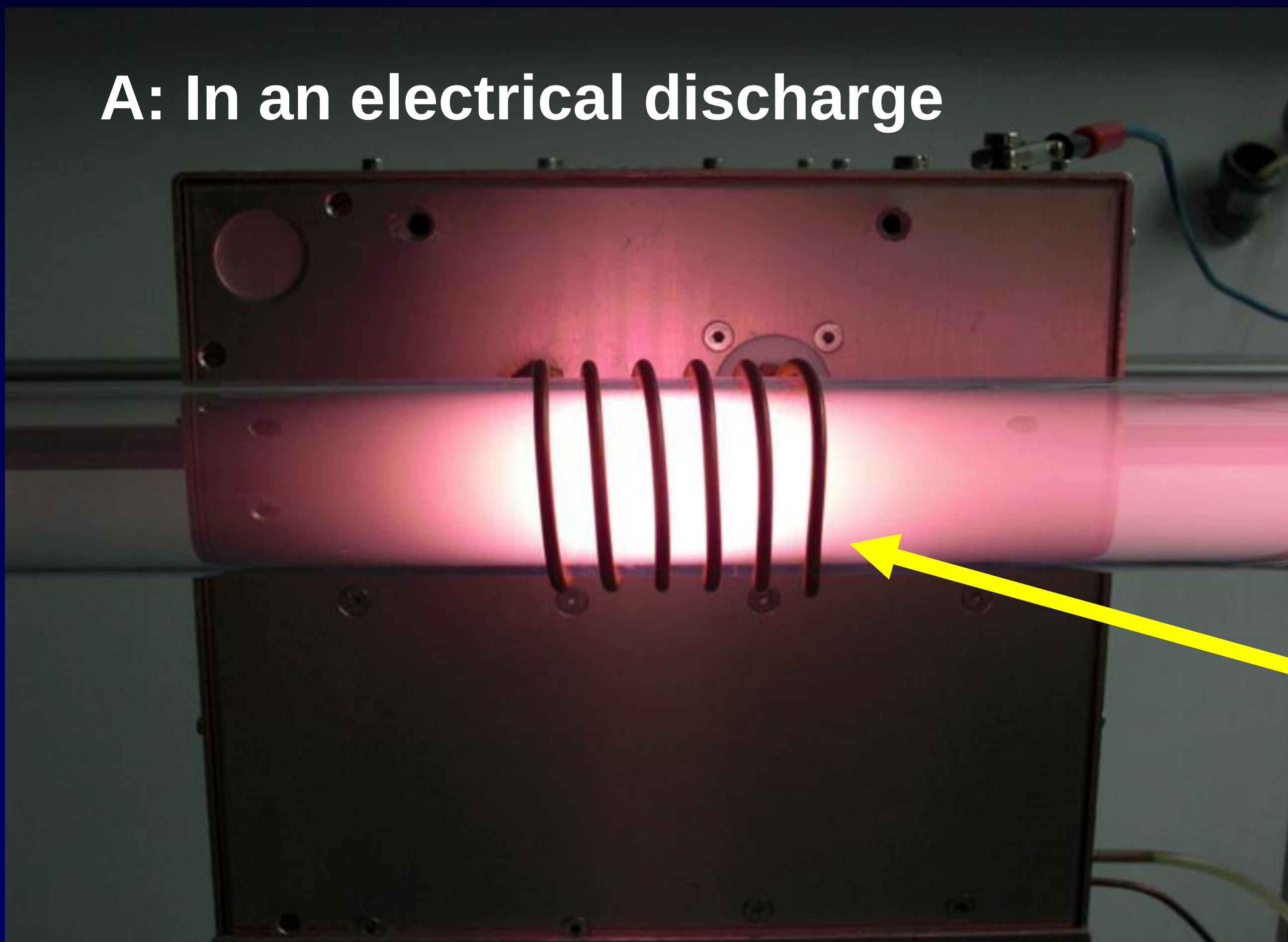


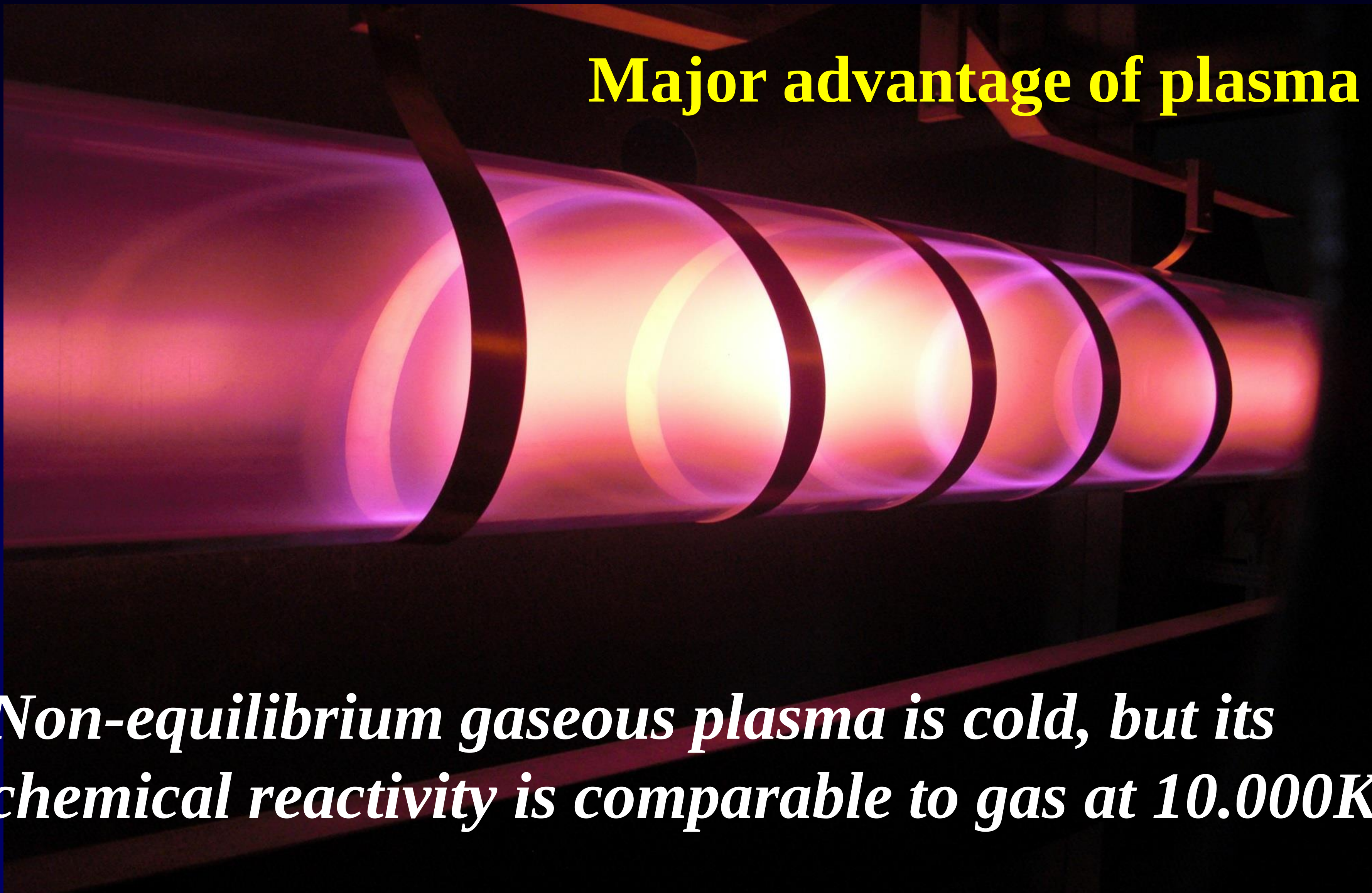
$$m_e \, v_e = M \, v_M$$

$$W_k = \tfrac{1}{2} M v^2 \rightarrow$$ Kinetic energy of heavy molecule is negligible

ELECTRONS EXCITE MOLECULES EASILY BUT NOT HEAT THEM

Q: How do we create gas with substantial amount of free electrons?



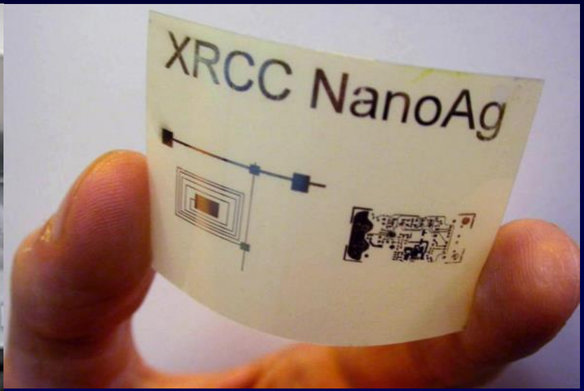


Major advantage of plasma

Non-equilibrium gaseous plasma is cold, but its chemical reactivity is comparable to gas at 10.000K!

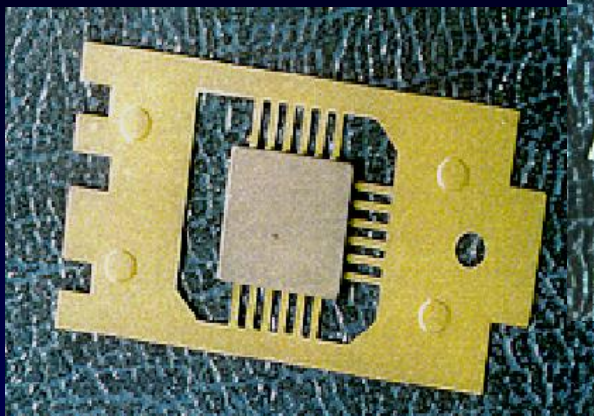
Applications

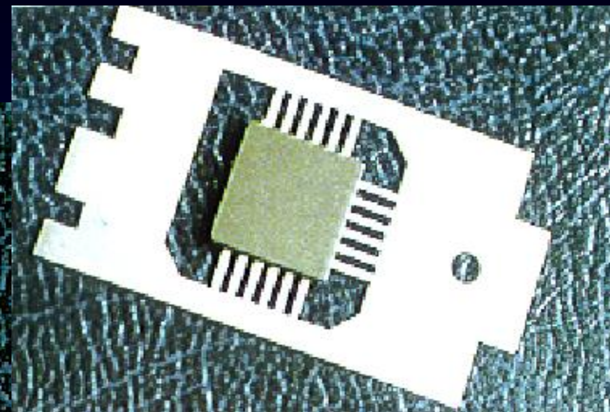
Activation of polymers for better adhesion (painting, printing)



