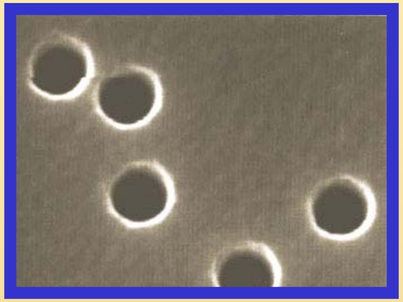
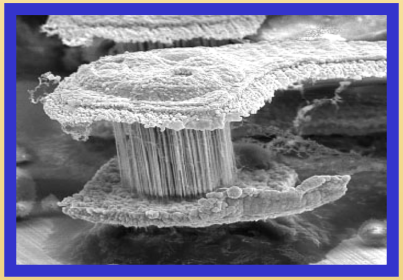
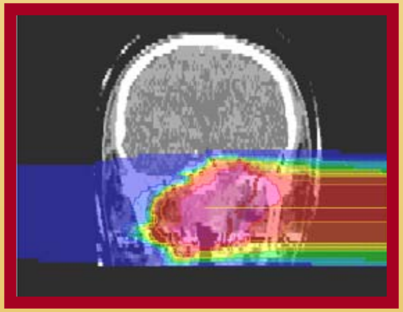
Nanostructuring and tumor therapy with swift heavy ions





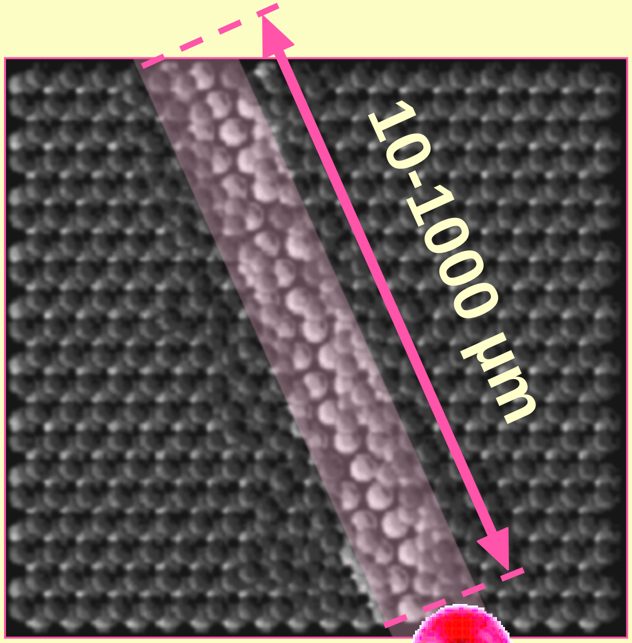


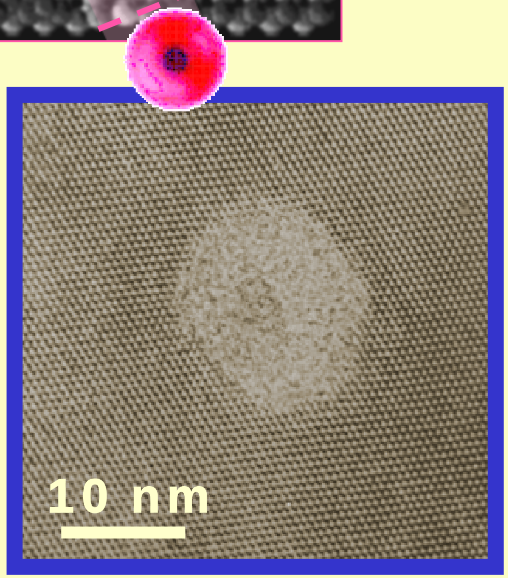
- latent tracks as nano-objects
- drilling holes by track etching
- nanowires
- single nanopores

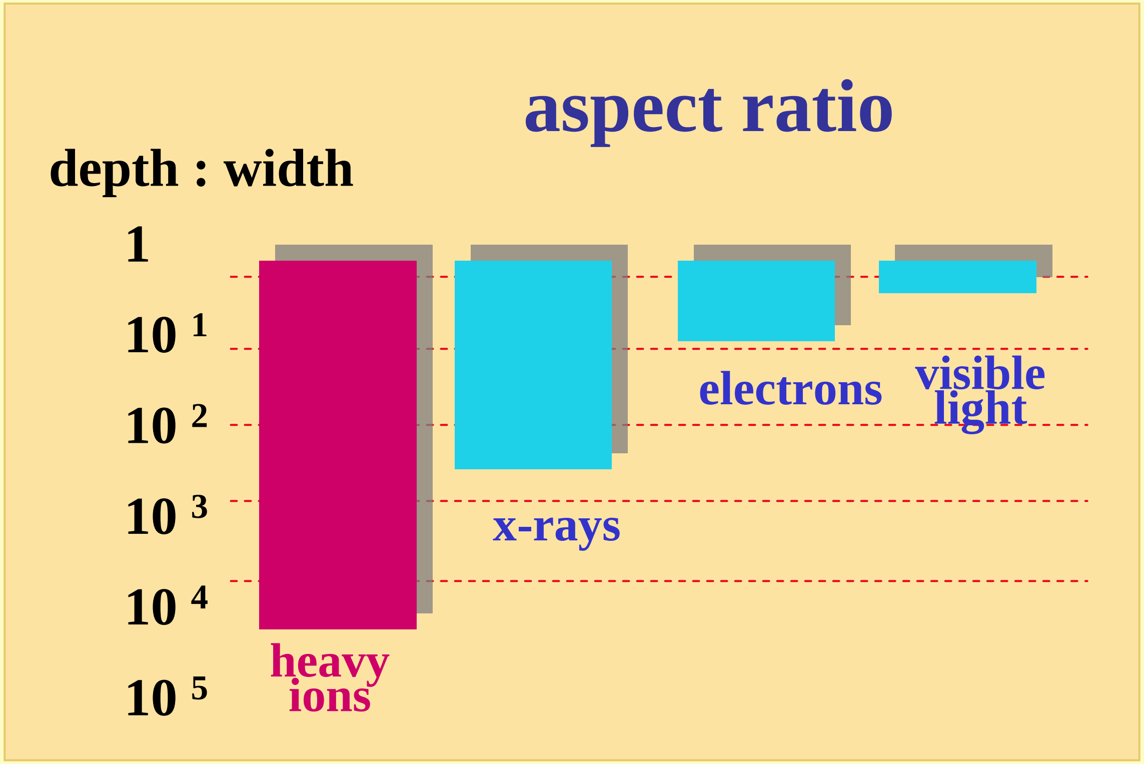
- hadron therapy project at GSI

Christina Trautmann, Gesellschaft für Schwerionenforschung, Darmstadt

MeV-GeV Ions as structuring tool





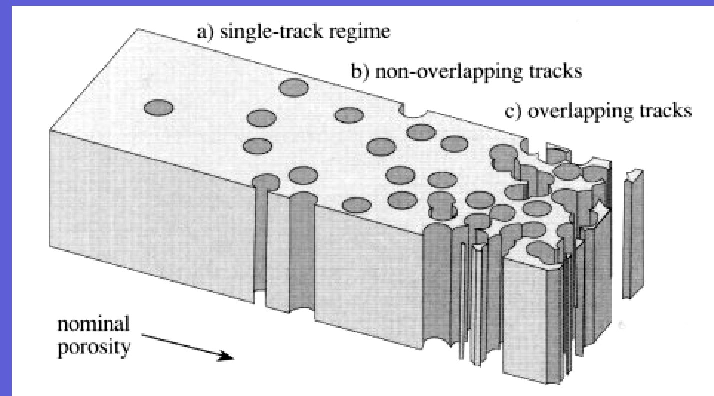


Irradiation Parameters

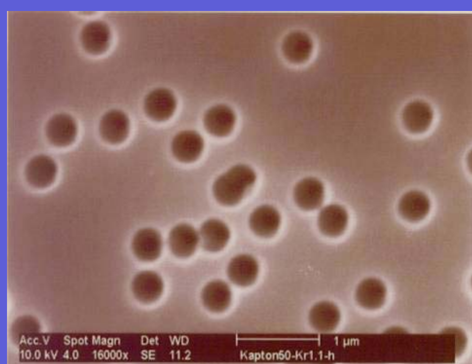
ion species ..C…Xe...U

energy (MeV/u)	range
1	10 µm
10	**100 µm**
1000	10 cm

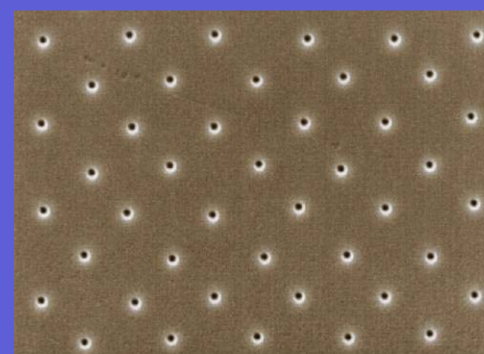
fluence: 1 …10^{14} ions/cm^2



random

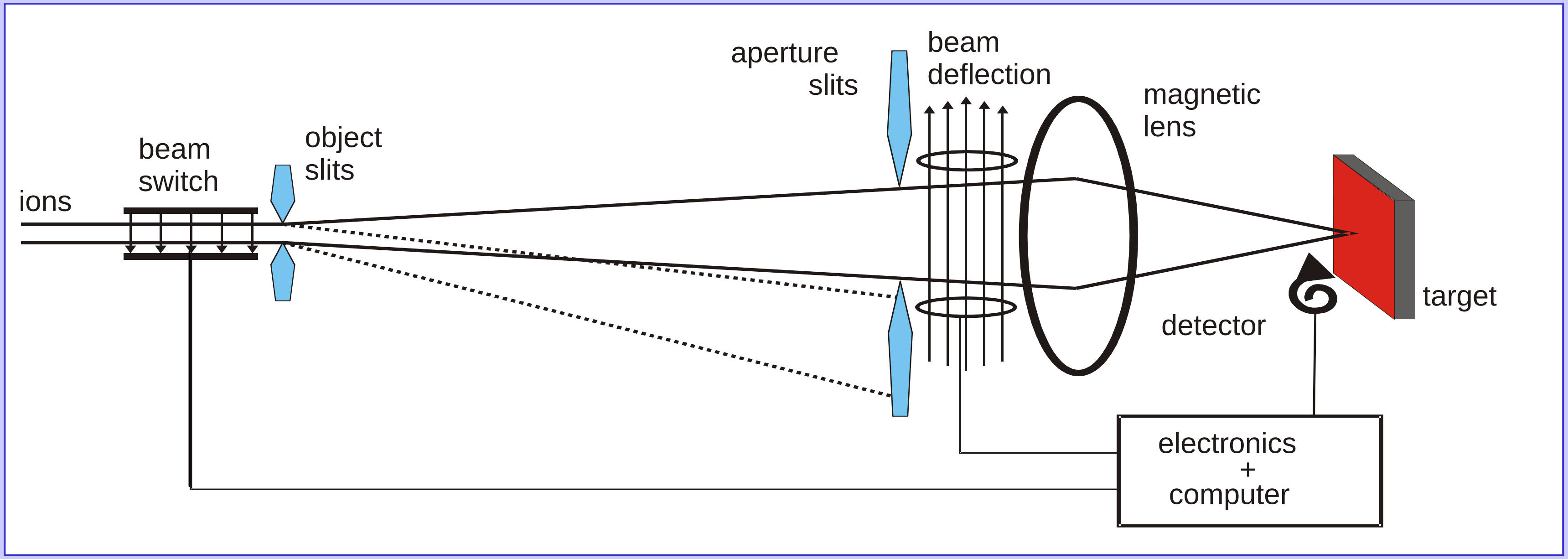


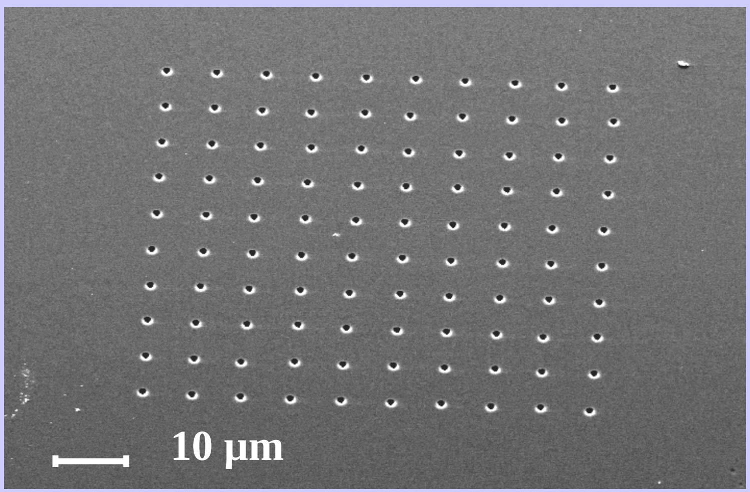
ordered

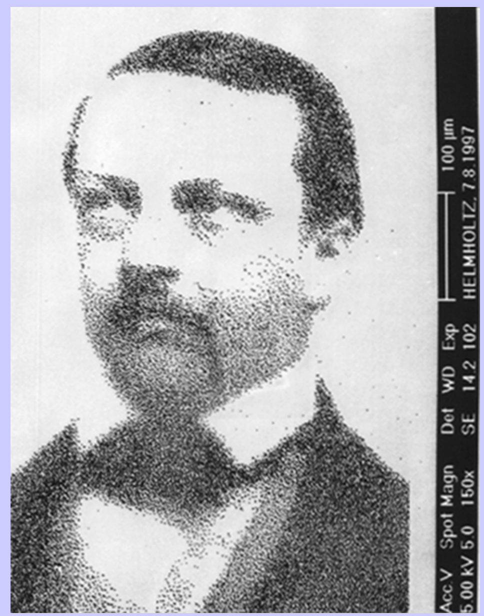


micro probe

Positioning of single ions with the heavy-ion microprobe

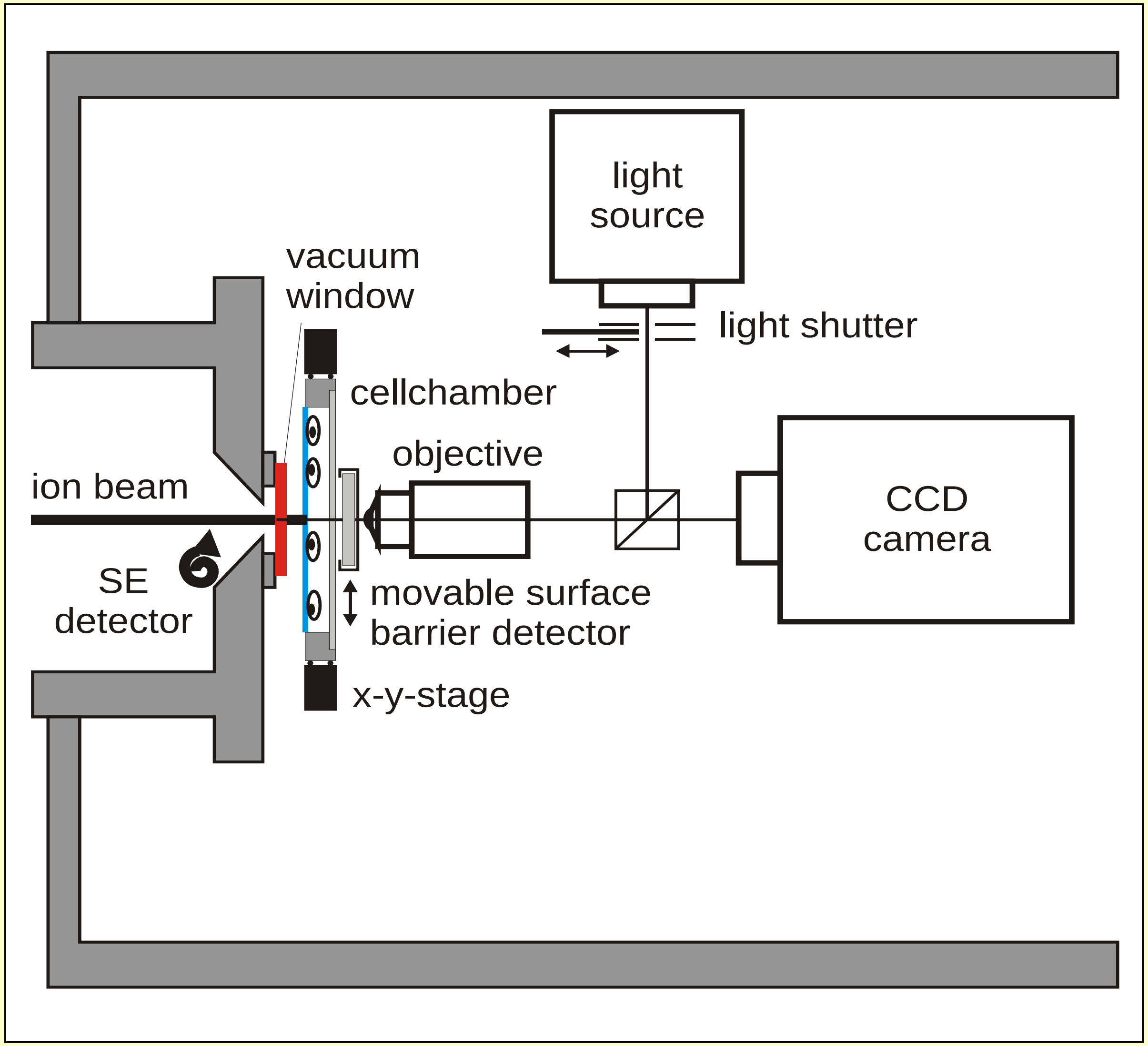




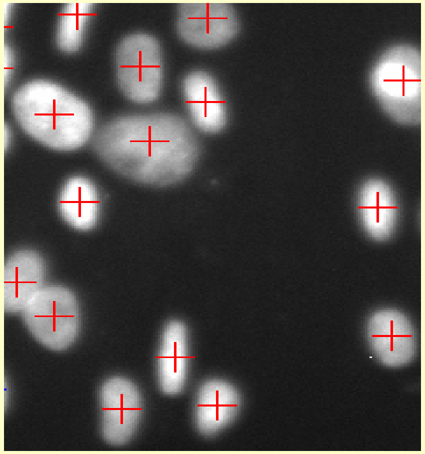


Fischer et al., NIMB 146 (1998) 587
MRS Bull. 25 (2000) 39

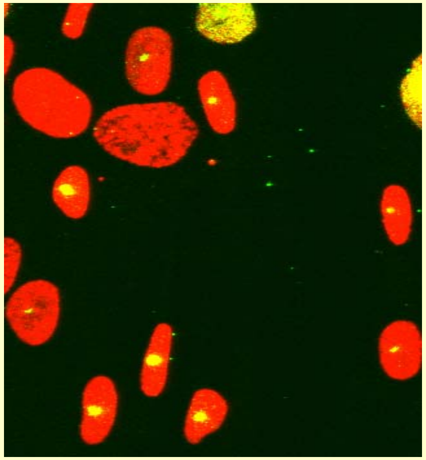
Irradiation setup for cell iradiation



- stained cell nuclei automatically indexed by microscope and CCD camera



- ion irradiation with microprobe
- hits made visible by immuno staining



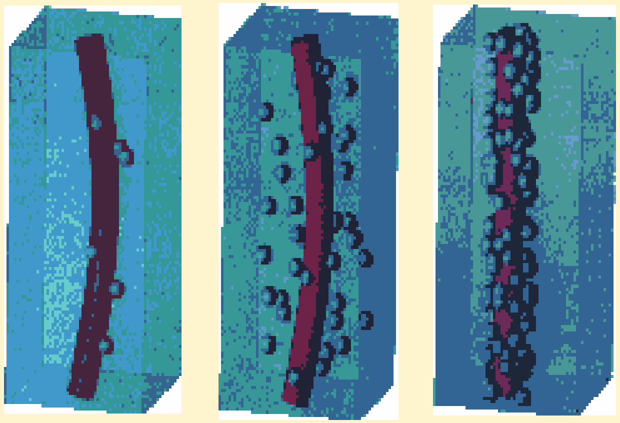
Fischer et al., NIMB 210 (2003) 285 Heiss, GSI (PhD Thesis, TU Darmstadt (2004))

Application of latent tracks

- pinning centers in superconductors
- tracks as nanowires
- nano-magnetic structures
- shaping of nanoparticles

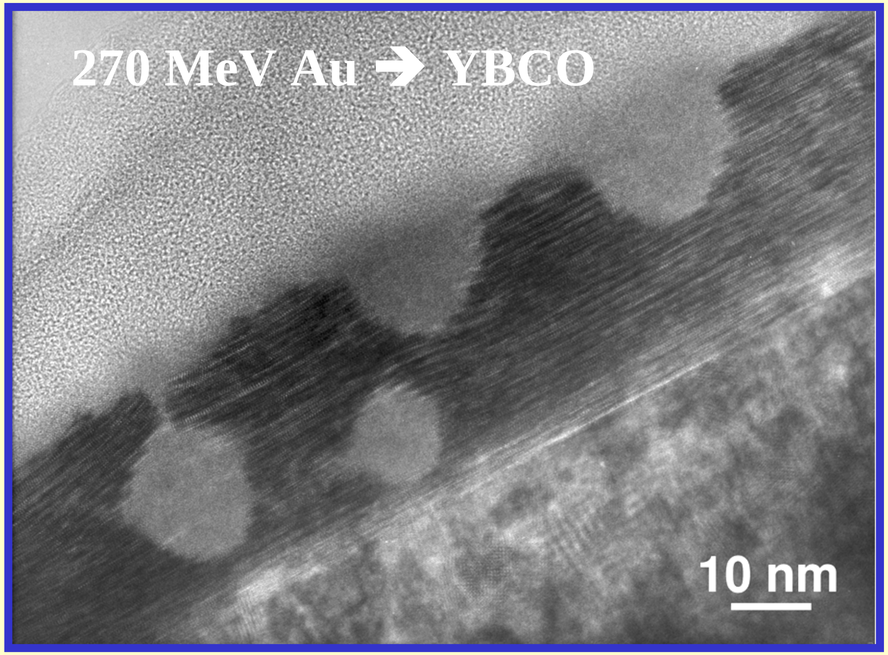
Tracks in superconductors

columnar defects



ideal pinning centers
for
magnetic flux lines

oriented & sharp internal interfaces



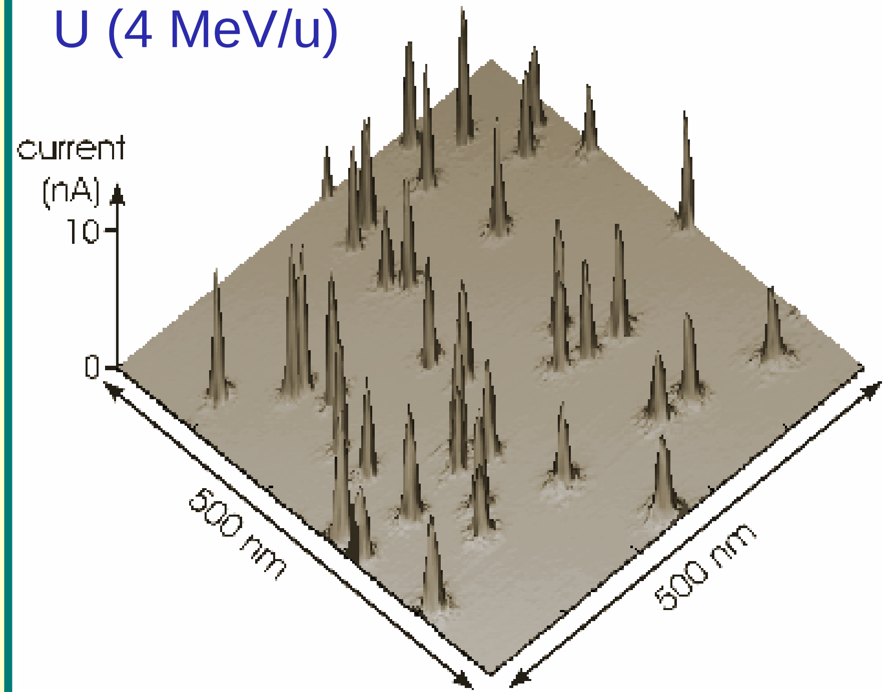
anomalous surface currents
layer : a few ξ_0 ~ 15 Å
for T < 15 K

H. Walter et al. PRL 80 (1998)

Conducting tracks in diamond-like carbon films (DLC)

AFM with conducting tip

U (4 MeV/u)

