Trento Institute for
Fundamental Physics
and Applications

Heavy ions in therapy and space

Marco Durante, TIFPA

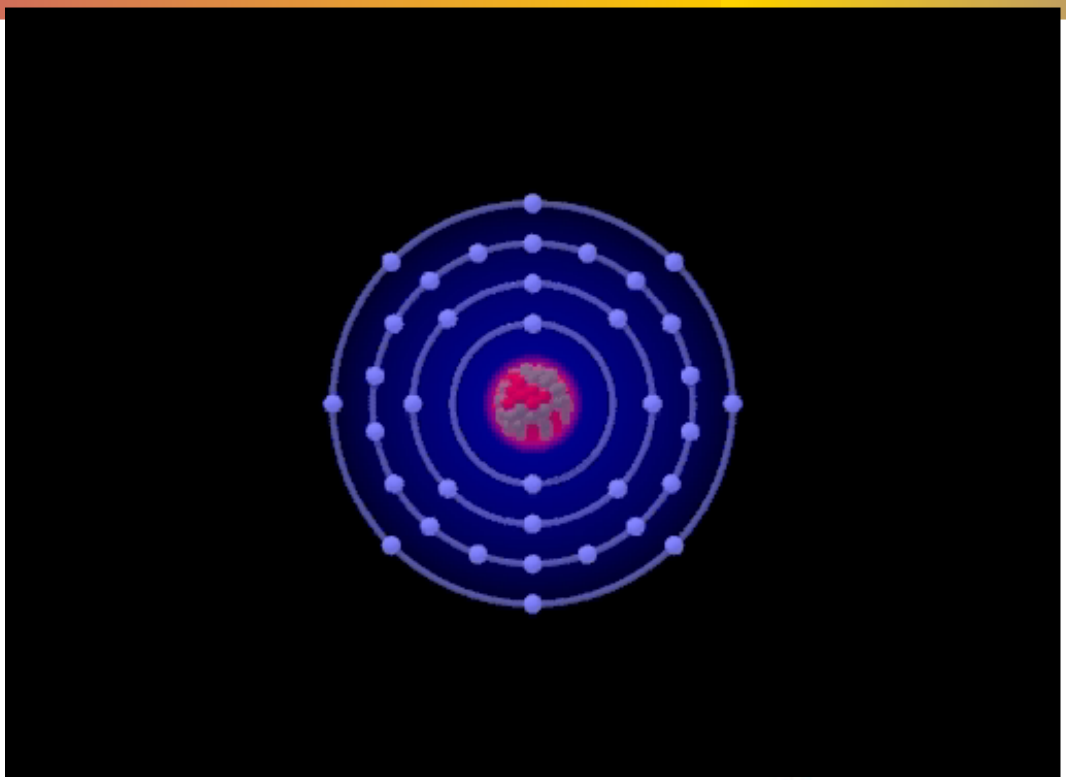
www.tifpa.infn.it

9.6.2016

UNIVERSITA' DEGLI STUDI DI PAVIA

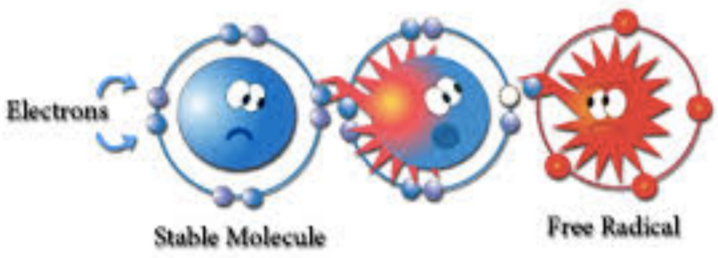
DOTTORATO DI RICERCA IN FISICA

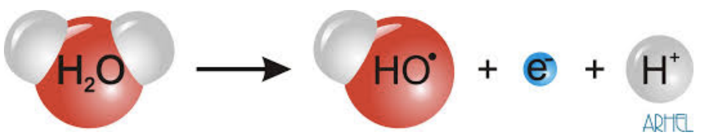
How does radiation injure people?



Direct ionization of biological molecules

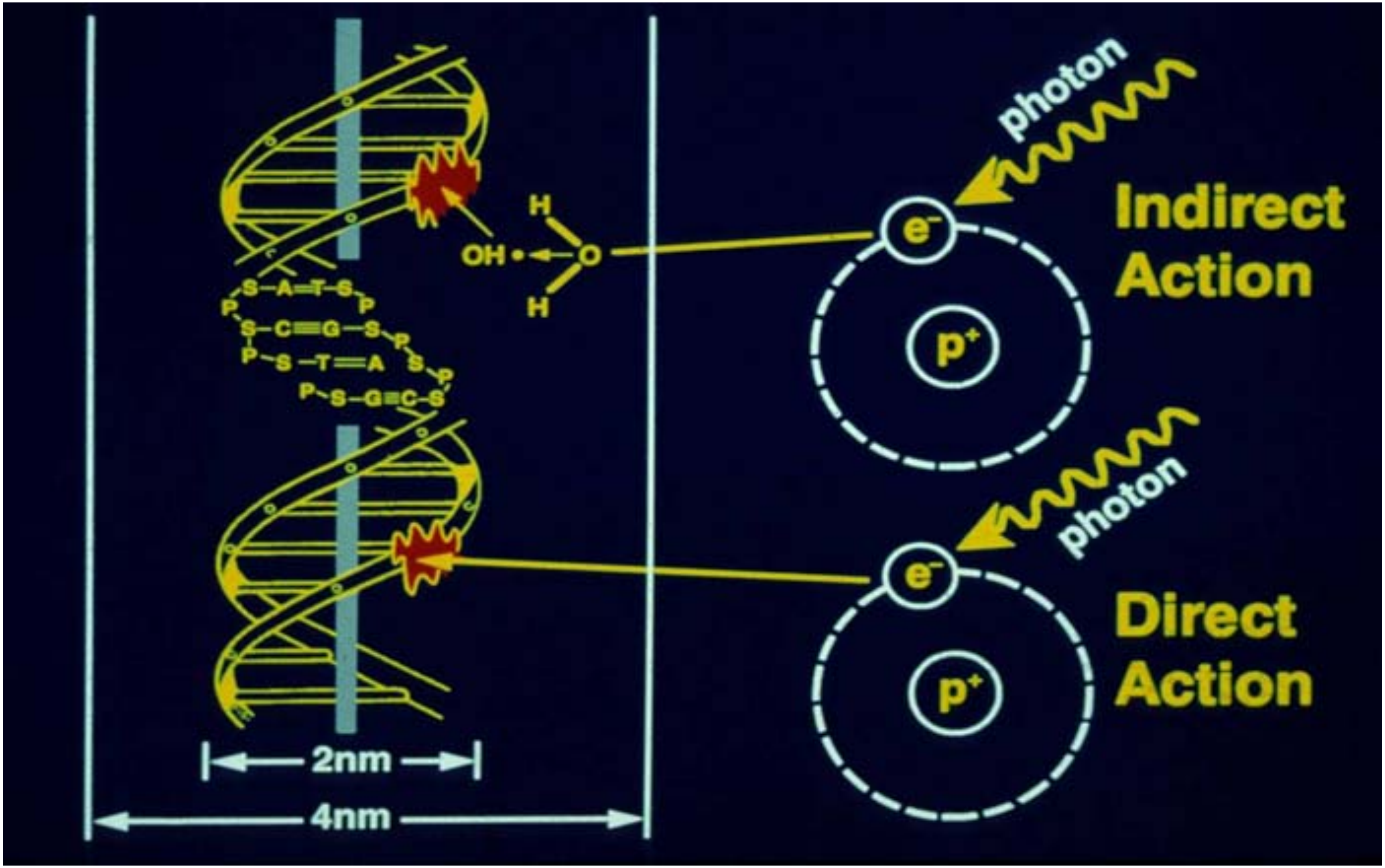
Indirect effect through formation of free radicals in water



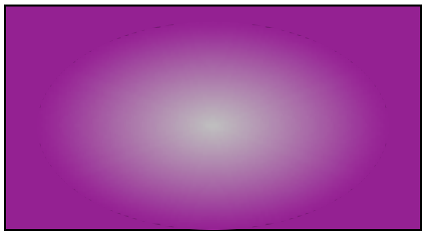


The most unkindest cut of all

(W. Shakespeare, Julius Caesar)

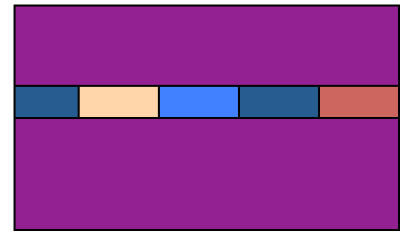


How does this damage from ionizing radiation effect our bodies?