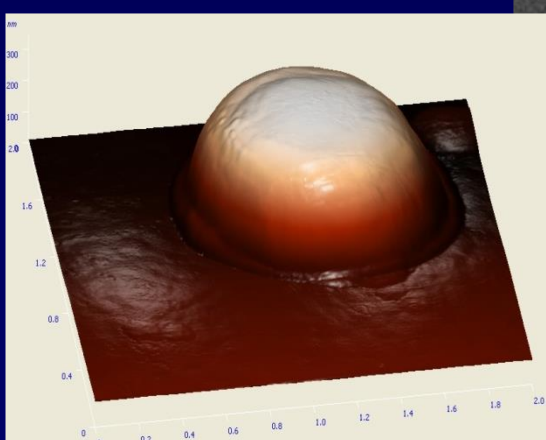
Functional textiles

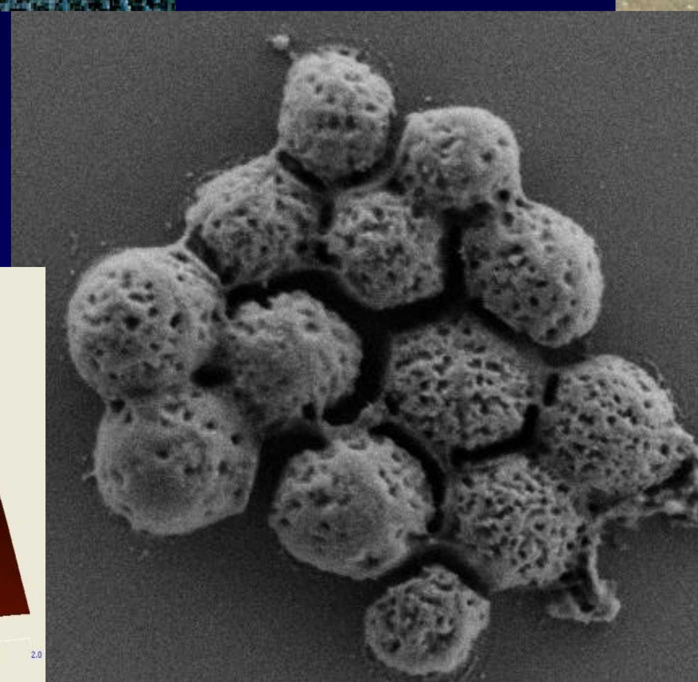
Discharge cleaning



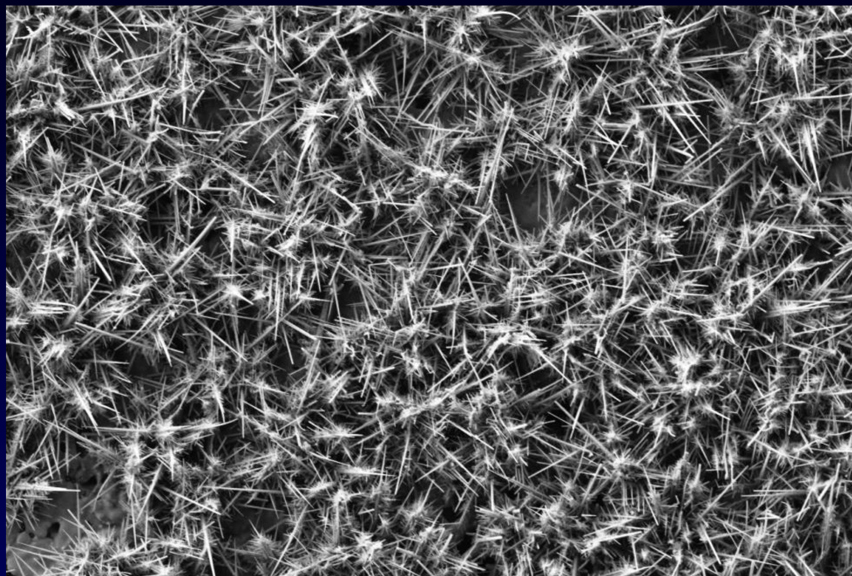


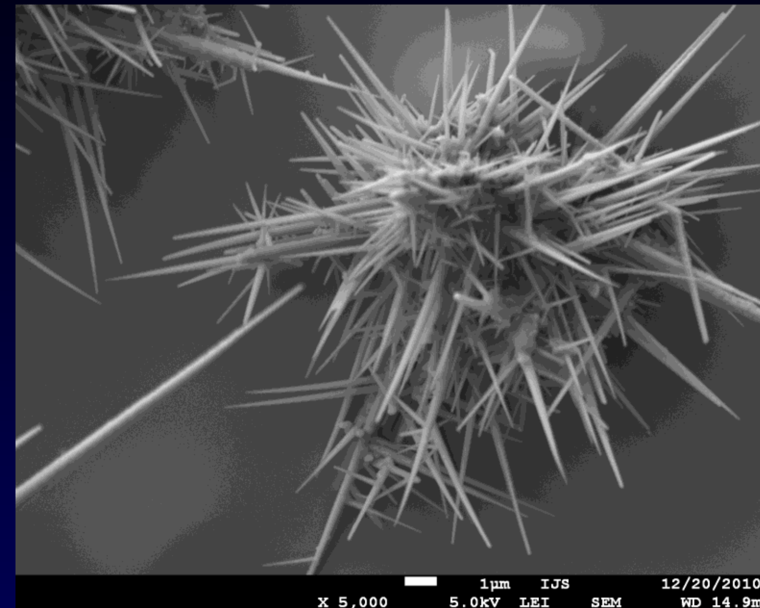
Sterilization

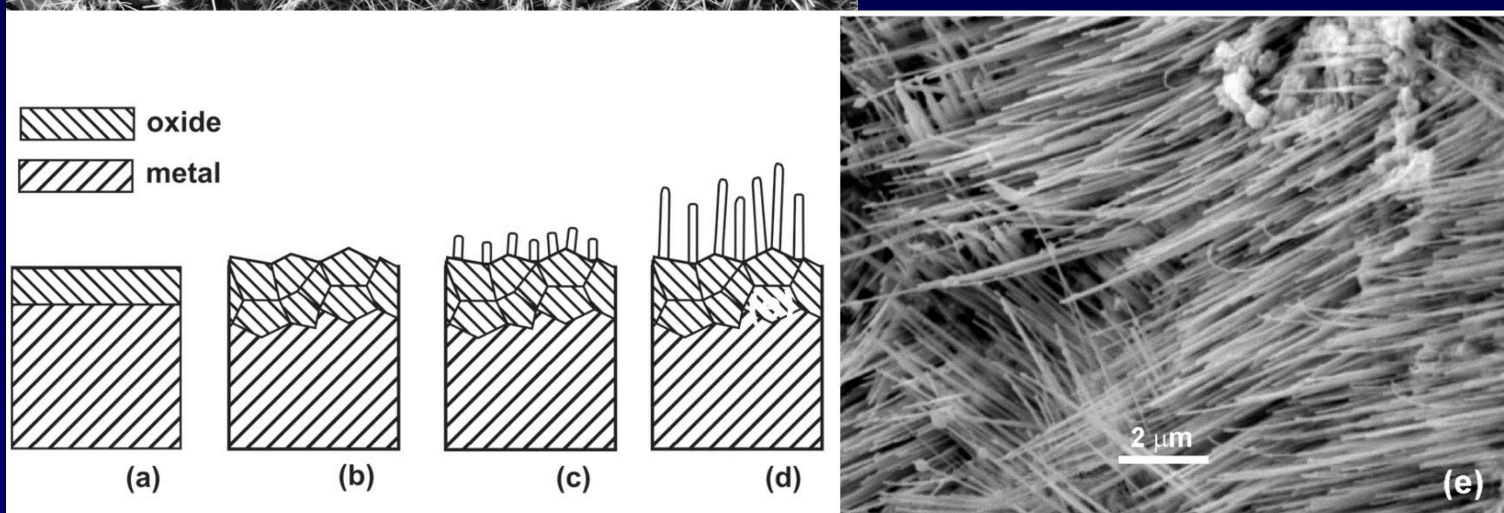




Synthesis of nanoparticles







Cardiovascular diseases represent the major cause of death in wealthy countries

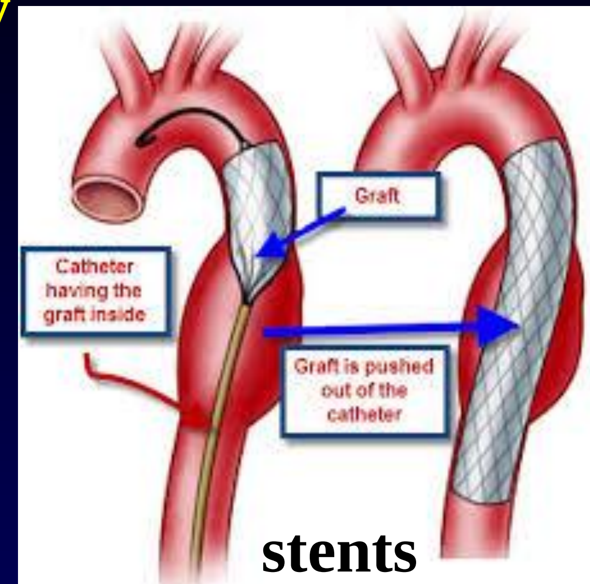
Only in USA, the costs annual exceed 500 billion $

stress

improper diet

smoking

Curing of cardiovascular diseases is by surgery



stents


Heart valves

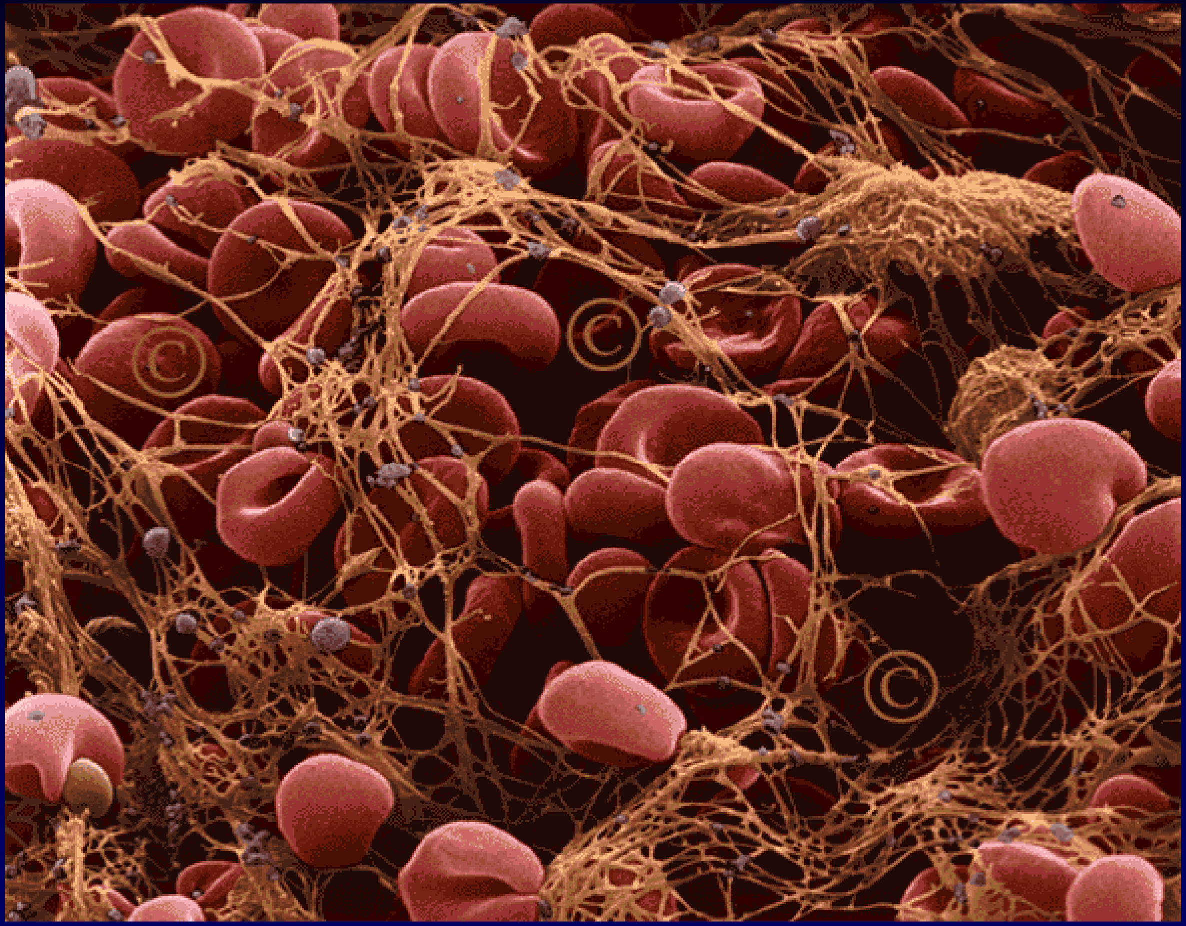

Vascular grafts

A common post-surgery complication is thrombosis

Coagulation cascade

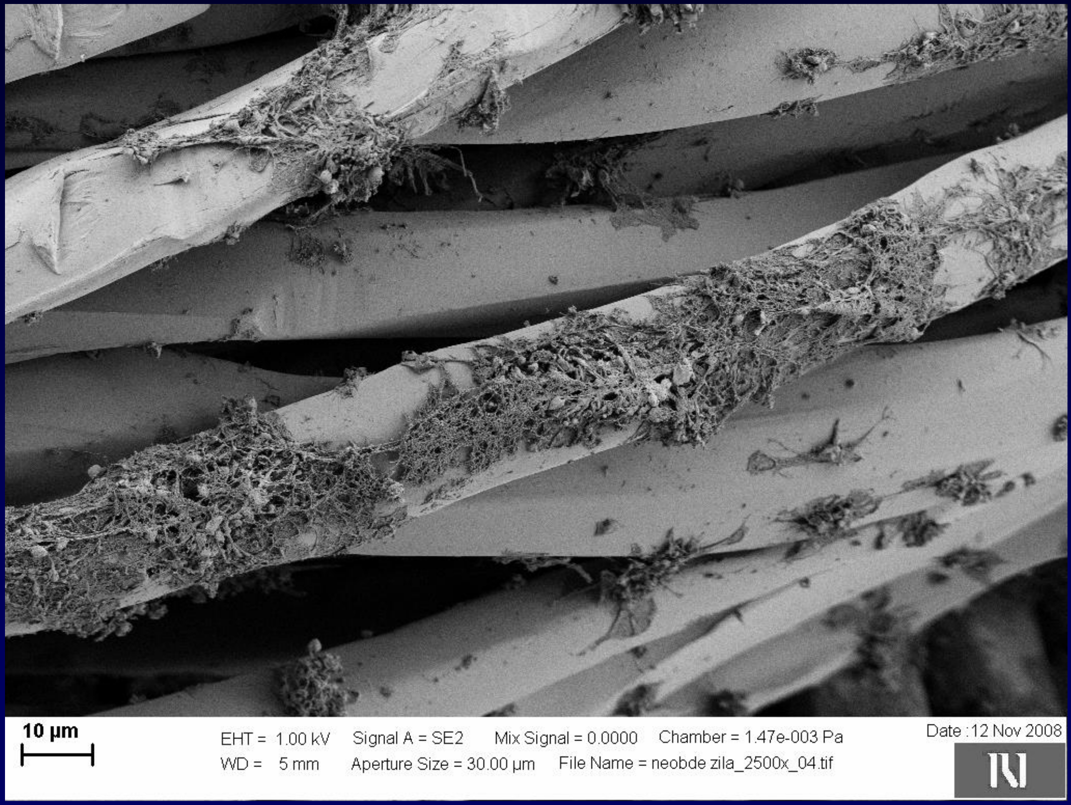
Fibrinogen to fibrin fibres

fibrin fibres form a network capturing erythrocytes



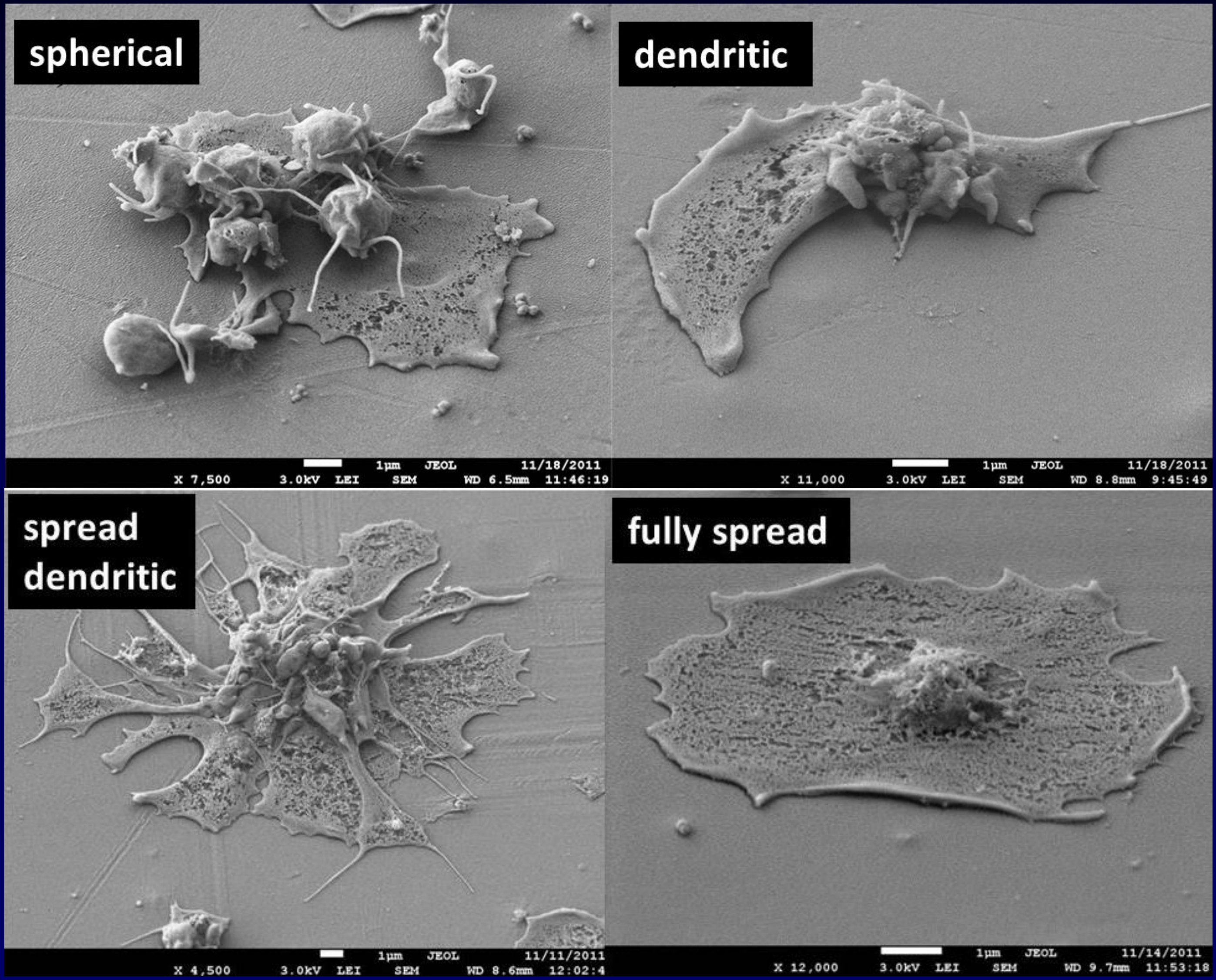
http://www.ldeo.columbia.edu/micro/images.section/pages/bloodclot.html