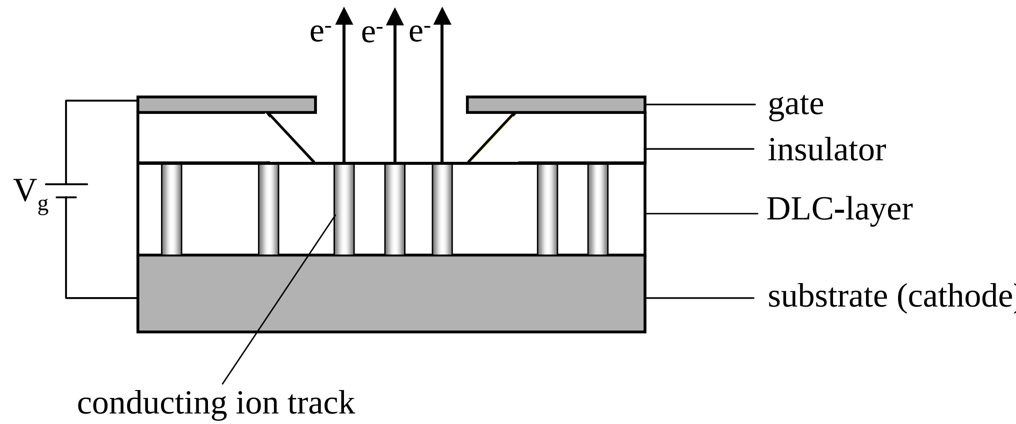


100-nm DLC (70-80% sp^3)

diamond sp^3 → graphite sp^2

el. conductivity:	σ (track)	~ 1 S/cm
	σ (graphite)	~ 250 S/cm

possible application as electron emitters

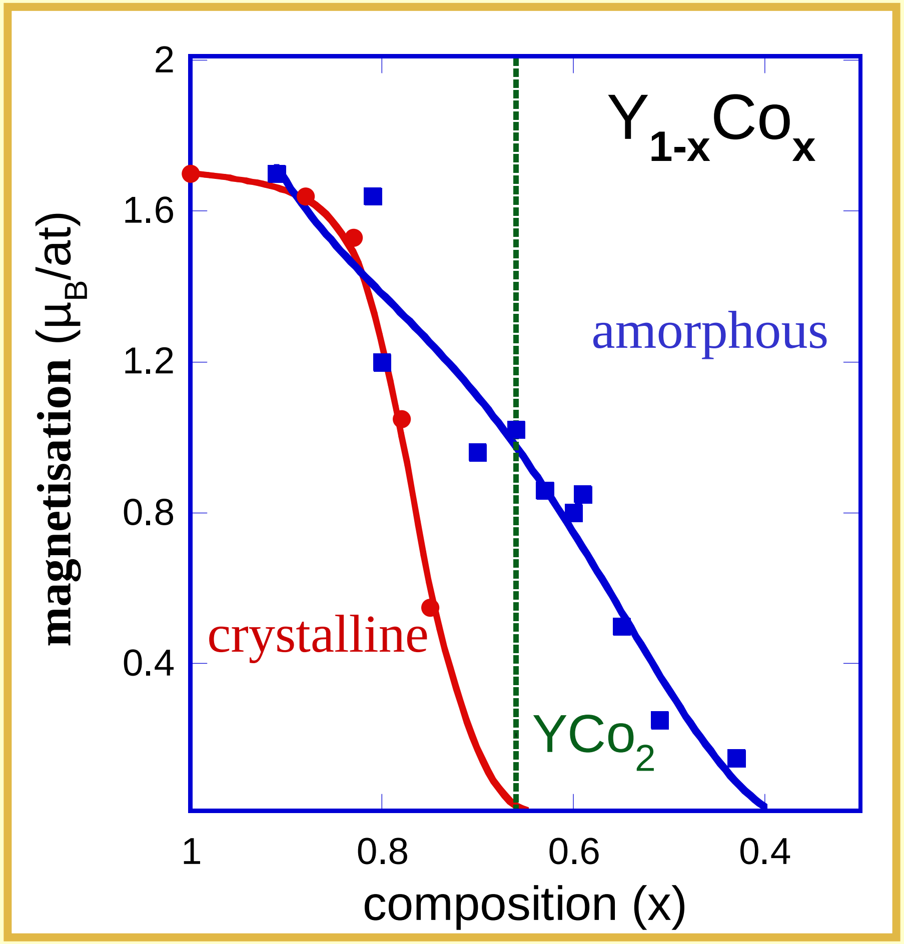


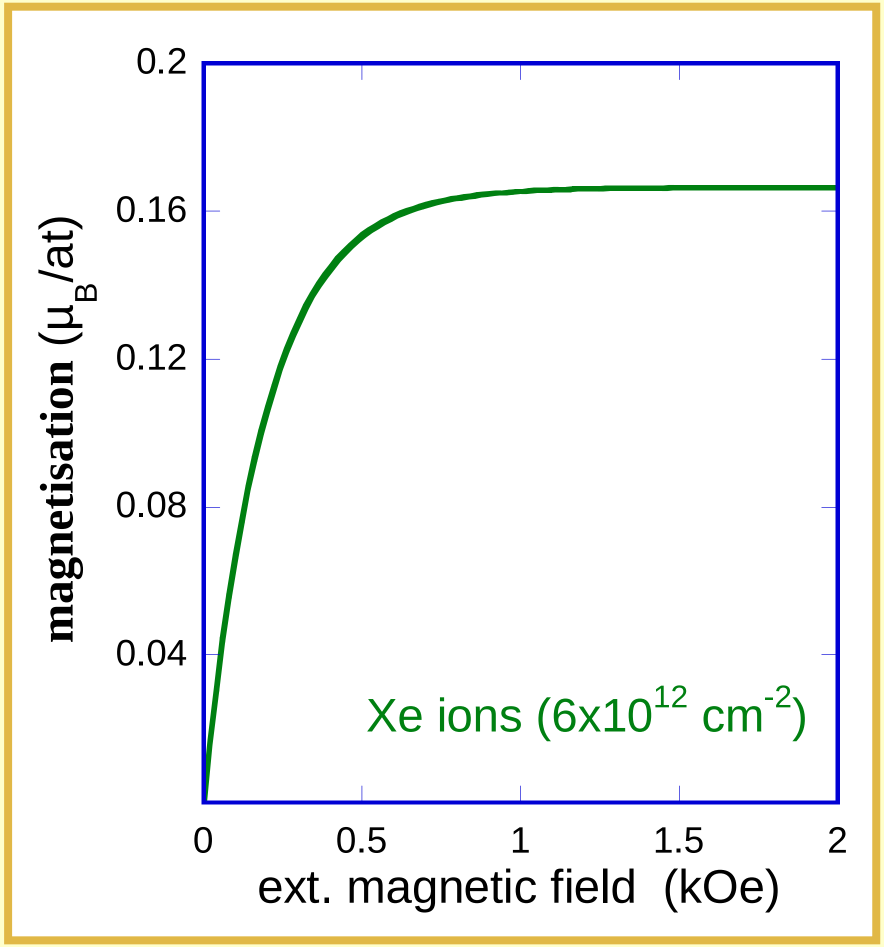
Zollondz et al., Diamond and related materials 12 (2003) 938

Krauser et al., J. Appl. Phys. 94 (2003) 1959

Ion induced magnetisation in YCo_2

irradiation ➔ amorphisation ➔ magnetisation





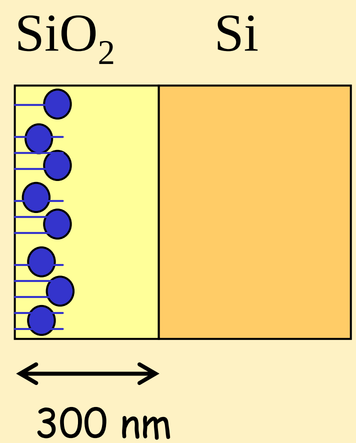
Givord et al., J. Appl. Phys. 76 (1994) 6661
Ghidini et al., J. Magn. Mat. 140 (1995) 483

Ion-induced deformation of nano-clusters embedded in vitreous SiO_2 matrix

ion implantation (600°C)

Co^+

160 keV
10^{13} - 10^{14} ions/cm^2
R=120 nm

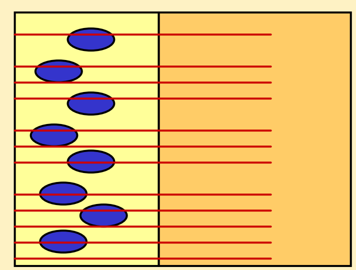


nucleation and growth of Co nanoparticles (~10 nm)

ion irradiation (RT)

^{127}I

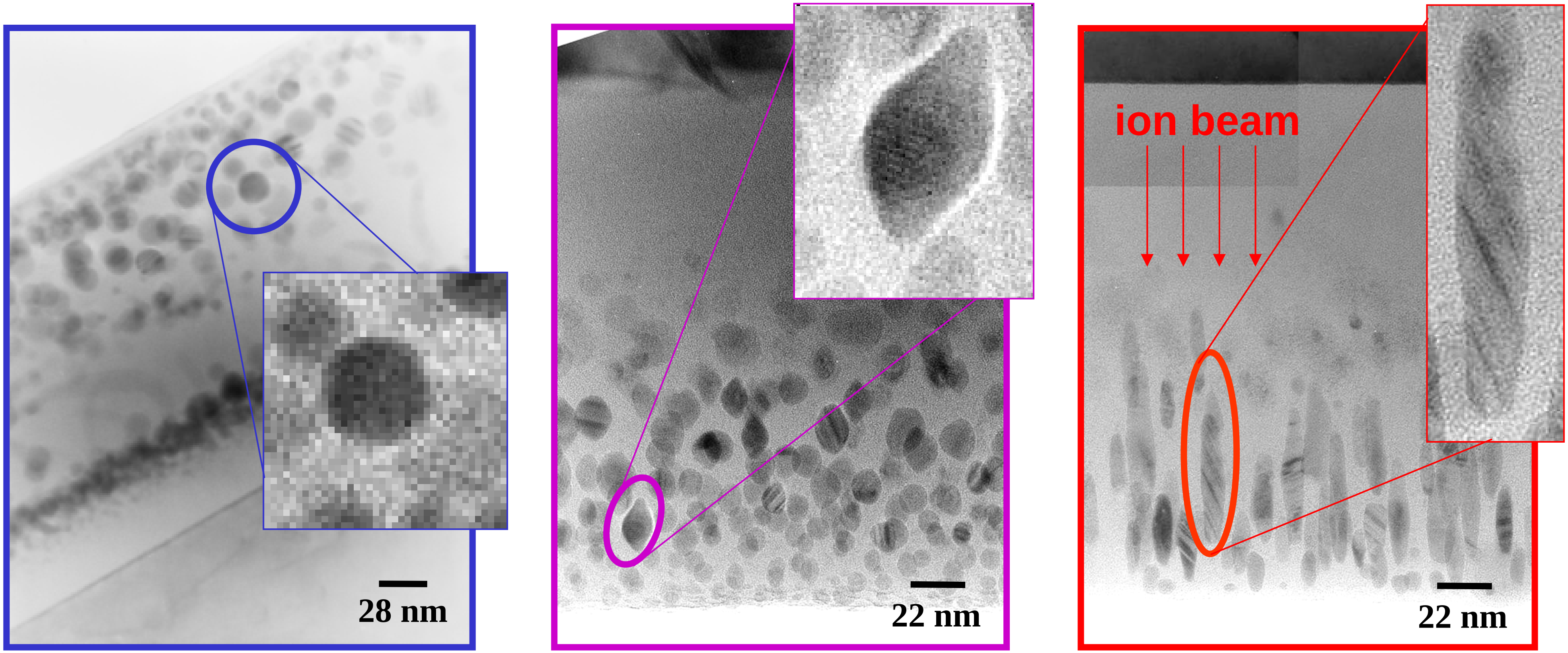
200 MeV
10^{13} - 10^{14} ions/cm^2
R=15 µm



deformation from spherical to cigar-shaped particles

D'Orleans, PhD thesis, Univ. Strasbourg (2003)

Changing spherical nanoclusters into cigar-shape



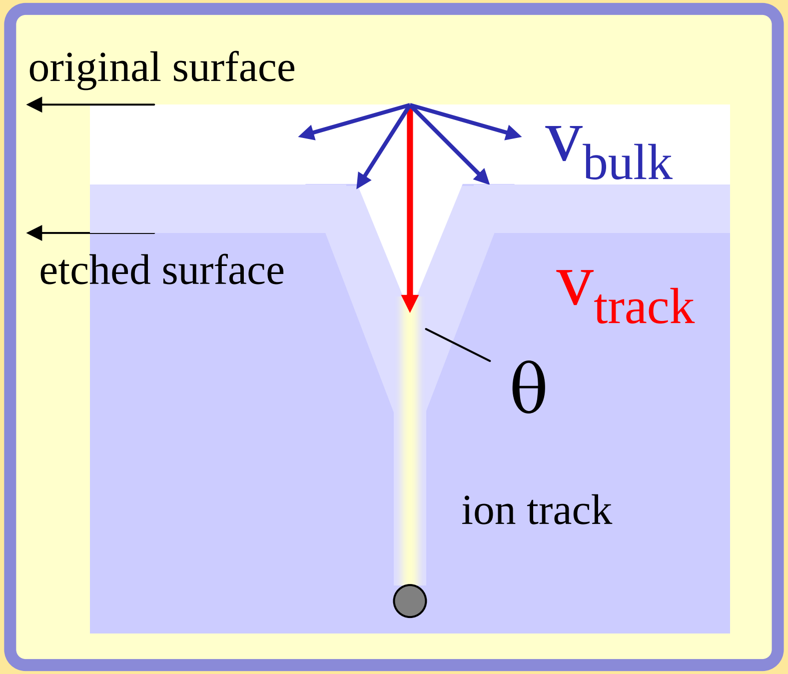
10^{17} Co cm^{-2}
Implantation at 873 K

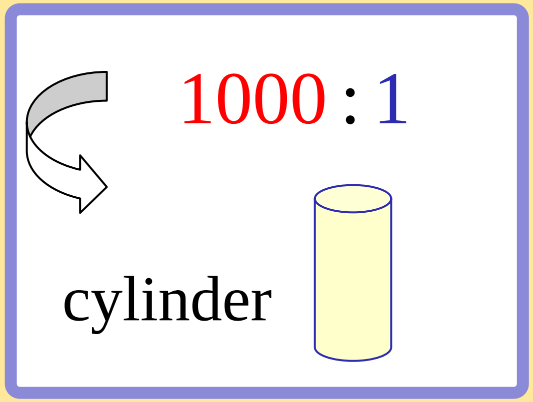
+ 10^{13} ions cm^{-2} + 10^{14} ions cm^{-2}
Post-irradiation with I ions (200 MeV)

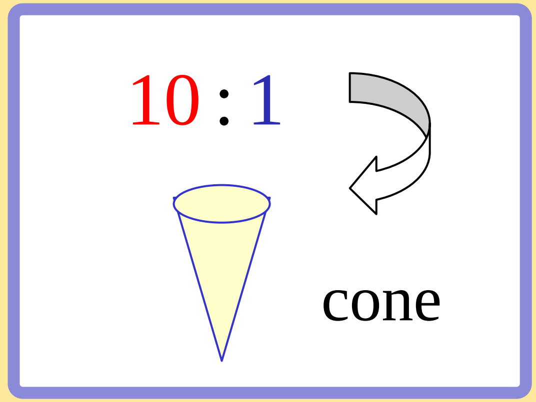
D'Orleans et al., Phys. Rev. B.67 (2003) 220101

Chemical etching of ion tracks

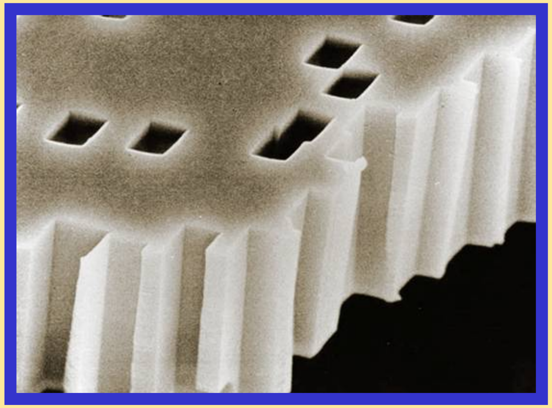
$v_{track} : v_{bulk} = \sin\theta$ ➔ pore geometry



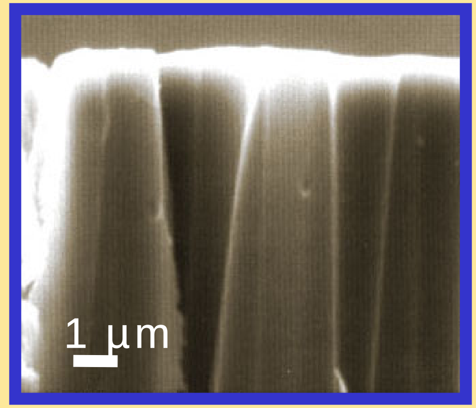




chemical etchant
(e.g., NaOH, NaOCl, H_2SO_4)

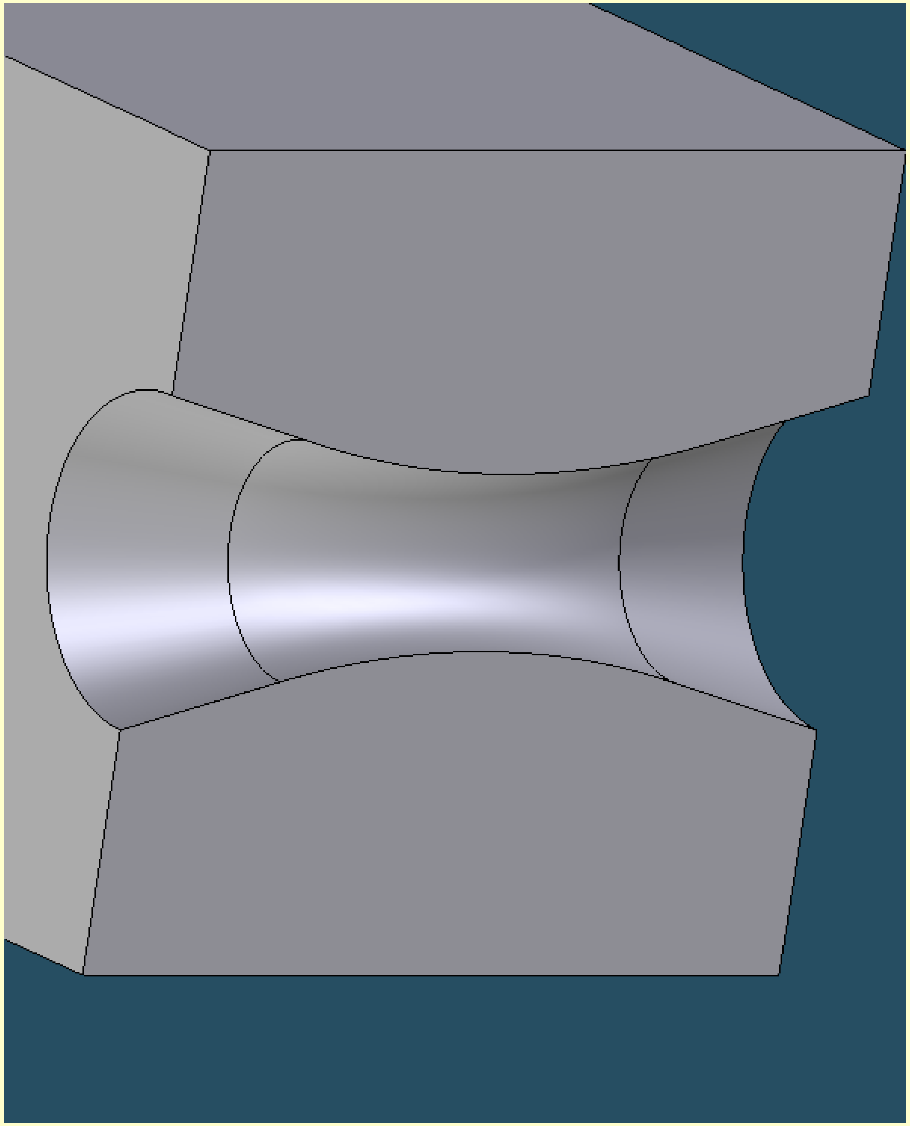


mica



Kapton

Track etching



Andrew Akimenko, JINR, Dubna, 2004

Track etching process

bulk etch rate v_{bulk}

polymer property
etchant composition
concentration
pH value
temperature….

storage
post treatment
vis, UV
solvents
aging….

track etch rate v_{track}

energy loss
irr. temperature
atmosphere...

POLYMERS

polyethylene terephthalate **(PET)**
(Mylar, Hostaphan)

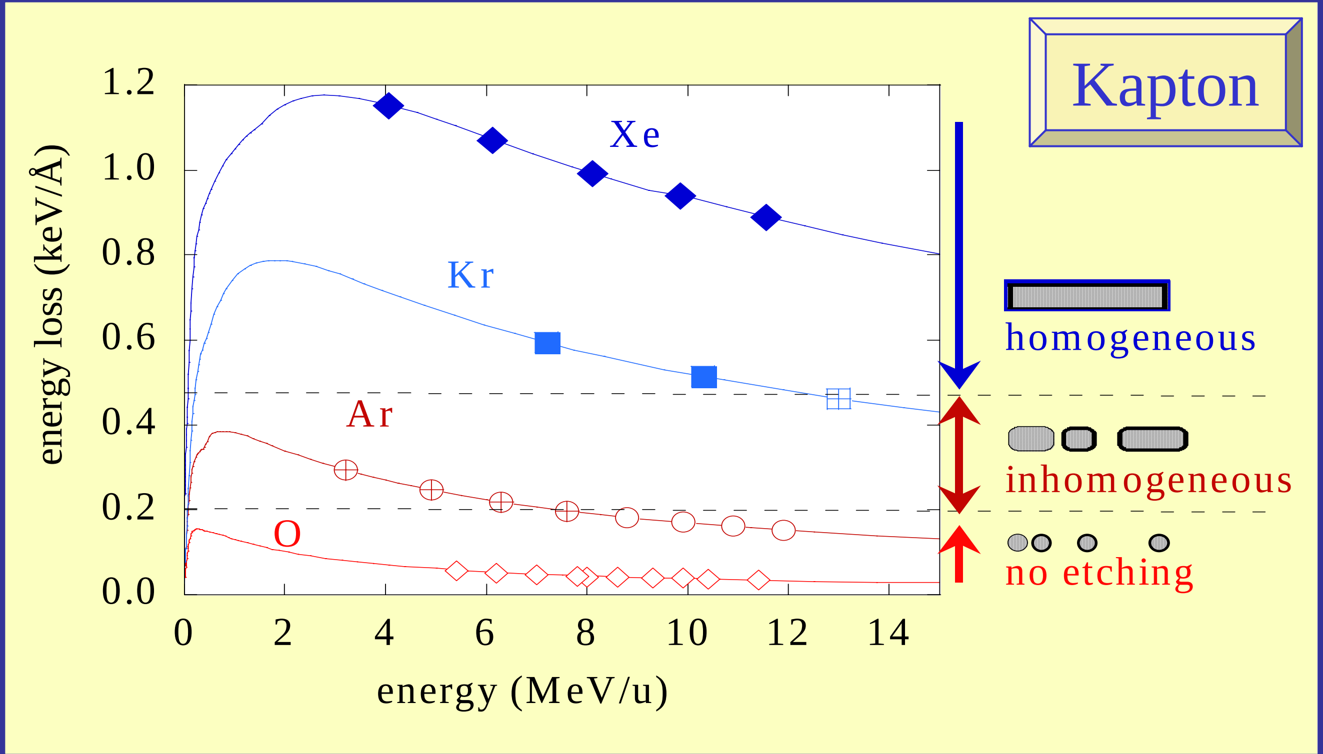
polycarbonate **(PC)**
(Lexan, Makrofol, CR39)

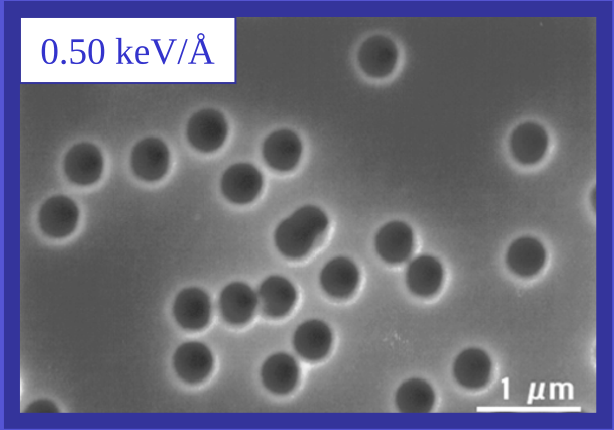
polyimide **(PI)**
(Kapton, Upilex)

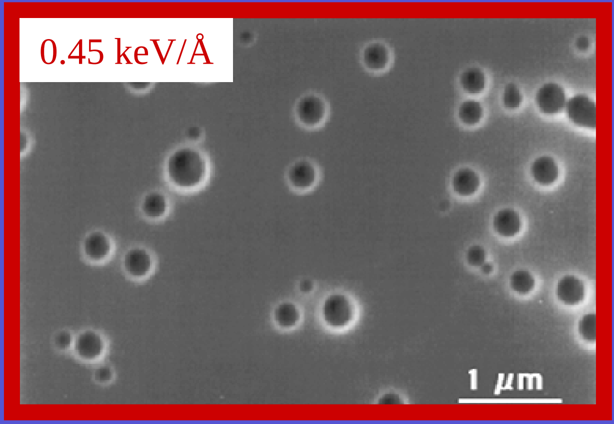
polypropylene **(PP)**

polyvinyidene fluoride **(PVDF)**

Damage morphology and track etching



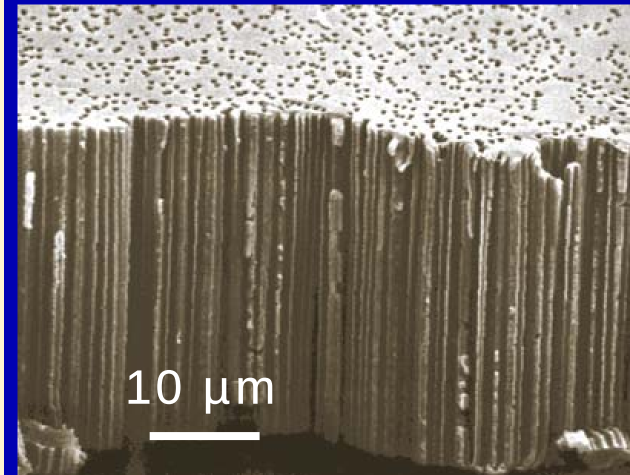




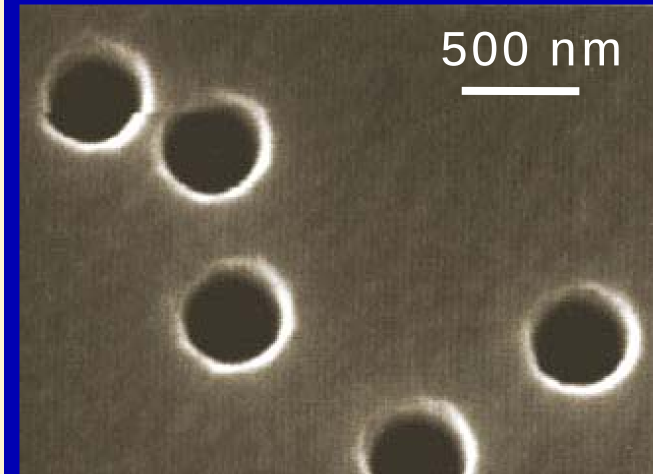
etch threshold	(keV/ Å)
polycarbonate (Makrofol)	0.2
polyimide (Kapton)	0.5
SiO_2 quartz	1.0
$Y_3Fe_5O_{12}$	2.0
metallic glass	3.6