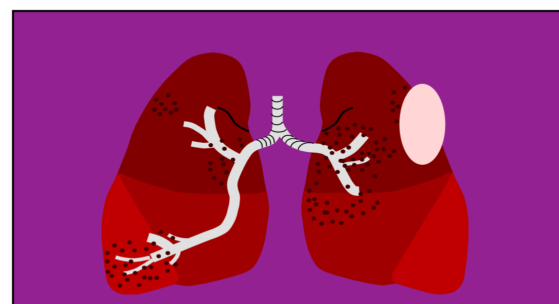


Sufficient Cell Killing

Radiation Sickness



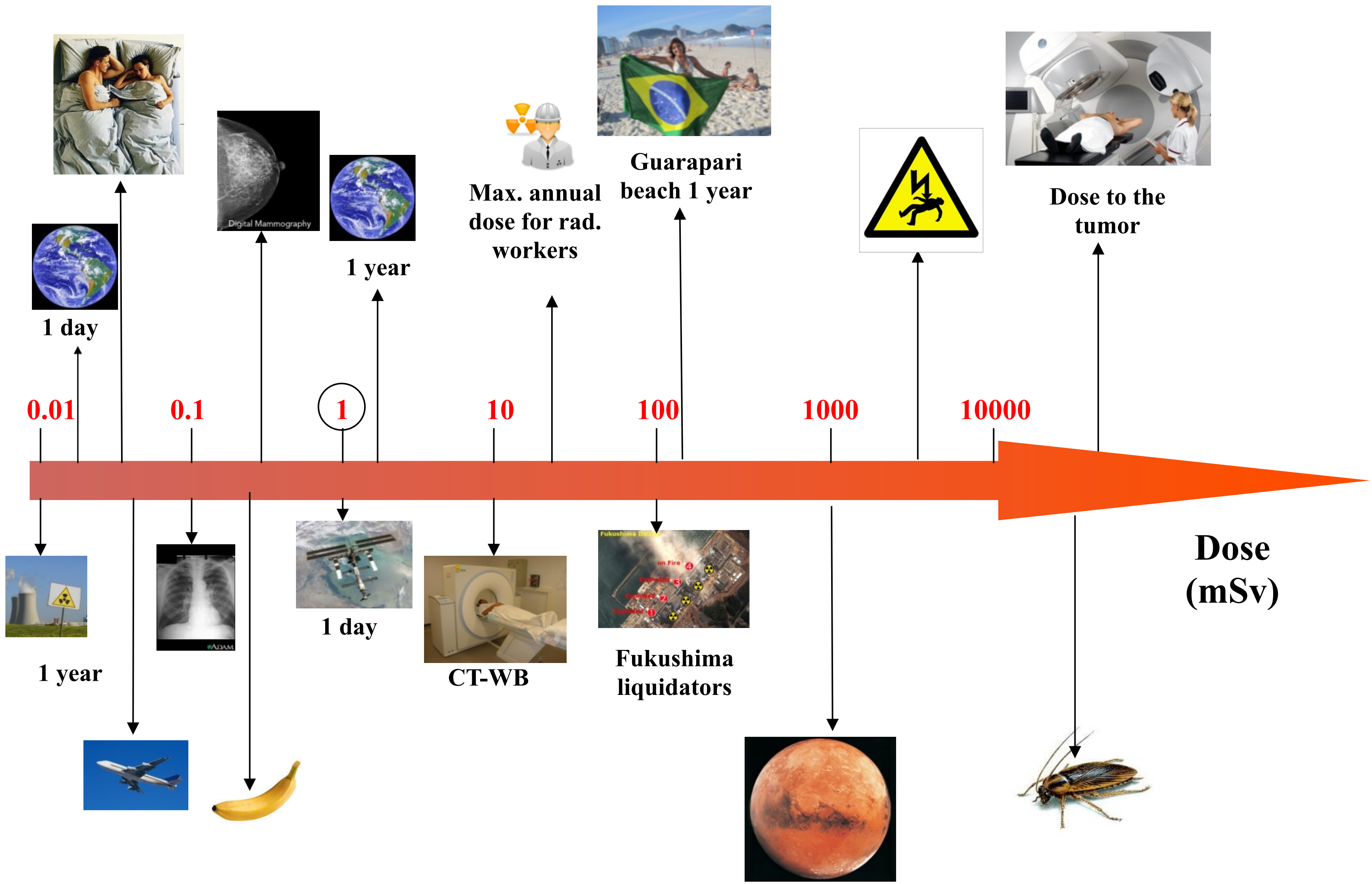
Sufficient Genetic Alterations



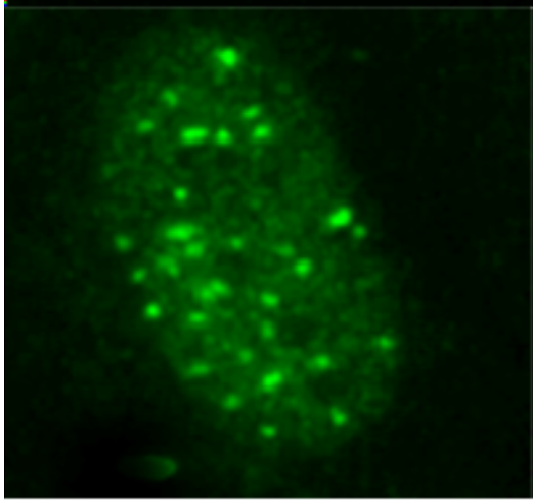
Cancer

Radiation effects depends on the DOSE

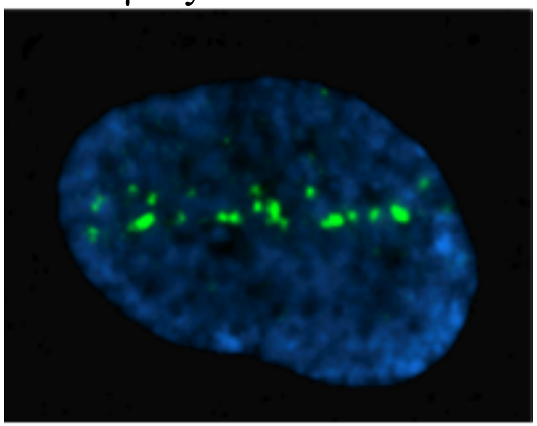
Dose is an energy per unit mass and is measured in Sievert = Joule/kg