Fibrin fibres accommodate quickly upon incubation of an artificial blood vessel with blood



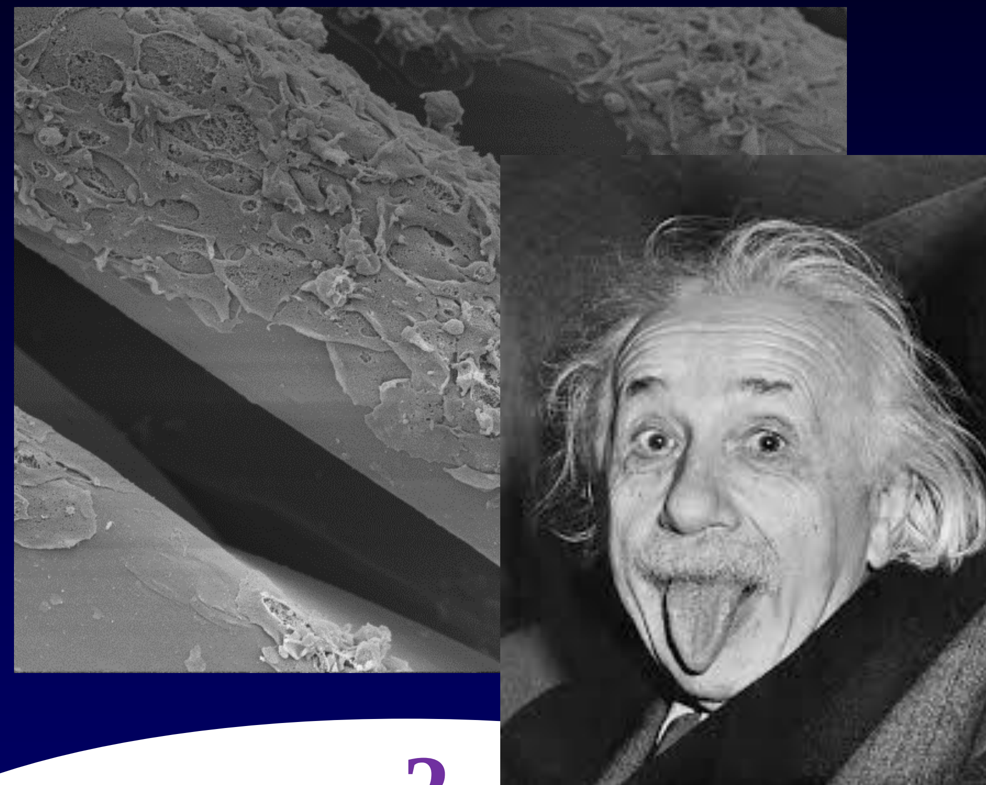
Vascular grafts are made from knitted polymers, often PET

Coagulation cascade is stimulated by platelet activation



Platelets‘ shape change upon activation

Activation of blood platelets on polymer surface is due to insufficient biocompatibility



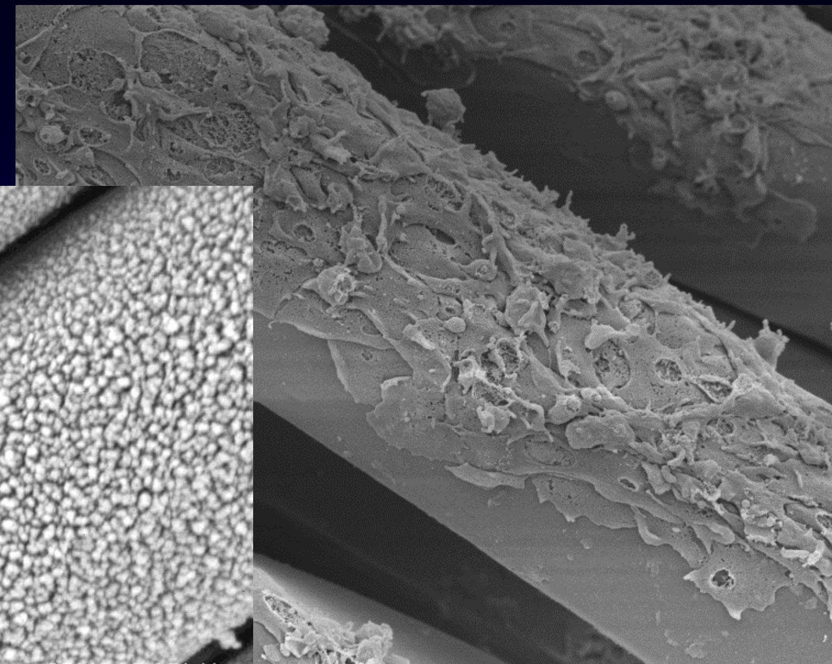
Possible solutions:

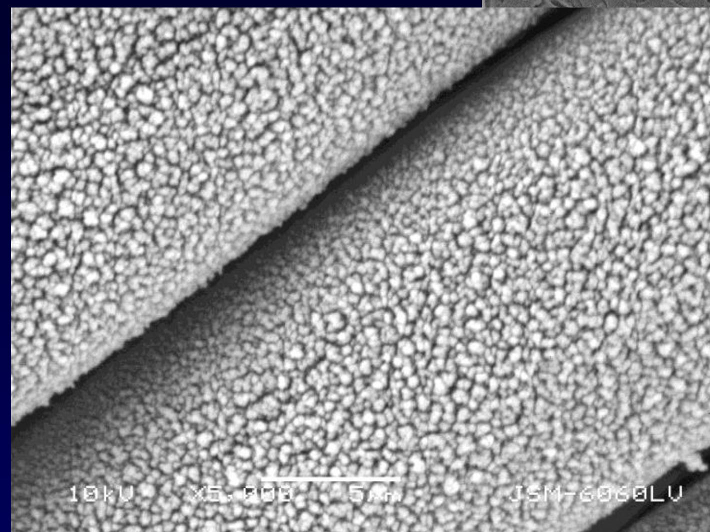
1.
Coat with heparin

Gaseous plasma treatment

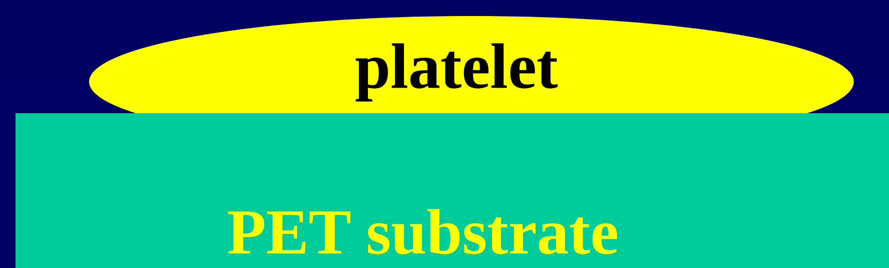
2.
Make the contact area minimal by nano-structuring

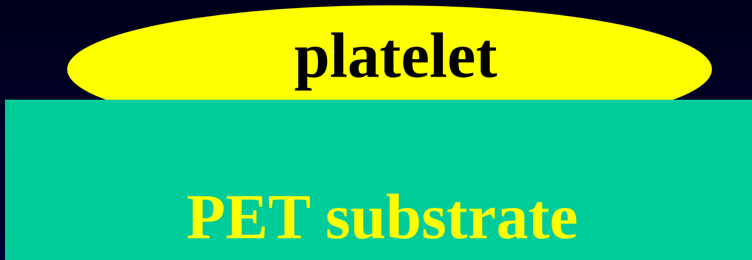
Platelets spread on smooth surface of polymer

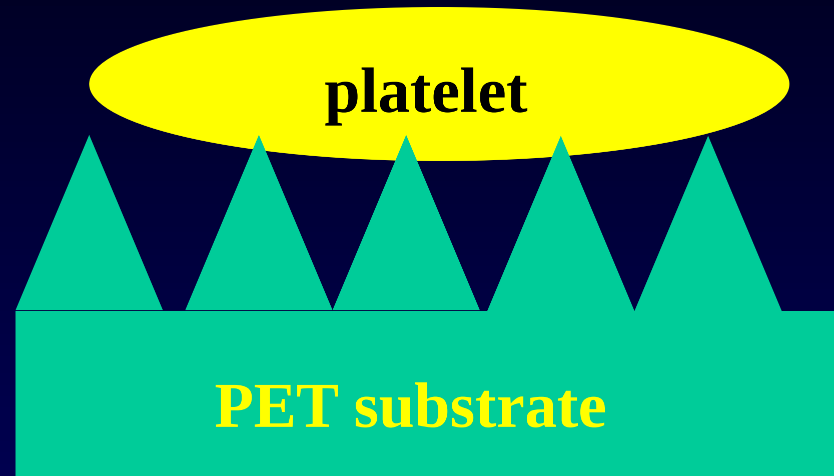




Minimize the contact area!

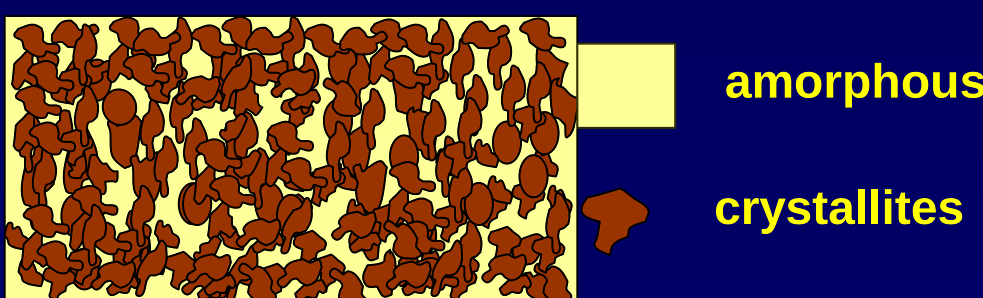






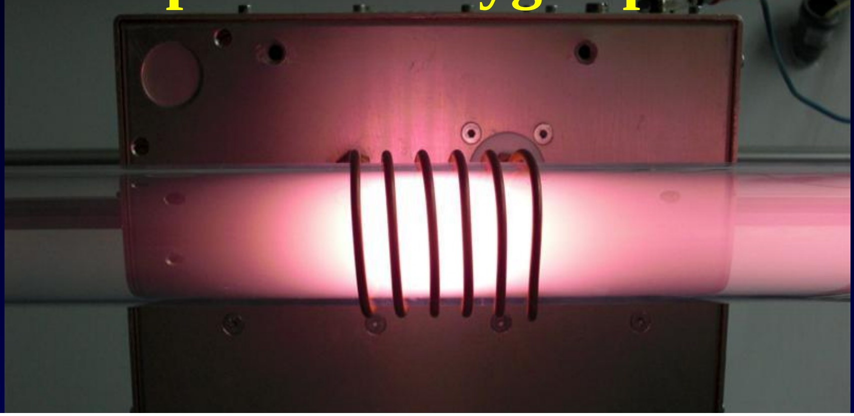
Contact area is minimized by making substrate rough on sub-micron scale

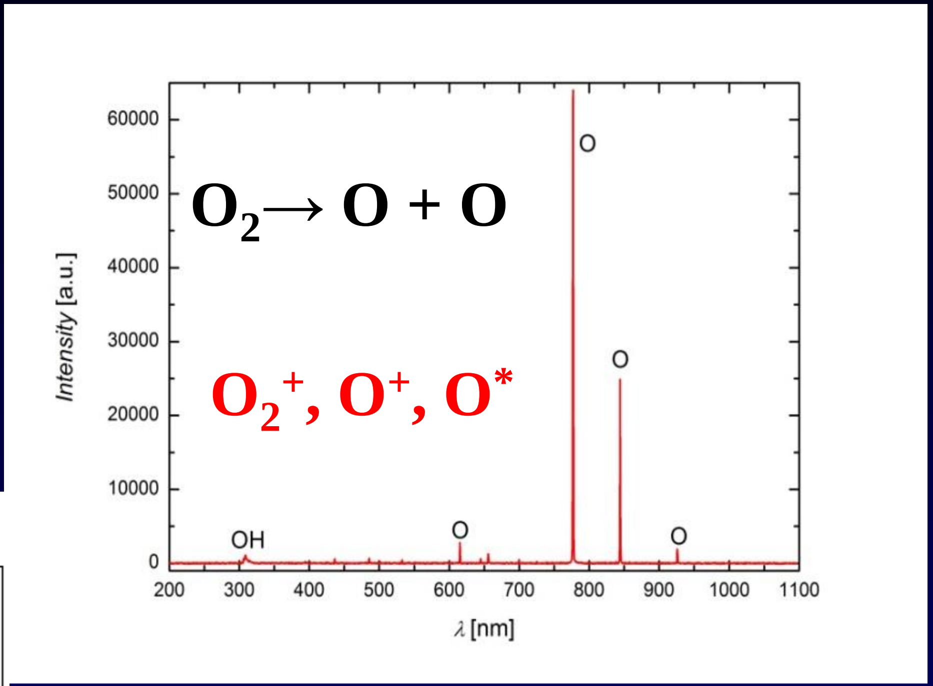
PET polymer for vascular grafts is semi-cristalline

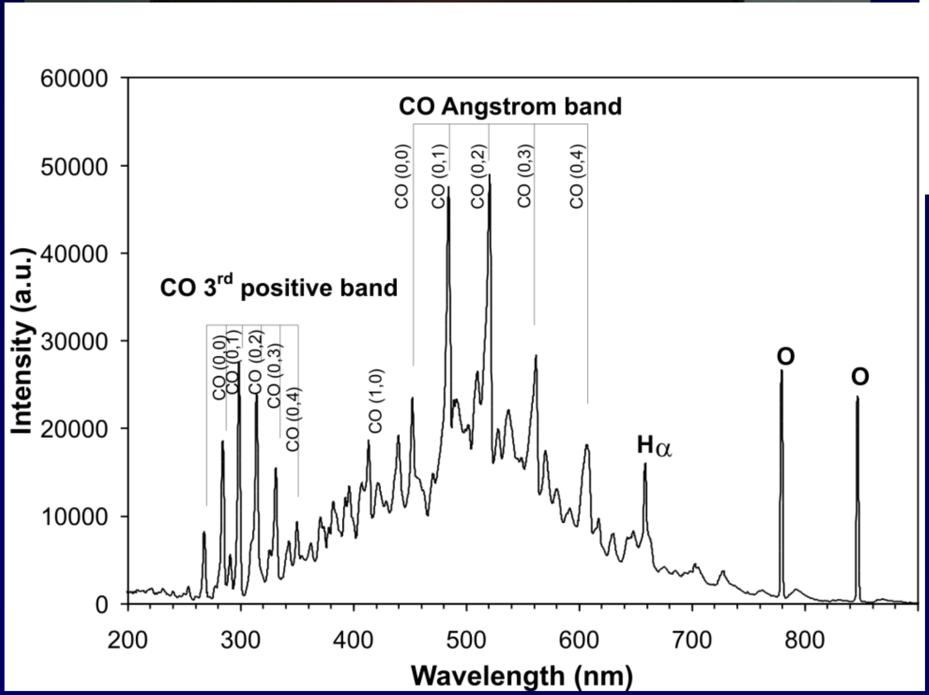


SELECTIVELY ETCH THE AMORPHOUS PHASE AND YOU WILL MAKE MATERIAL ROUGH ON SUB-MICRON SCALE

Low-pressure oxygen plasma







Reactive oxygen species cause low-temperature „burning“ of polymer

Etching rate depends on crystallinity (nm/s)