NIMB 116 (1996) 429

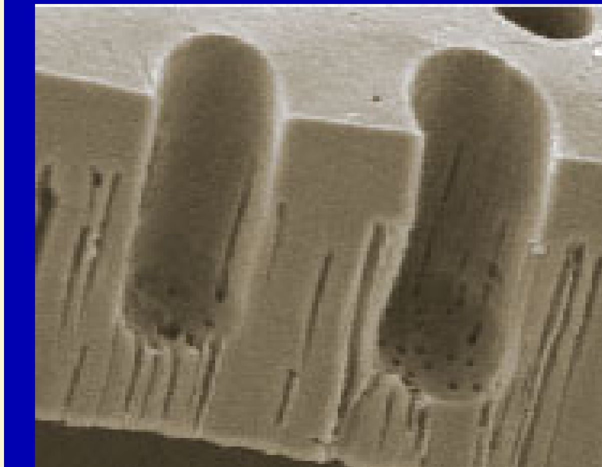
Possible pore geometries



ion track membrane



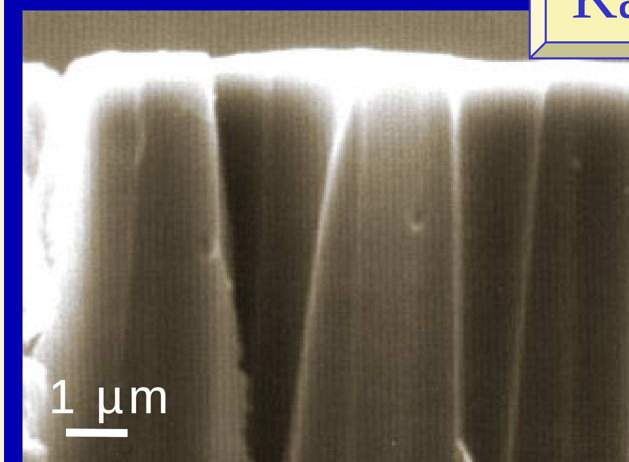
cylindrical pores



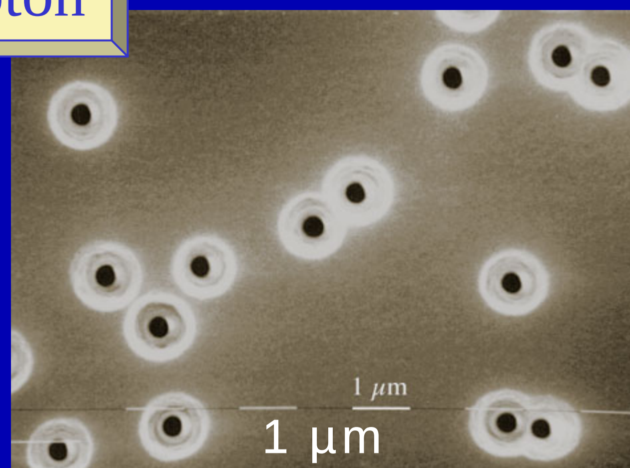
perfor. dead-end pores

Kapton

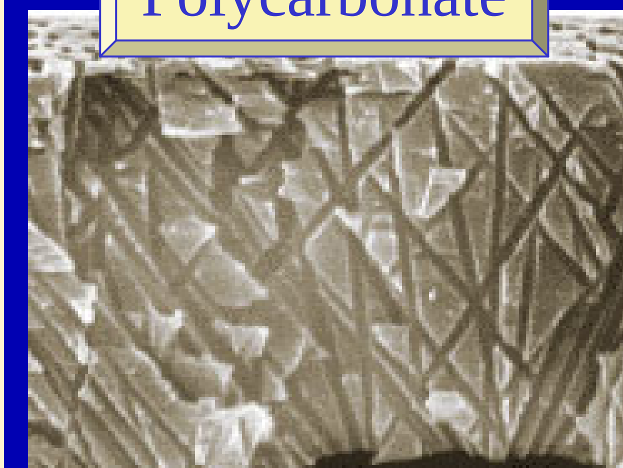
Polycarbonate



conical pore shape



cone-shaped entrance



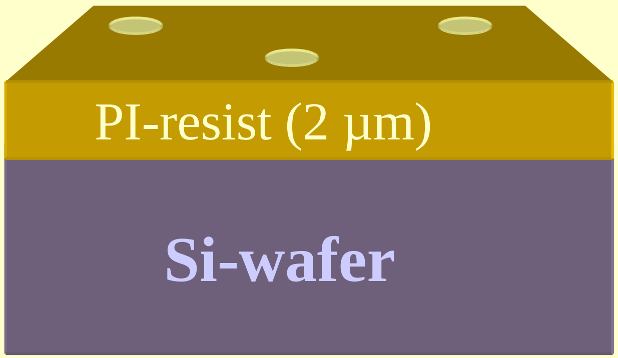
intersecting pores

NIMB 111 (1996) 70

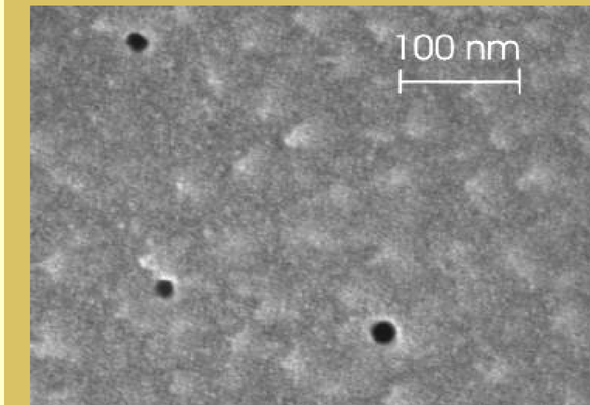
P. Apel, NIMB 208 (2003) 11

Compatibility of silicon and ion-beam technology ?

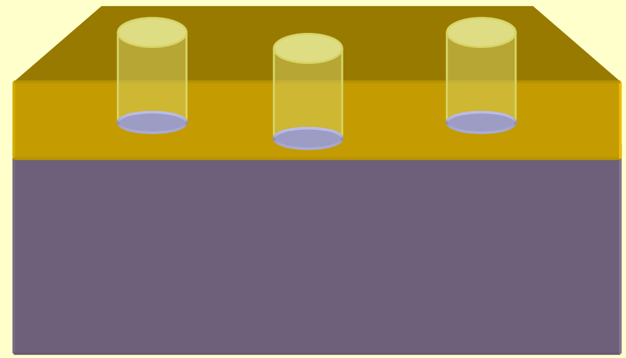
Resist / Si



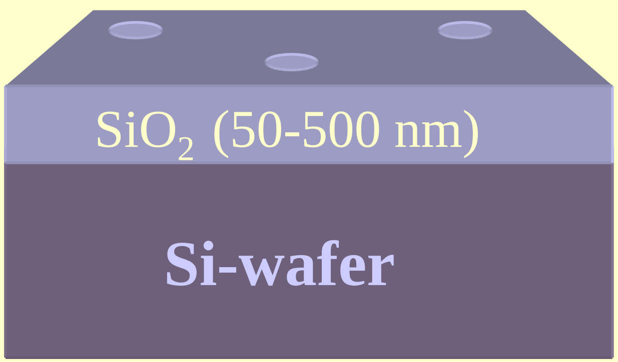
etched ion tracks in resist (~10 nm)



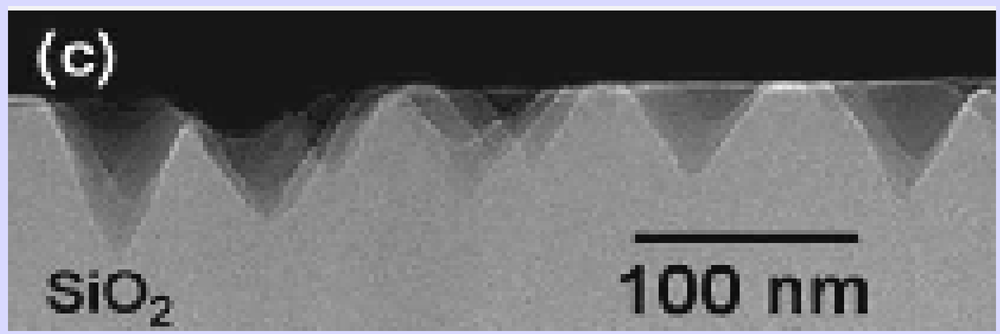
Skupinski et al. (Uppsala, 2003)



SiO_2 / Si



cross section of etched ion tracks in SiO_2 film



Milanez Silva et al. NIM B 206 (2003) 486

Commercial ion track membranes

Irradiation: Berlin (HMI)
Louvain-la-Neuve
Brookhaven, N.Y.
Dubna .....

e.g. Whatman/Nuclepore
Oxyphen …..

Industrial application

filters for particle analysis
cell separation
cytology
biosensors
water barrier systems
controlled drug release
water-sealed housings for electronic devices
water purification
epifluorescence microscopy

Self-adhesive membrane discs

Membranes (typical parameters)

polycarbonate, PET (6-10 µm thick)

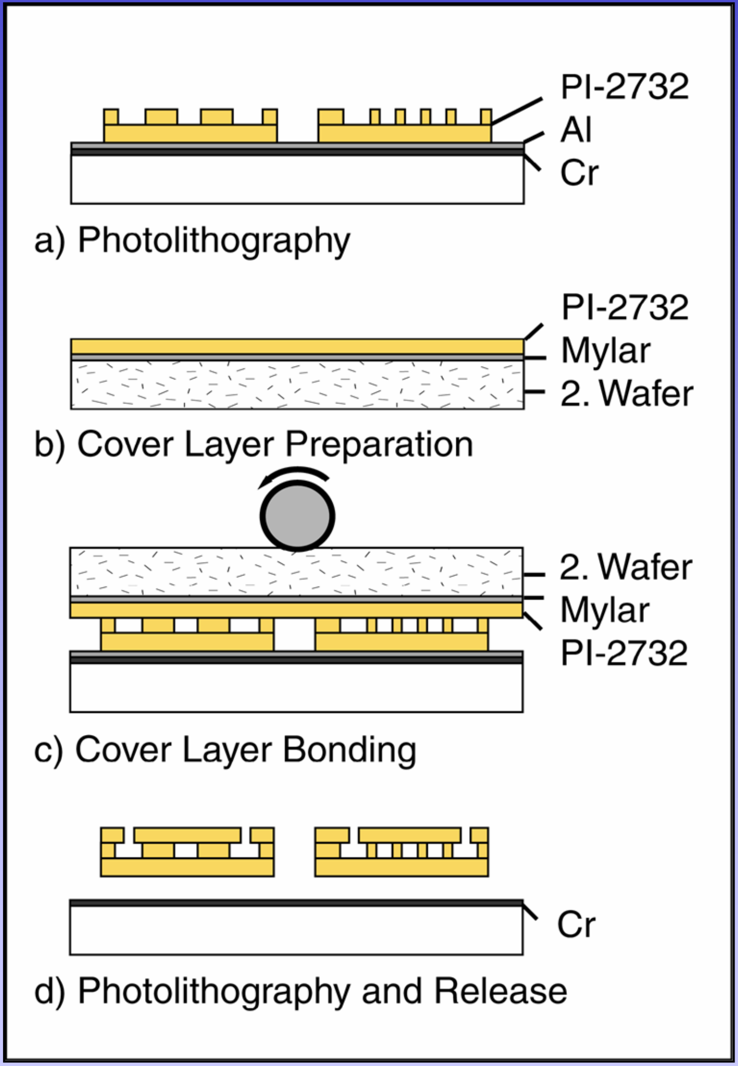
pore size: 15 nm -10 µm

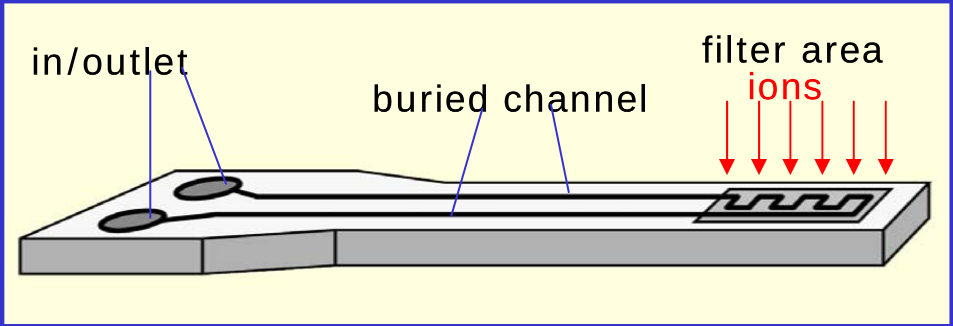
pore density: 10^5 - 10^9 cm^{-2}

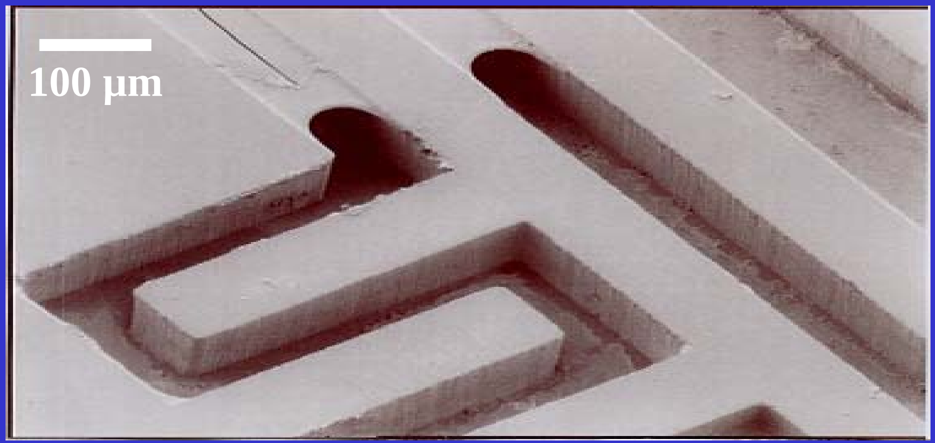
Capillary-pore membranes

Heat-sealable membrane for controlled release of substances

Microfluidic devices
fabricated by photolithography, bonding, and annealing



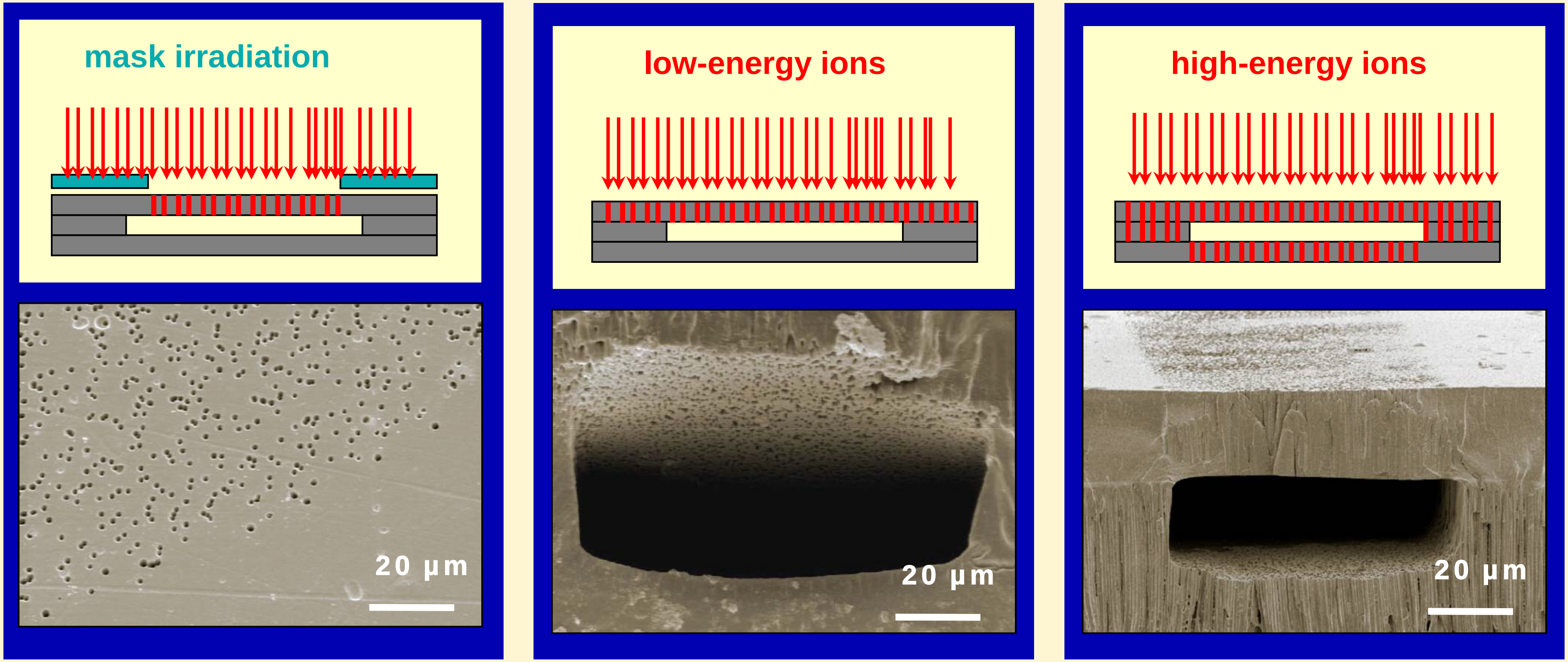




increased filter area by meander structure

Metz, PhD thesis, EPFL Lausanne (2003)

Micro-systems and ion track technology

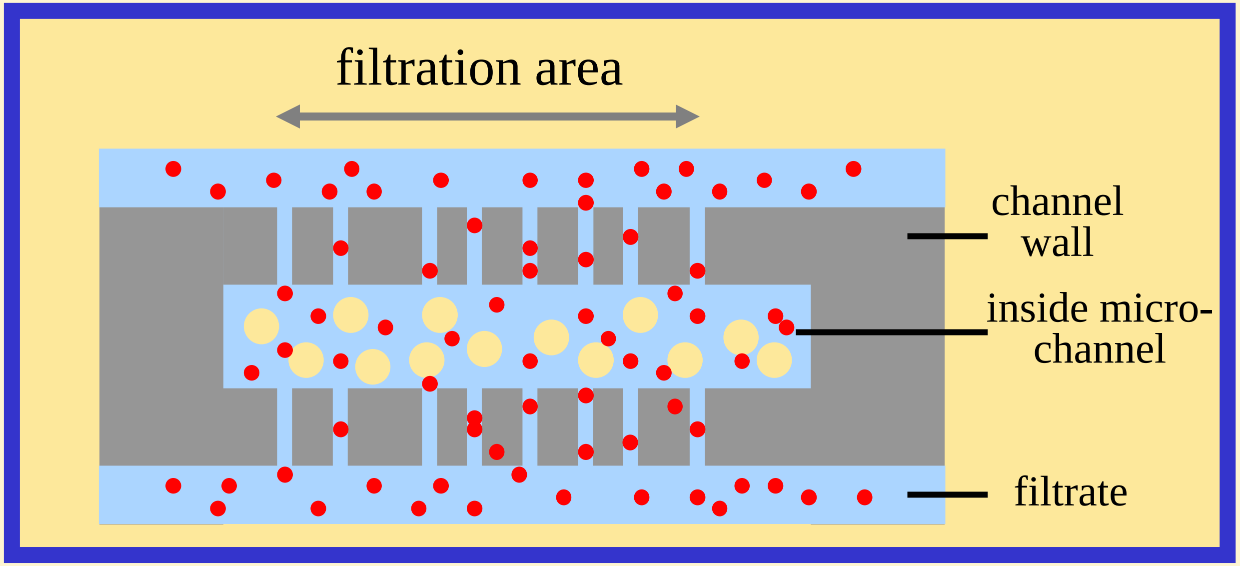


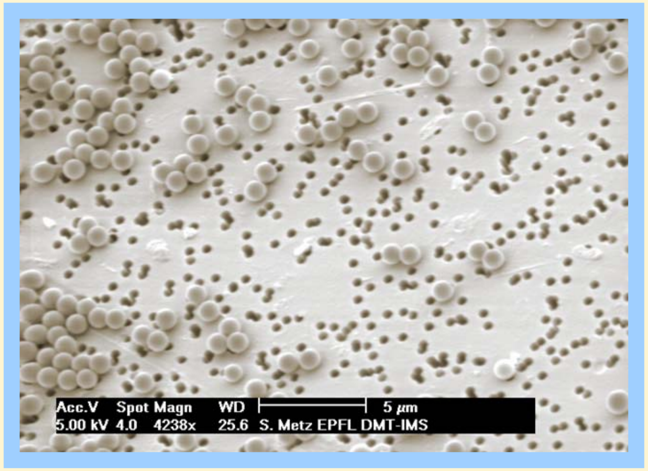
integrated nanoporous membrane ➔

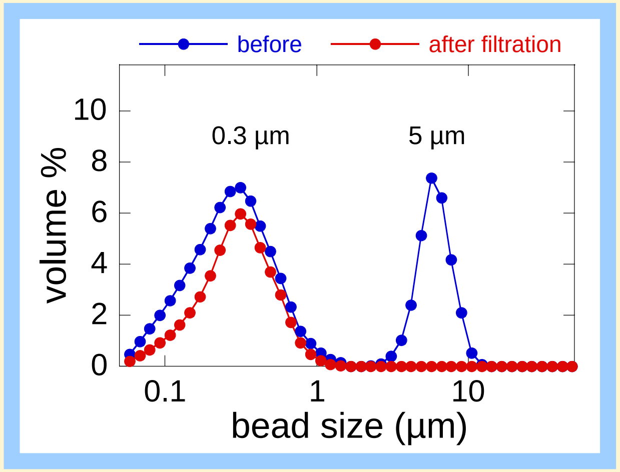
- mask irradiation defines filter area
- ion energy defines filter layer
- ion fluence defines pore density
- etching defines pore size

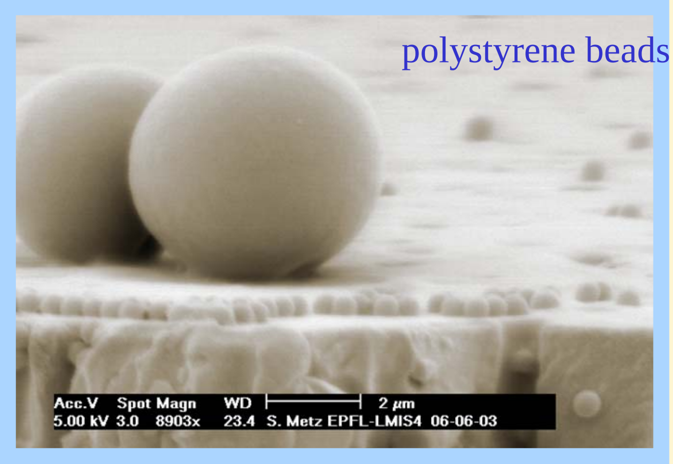
Metz et al. J. Micromech. & Microeng. 14 (2004) 324