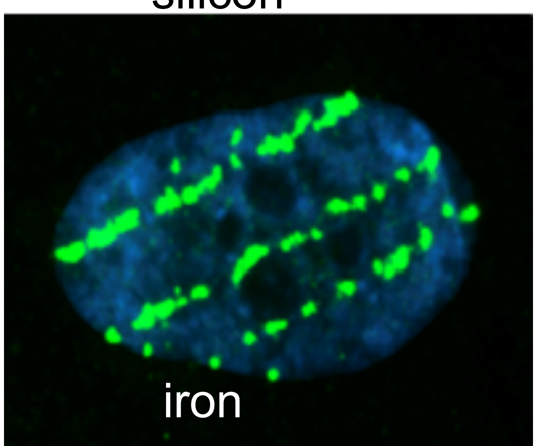
Charged particles

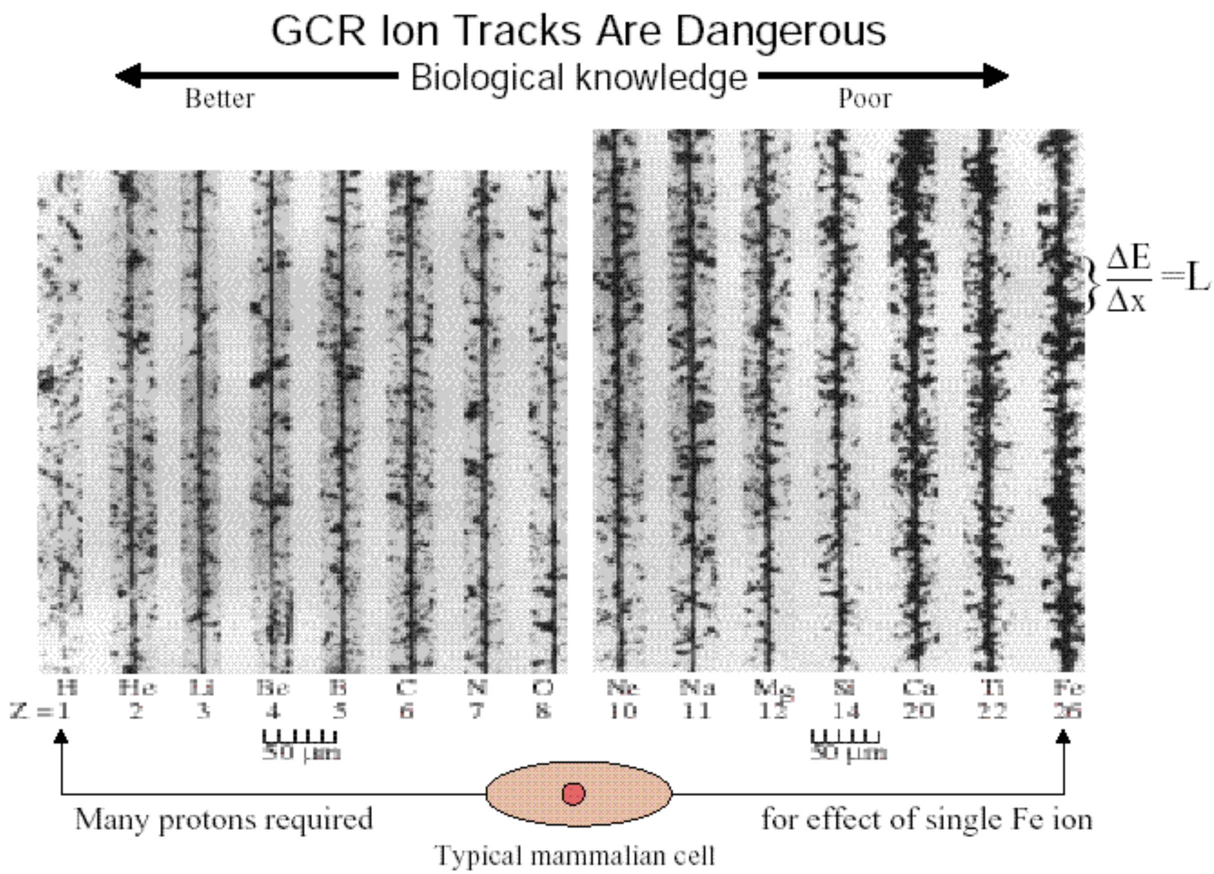


γ-rays



silicon

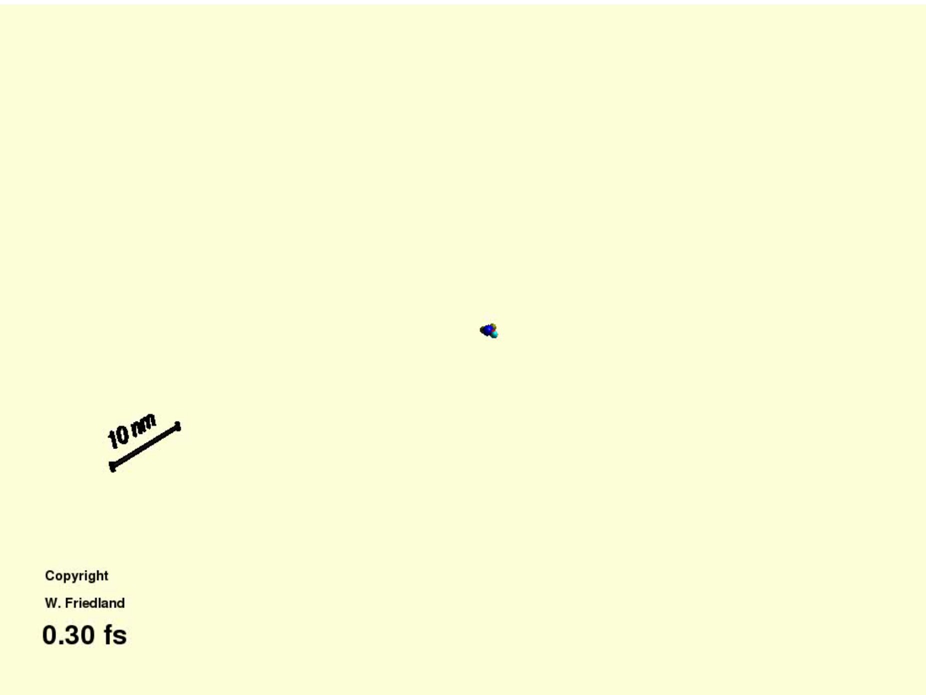




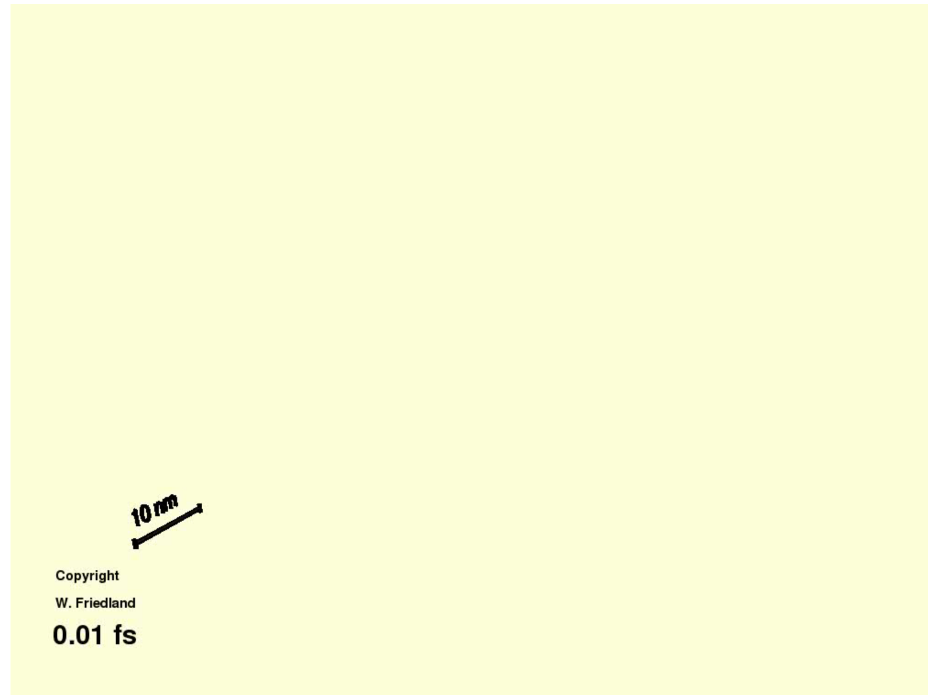
Cucinotta and Durante, *Lancet Oncol.* 2006

Light vs. heavy ions at the same linear energy transfer (LET=140 keV/μm)