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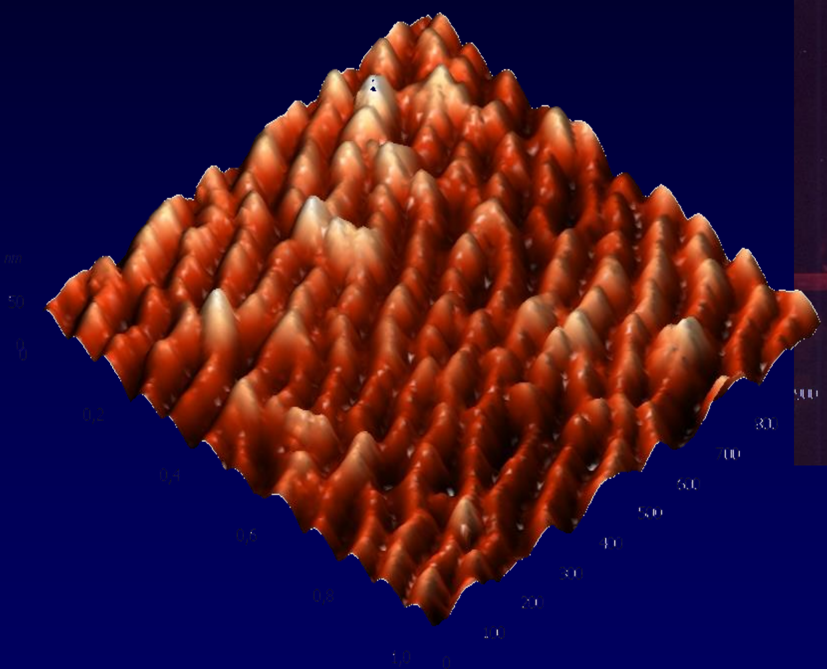
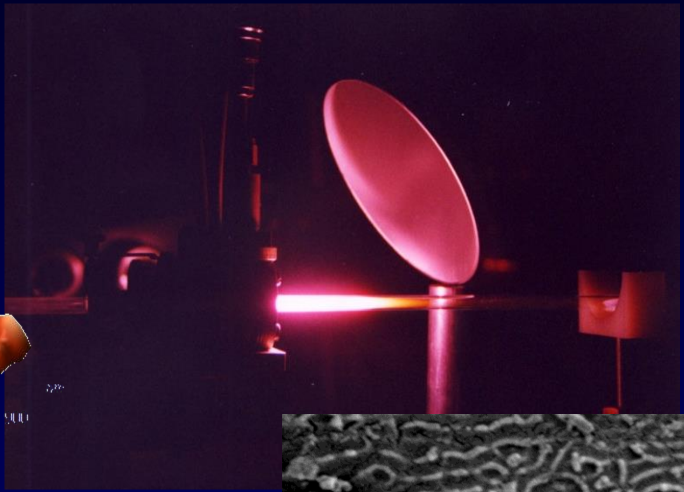
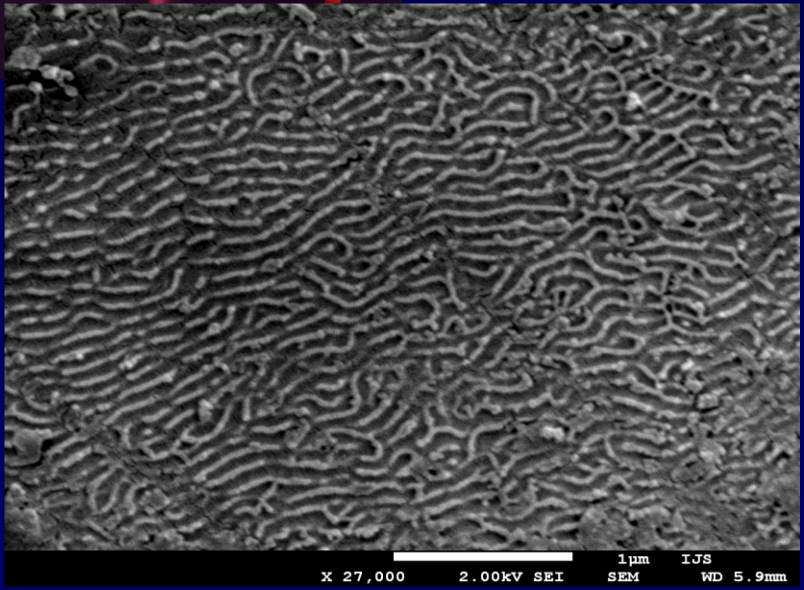
Department of Surface Engineering

Non – equilibrium oxygen plasma is an excellent medium for selective etching of carbon-containing materials



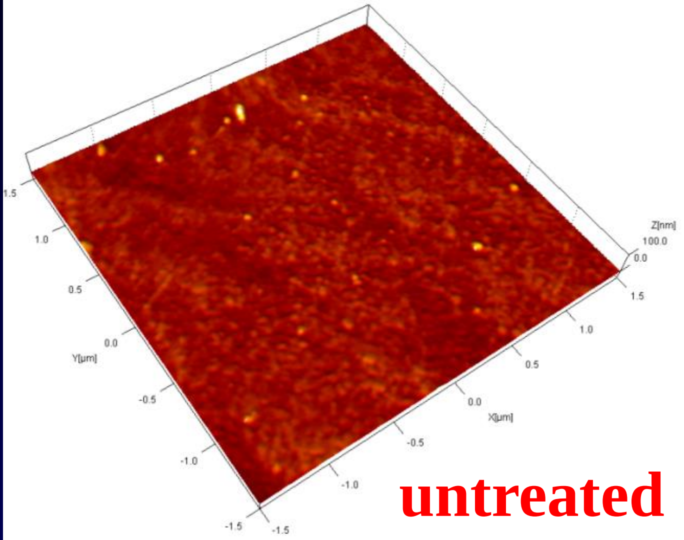


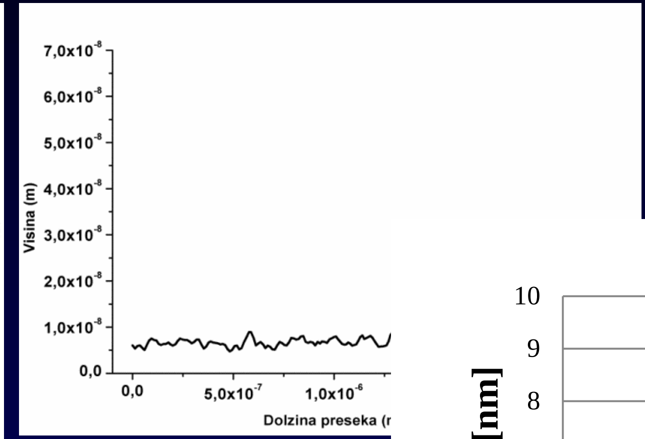
SEM image - optimal roughness



AFM image of plasma treated originally smooth semicristalline PET foil

Surface morphology changes upon plasma treatment





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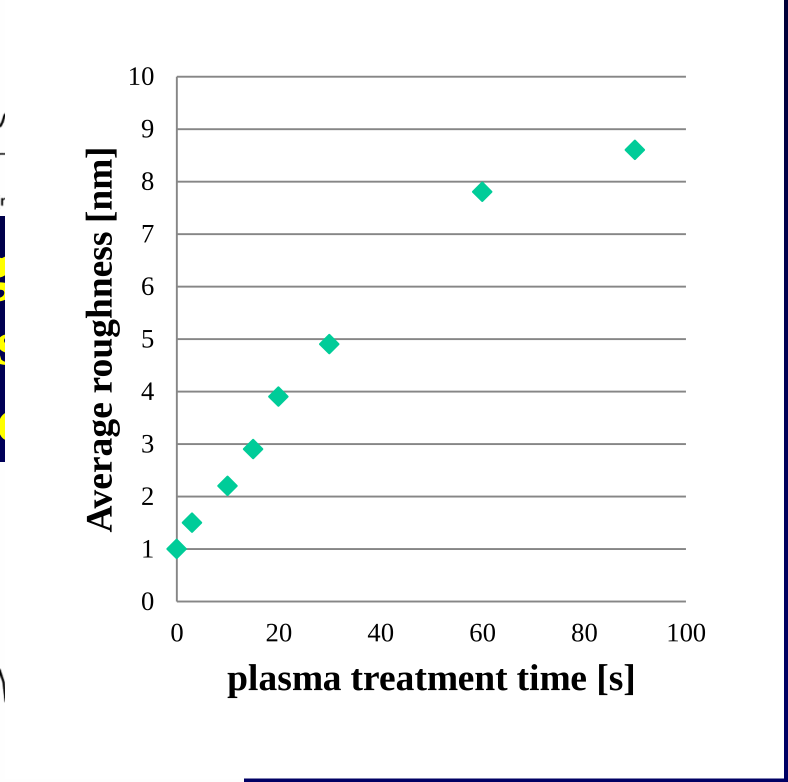
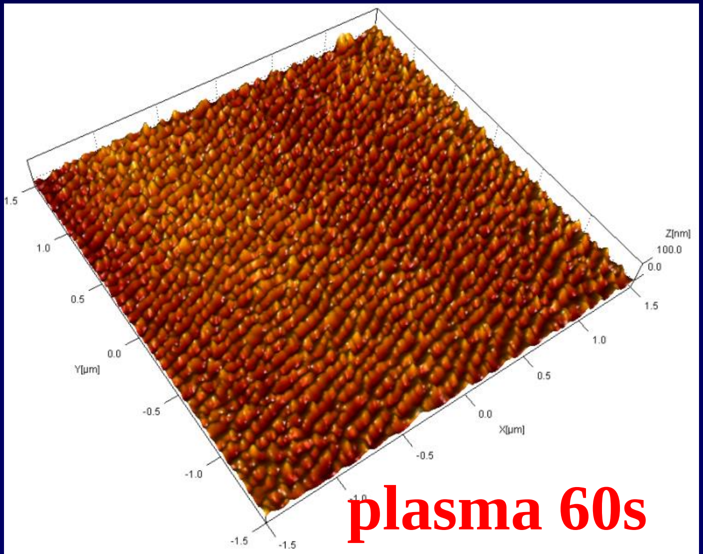
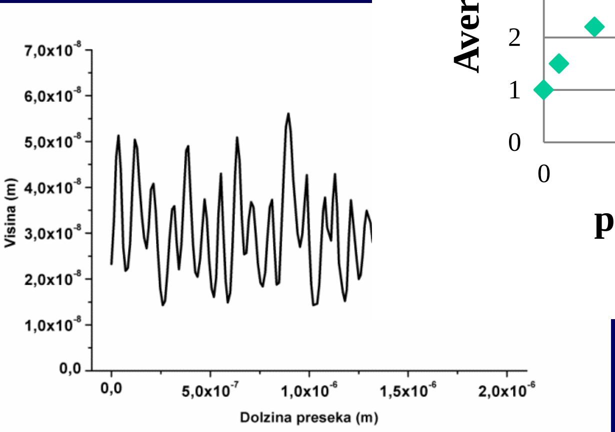
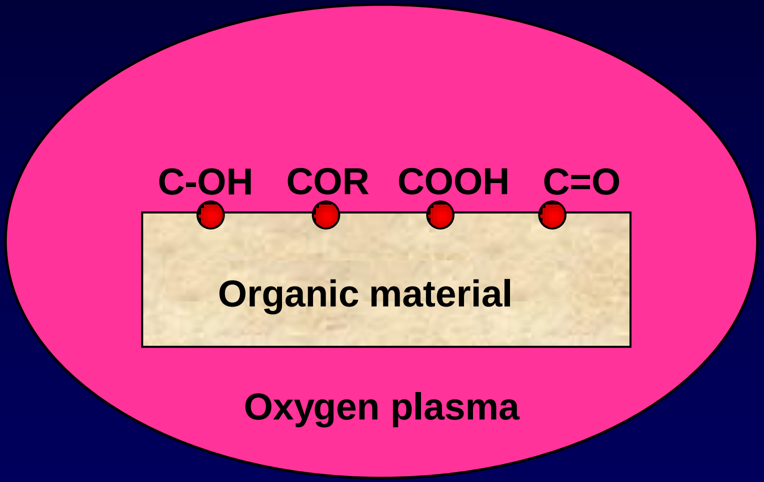