Microfluid filtration with nanopores

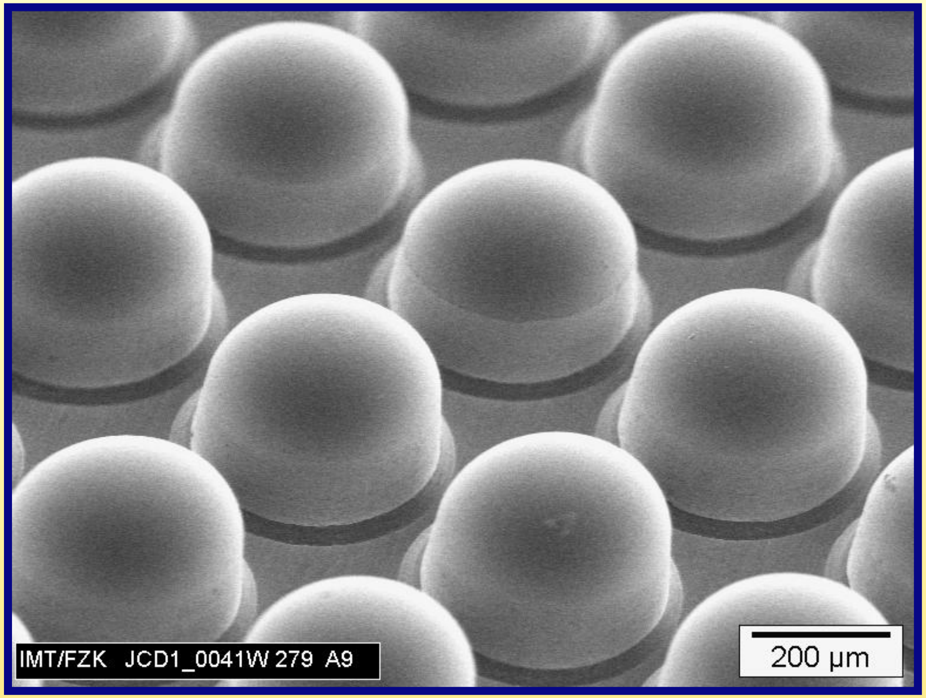


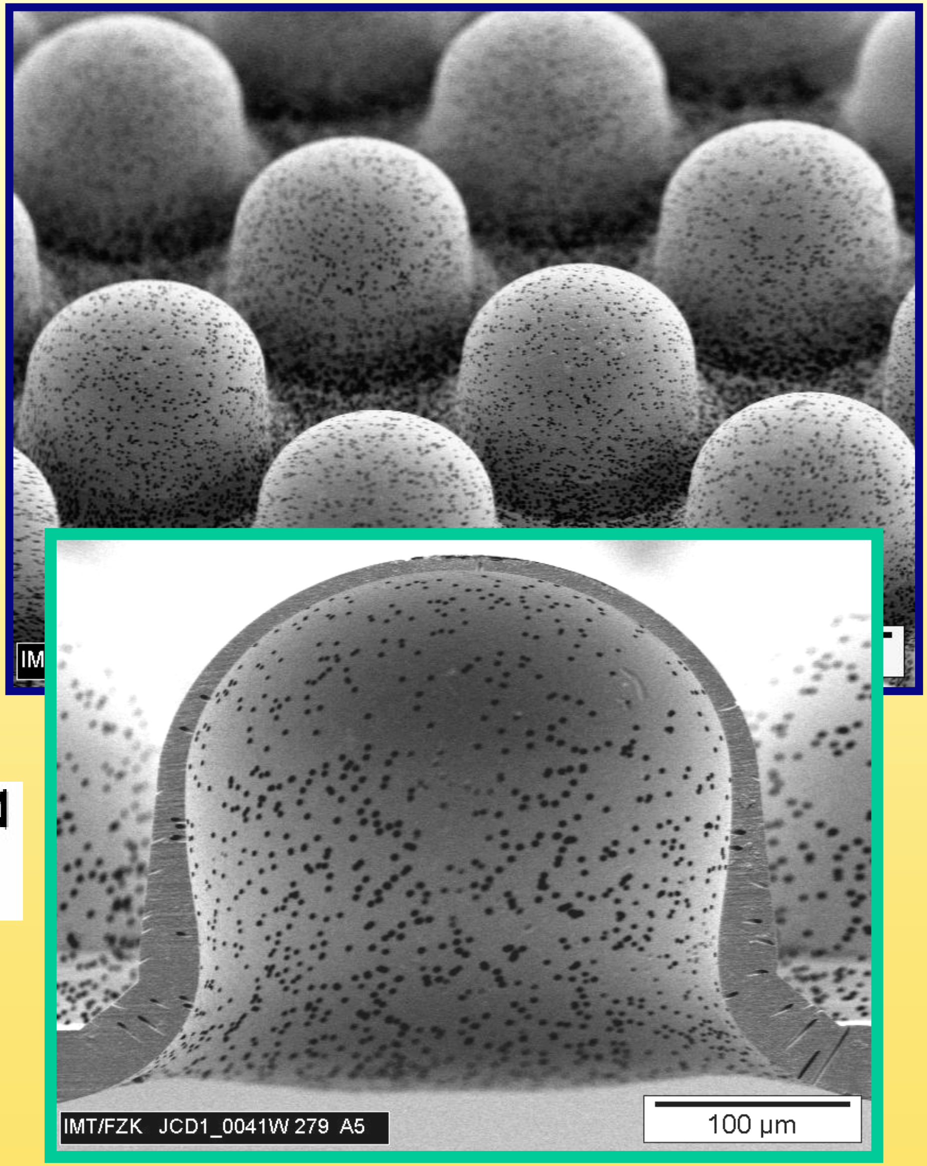


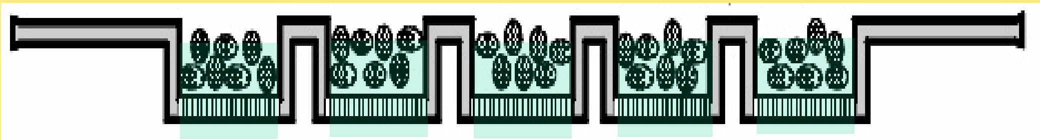




Perforation of thermoformed microcontainers



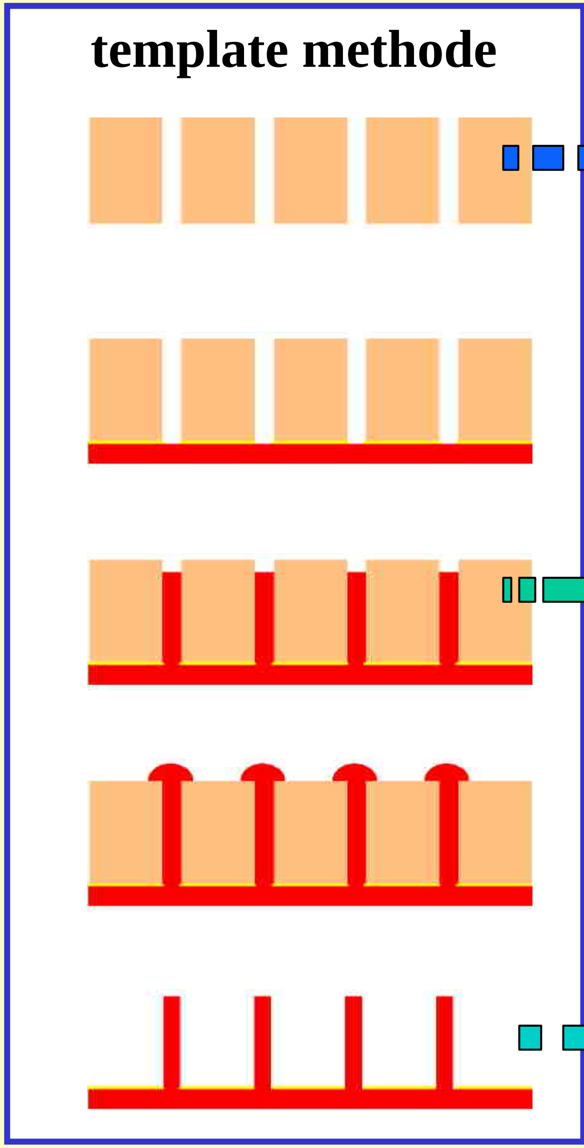


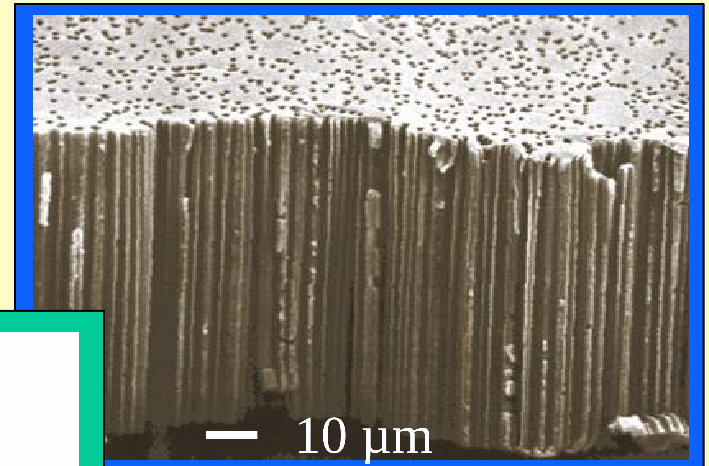


drainage during growth of cell cultures
in liquid medium

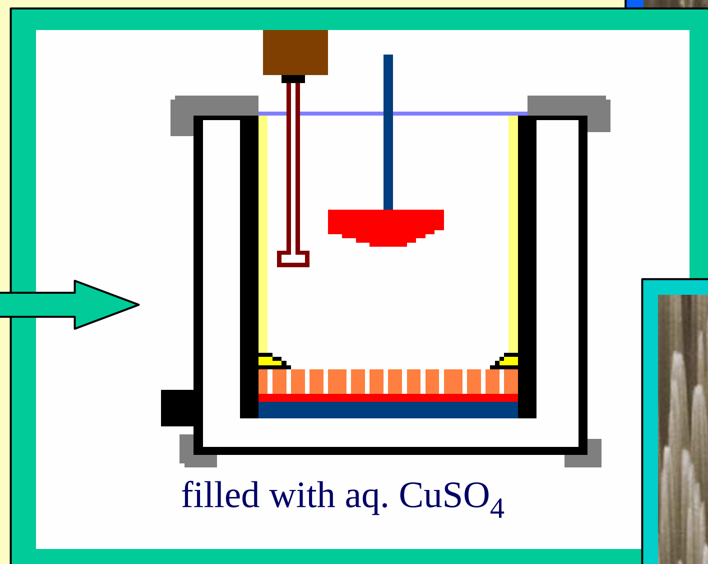
S. Giselbrecht, Forschungszentrum Karlsruhe

Ion track membranes as templates

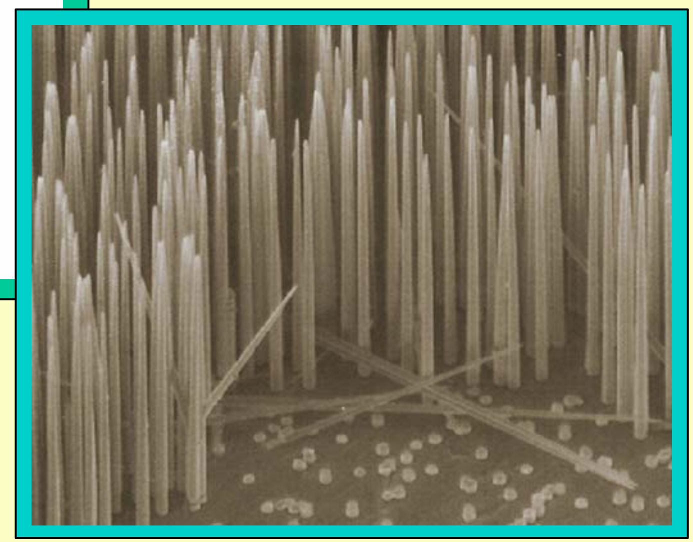




etched ion track membrane



filling of pores in galvanic cell

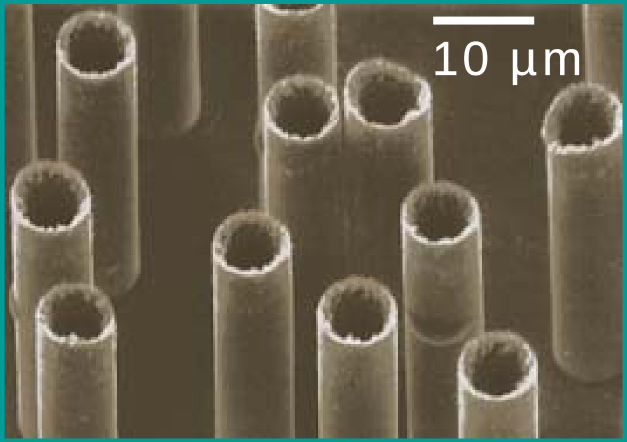


free-standing metal needles

Dobrev et al. J. Vac. Sci. Technol. B 19 (2001) 1385

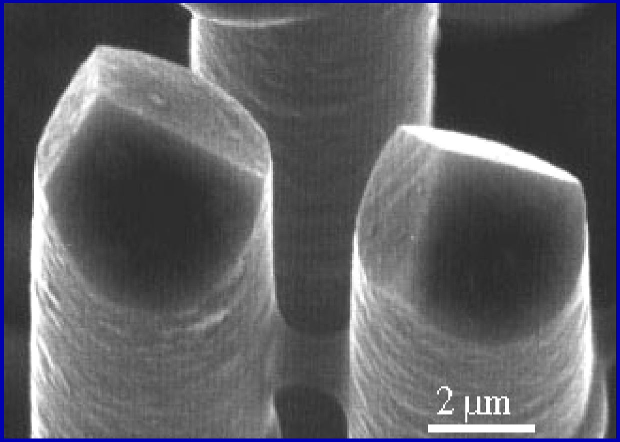
Microneedles and nanowires

metallic micro-tubes



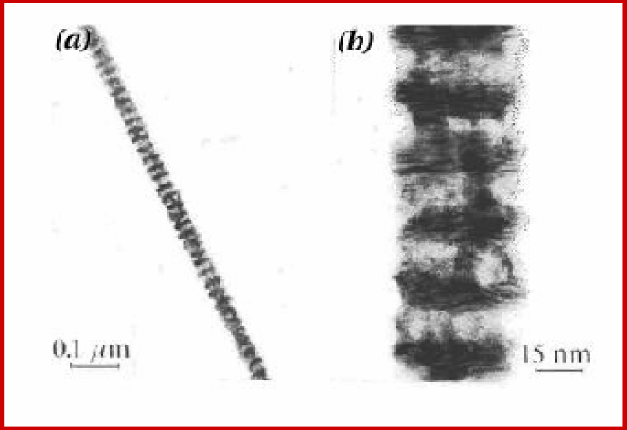
D. Dobrev et al. (GSI)

single-crystalline Cu needles



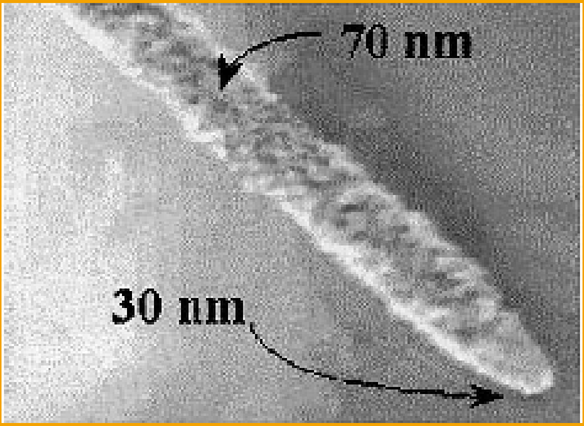
E. Toimil et al. Adv. Mater. 13 (2001) 62

10-nm thick multilayers of Co / Cu



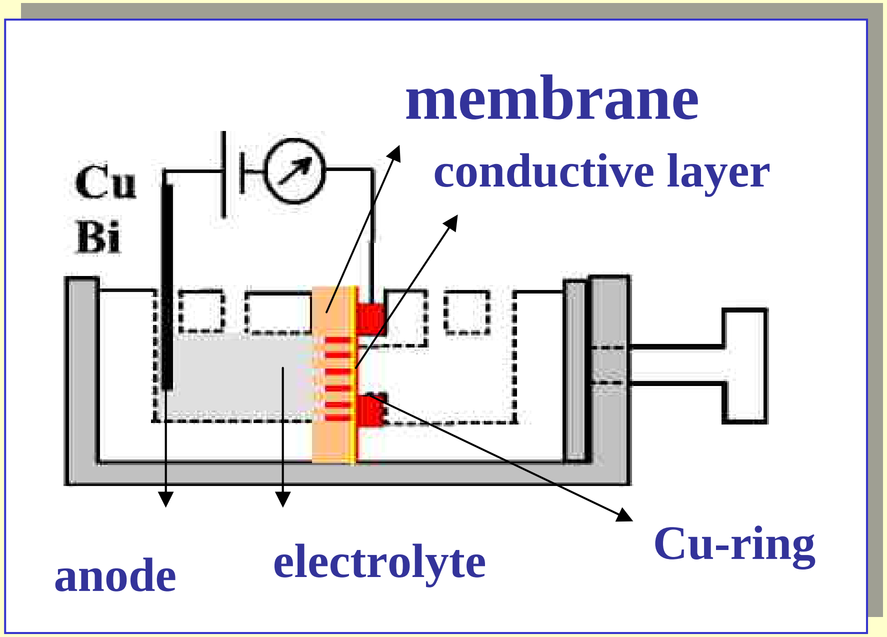
L. Piraux et al., Louvain-la-Neuve

toothpick-shaped Co nanowire

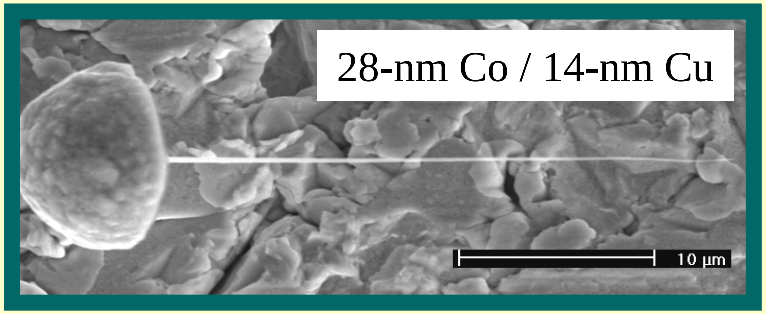


E. Ferain., NIM B 174 (2001) 116

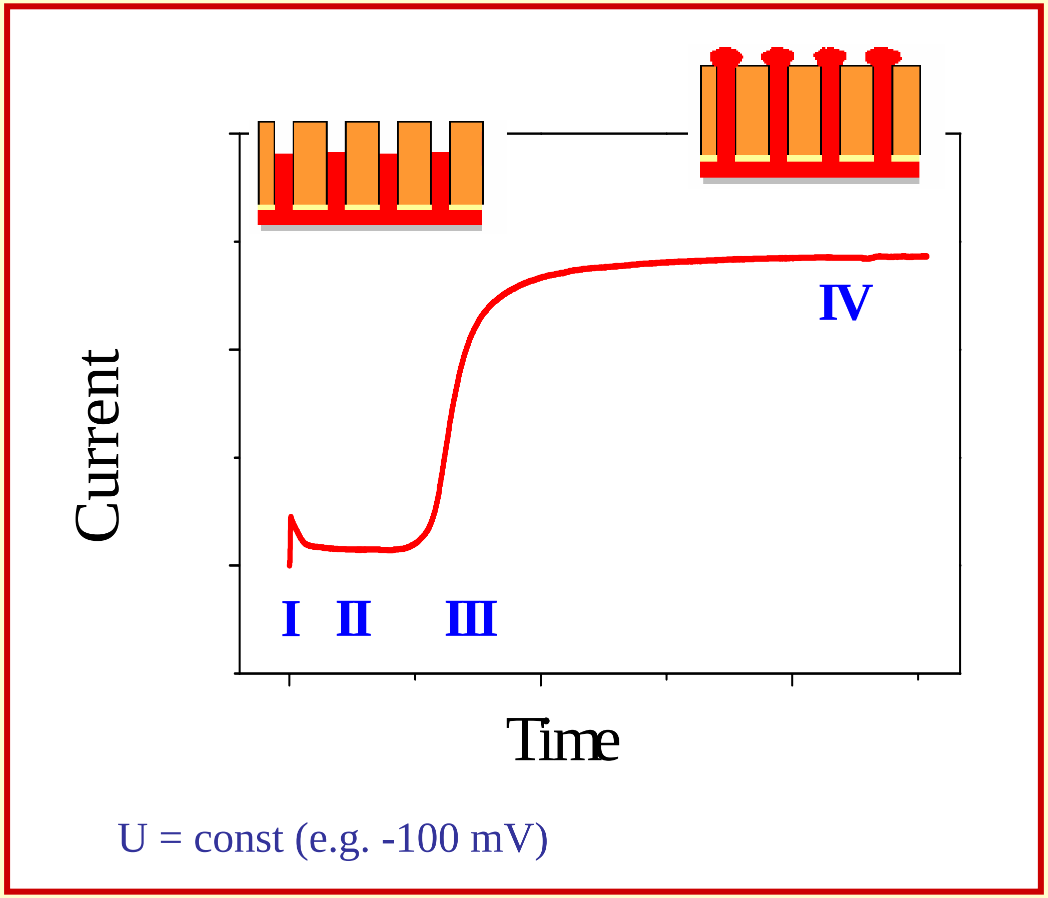
electrochemical deposition process



material: Au, Bi, Cu, Fe, Ni....
Cu/Co, Cd/Te,...



I.Enculescu et. al. (2004)

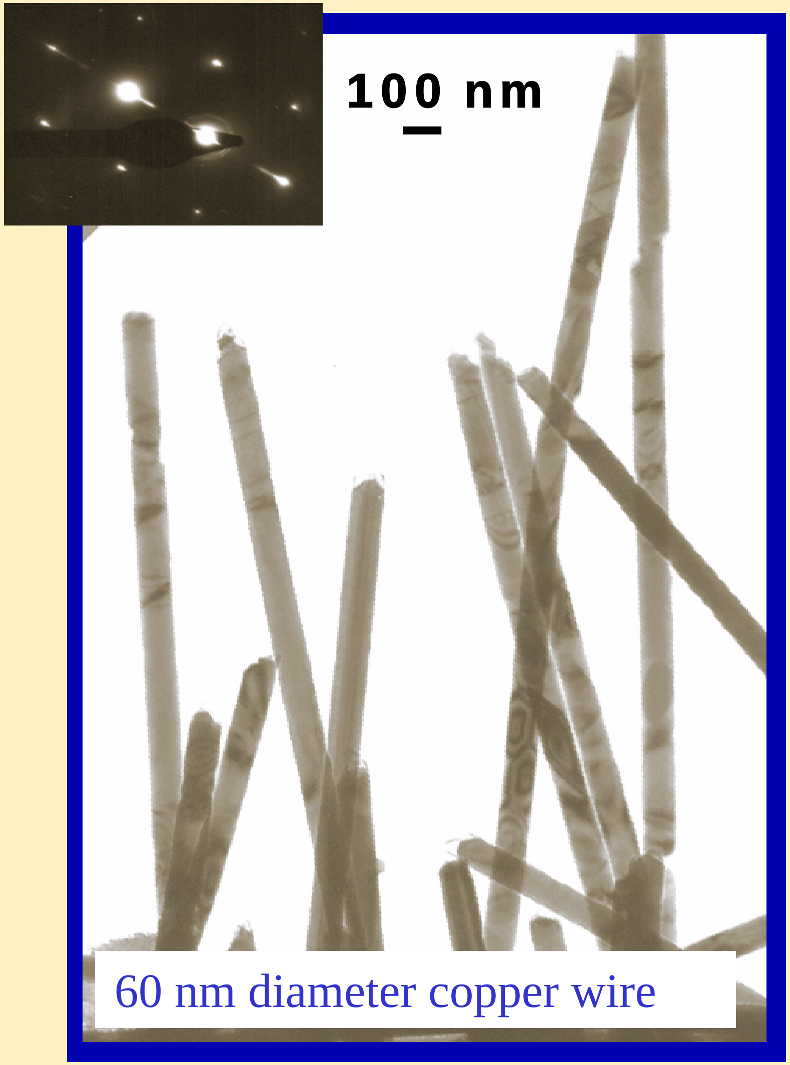


Single-crystalline Cu-nanowires

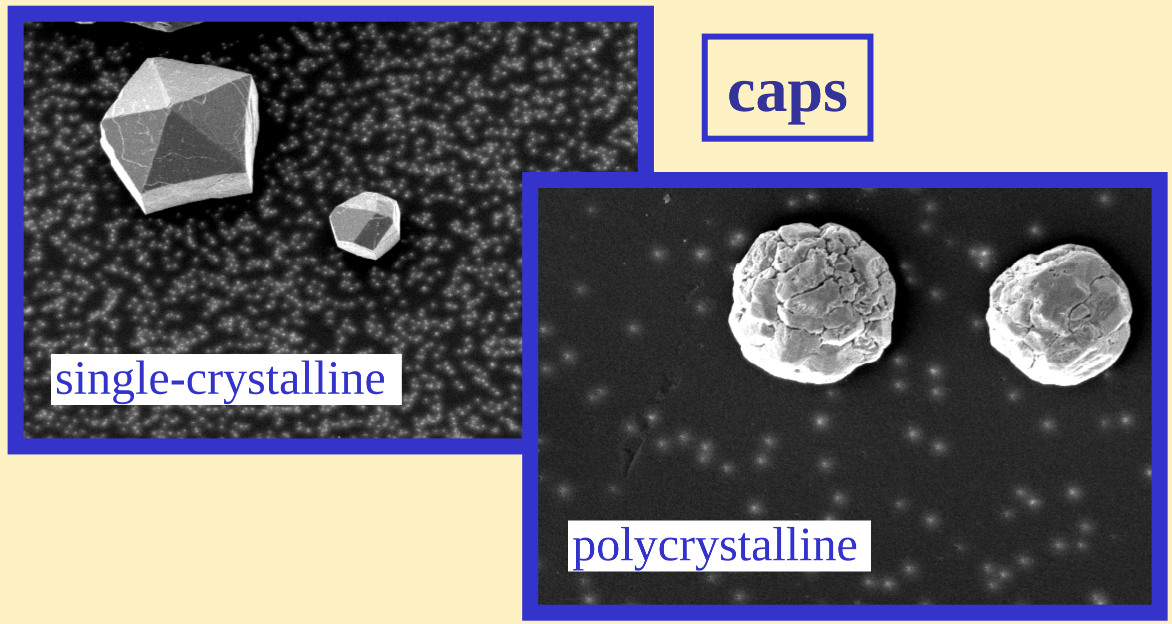
- high deposition temperature
- low over-voltage