α-particles, 2 MeV



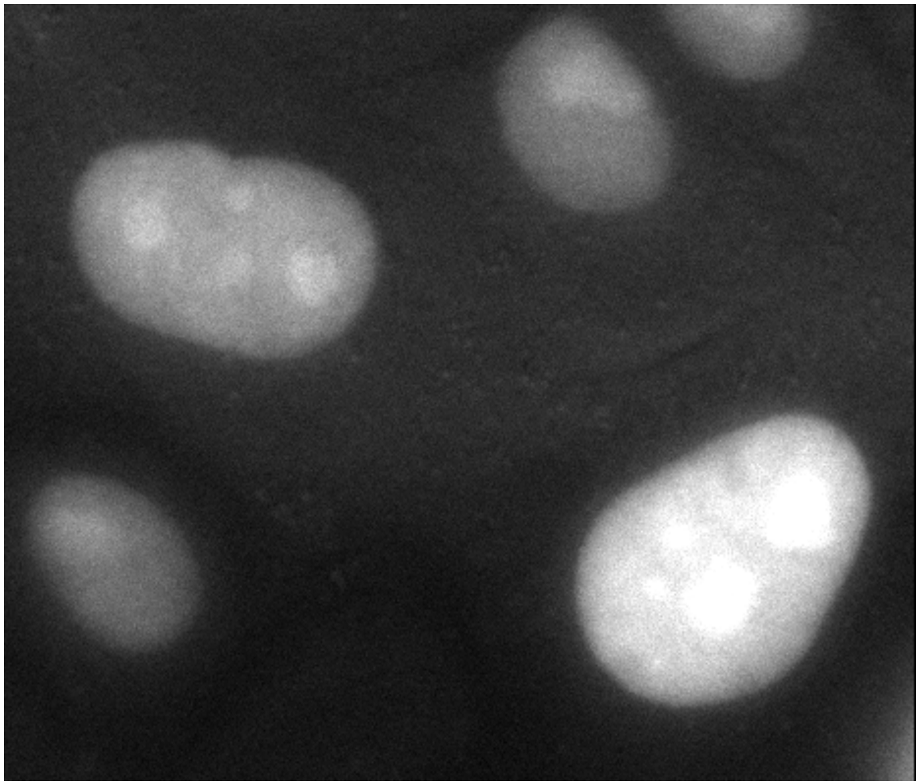
Fe-ions, 1 GeV/n

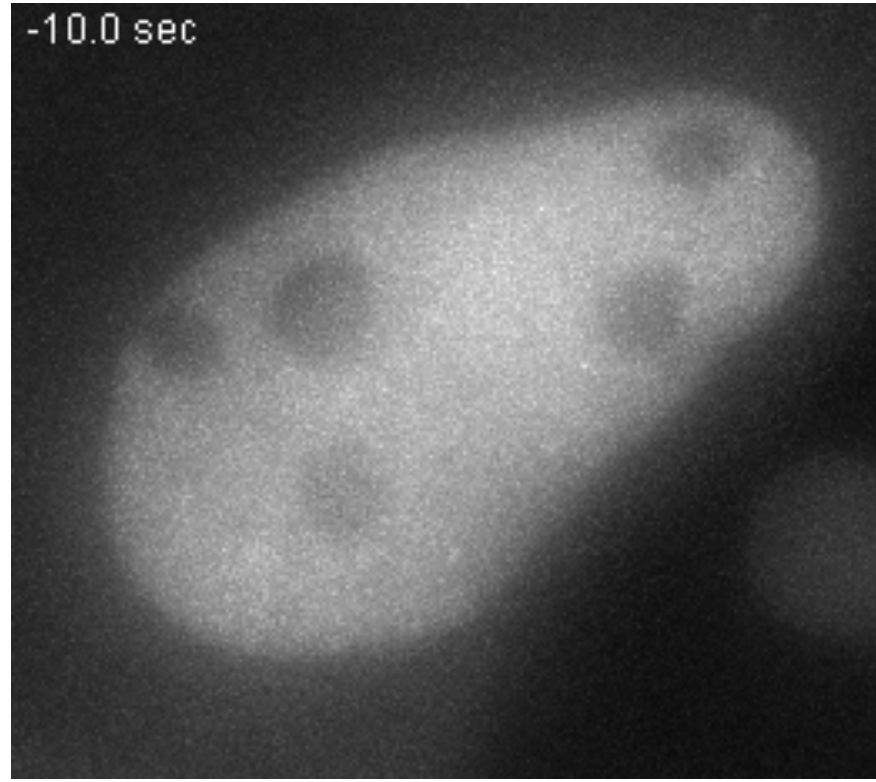


courtesy of Werner Friedland

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Beamline live cell imaging





Uranium 11 MeV/n, 90°

Human cells

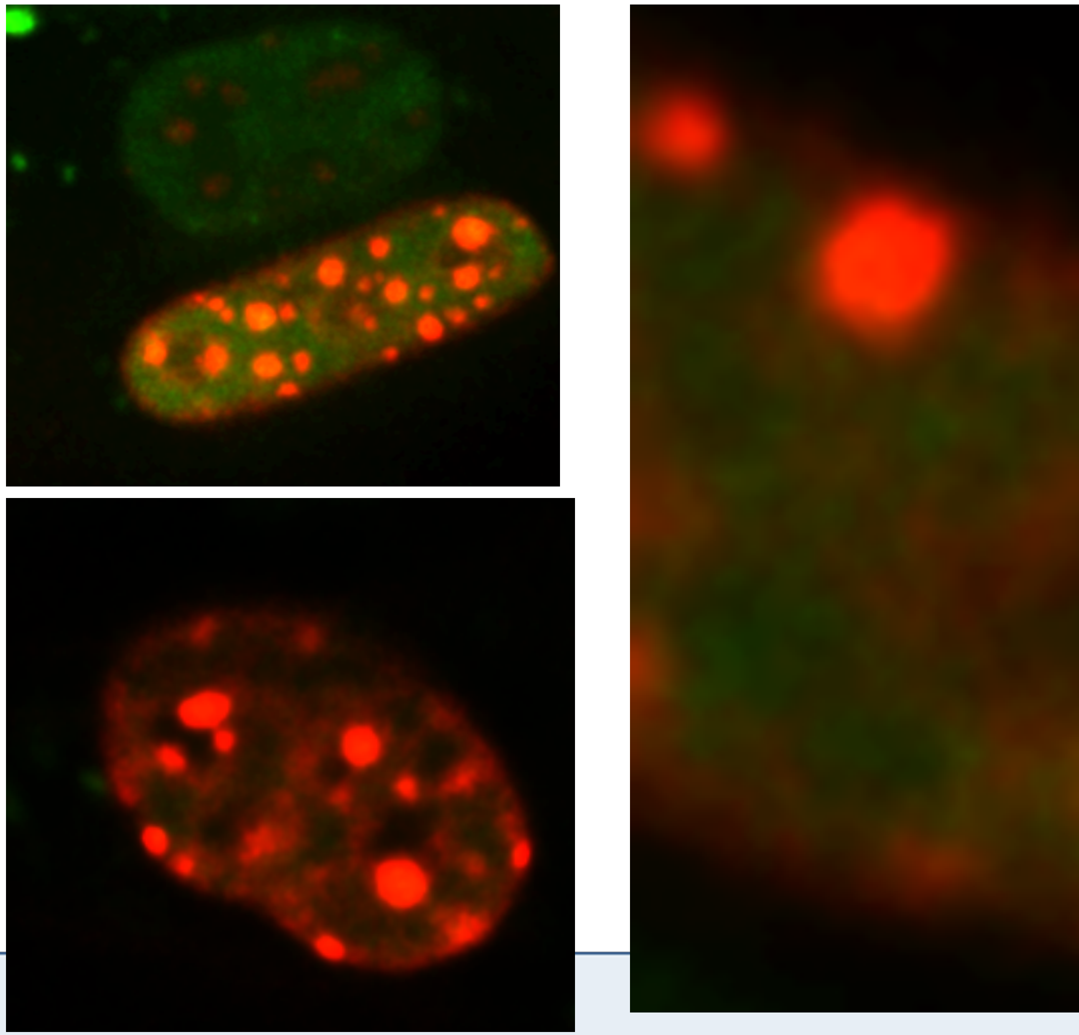
GFP- APTX (Aprataxin)

Iron 1 GeV/n, 0°

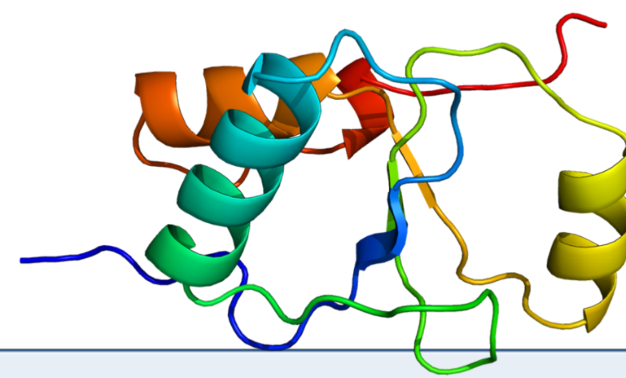
Human cells

GFP-Nijmegen breakage syndrome 1 (NBS1)

Jakob *et al. Proc. Natl. Acad. Sci. USA* (2009)

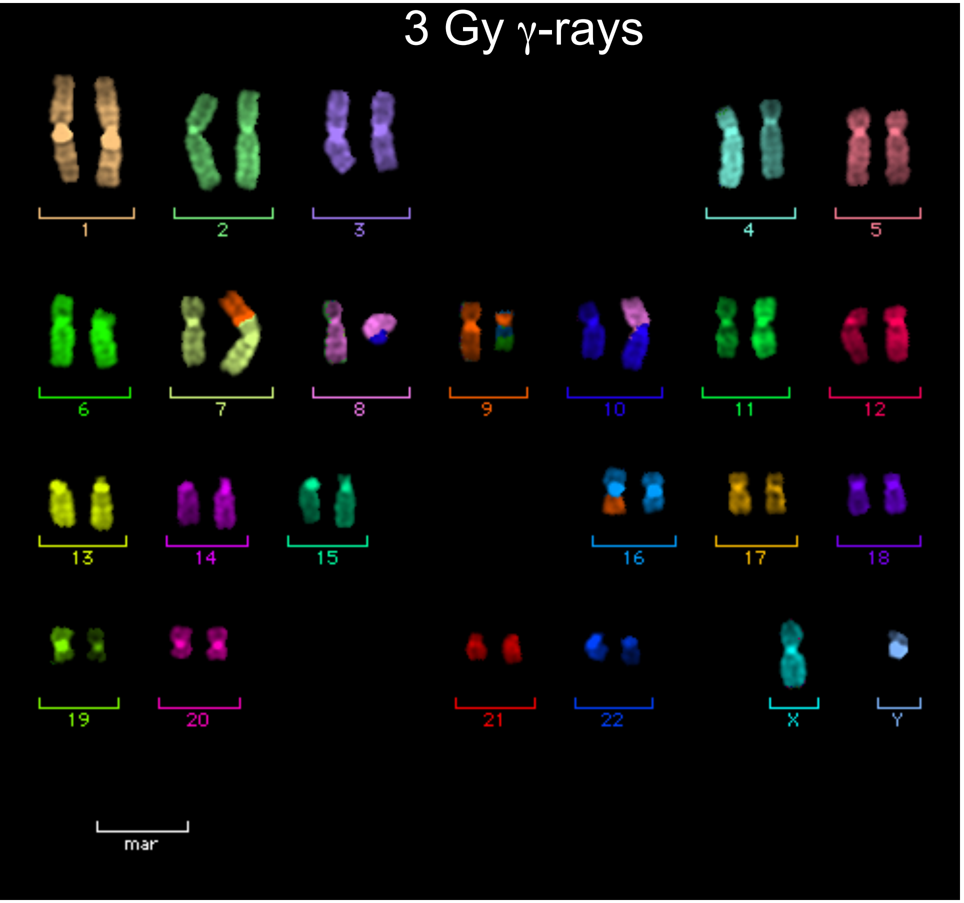


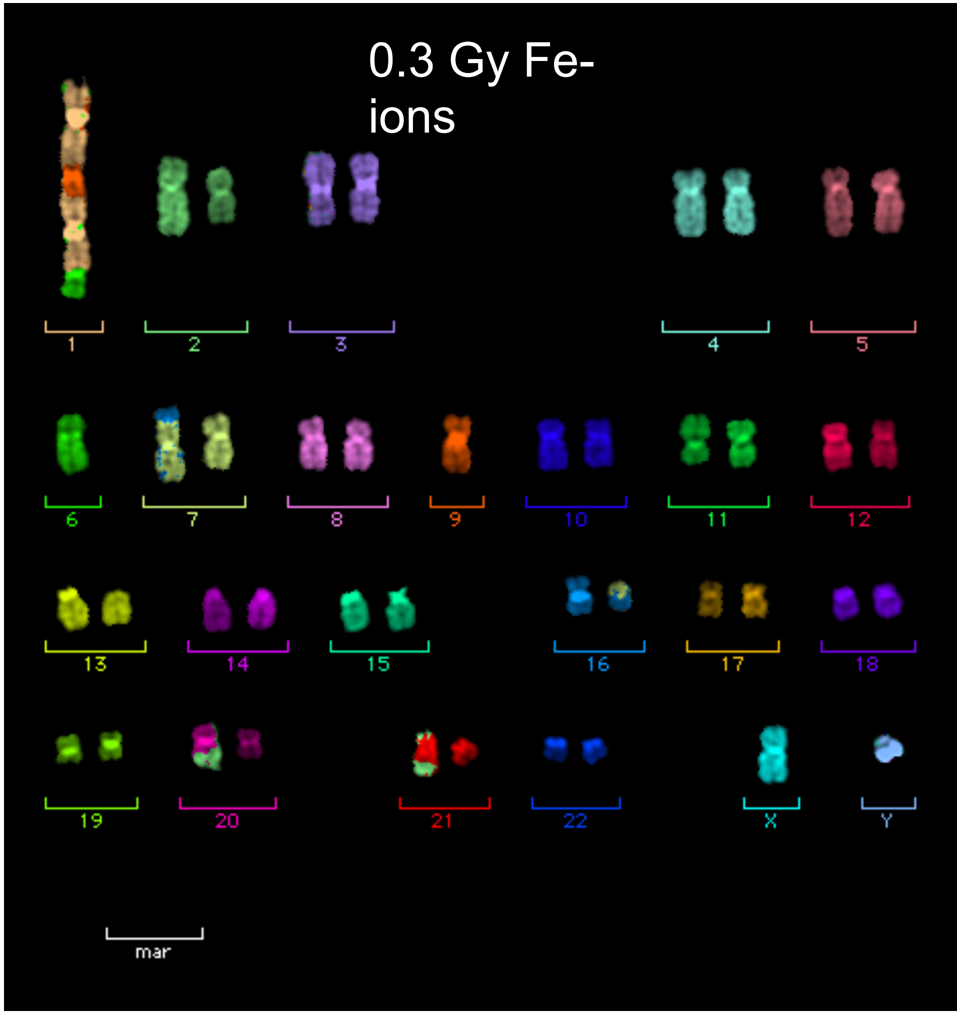
X-ray repair complementing defective in Chinese hamster cells 1 (SSB and b-excision repair pathways)