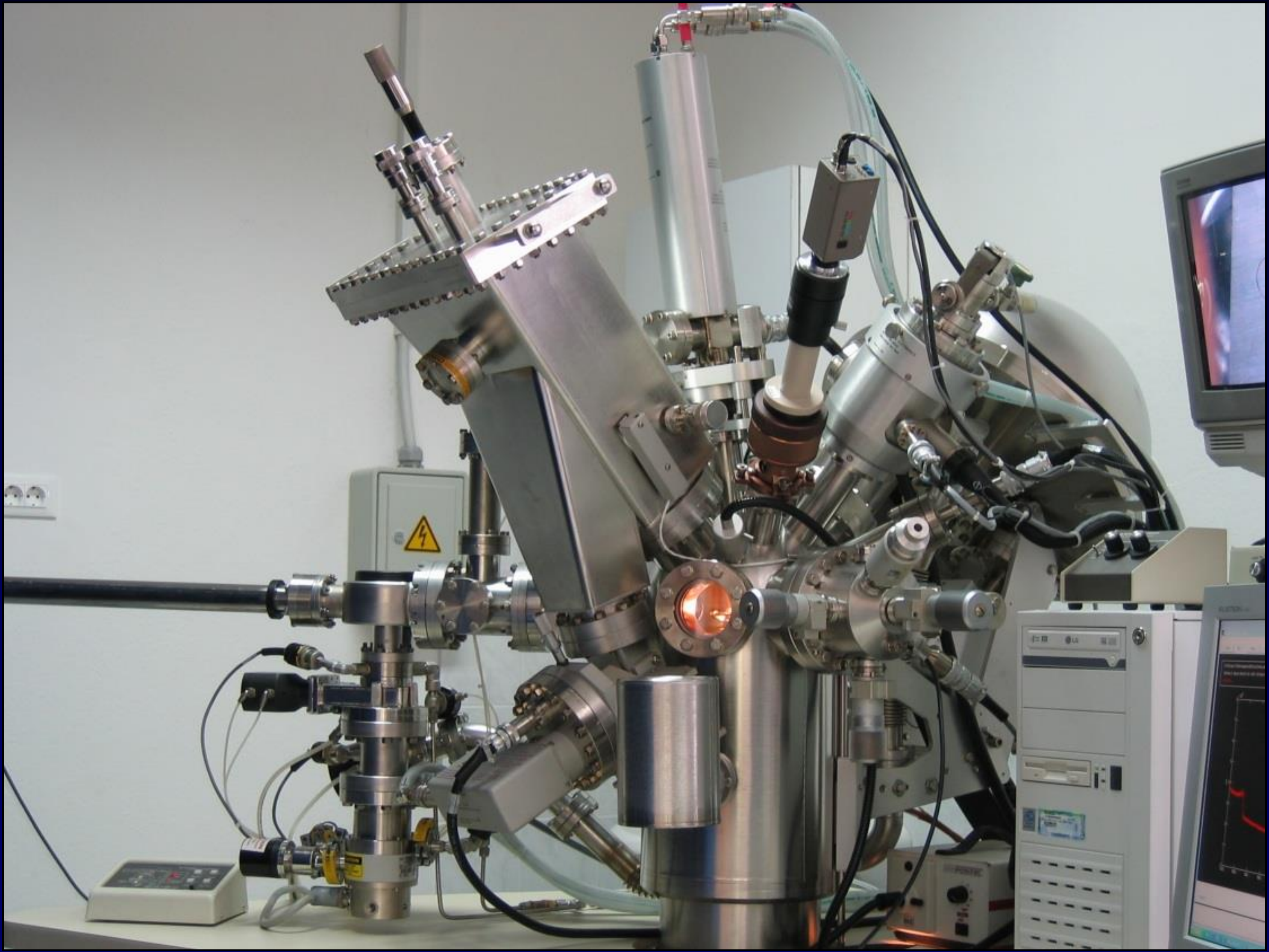
Plasma radicals readily interact chemically with the surface of organic materials



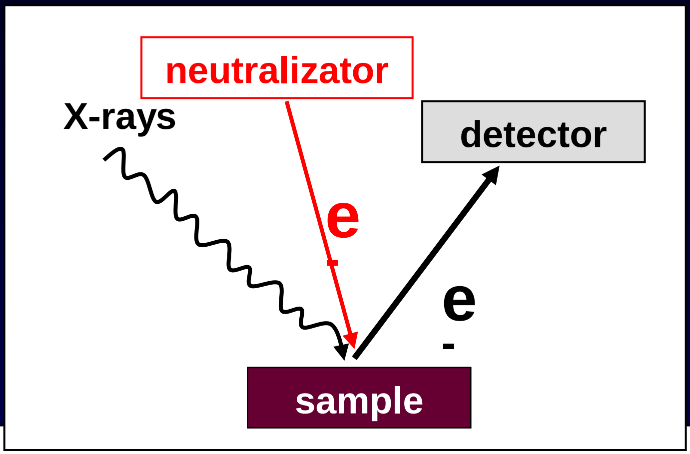
O – atoms are incorporated into the surface layer of polymer forming O-rich functional groups.

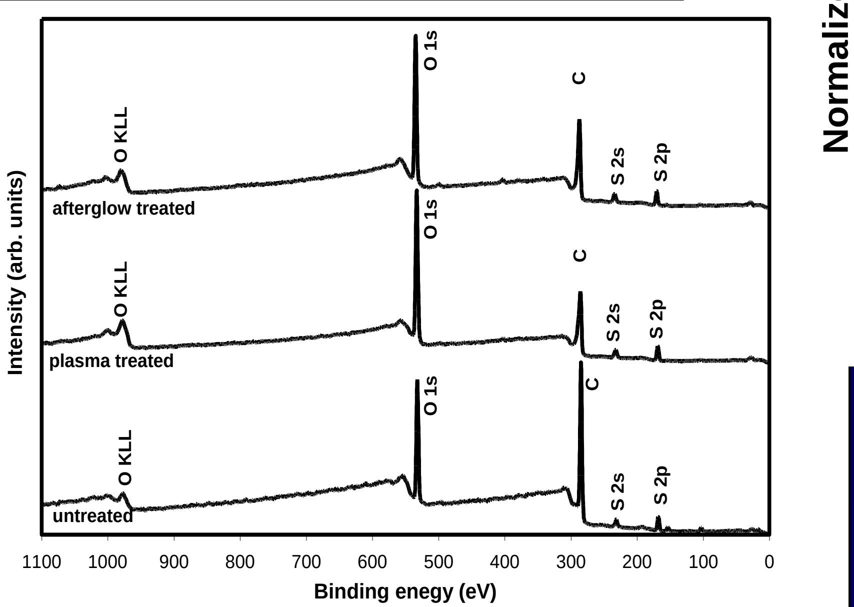
Hydrophilicity is improved dramatically

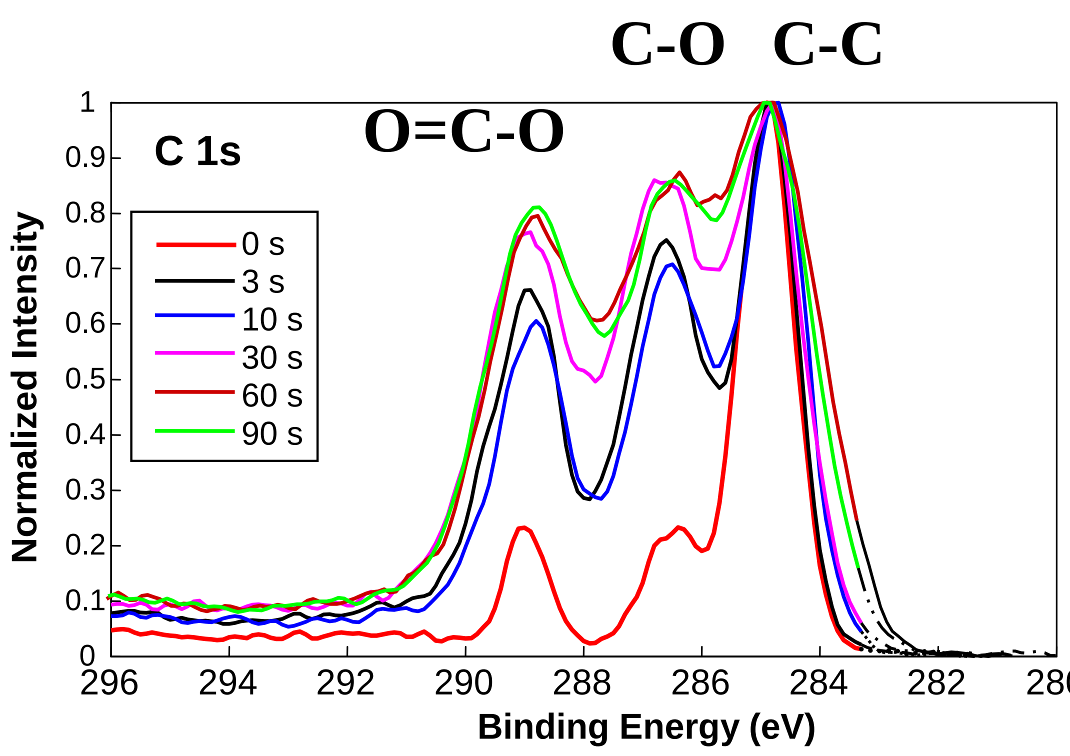
Surface functional groups are determined using XPS (ESCA) instrument