→ low deposition rate

→ higher crystallinity

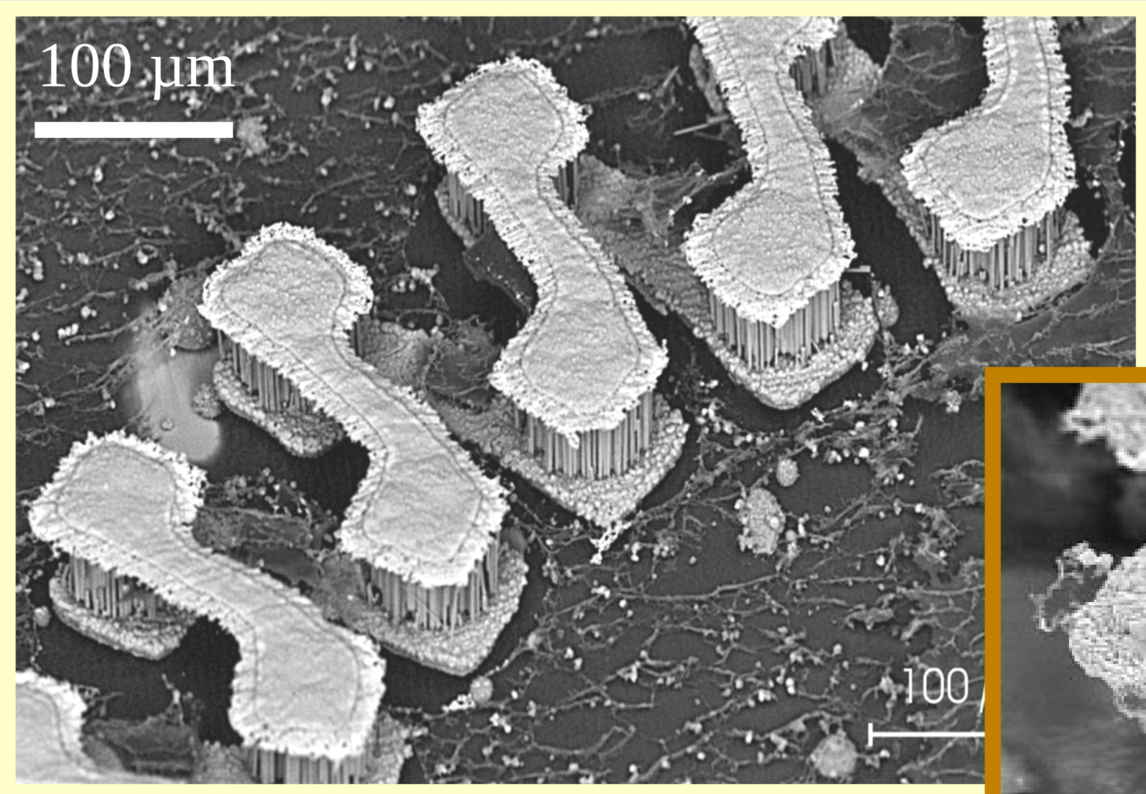


caps

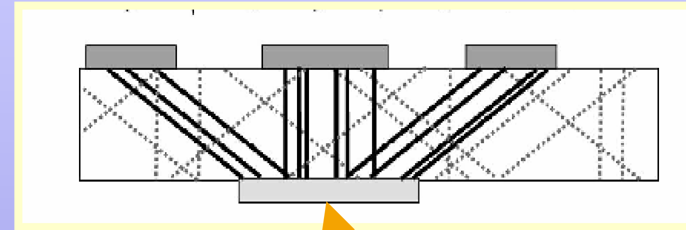


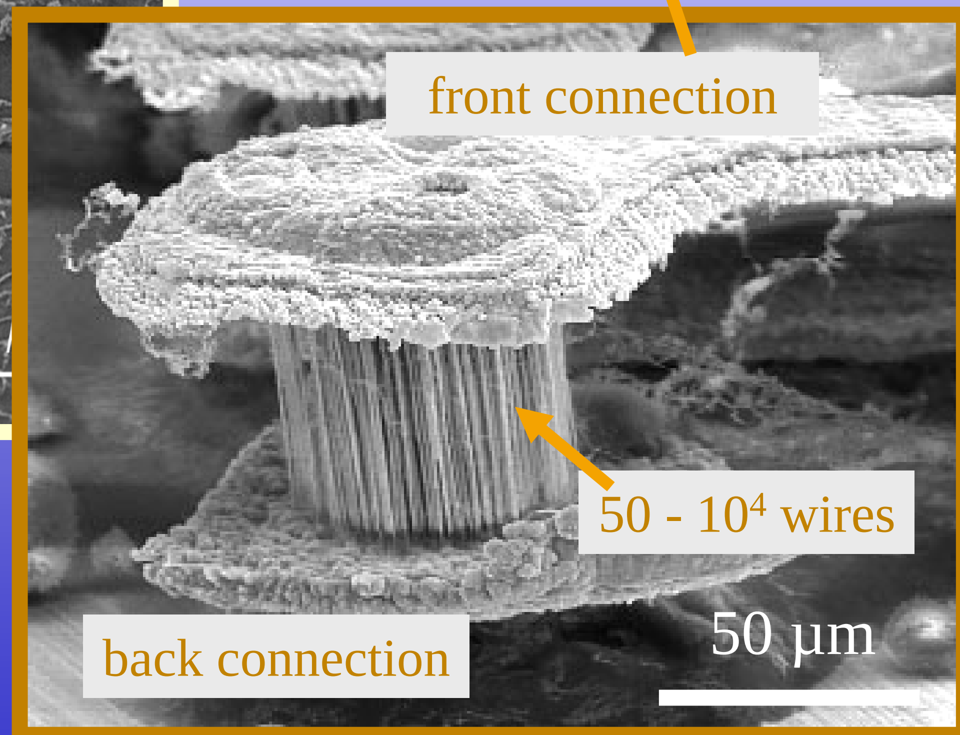
E. Toimil, PhD thesis, Univ. Heidelberg (2001)

Electrical connections using wire ensembles



tilted wire ensembles



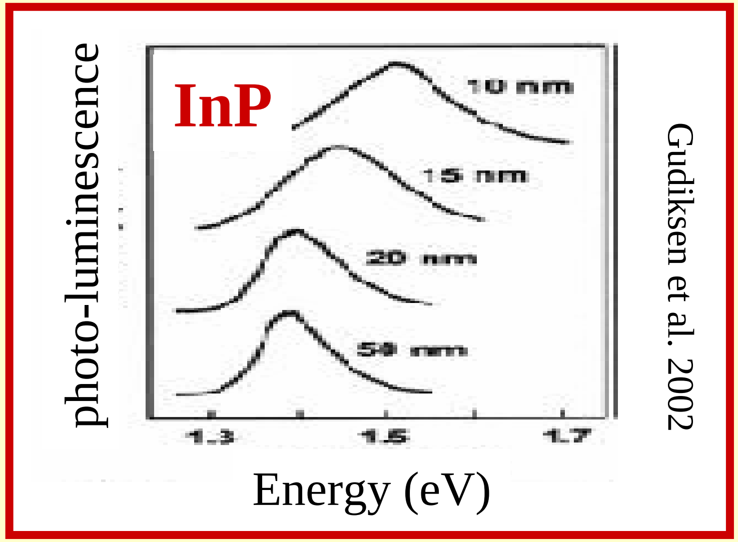


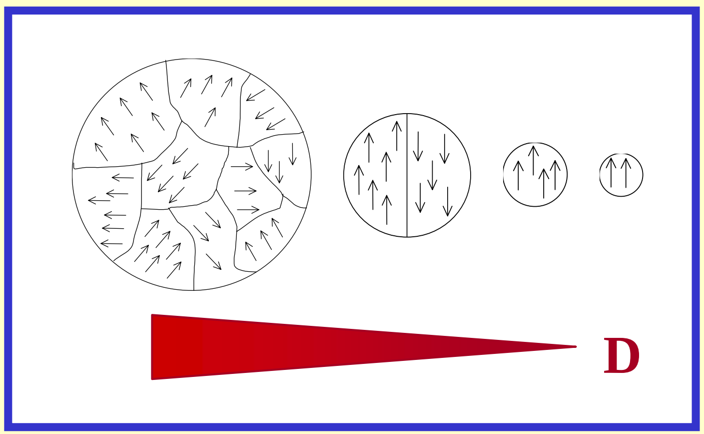
- polyimide flexible circuit boards
- contacts by lithography
- adjustable wire density, length
- prospective applications:
  micro-wave filters,
  sensors, etc.

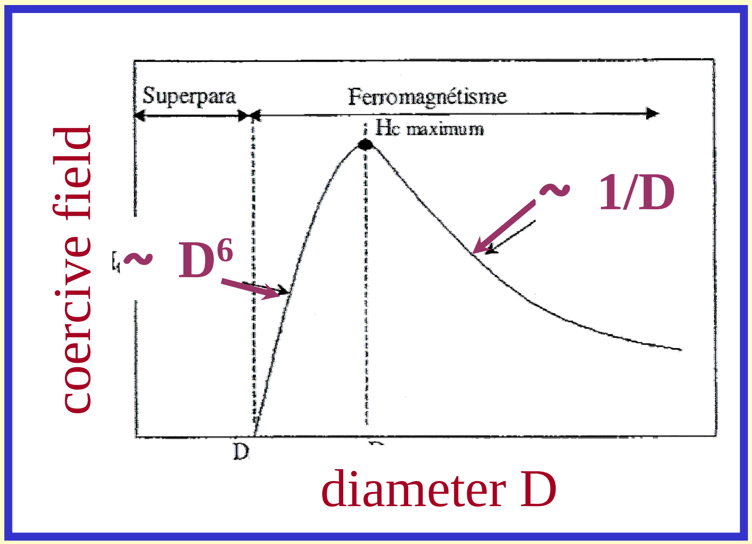
Lindeberg, PhD thesis, Univ. Uppsala, 2003
Lindeberg et al., Sens. Actuat. A 105 (2003) 150

Material property change versus particle size

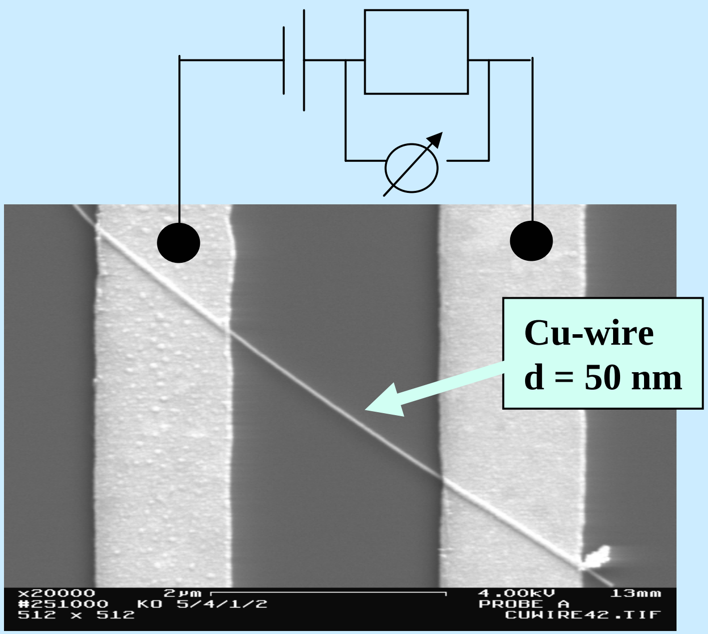
- optical
- electronic
- mechanical
- magnetic...

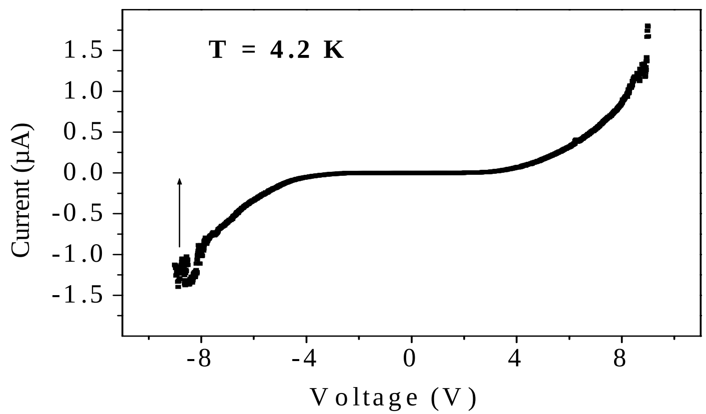






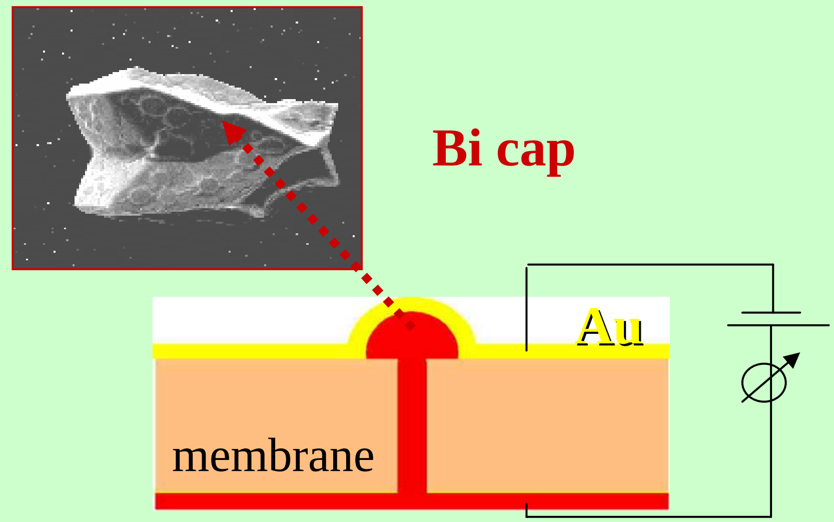
Electric measurements on single nanowires

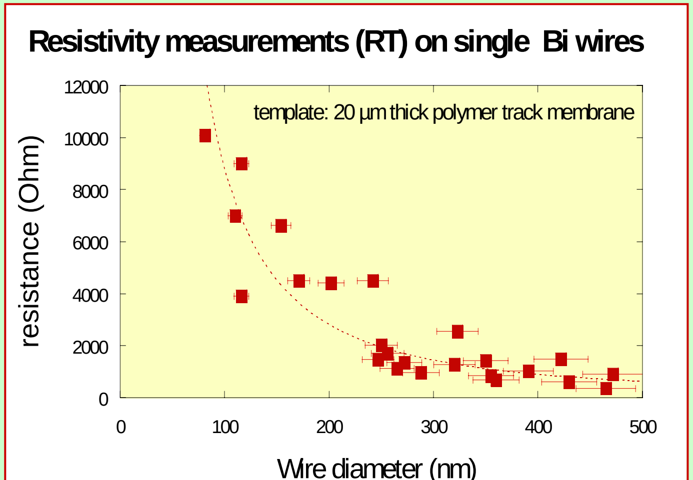




Toimil et al., Appl. Phys. Lett. 82 (2003) 2139

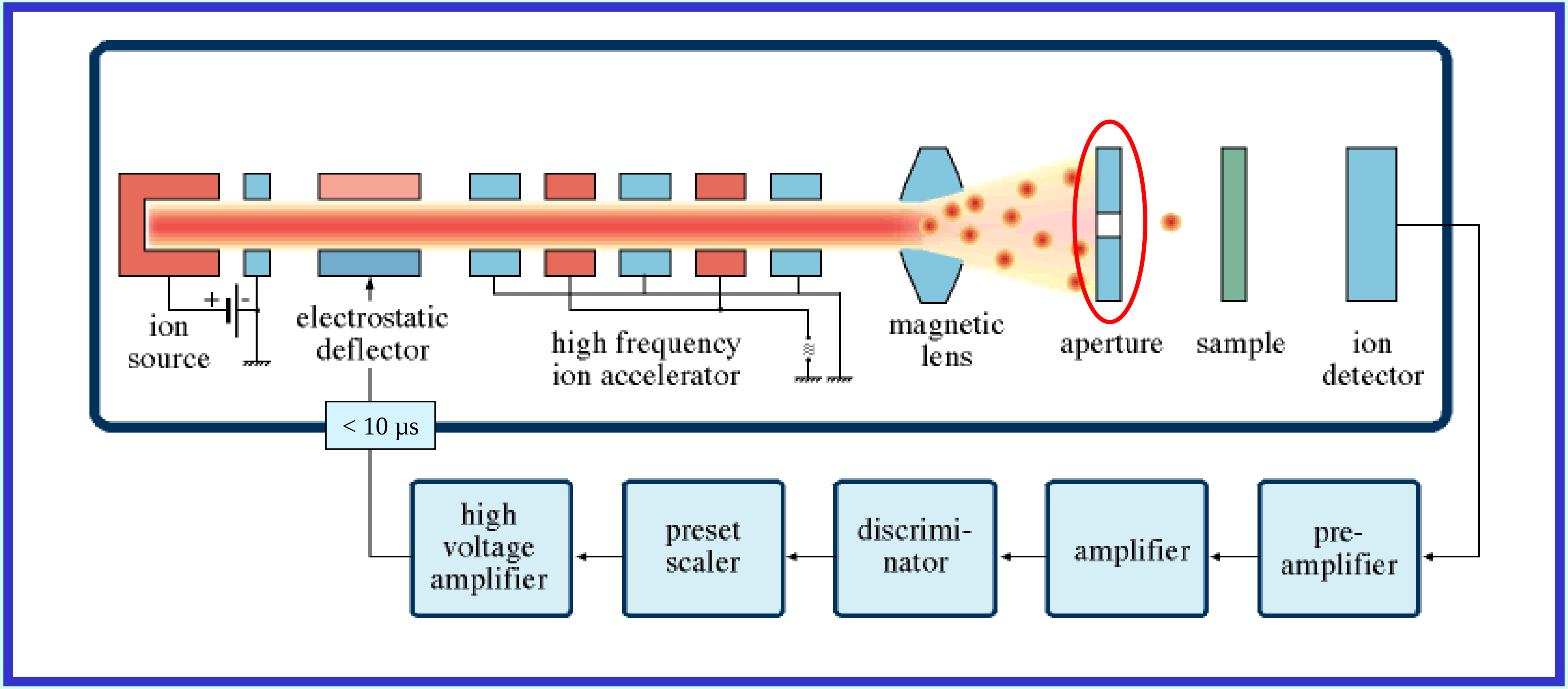
single-wire deposition





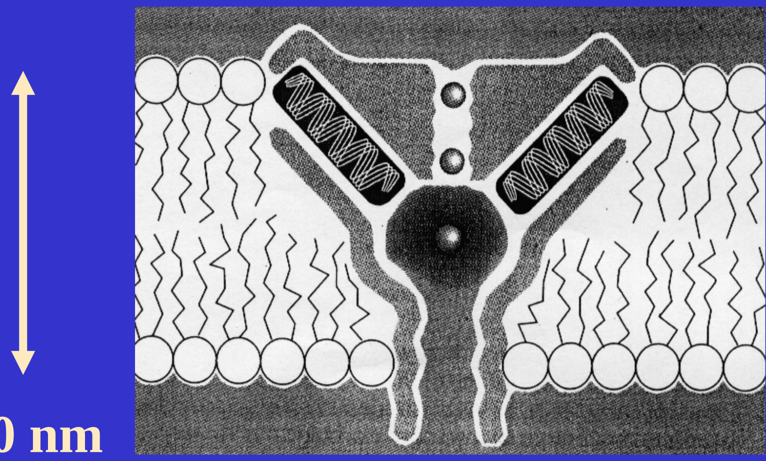
Enculescu et al..; Appl. Phys. A 77 (2003)751
T. Cornelius, N. Chtanko, E. Toimil (GSI)

Single ion irradiation



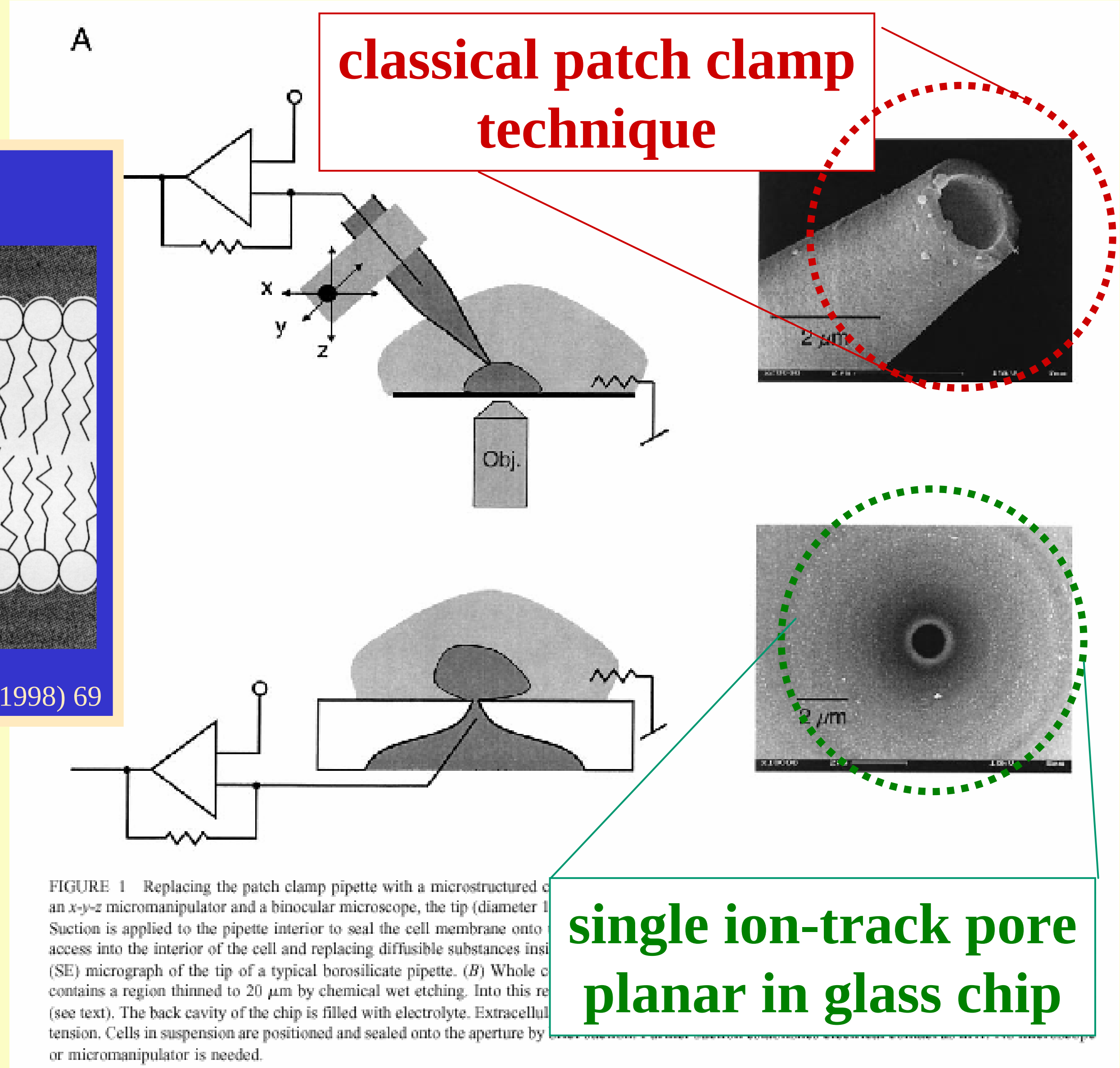
Ion currents through lipid bilayers of bio-membranes

lipid bilayers



10 nm

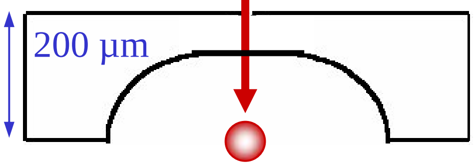
Doyle et al. Science 280 (1998) 69



Fertig et al., Biophys. Journal 82 (2002) 3056

Planar glass chip with single pore for cell biology

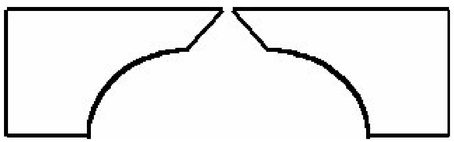
single ion irradiation of pre-etched glass chip

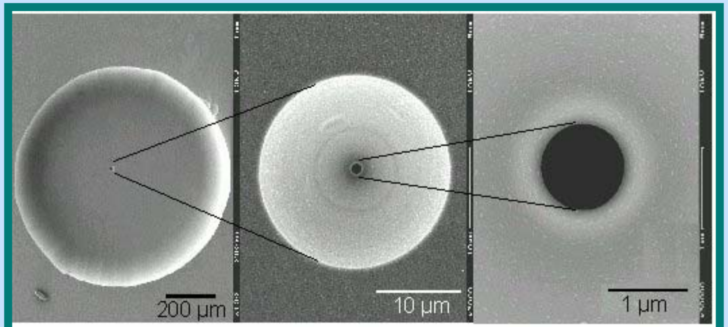


track etching

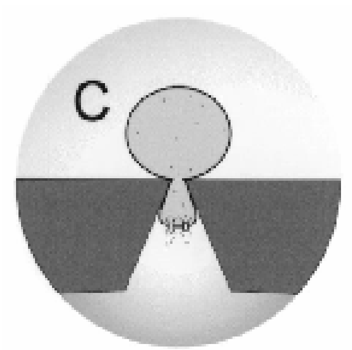
↓

pore aperture ~ 1 µm





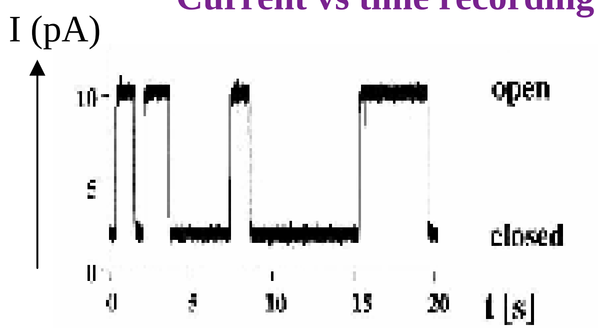
cell positioning via suction



Advantages of planar geometry

- improved sealing > 5 GΩ
- low capacitance < pF
- low noise
- good time resolution
- cell positioning without microscope