Jakob et al. Nucl. Acids Res. 2011

Chromosomal aberrations induced by heavy ions

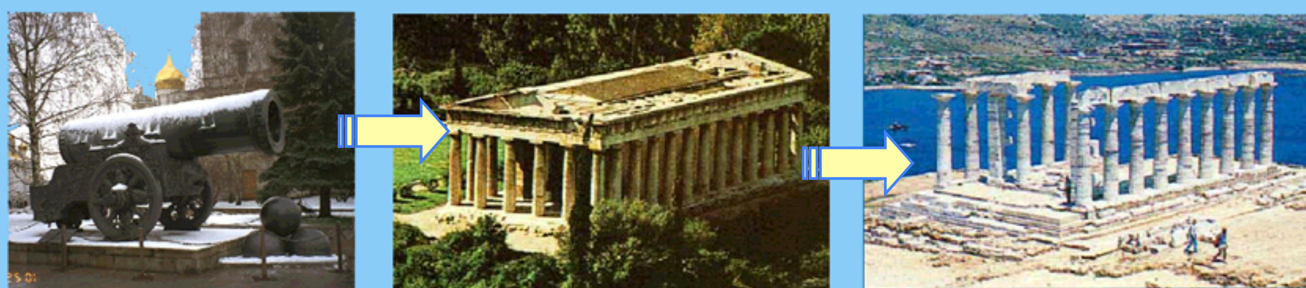




Durante *et al.*, *Radiation Research* 2002

An Analogy for Structured Energy Deposition and its Consequences

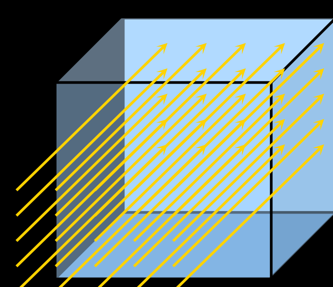
Low LET radiation produces isotropic damage to organized targets.



High LET radiation produces correlated damage to organized targets.

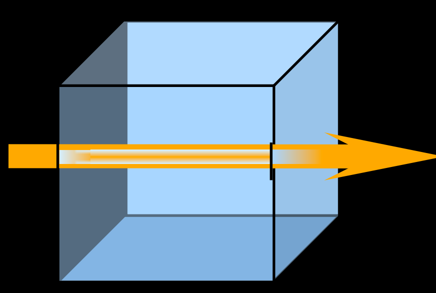
LET: Linear Energy Transfer

1 Dose Unit



Low LET radiation deposits energy in a uniform pattern

1 Dose Unit

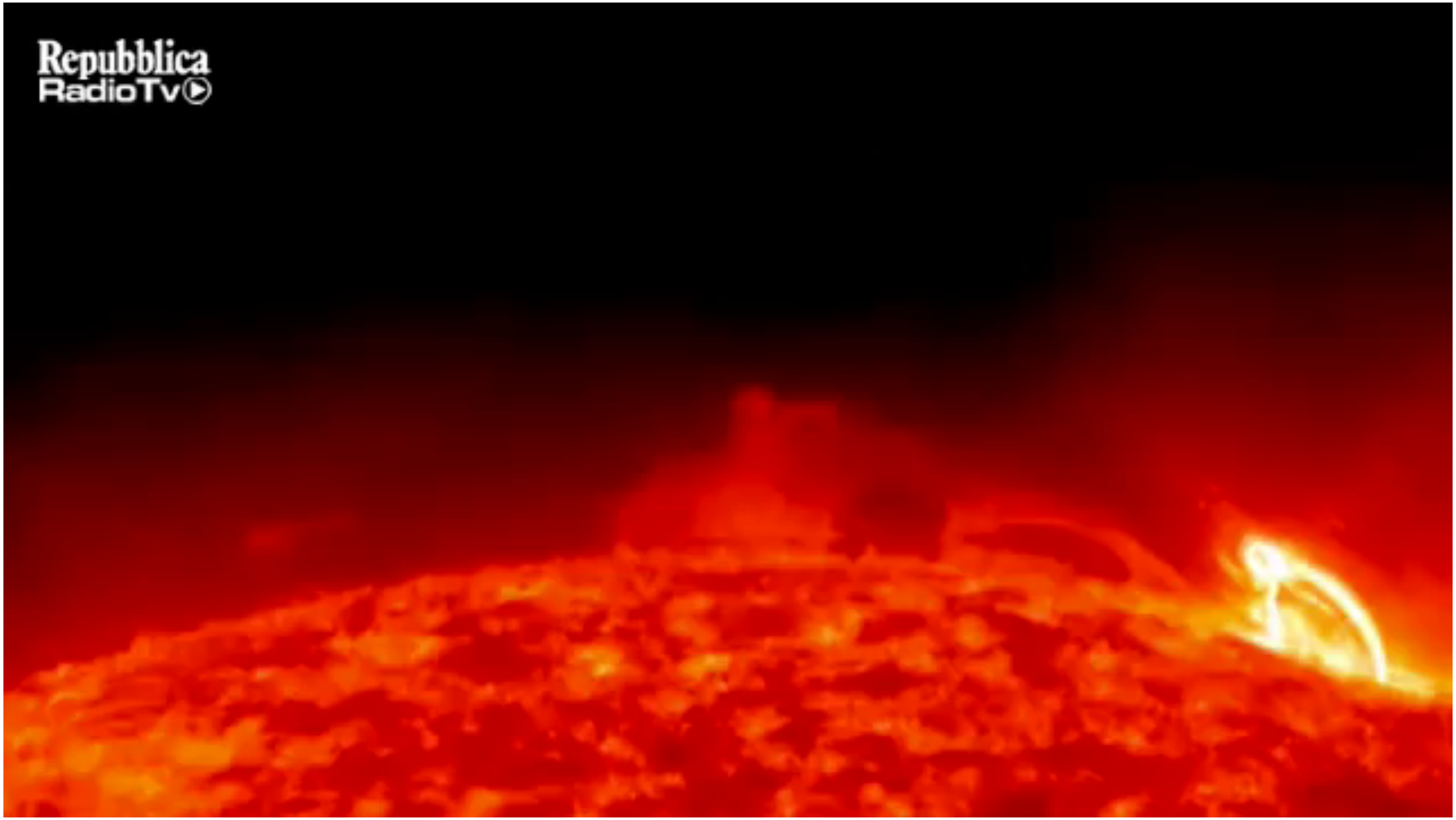


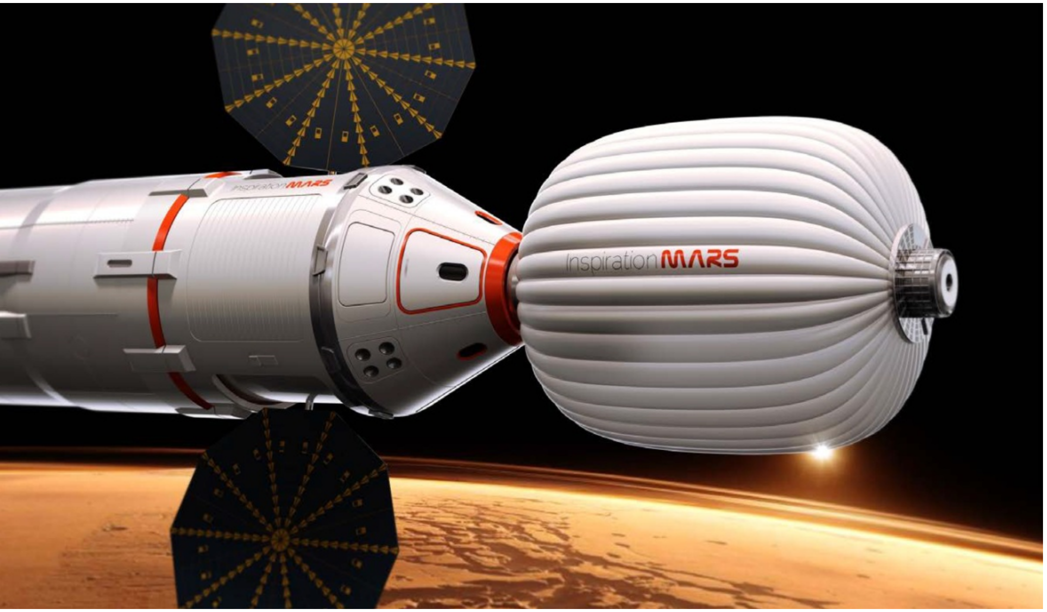
High LET radiation deposits energy in a non-uniform pattern

Why are we interested in energetic heavy ions?