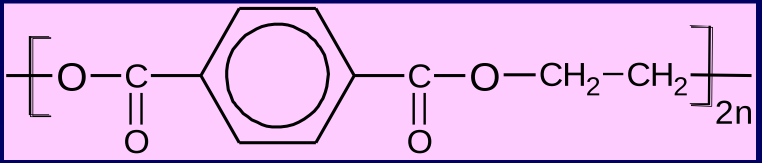


Photoelectron spectrum gives composition in few nm thick film

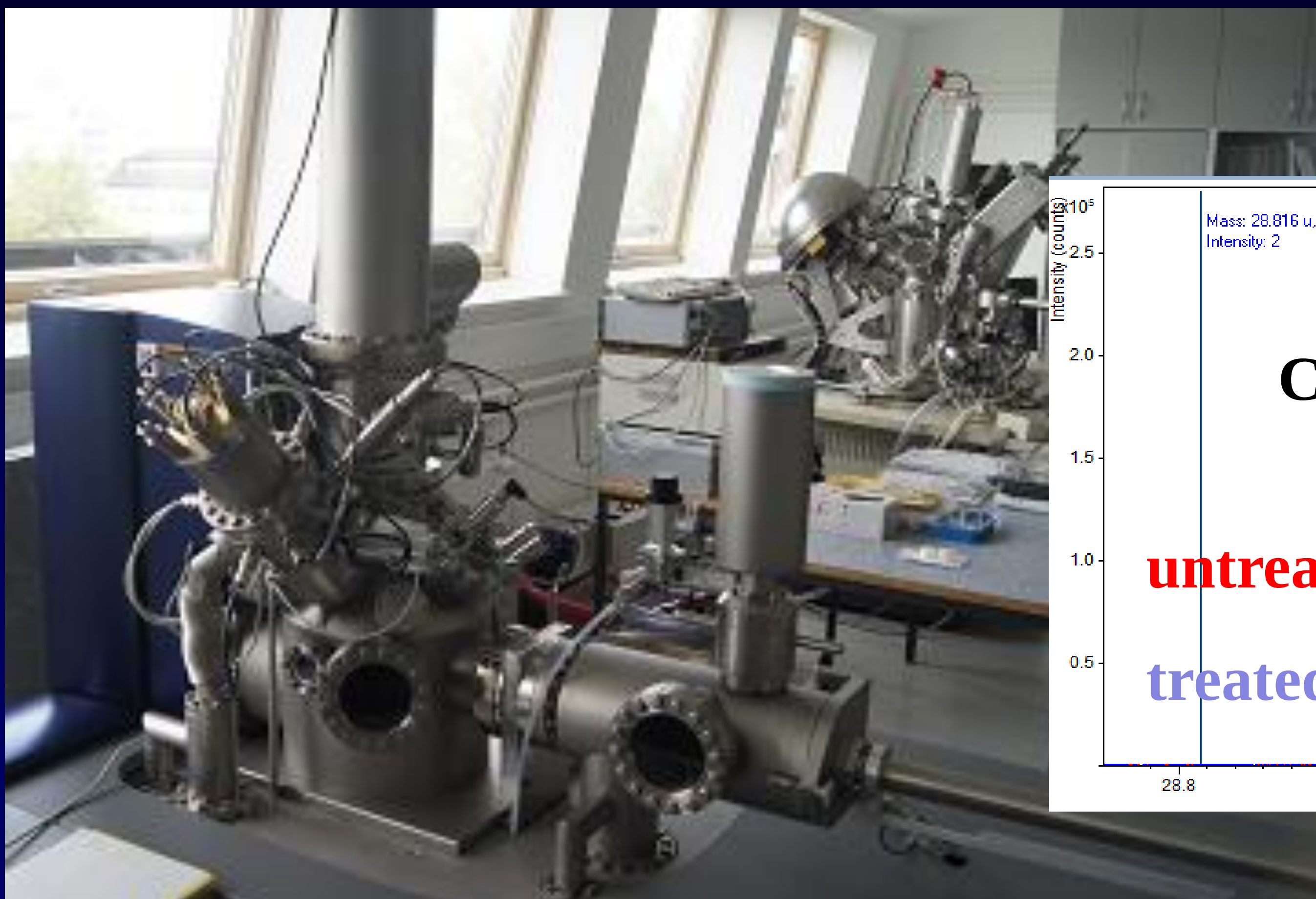


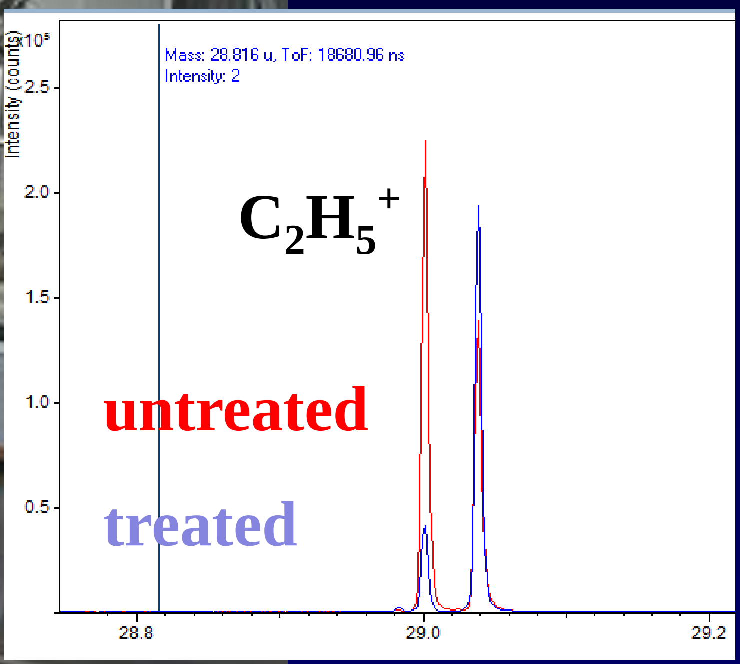




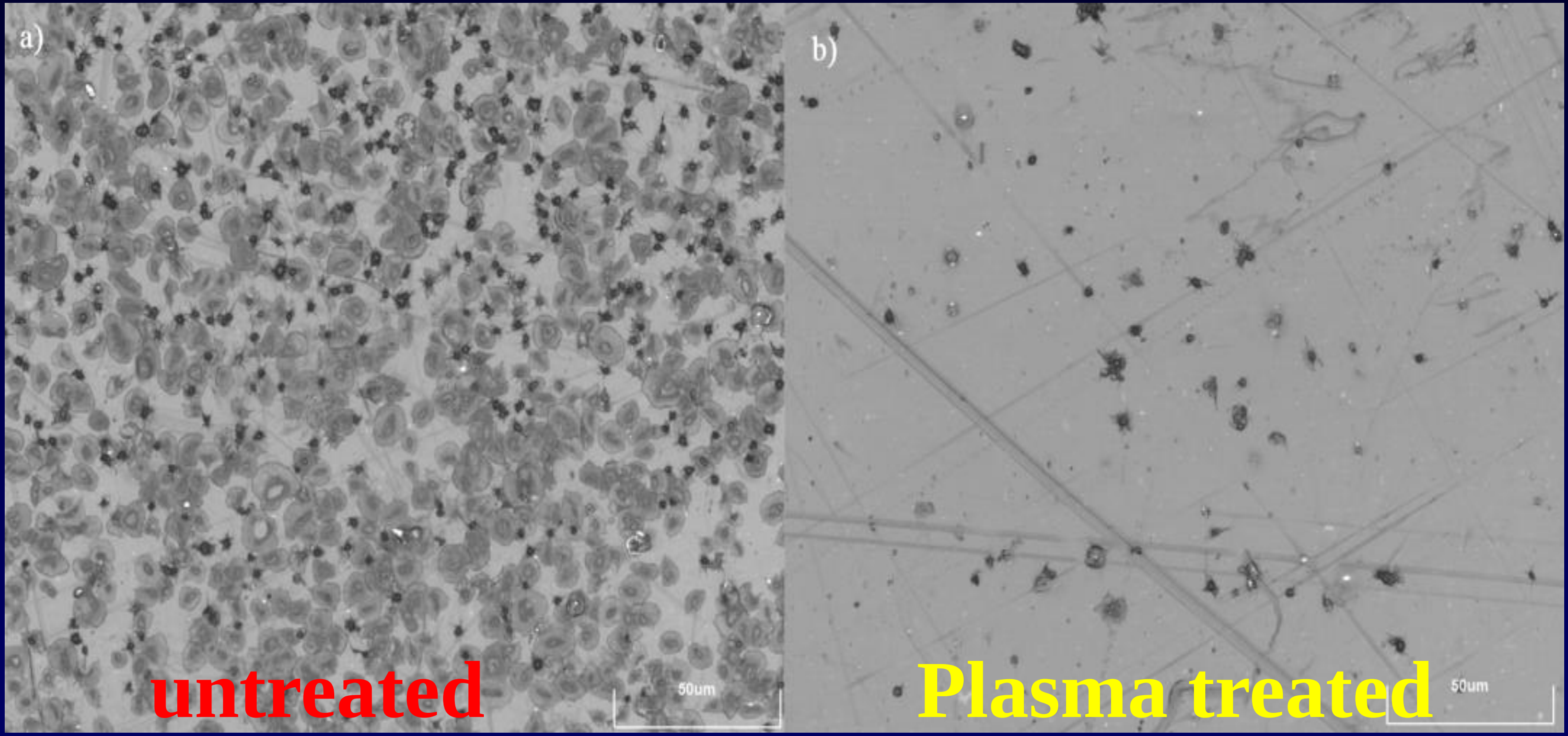


ToF-SIMS shows extremely high concentration of O-rich functional groups on the very surface



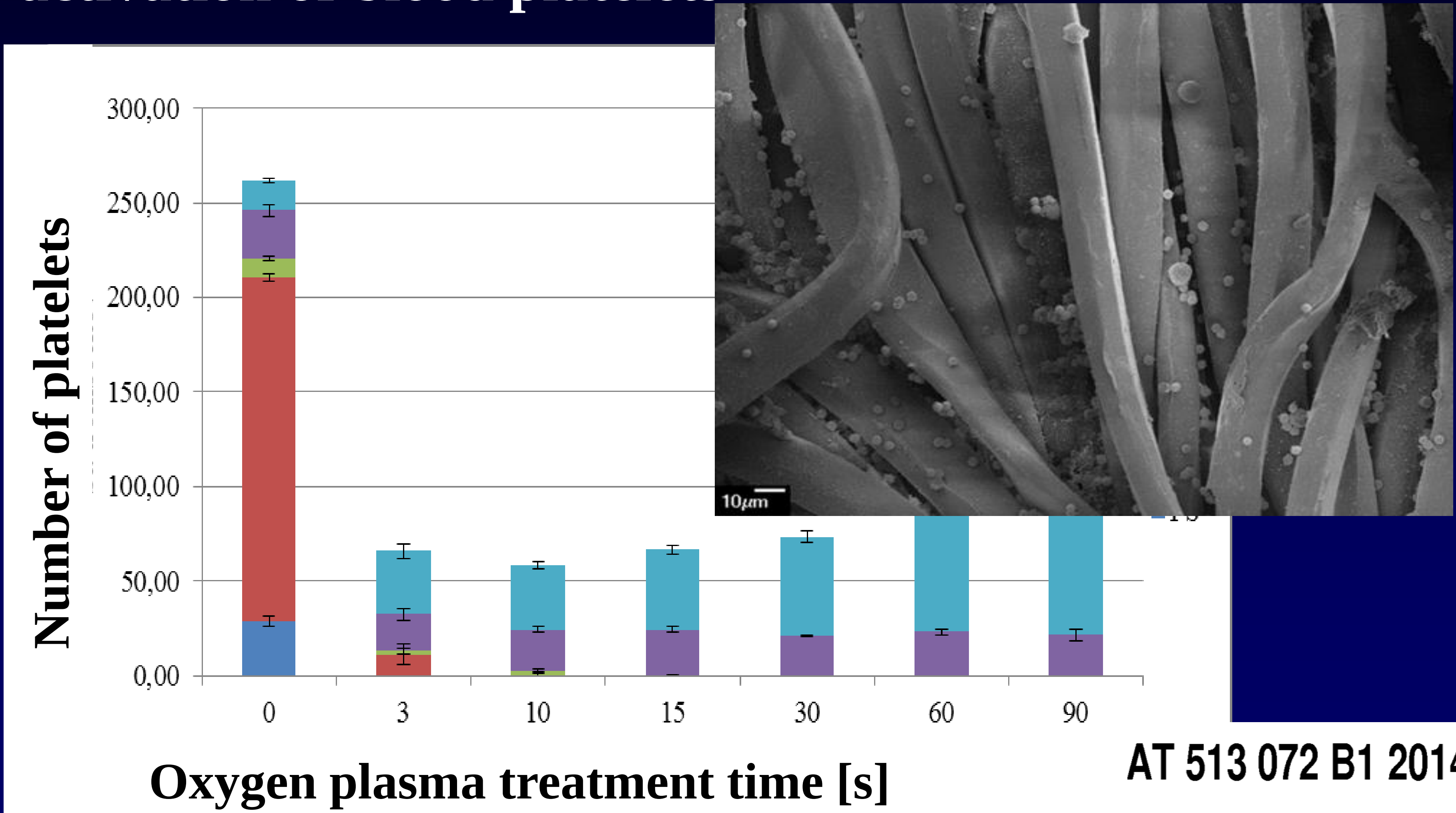


Even a brief treatment by oxygen plasma prevents activation of blood platelets



PET foils are used instead of real vascular grafts for quantification

Even a brief treatment by oxygen plasma prevents activation of blood platelets



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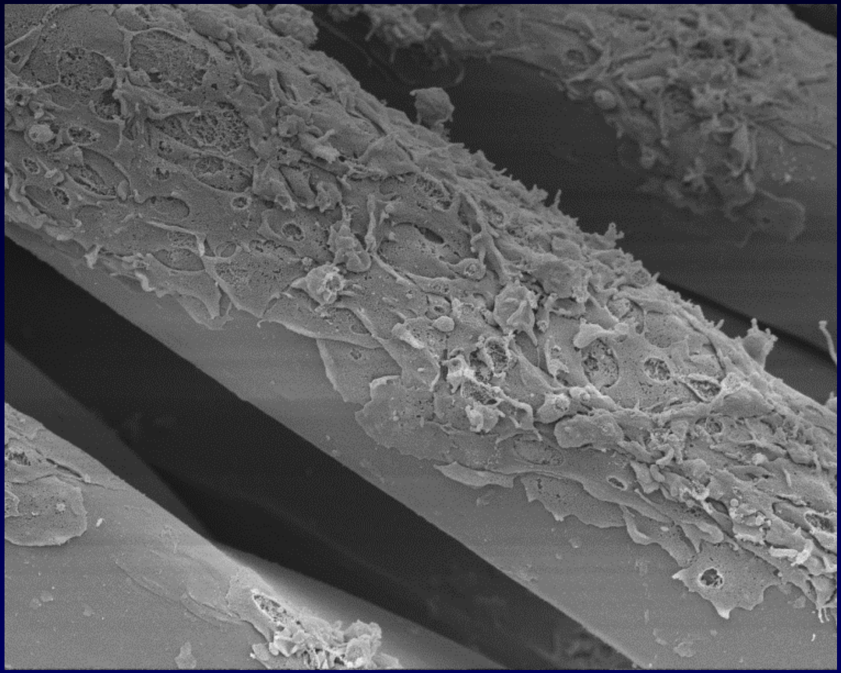
Activation of blood platelets on polymer surface is due to insufficient biocompatibility



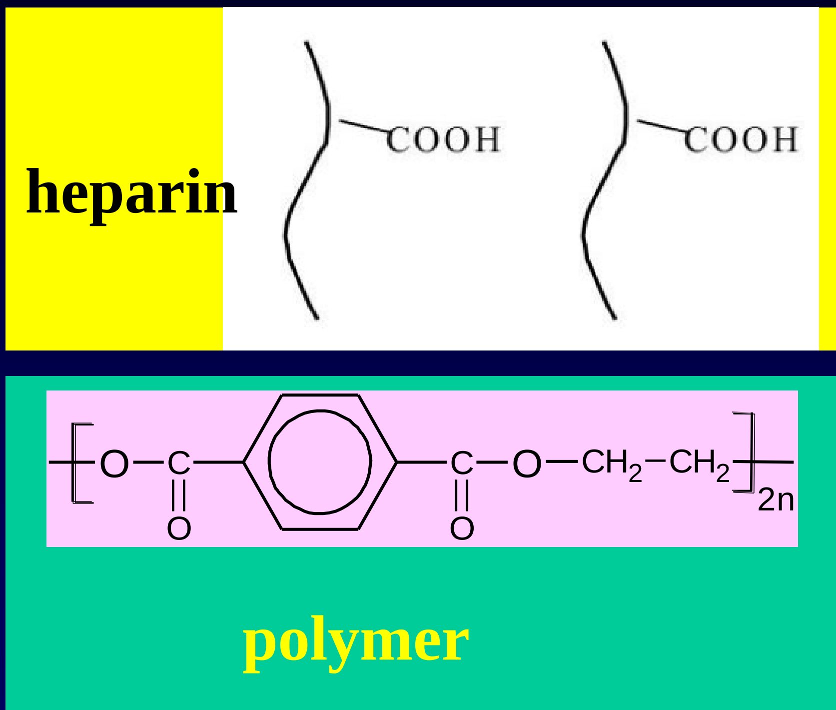
Possible solutions:

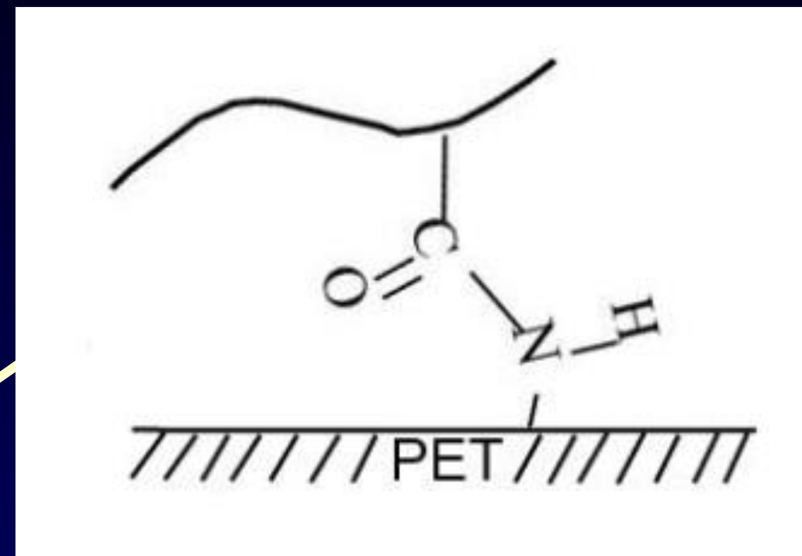
1.
Coat with heparin

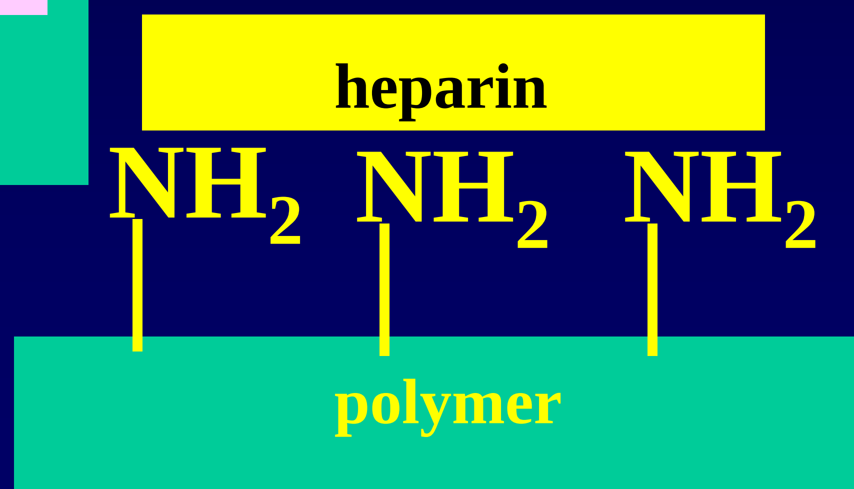
Gaseous plasma treatment

2.
Make the contact area minimal by nano-structuring

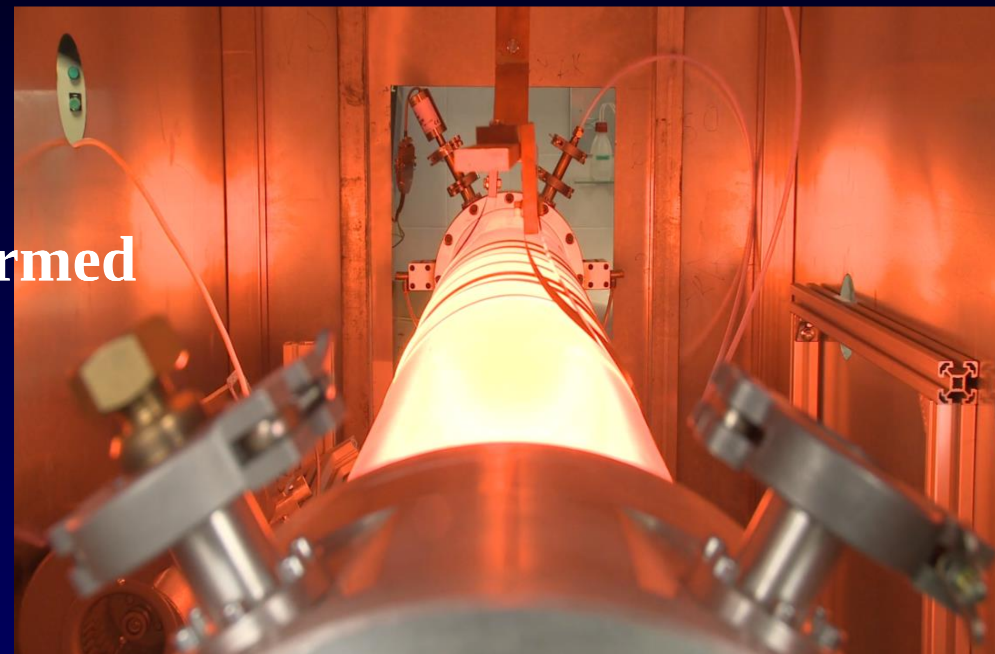
Another approach: coating of polymer surface with heparin