Current vs time recording

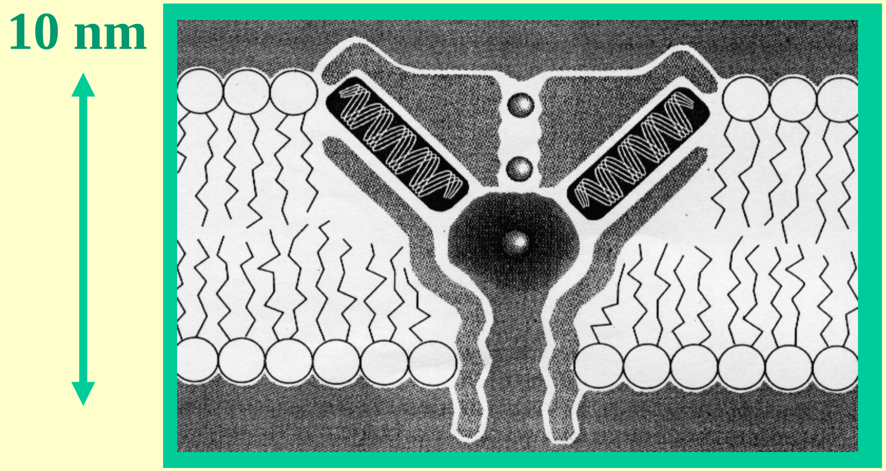


Gramicidin A channels in artificial bilayer

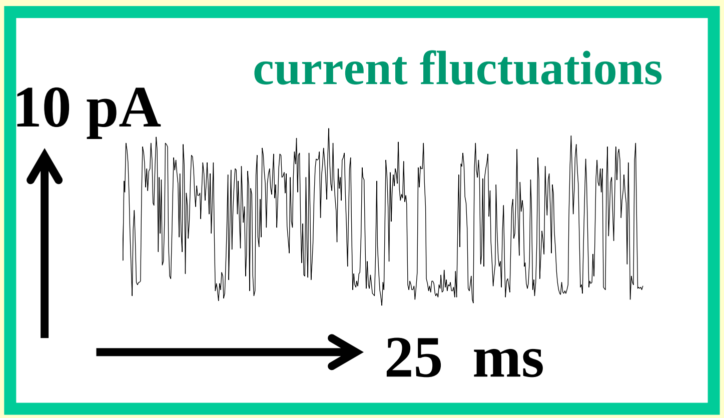
Fertig et al., Appl. Phys. Lett. 81 (2002)
Phys. Rev. E 64 (2001) 040901

Model pores for biological membranes

bio-membrane

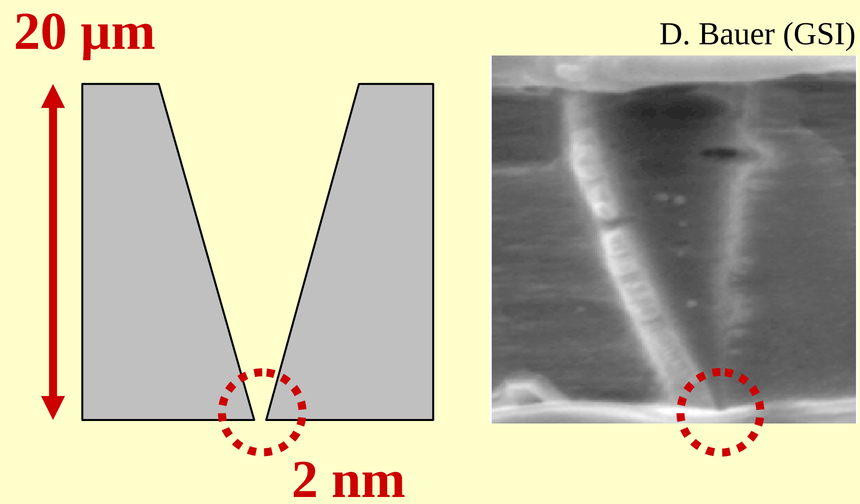


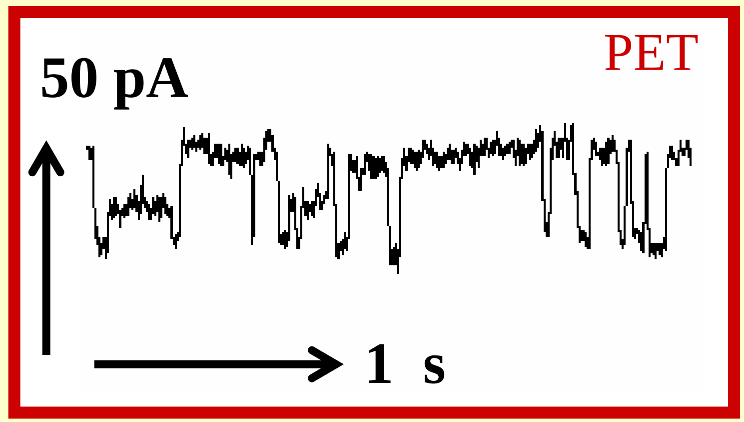
Doyle et al. Science 280 (1998) 69



P.N.R. Usherwood (Nottingham, U.K.)

polymer membrane





Siwy et al., PRL 89 (2002)

detection and identification of of biomolecules

1985

red blood cell

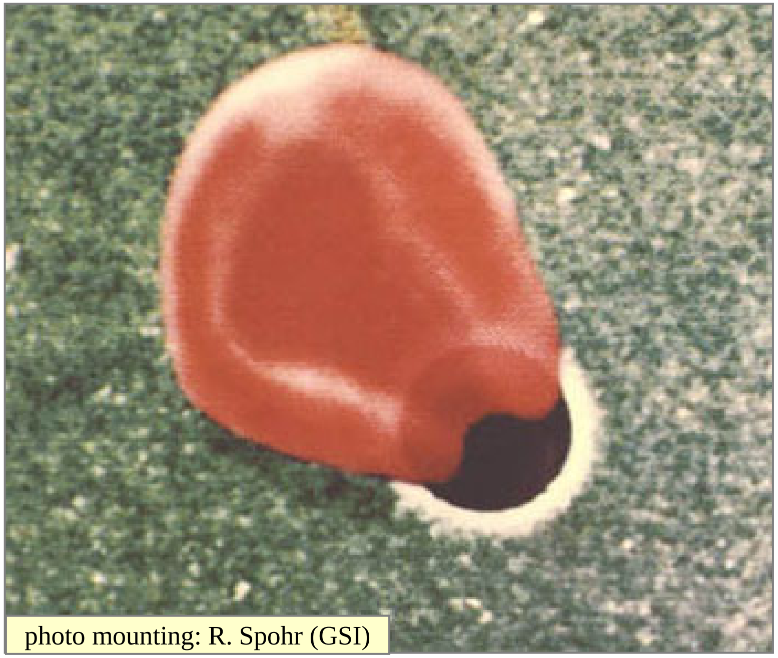


photo mounting: R. Spohr (GSI)

pore and cell dimensions:
3-10 μm

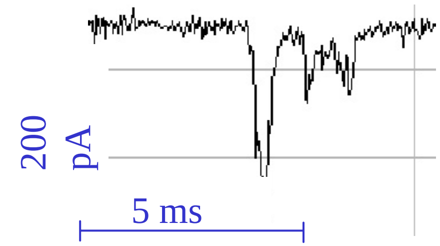
:1000

2003

DNA

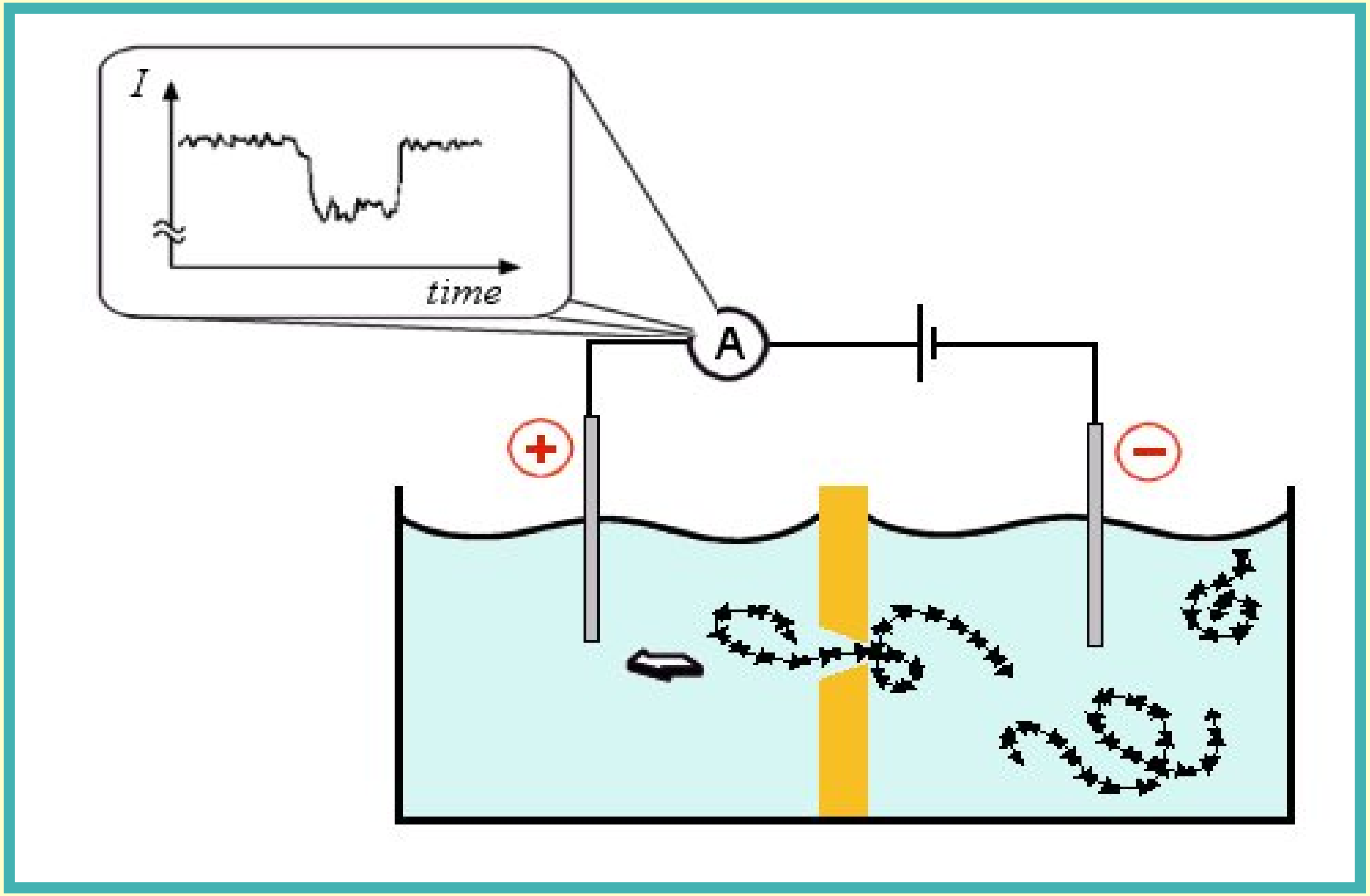
pore ~ 2-3 nm

Conductivity measurement of DNA transport through single nanopore (5 nm)

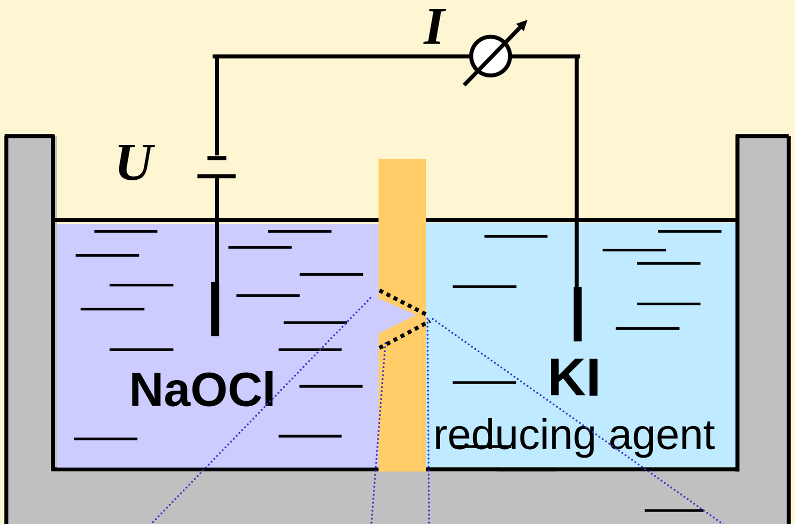


Mara et al., Nano Lett. 2004

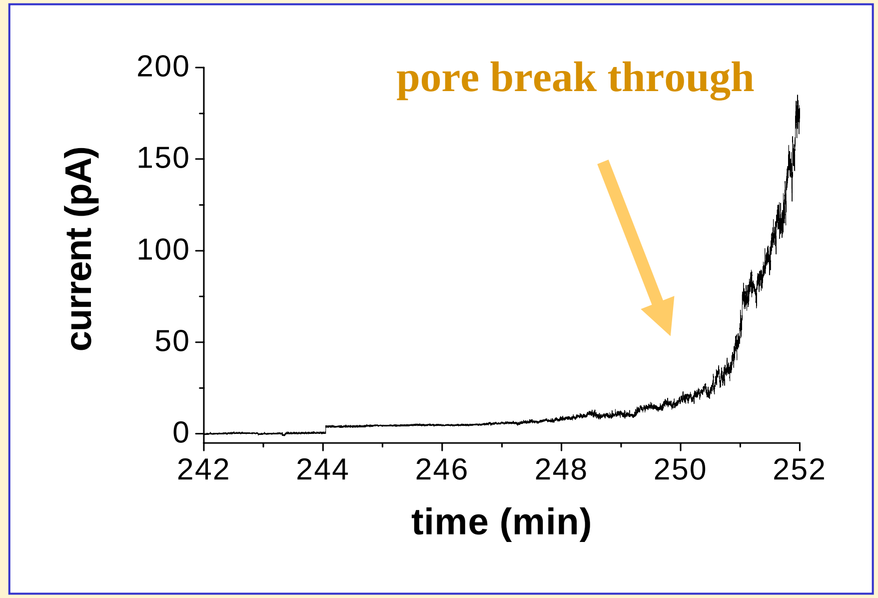
Single-molecule detection with nanopores

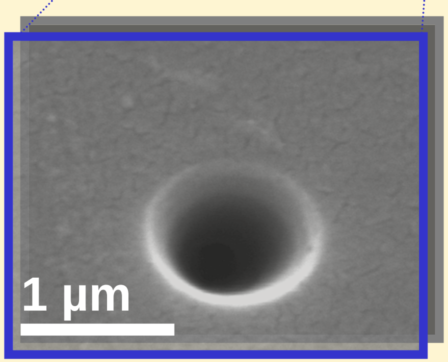


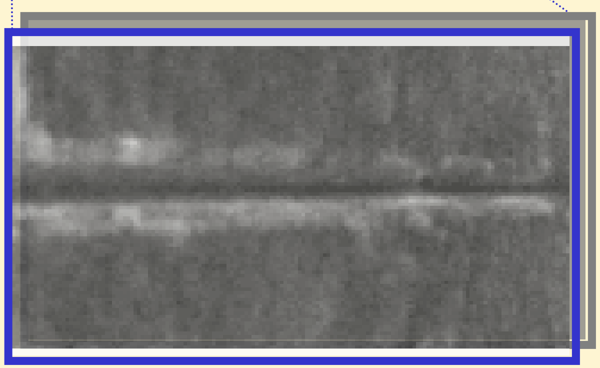
Single nanopores by electro-stopping



Kapton:etch stop: $OCl^- + 2\,H^+ + 2\,I^- \rightarrow I_2 + Cl^- + H_2O$







large opening

small opening

d ≈ 2 nm

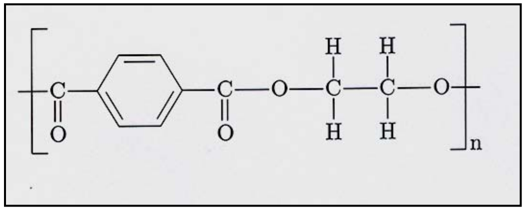
$R = 4\,L\,/\,\pi\,\kappa\,D\,d$

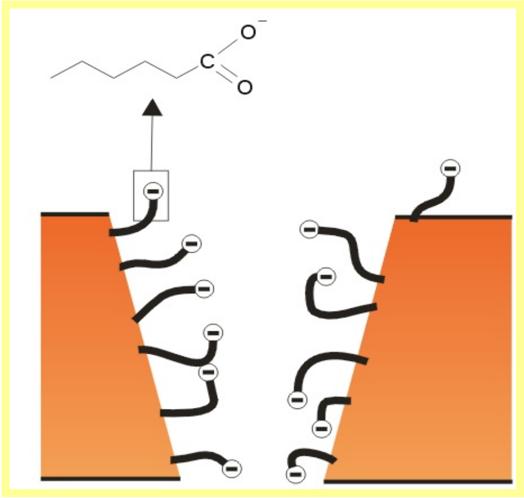
R	resistance
κ	conductivity of KCl
L	length of the pore

Z. Siwy et al., Appl. Phys. A 76 (2003) 781

Rectification depends on surface charges

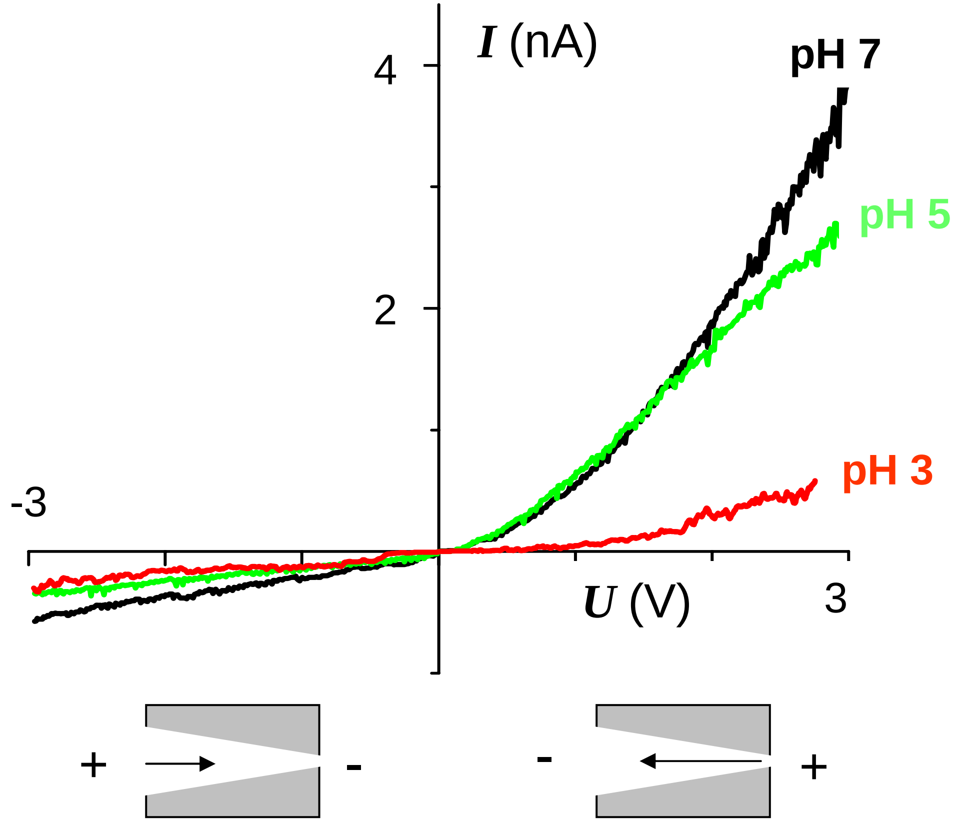
Pores are negatively charged





Pores are cation selective

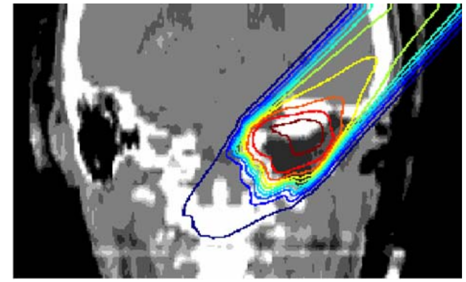
Rectification depends on pH



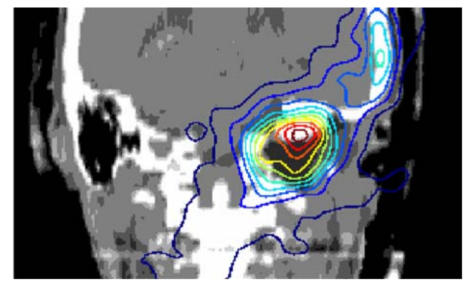
Siwy et al., Europh. Lett. 60 (2002)

Radiotherapy with heavy ions

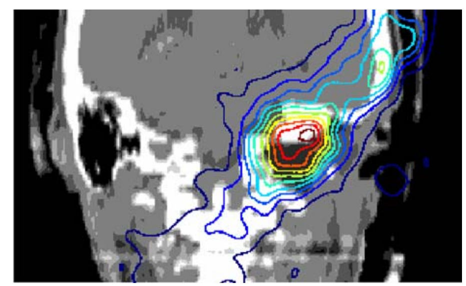
- why to use hadron beams?
- radiobiological model
- carbon therapy at GSI
- raster scanning
- future



required dose distribution



simulatated irradiation

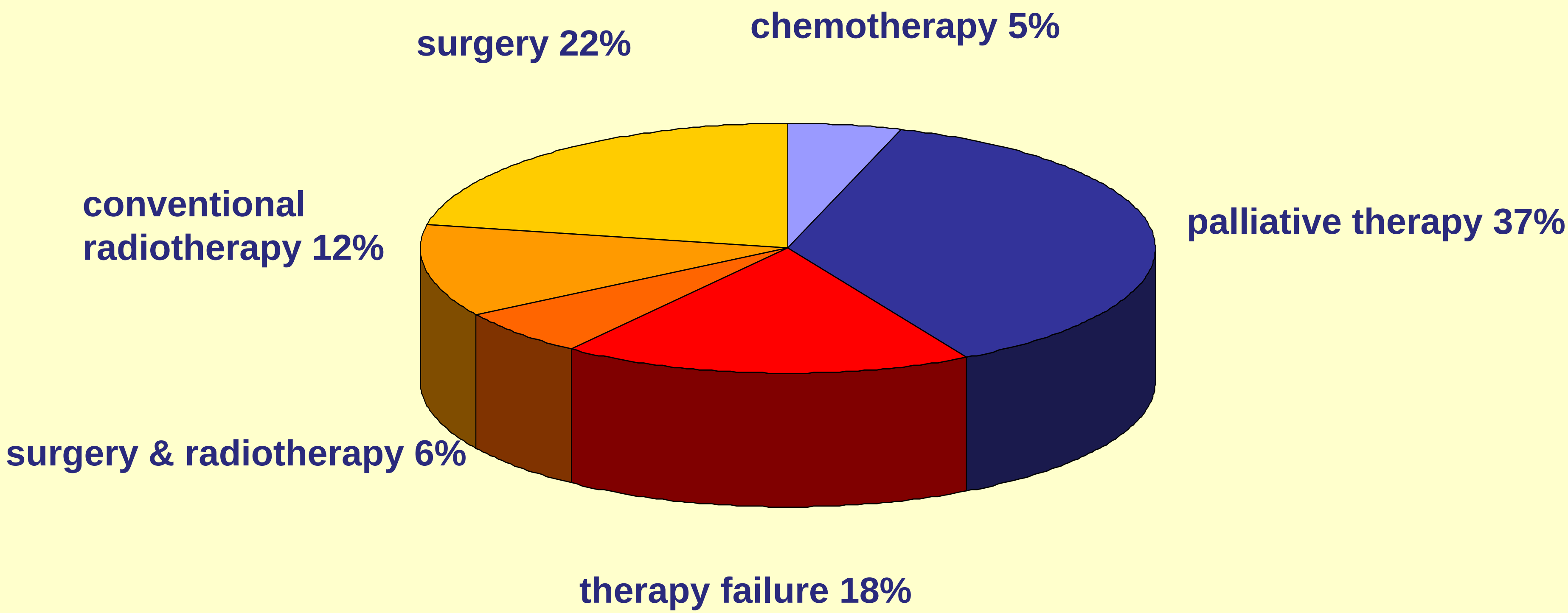


experimental dose data

List of various publications: http://www-aix.gsi.de/~bio/PUBS/pubs.html

Tumor therapy

localized tumors: 58%
metastases-forming tumors: 42%



For 18 % of all cancer patients therapy for localized primary tumor fails

due to limited dose application or difficult surgery

Hadron tumor therapy

1946: proposal by R.R. Wilson

1954: first proton beam for tumors in LBL (Berkeley, USA)

1975: treatment with heavy ions (Ne etc) at LBL

1990: center for proton therapy in Loma Linda (USA)

1993: center for ^{12}C-ion therapy in Chiba (Japan)

1997: tumor-conform irradiation with protons at PSI (Villingen, CH) and with ^{12}C-ions at GSI (Darmstadt, Germany)