Heavy ion radiation is not present naturally on Earth

Valentine’s Solar flare 14.2.2011





April, 3, 2013

The New York Times

Space & Cosmos

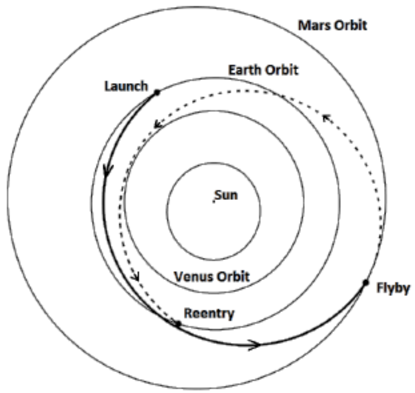
WORLD | U.S. | N.Y. / REGION | BUSINESS | TECHNOLOGY | SCIENCE | HEALTH | SPORTS | OPINION

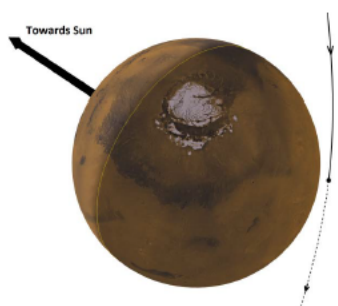
ENVIRONMENT SPACE & COSMOS

May, 30, 2013

Data Point to Radiation Risk for Travelers to Mars

- A 501-day "free-return" Mars flyby passing within a hundred miles of the surface
  - Only small correction maneuvers are needed during transit
- Simple mission architecture lowers risk
  - No entry into Mars atmosphere
- An exceptionally quick free return occurs twice every 15 years
  - 1.4 years duration vs. 2 to 3.5 years typical
  - Launch Jan 5, 2018, (or 2031)
  - Mars on 20 Aug 2018 (227 days)
  - Earth on 20 May 2019 (274 days)
  - At Mars, Earth is 38,000,000 miles away
- Video
  - http://www.youtube.com/watch?v=IBGIYNd2tmA





Tito, MacCallum, Carrico, Loucks

FISO 3 April, 2013

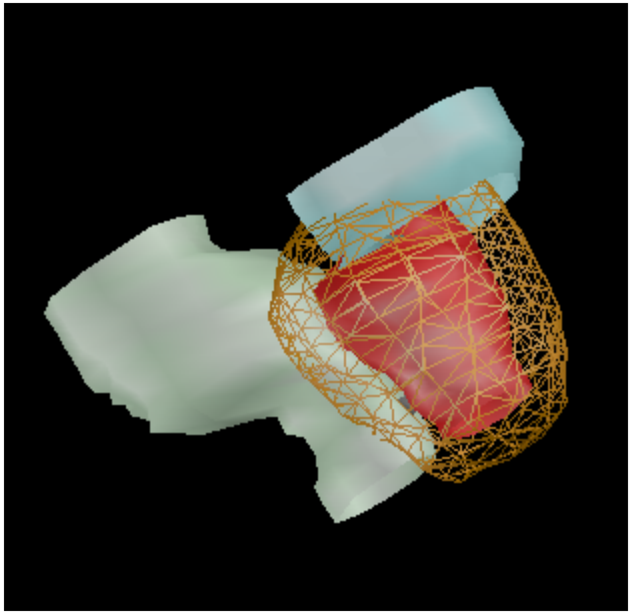
Dose=1.8 mSv/ dayx501x2=1.8 Sv

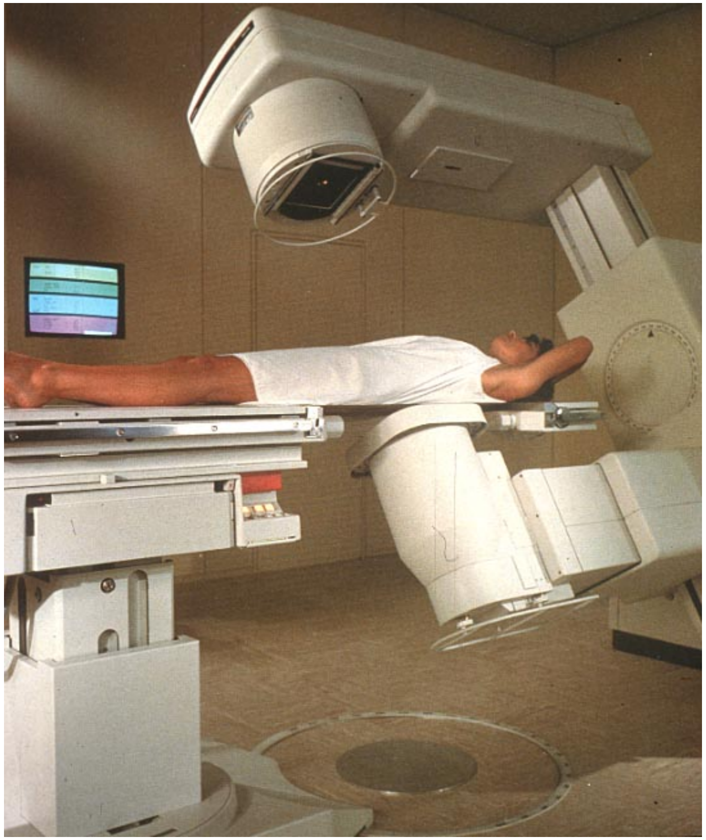
Health in Deep Space

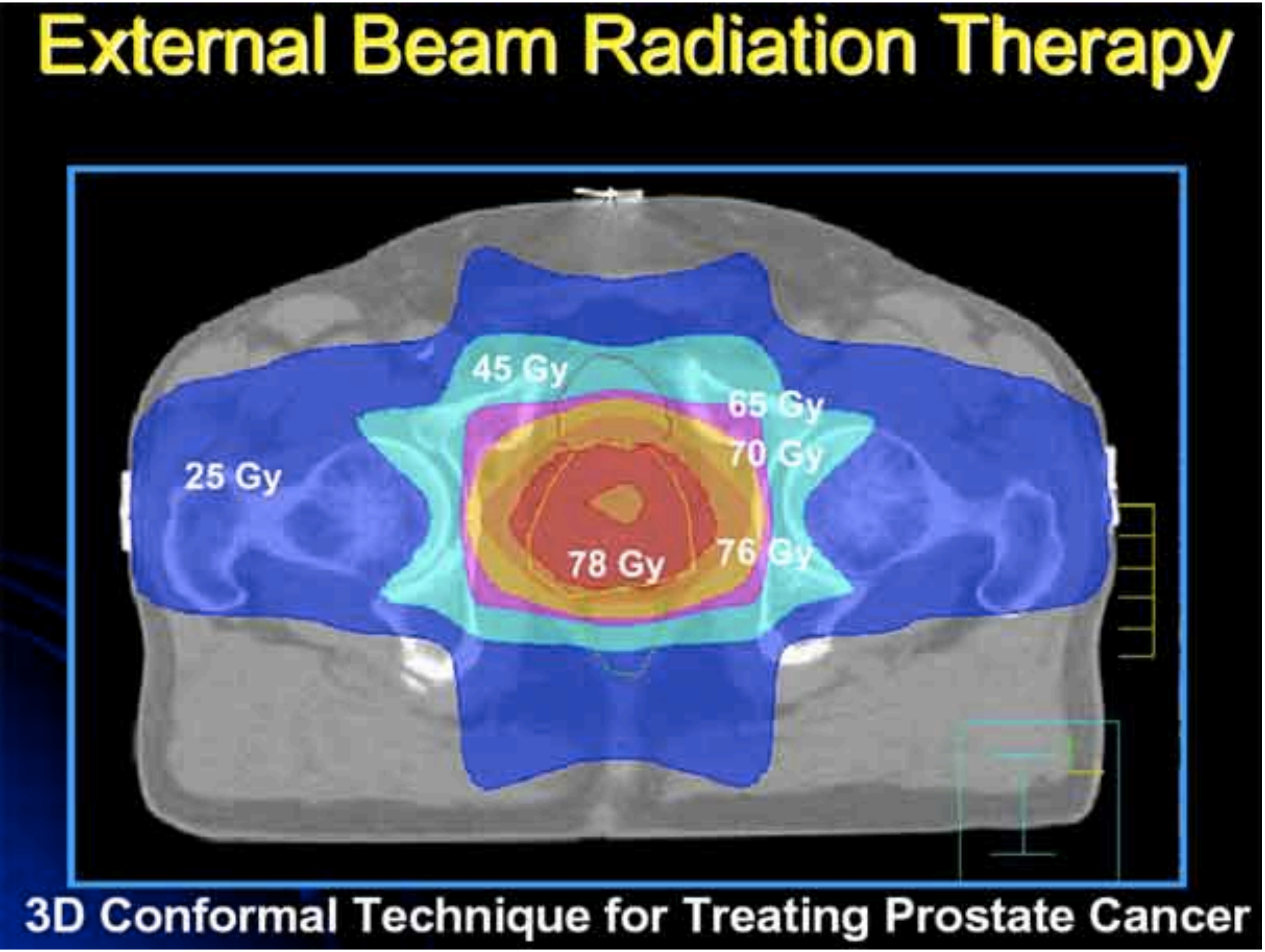
1. Protection from space radiation (particularly very high energy heavy ions)
2. Psychosocial and behavioural problems
3. Physiological changes caused by microgravity

Modified by Mike Lockwood

The good side of radiation: radiotherapy







Treatment planning

Generally, the total dose to the tumor is about 60 Gy, given in daily fractions of 2 Gy to spare the normal tissue

X-rays produced by LINACS (6-15 MV) are normally used

Side-effects of Radiotherapy

- Acute (<1 month)
- Depend on area(s) being treated
- Often fatigue can occur
- mucositis/esophagitis, nausea, diarrhea and redness of skin

Late (>1 month)