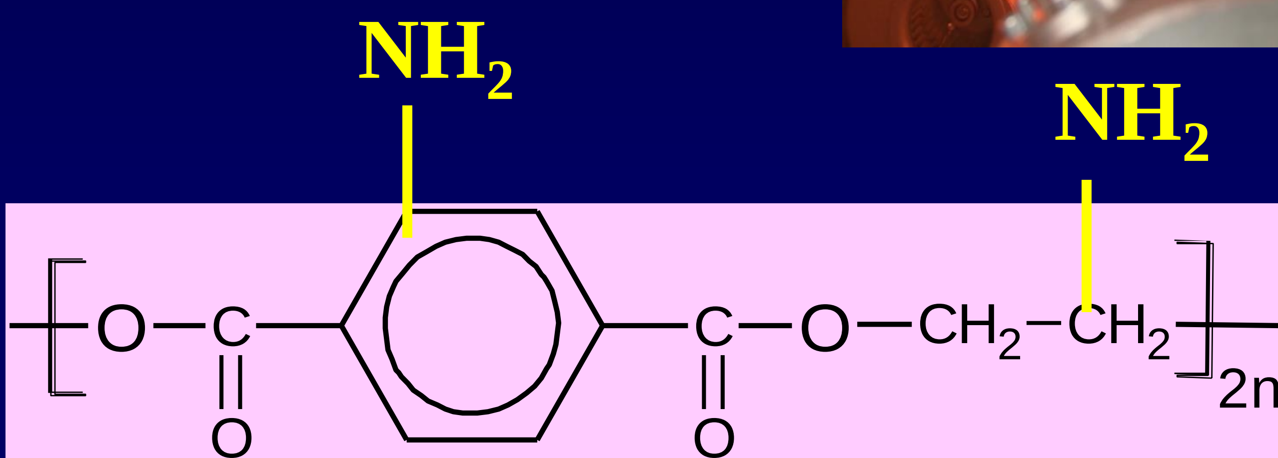




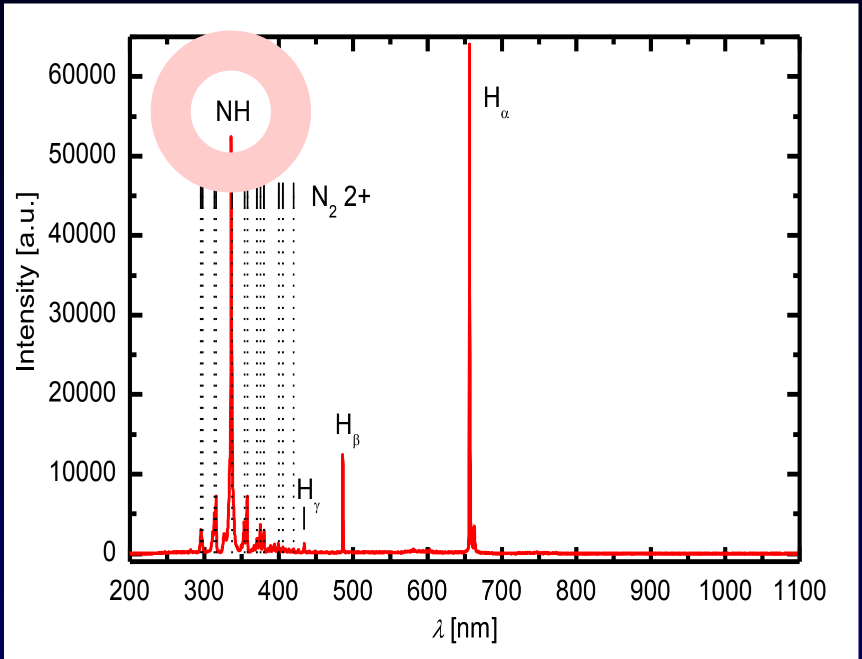
polyethylene terephthalate (PET) surface is functionalized with amono groups



Nitrogen plasma: N_2 is transformed to N_2^+, N_2^*, N, N^* etc



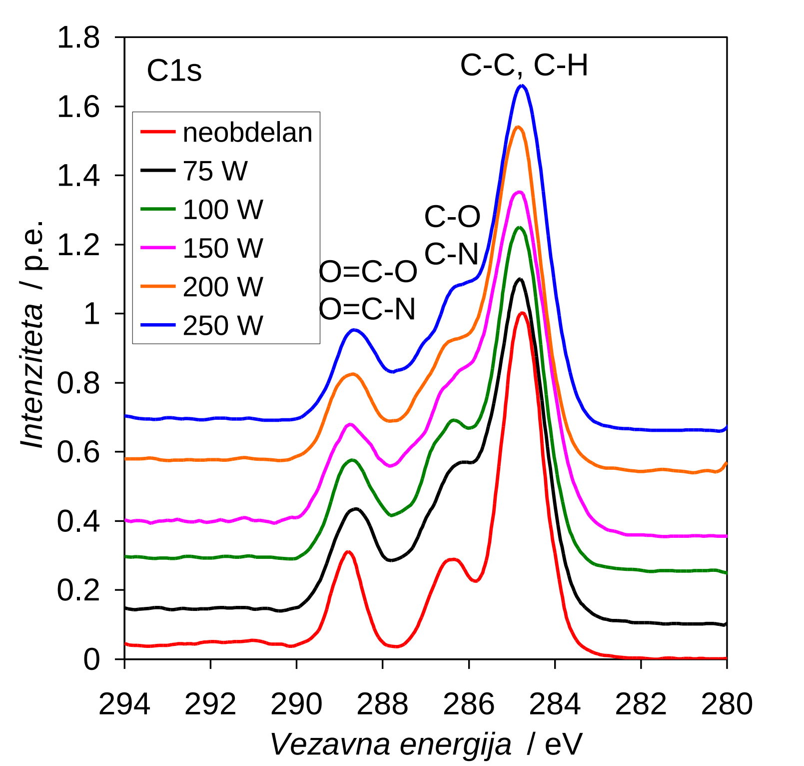
Composition after plasma treatment	C	N	O
untreated	74.7		25.3
NH_3	64.7	10.6	24.7
NH_3+Ar	65.8	9.6	24.5
N_2	61.2	2.9	35.8
N_2-H_2	64.5	4.2	31.4

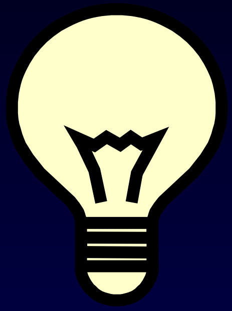


Best results are obtained by ammonia plasma treatment

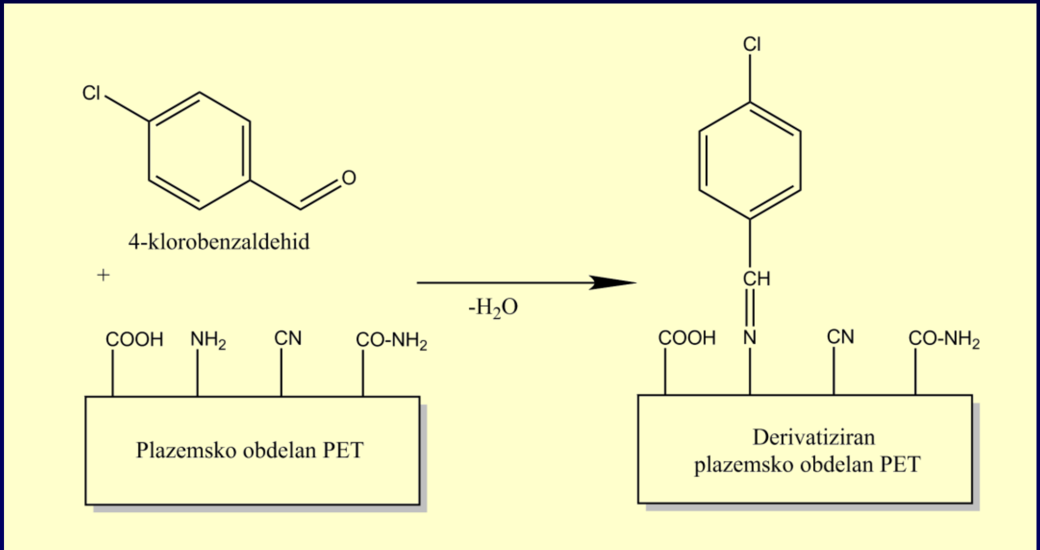
NH groups are created in amonia plasma

High-resolution C1s XPS peak cannot reveal amino groups





Derivatization by 4-chlorbenzaldehid



One can calculate concentration of amino groups from measured Cl content

Surface composition after derivatization

	C	N	O	Cl
NH_3	69.9	3.5	24.8	1.9
NH_3/Ar	70.2	3.0	24.5	2.3
N_2	65.0	1.4	33.1	0.5
N_2-H_2	66.6	2.1	30.5	0.8

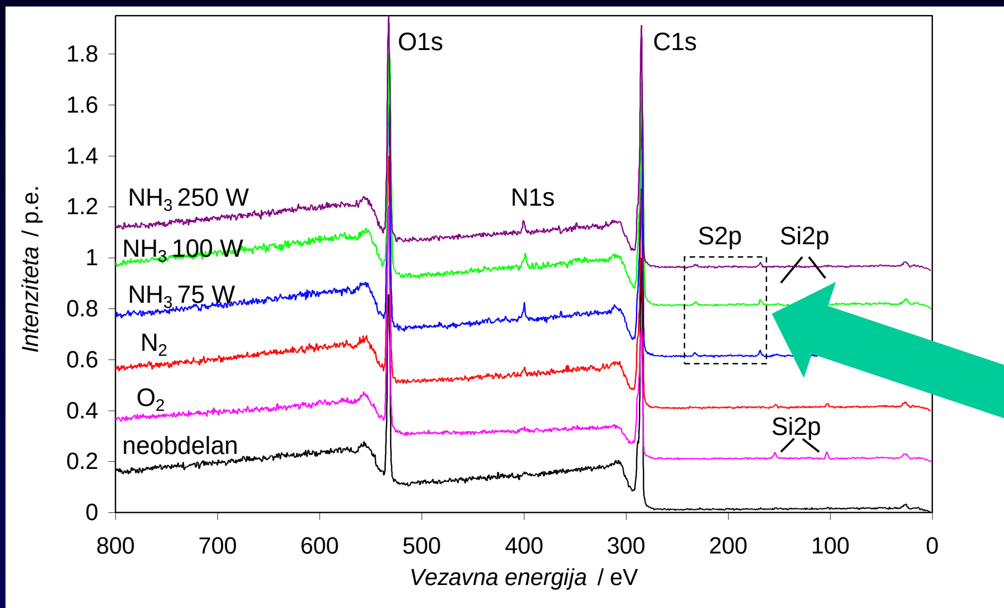
Power (W)	NH_2 /%
untreated	0,4
75 W	3,8
100 W	3,4
150 W	3,7
200 W	3,7
250 W	3,1
NH_3 + Ar	4,3
N_2	0,8
N_2 + H_2	1,3

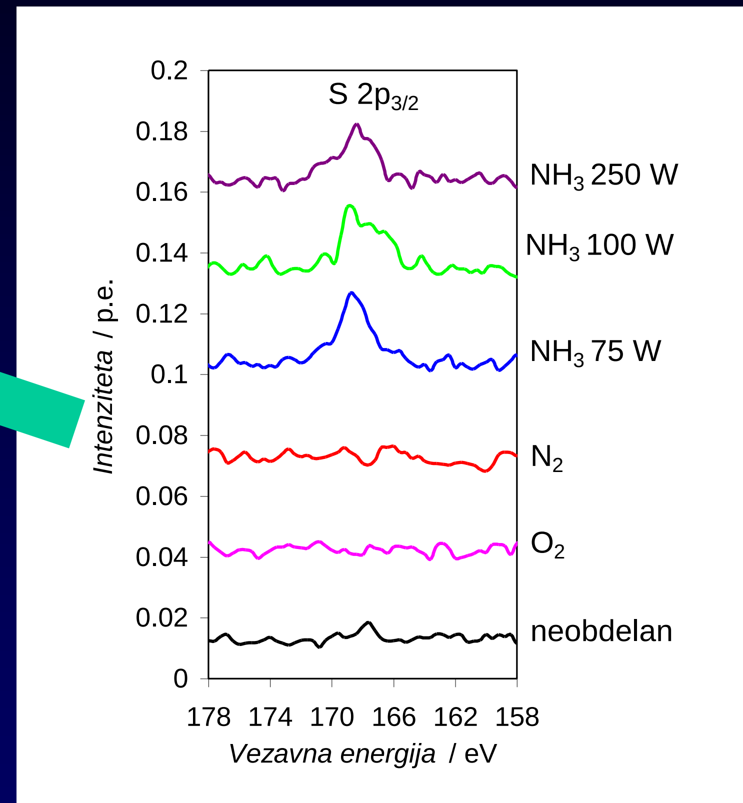
XPS gives average values over thickness about 5 nm