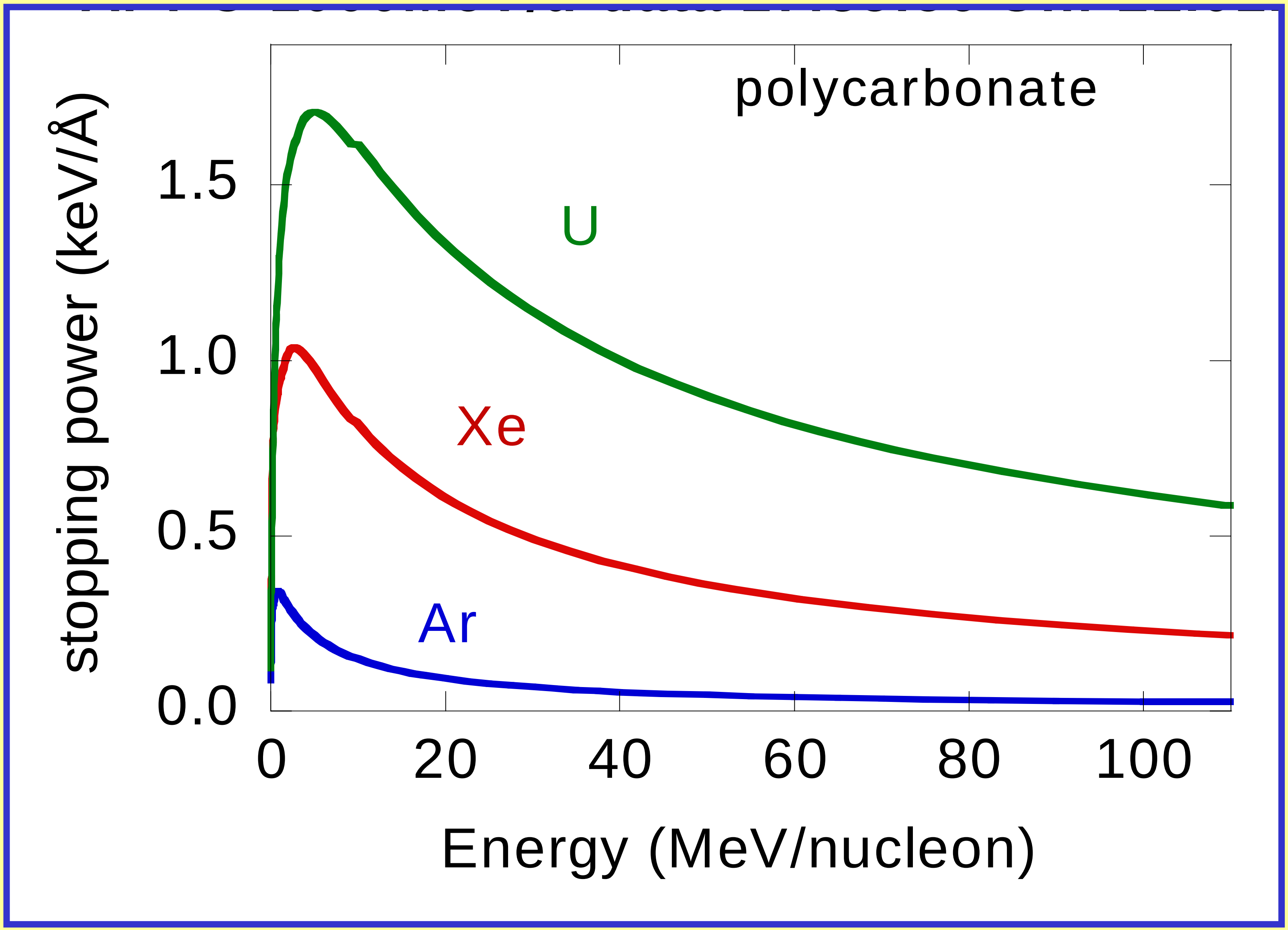
since 1997: clinical study in collaboration of

total: ~ 220 patients

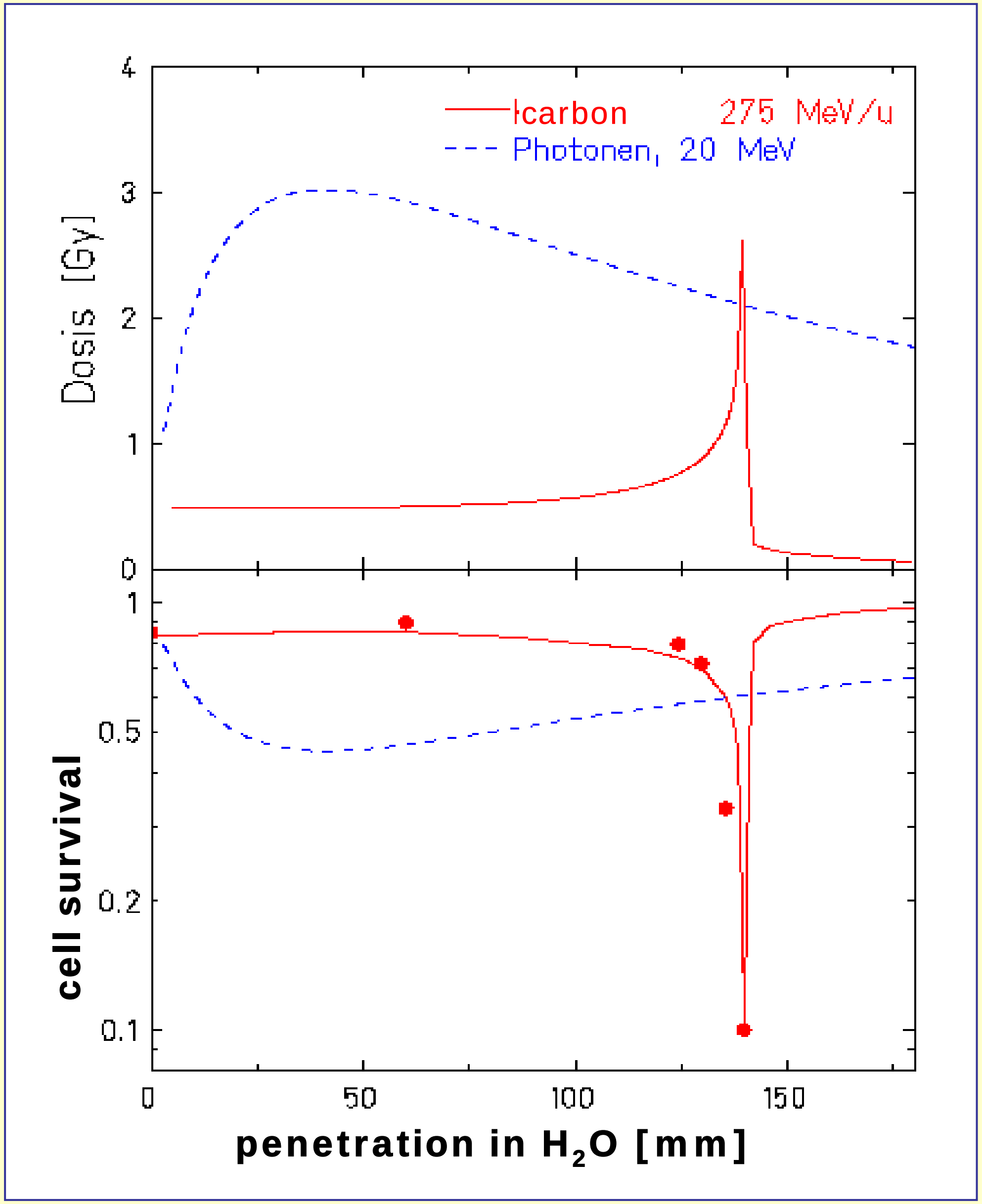
Aims of tumor therapy

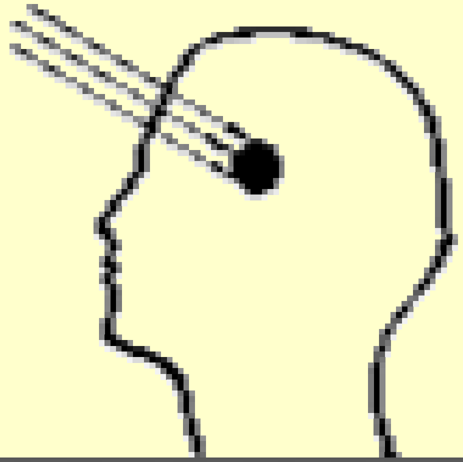
- apply lethal dose for tumor cells
- avoid critical regions (e.g. brainstem, organs, optic nerve)
- minimum dose for surrounding tissue

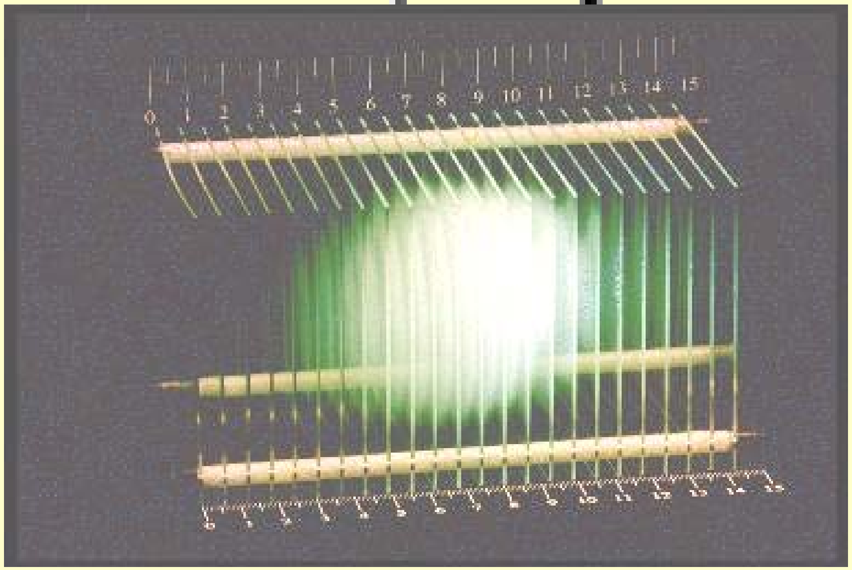
stopping power of energetic particles



Dose deposition by carbon ions and by photons

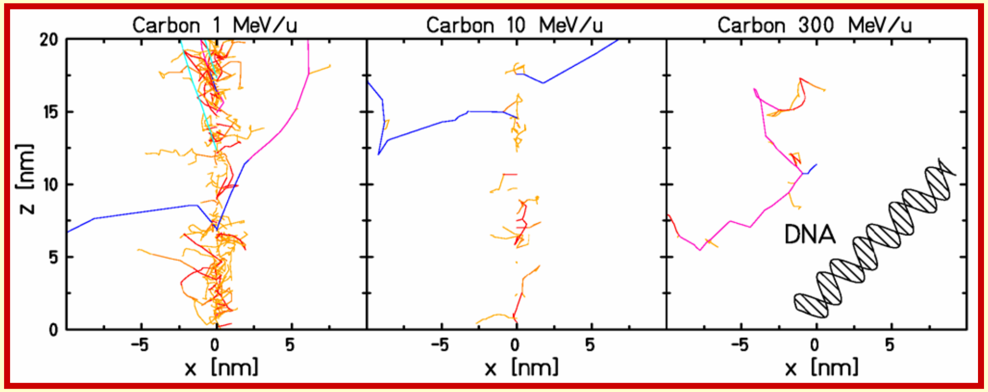




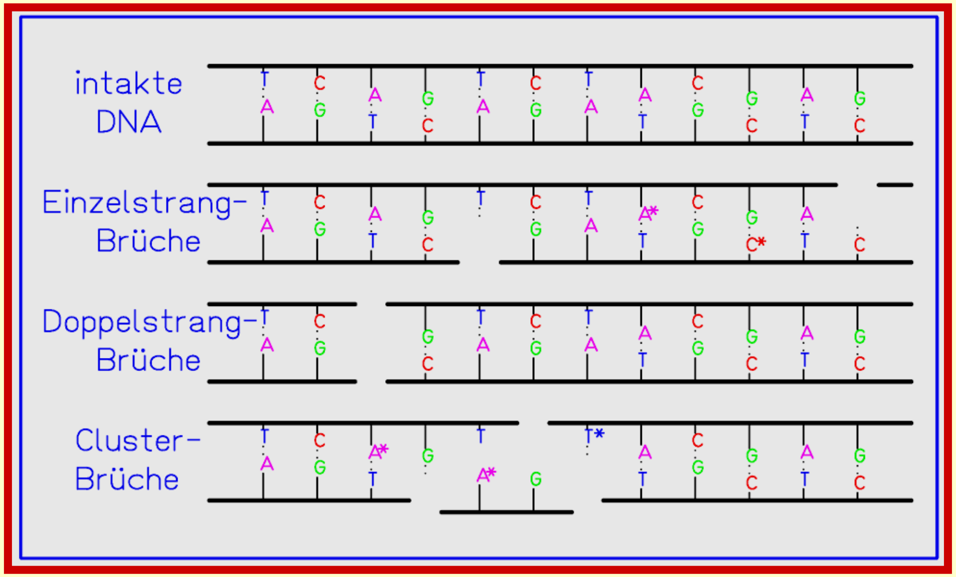


- Plastic slides in water irradiated with 270 MeV/u C ions
- Scanning over a spherical volume
- Track etching to make deposited dose visible

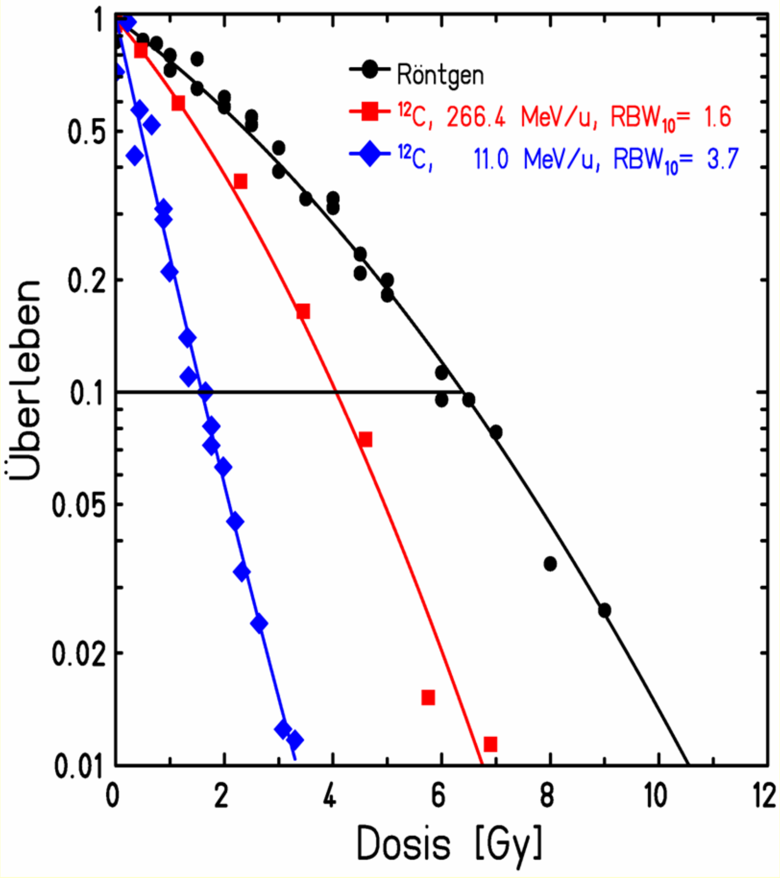
Monte-Carlo calculations of heavy-ions induced delta-electrons



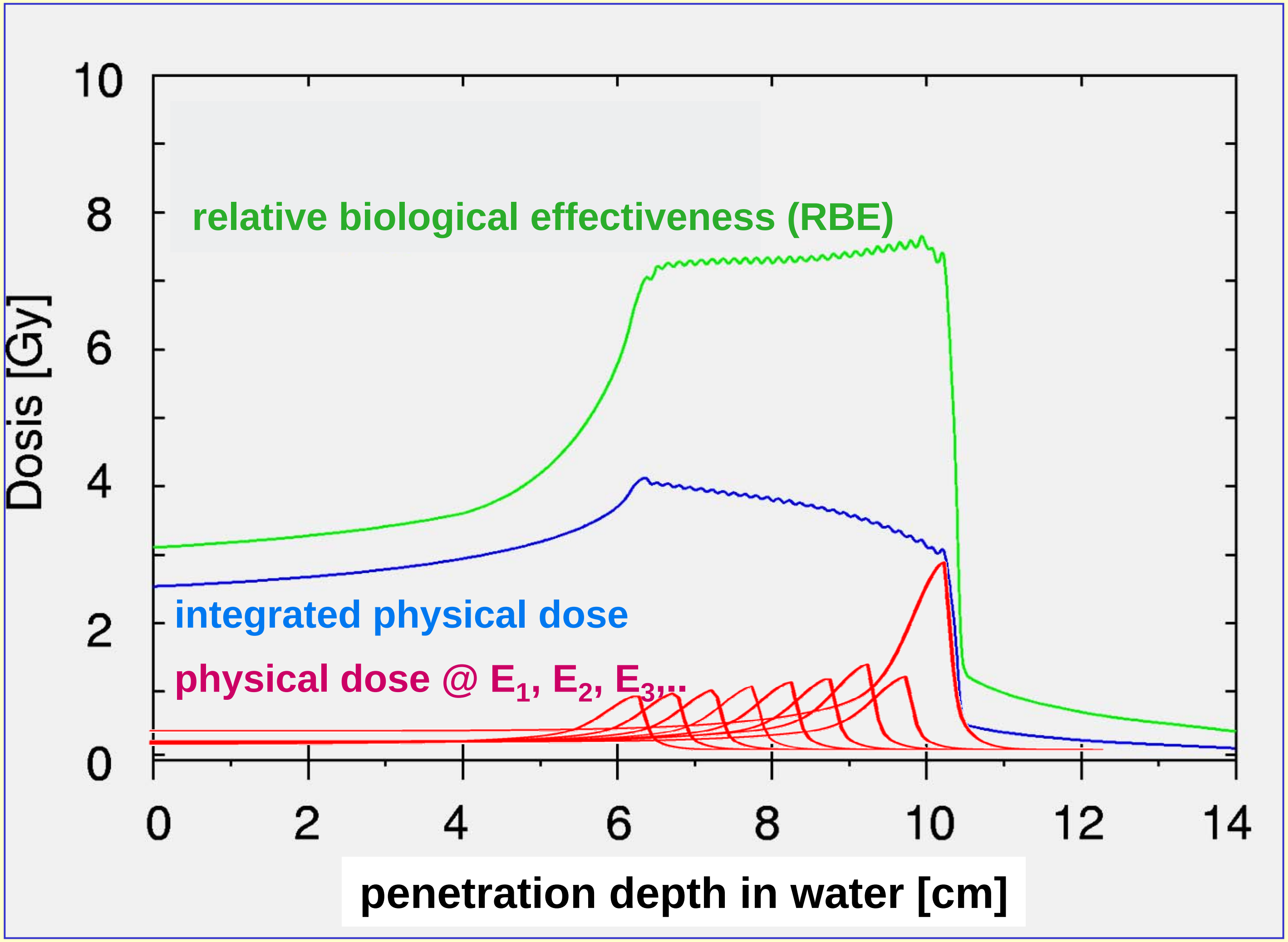
DNA damage



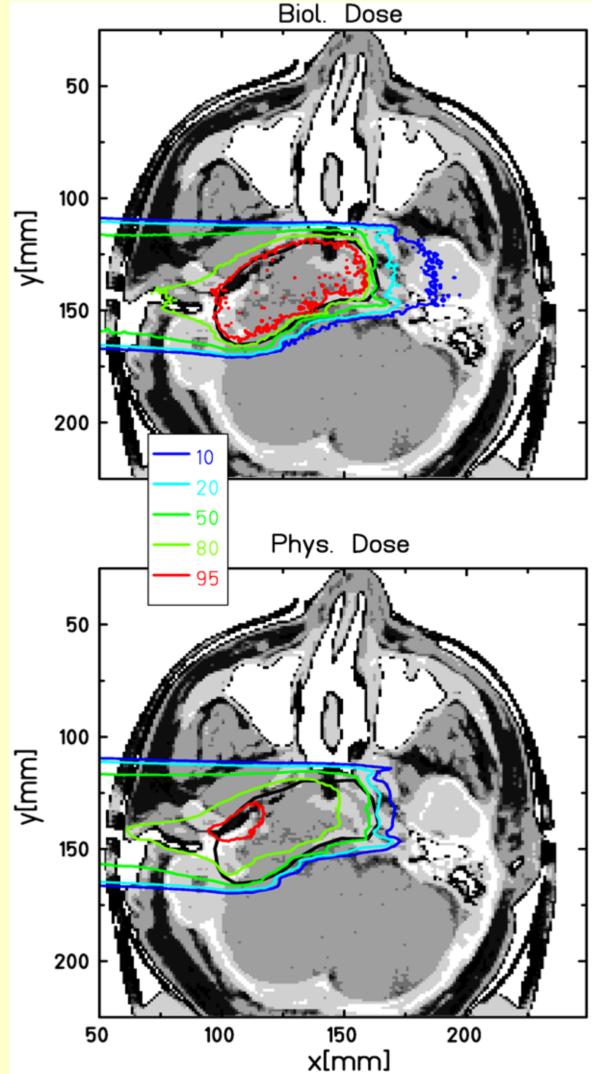
Survival curves: x-ray versus carbon ions



Dose distribution in tumor



biological dose



physical dose

medical planning
computer tomography

calculation of
treatment plan

medical operating

safety system
calibrations

GSI Darmstadt
DKFZ Heidelberg
Univ. Heidelberg
FZR Rossendorf

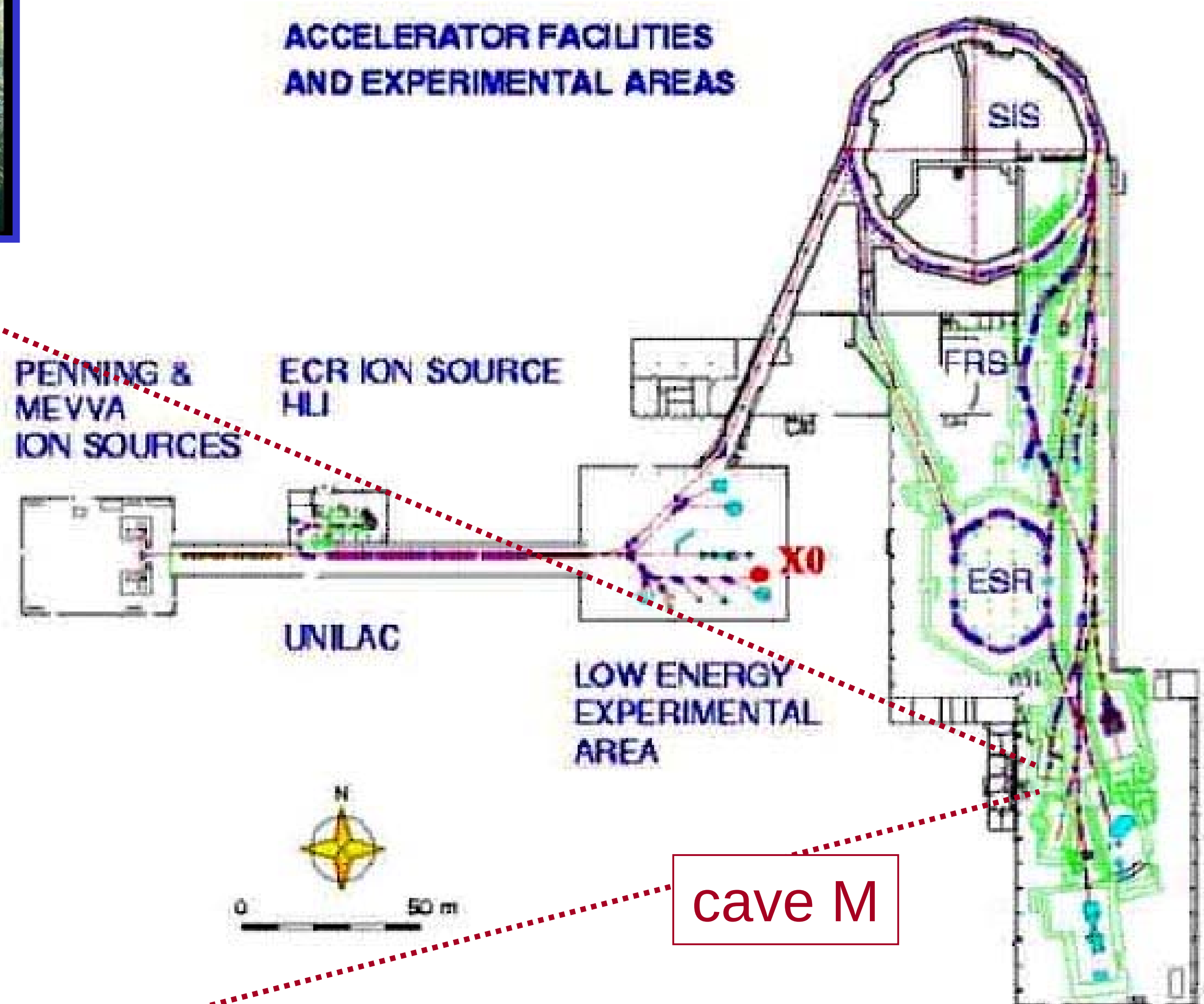
accelerator

PET camera

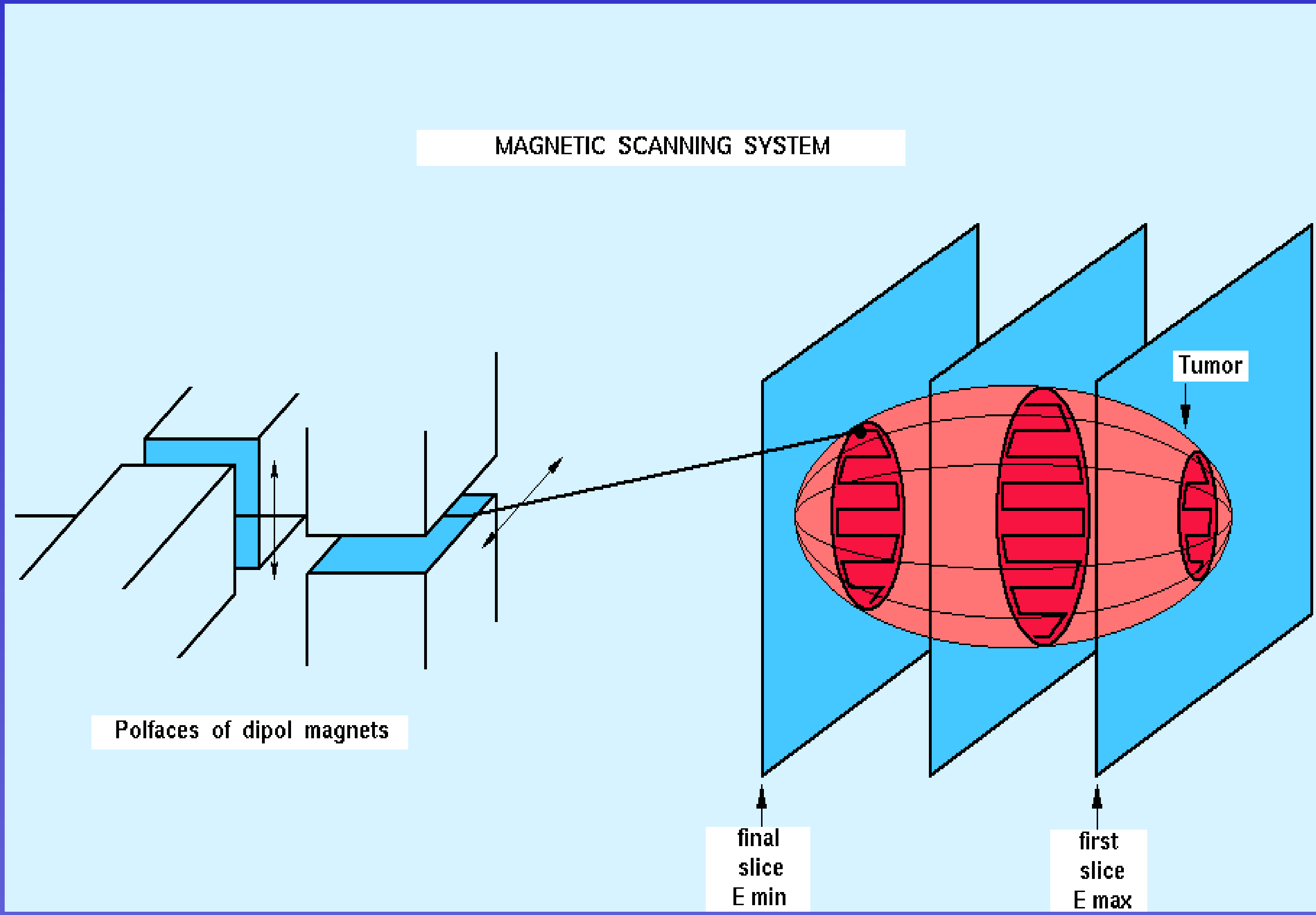
self controlled
scanning system

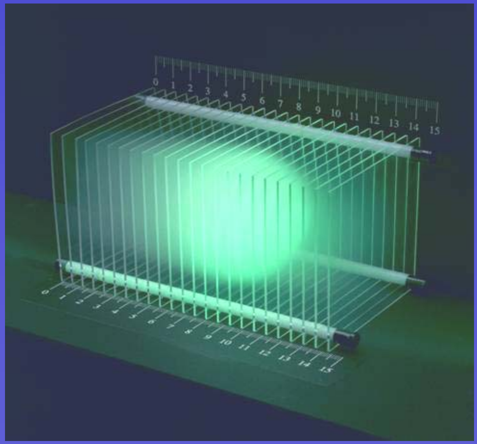
beam analysis

GSI


ACCELERATOR FACILITIES
AND EXPERIMENTAL AREAS
SIS
FRS
ESR
PENNING &
MEVVA
ION SOURCES
ECR ION SOURCE
HLI
UNILAC
X0
LOW ENERGY
EXPERIMENTAL
AREA
N
0
50 m
cave M