Pneumonitis/fibrosis of lungs

Hypothyroidism

Xerostomia

Enteritis

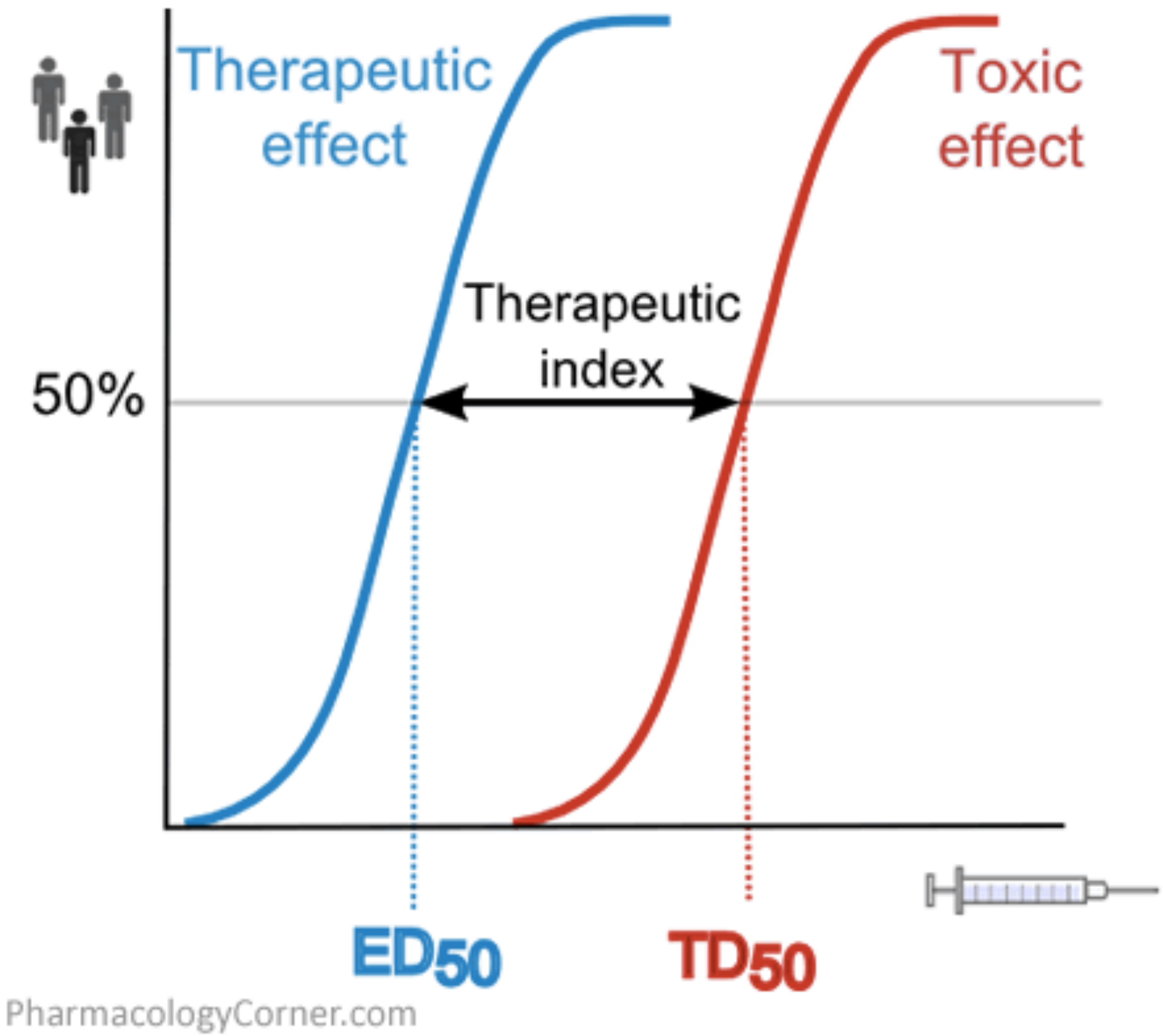
Infertility/menopause

Long-term (10-20 years)

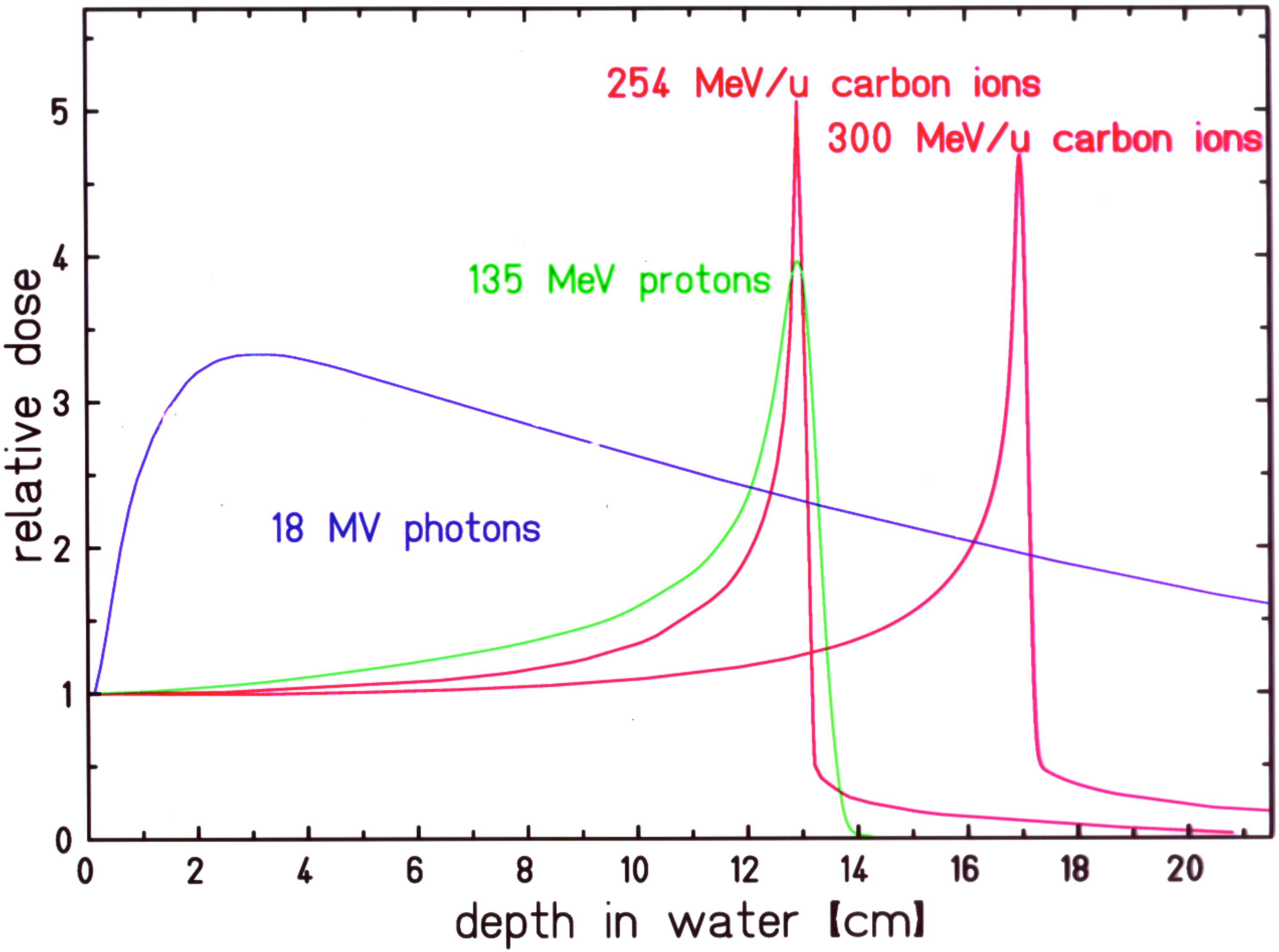
Increased risk of secondary cancers

Increased heart disease if chest region treated

Therapeutic window



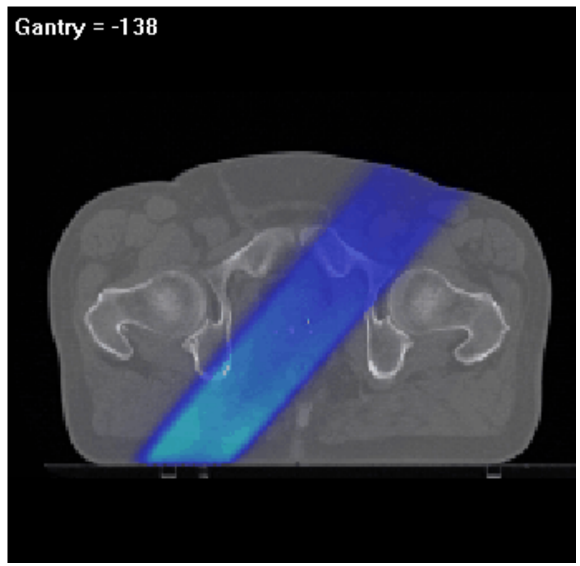
Depth dose distribution of various radiation modalities



X-ray dose decrease with depth
We have to cross-fire on the tumor from many angles