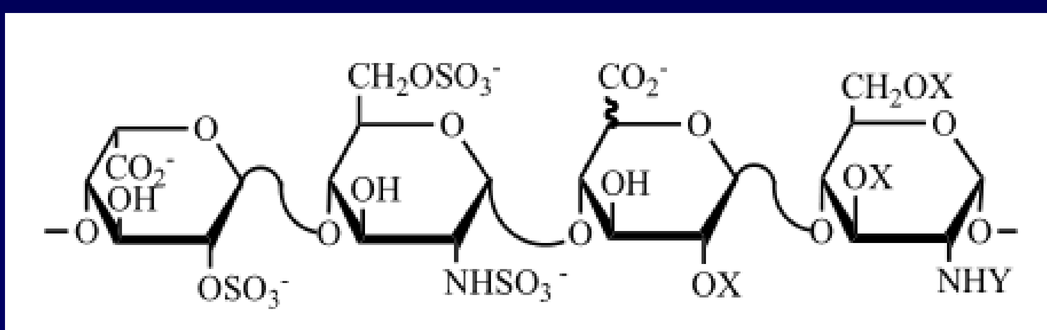
Amino-groups conc. up to around 4%

Surface is saturated with NH_2 groups after plasma treatment

Functionalized PET was incubated with heparin

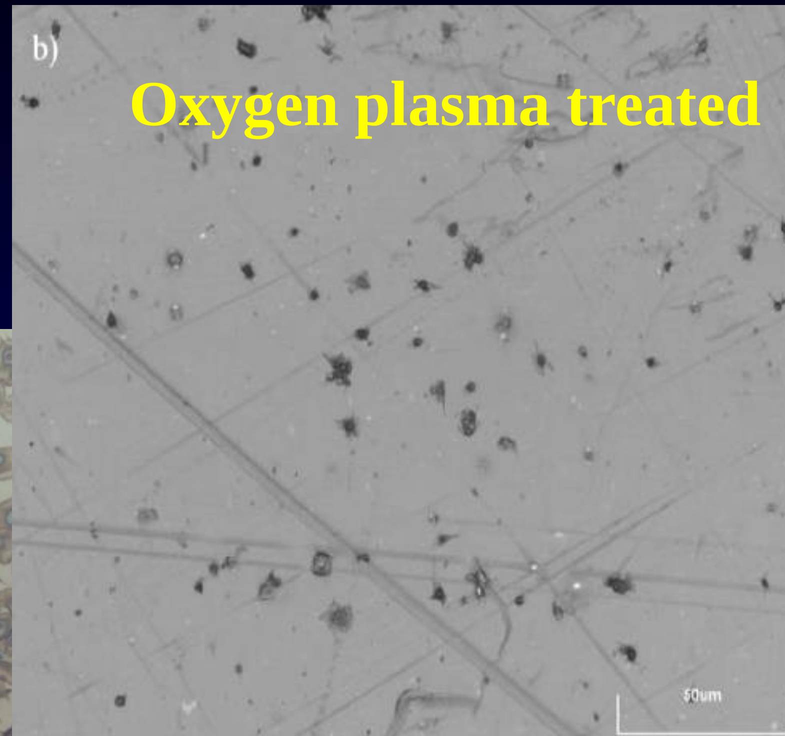


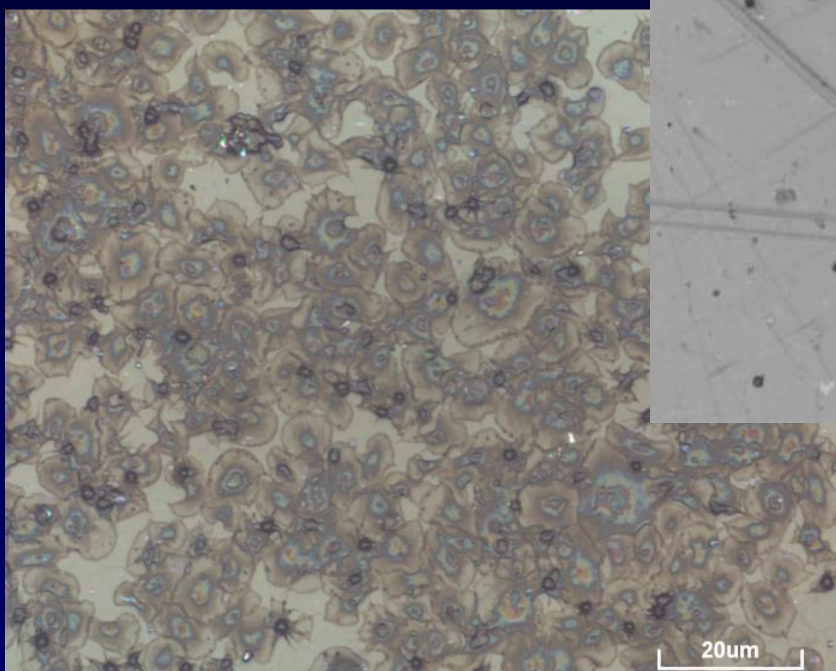


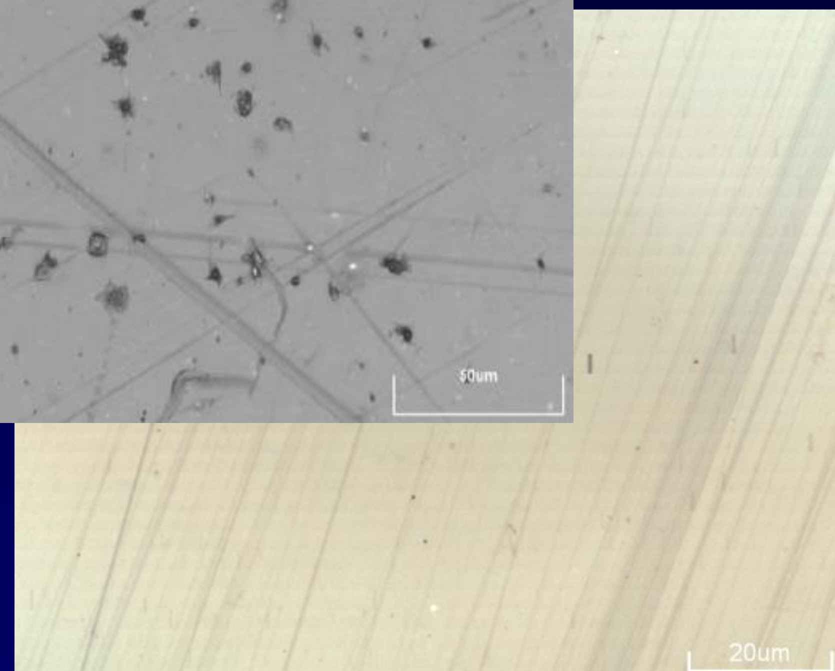


Ultra-thin layer of heparin is formed

Incubation with blood

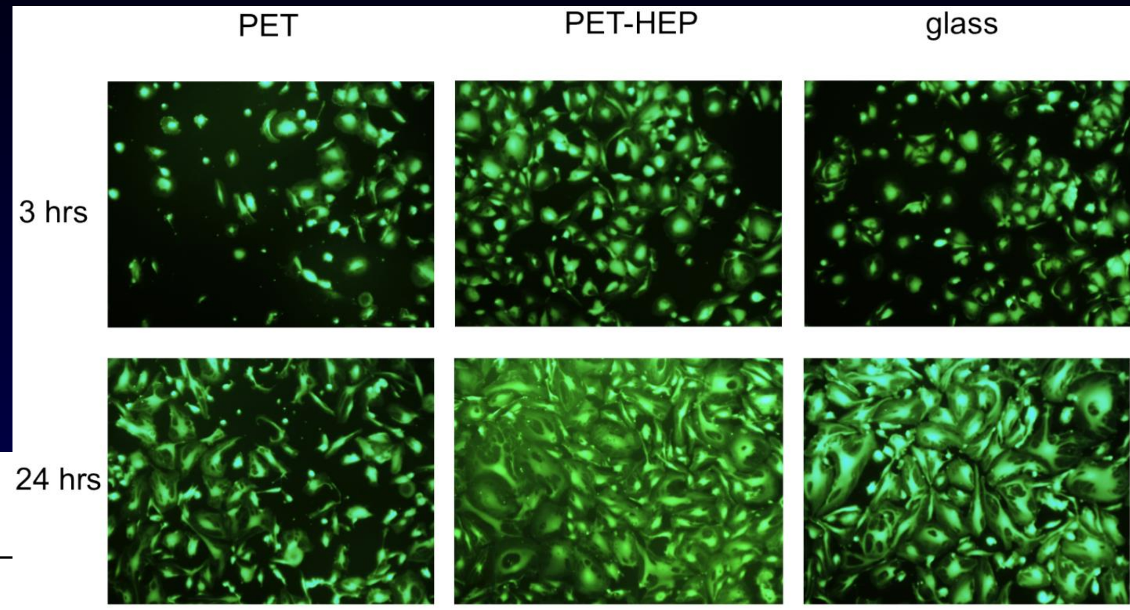


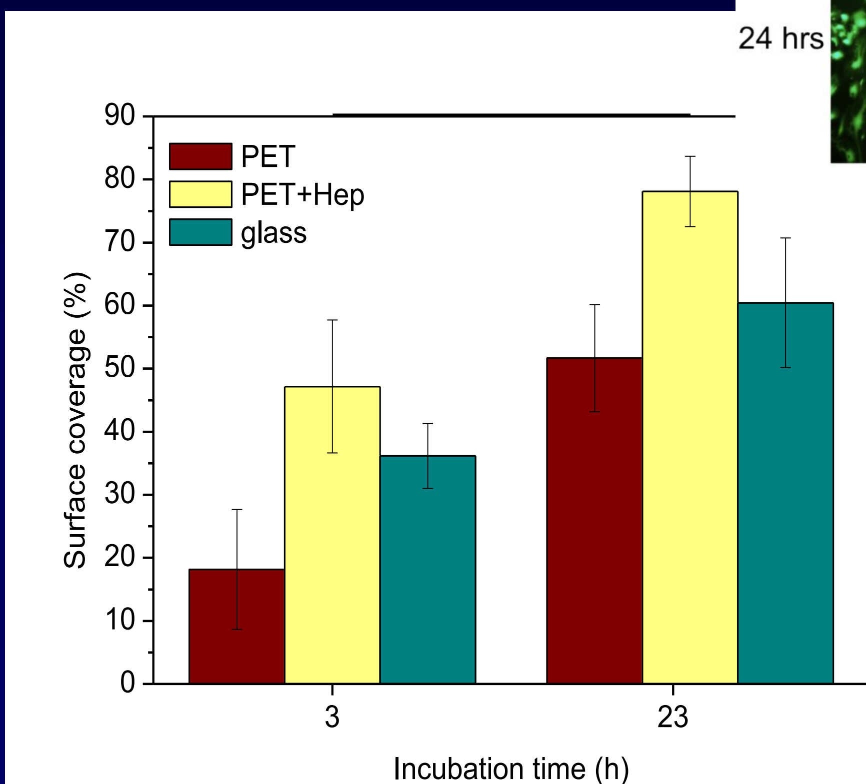




Optical microscopy for untreated (left) and treated (right) PET

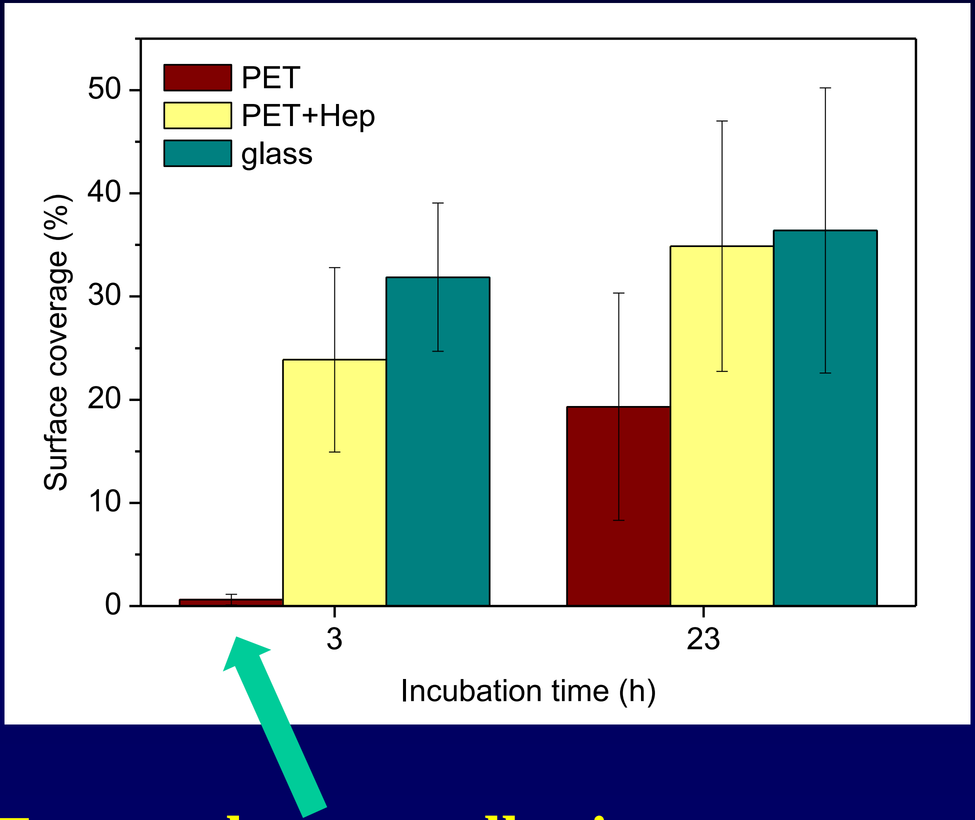
Incubation with human umbilical vein endothelial cells (HUVEC)





Samples coated by heparin allow for improved adhesion of HUVEC cells

Incubation with human microvascular endothelial cells (HMVEC)



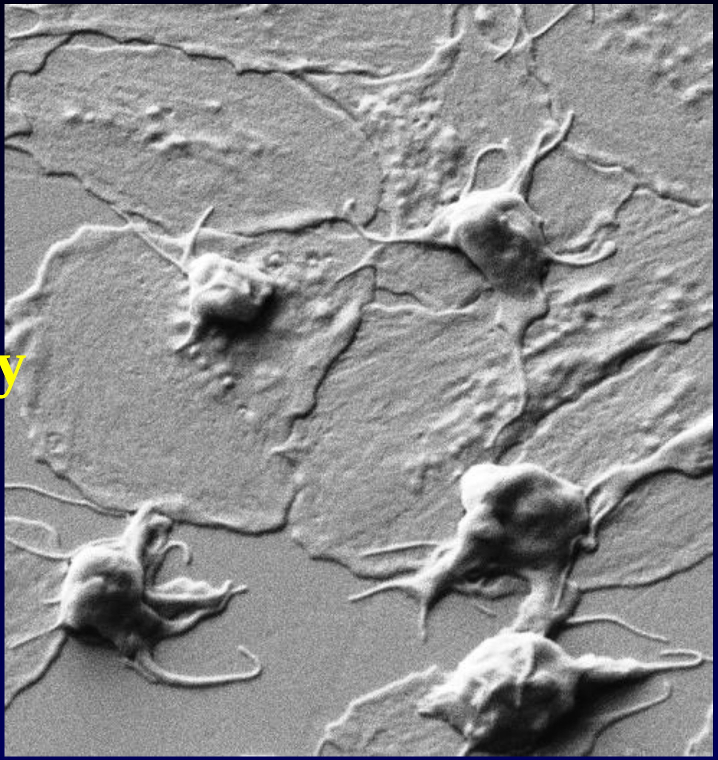
M. Kolar, A. Vesel, M. Modic, I. Junkar, K. Stana-Kleinschek, M. Mozetic,

Method for immobilization of heparin on a polymeric material:

patent application number GB 1416593.0. London: Intellectual Property Office (2014)

Extremely poor adhesion on untreated substrates

Conclusions:



- Vascular grafts made from PET have excellent mechanical and chemical properties but poor hemocompatibility
- Nanostructuring + functionalization with polar groups helps
- Best results are obtained by covalent bonding of heparin
- NHx radicals from ammonia plasma allow for functionalization of PET with amino groups
- Endothelization is improved

Most results taken from theses:

- Martina Modic, Hemostatic response of plasma treated artificial grafts (2012)
- Metod Kolar, Modification of PET biocompatibility by immobilisation of heparin (2015)

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