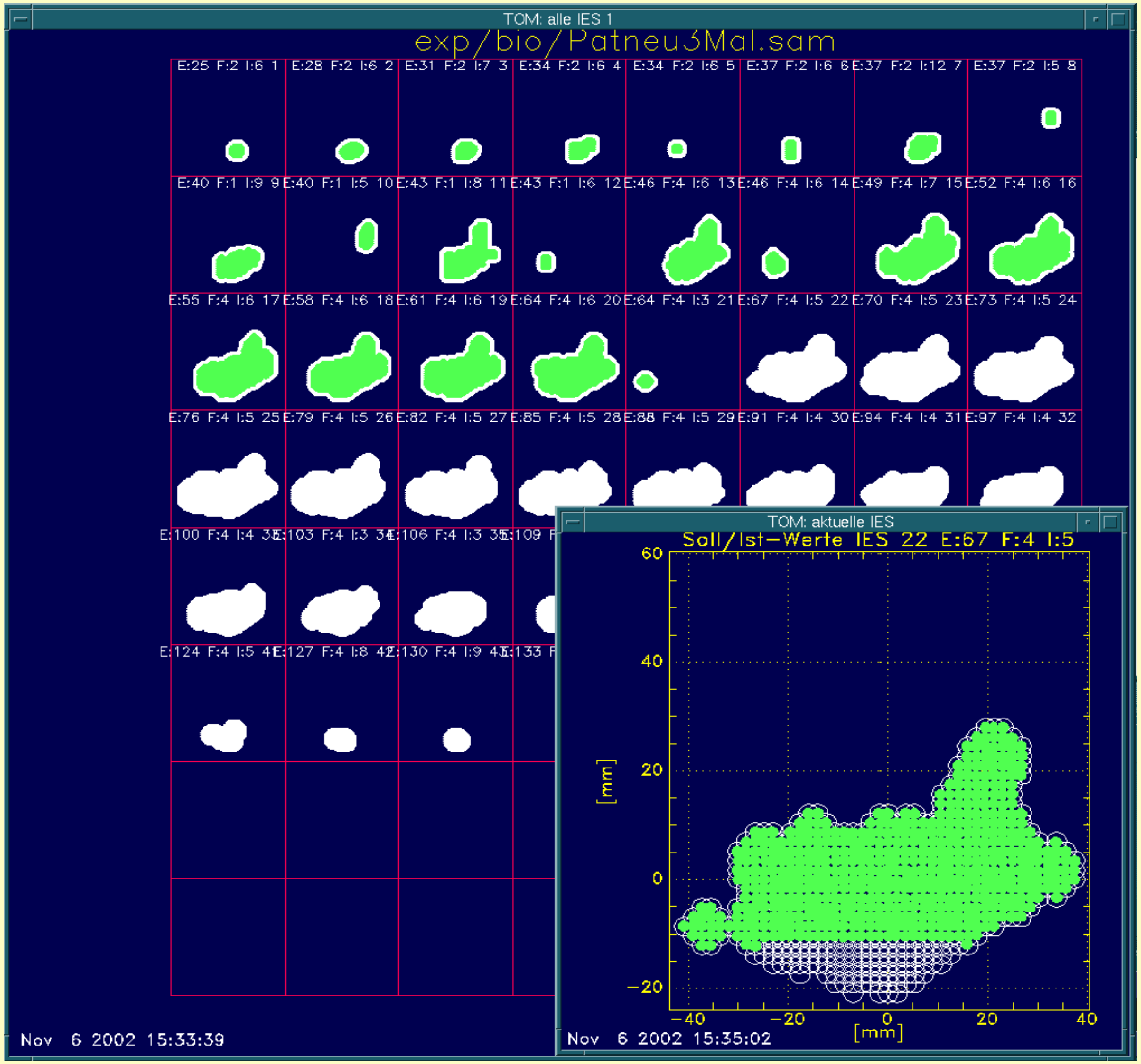
Principle of 3-D raster scanning system

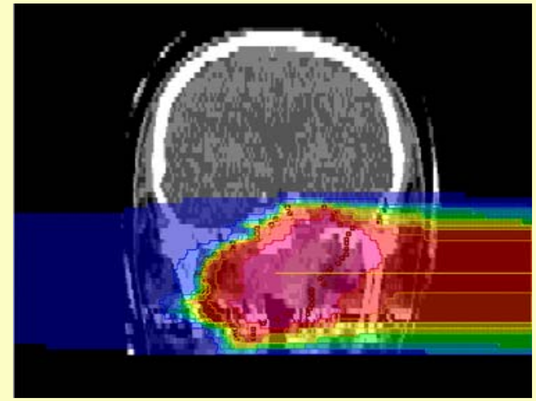


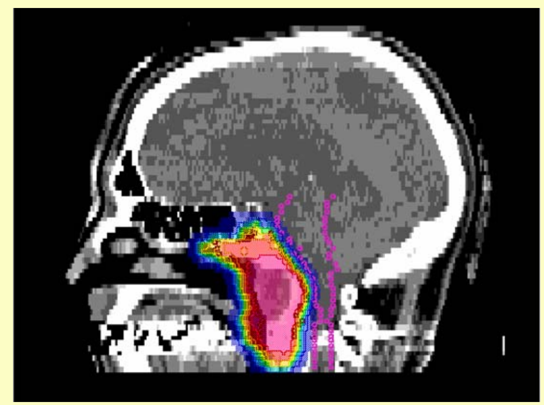


- 2-D raster scanning in x and y by magnetic deflection
- Depth variation by beam energy adjustment
- irradiation in slices (40-60)

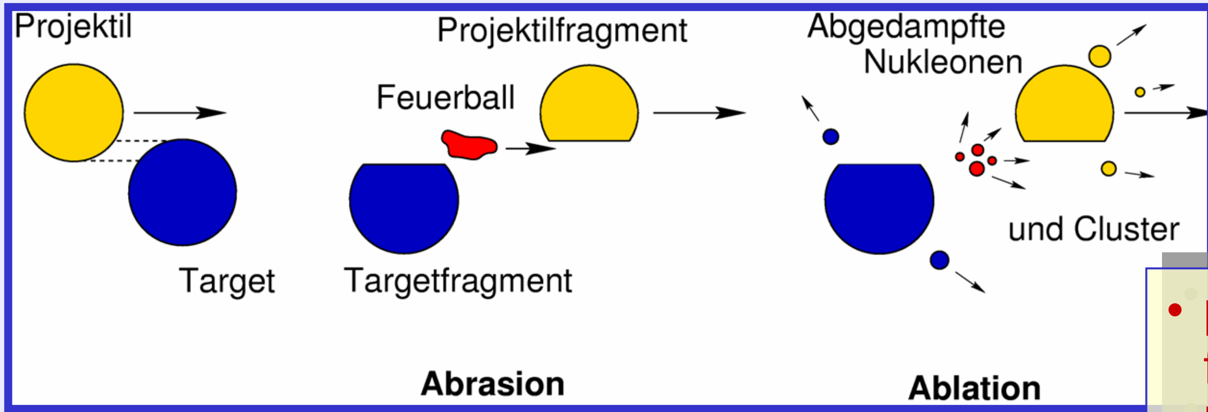
Therapie Online Monitor (TOM)



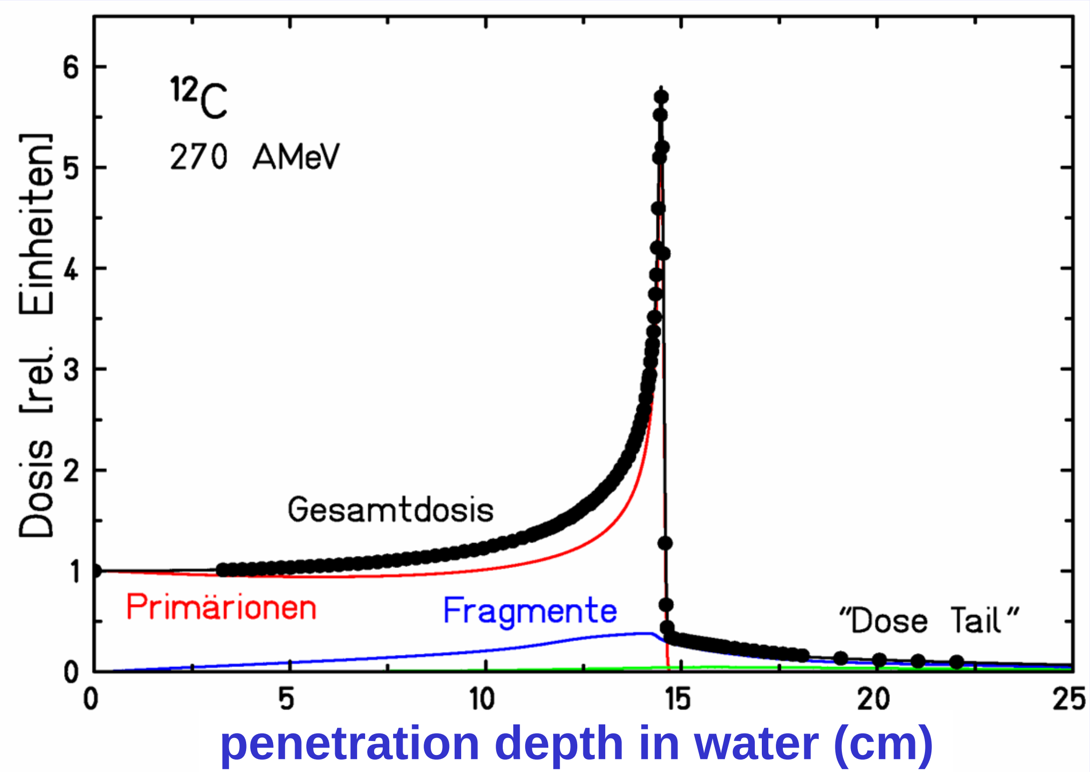


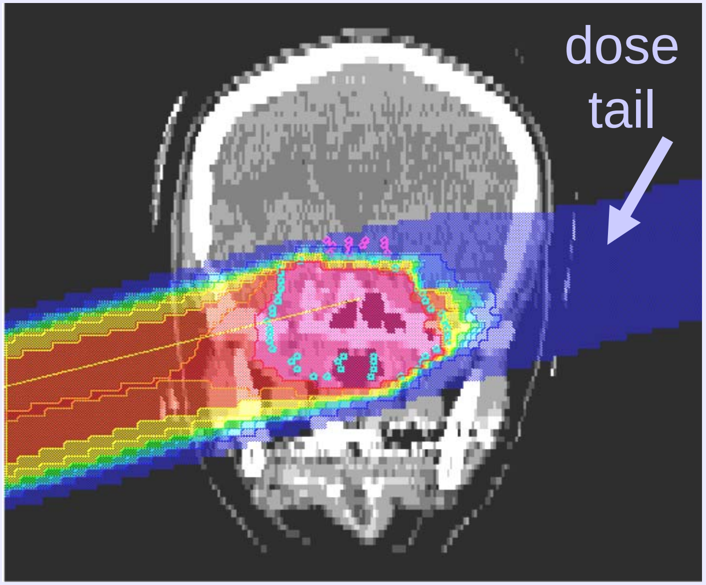


Fragmentation by nuclear collision processes

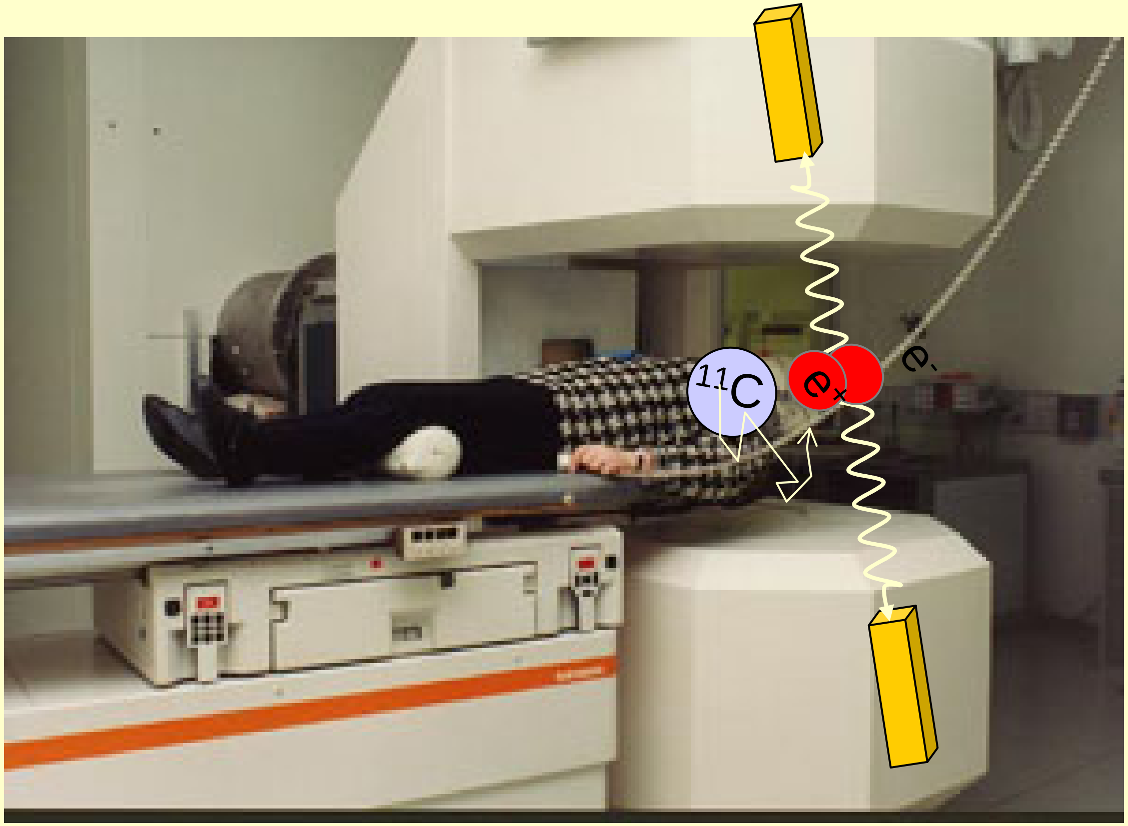


- production of lighter projectile fragments
- lighter fragments → larger ranges
- larger angular straggling
- dose tail behind Bragg maximum





Positron emission tomography (PET)



fragmentation of ^{12}C-Ionen

^{11}C and ^{10}C positron emitters

$T_{1/2}(^{11}C) = 20$ min
$T_{1/2}(^{10}C) = 19$ s

annihilation: $e^+ + e^- \rightarrow 2\gamma$

gamma emission
(180°, 511 keV)

gamma detection = dose control

Tumors eligible for carbon ion radiotherapy so far:

skull base tumors:

- chordoma
- chondrosarcoma
- mal. schwannoma
- atyp. meningeoma
- adenoidcystic ca.

tumors close to the spinal chord:

- sacral chordoma
- chondrosarcoma
- soft tissue sarcoma

tumors not eligible

- rapidly growing tumors
- metastasis forming tumors
- by law: children under 18

Status

- ~ 220 patients
- 70 % exclusively with ^{12}C-ions
  30 % with photons + ^{12}C-ions
- recognition of ^{12}C-ion therapy as standard therapy
- > 400 days of clinical operation

Typical treatment at GSI

Positioning of patient

- control via x-ray

Irradiation

- 20 fractions per patient on 20 consecutive days
- 2 -12 min per fraction
- tumor volume: 50 -3200 cm^3

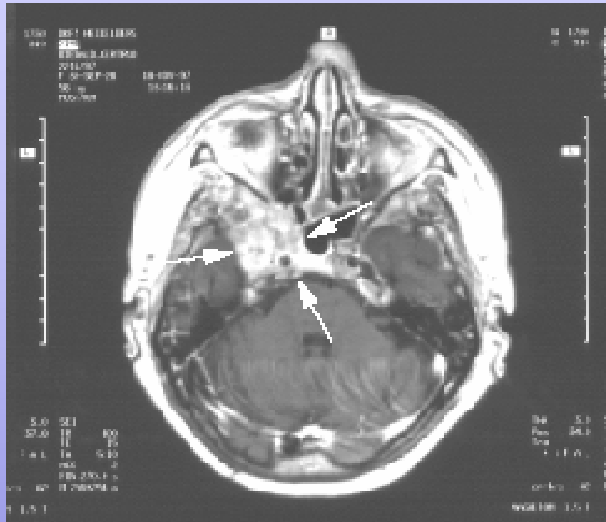
Control of irradiated volume via

- position- and energy monitors
- PET „in“ patient

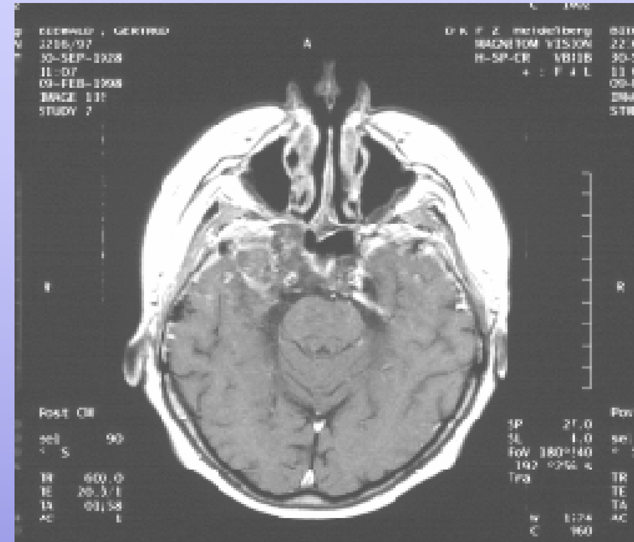
petroclivial chondrosarcoma:
(brain tumor)

after incomplete surgery

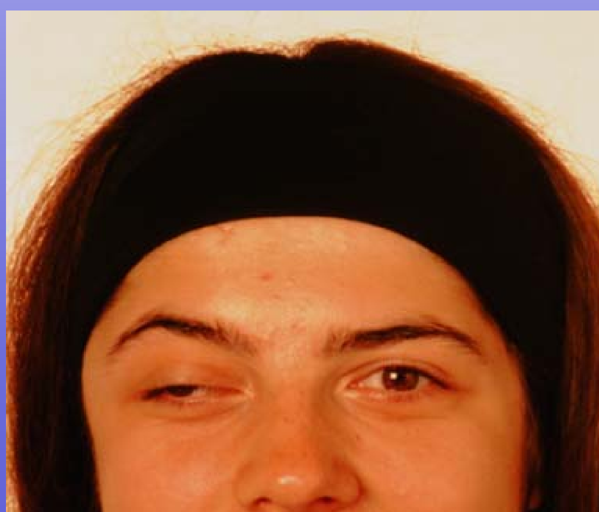
post-operative irradiation with ^{12}C-Ionen



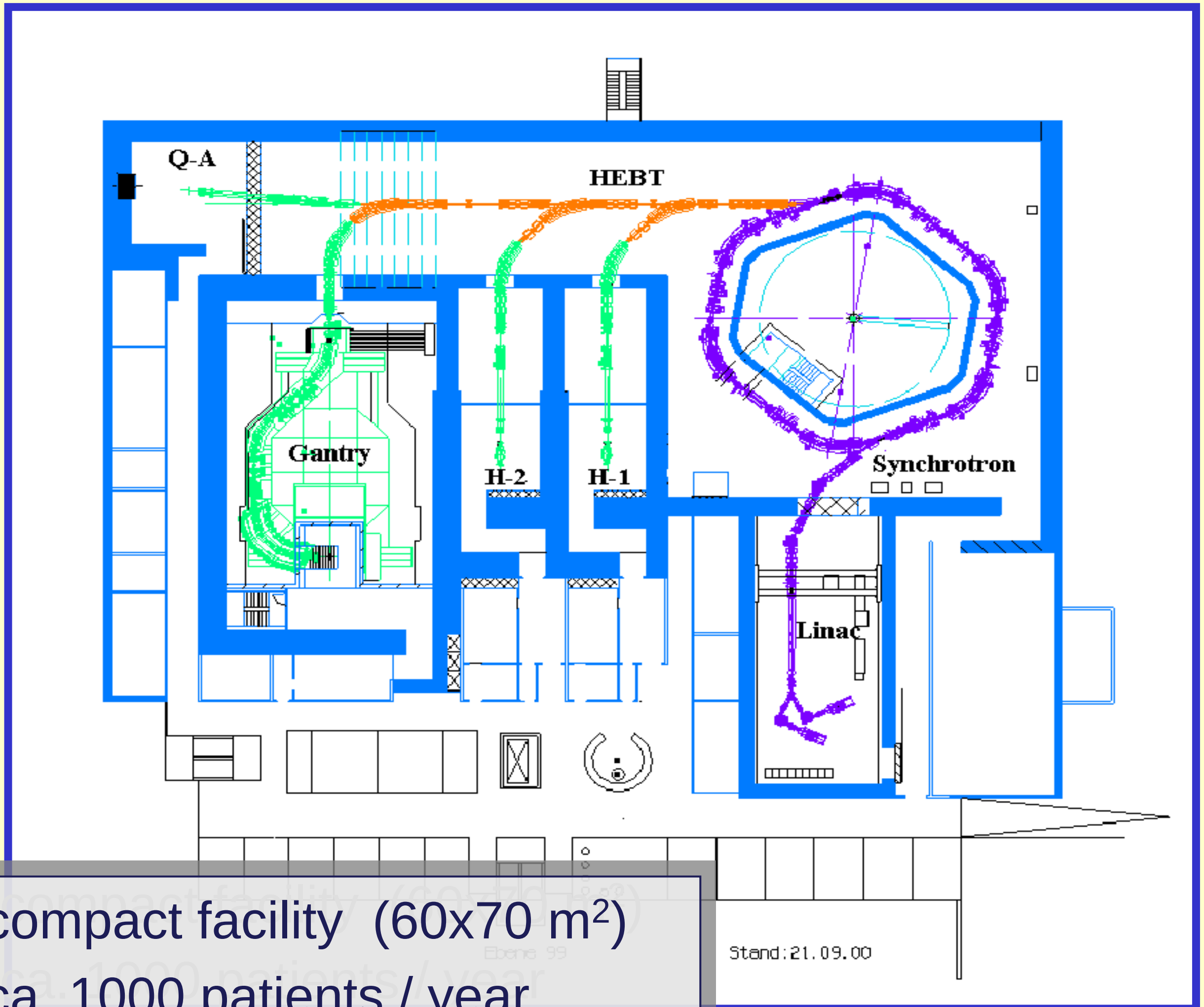
before treatment



6 weeks after carbon therapy



Dedicated therapy center in Heidelberg



- Gantry
- irradiation chair
- improved dosimetry
- moving tumors
- etc

- compact facility (60x70 m^2)
- ca. 1000 patients / year
- project start: 2002
- operation: 2007