Single field

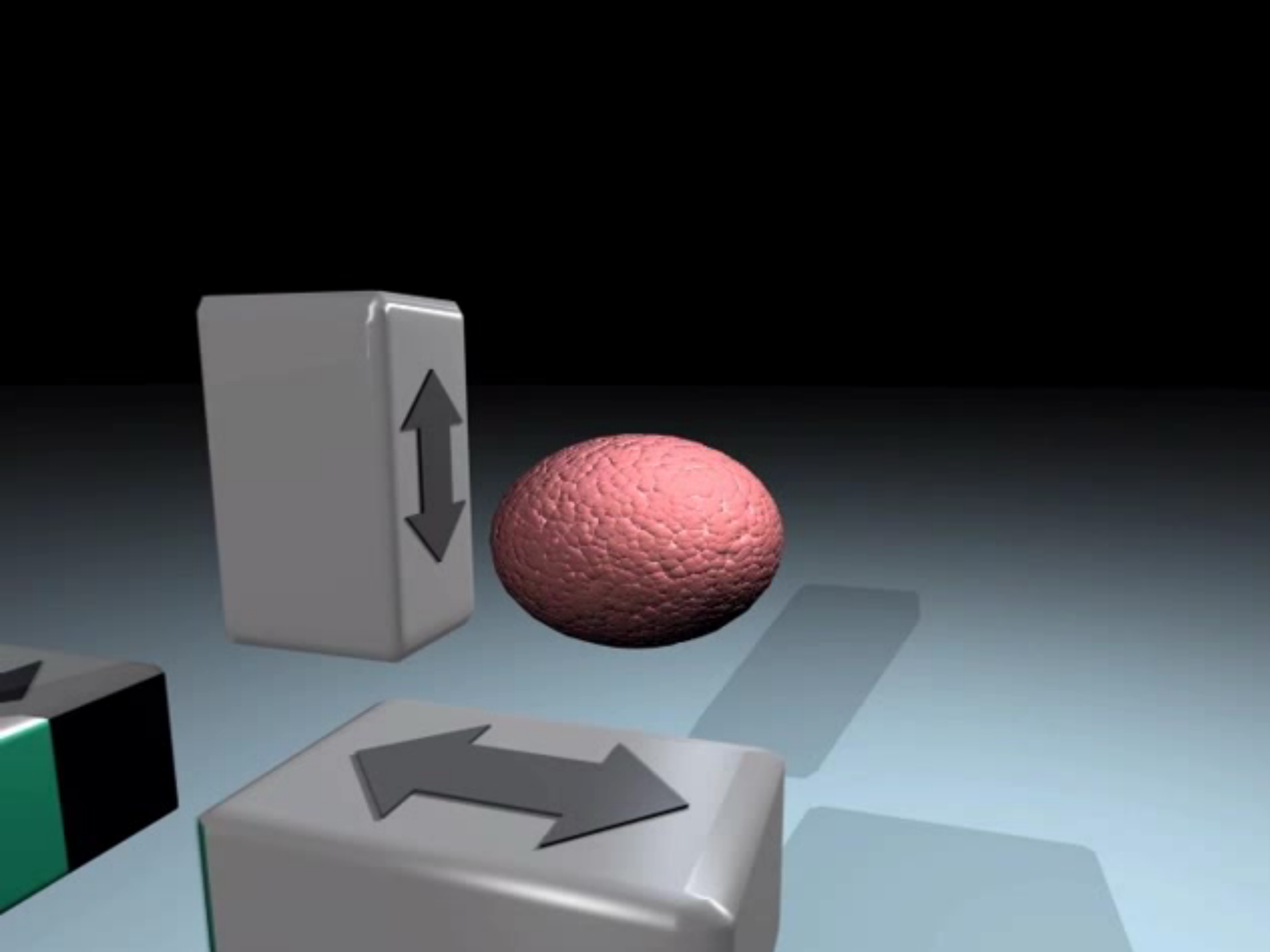
Dose per field



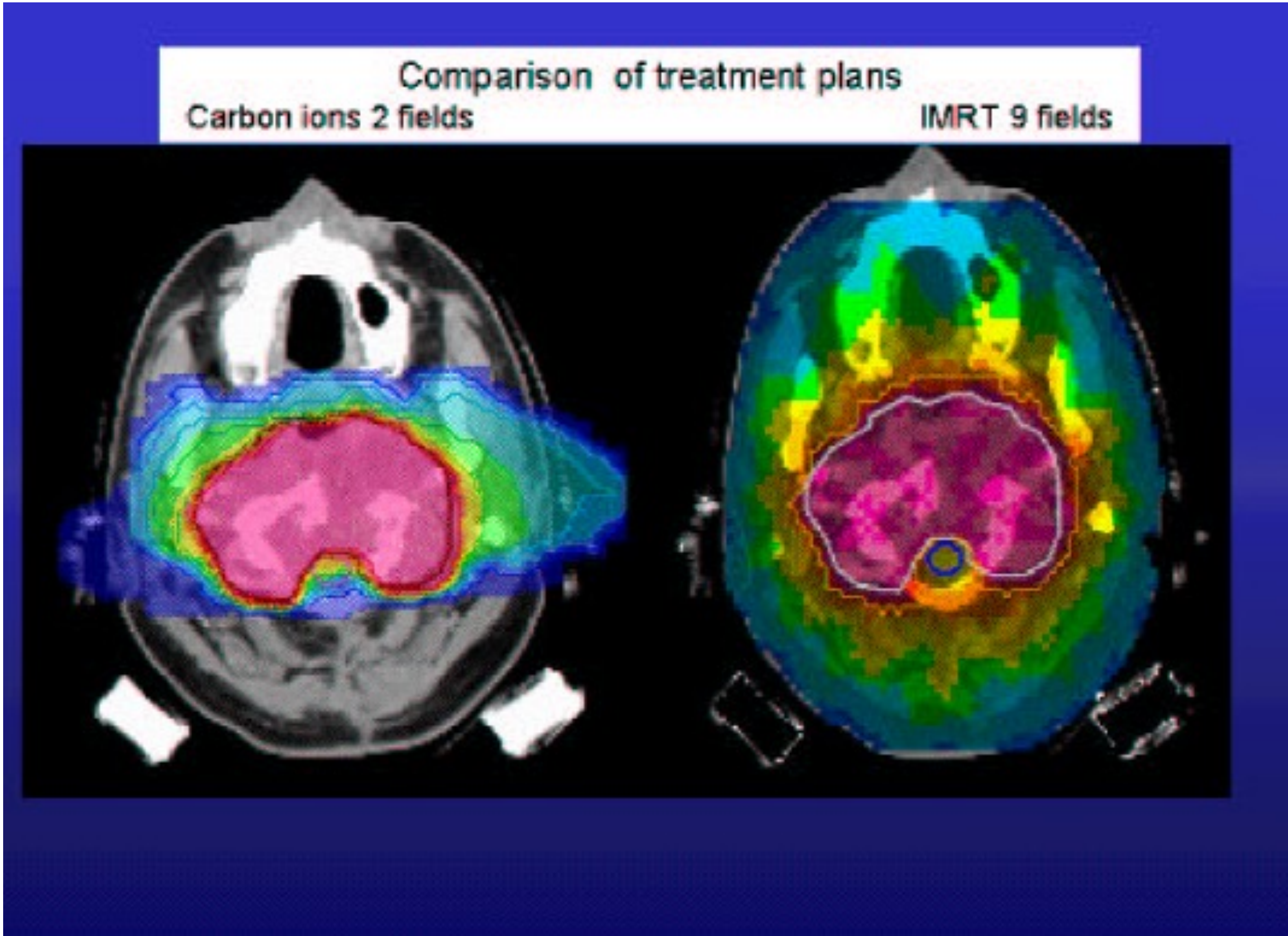
Total dose

Excellent target conformity
Large normal tissue volume irradiated

Courtesy B. Mijnheer



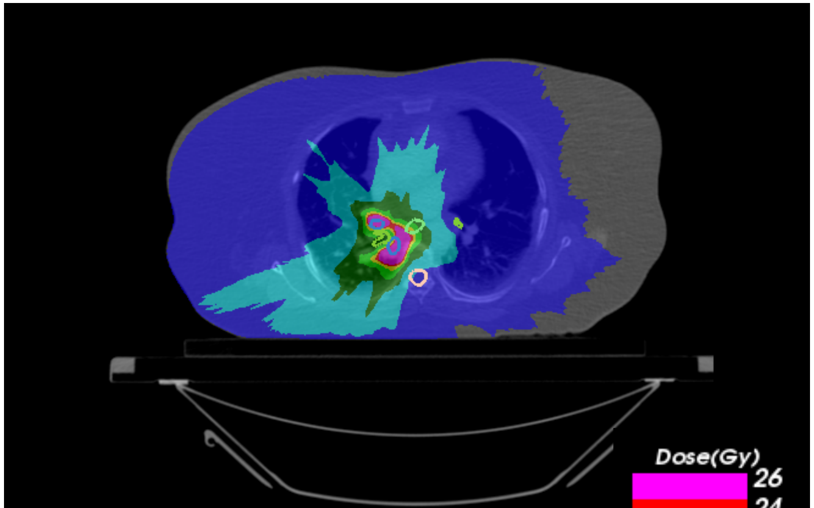
C-ions vs. X-ray therapy



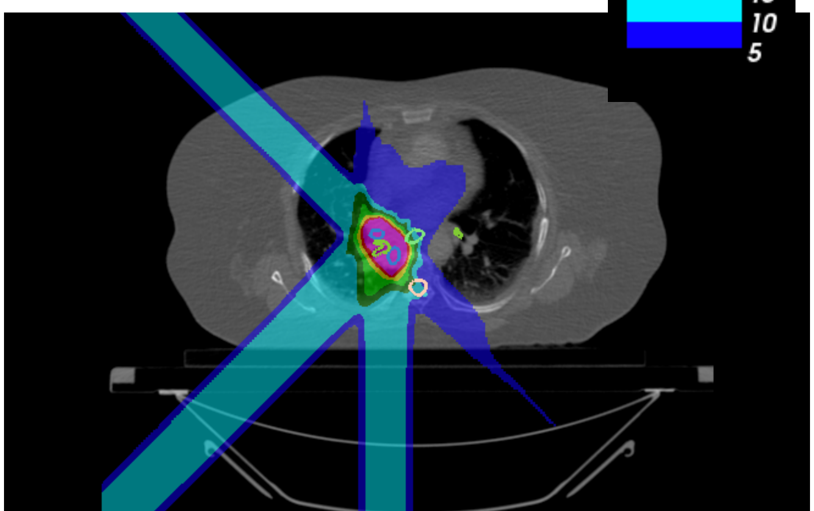
Lung tumors: SBRT vs. C-ions

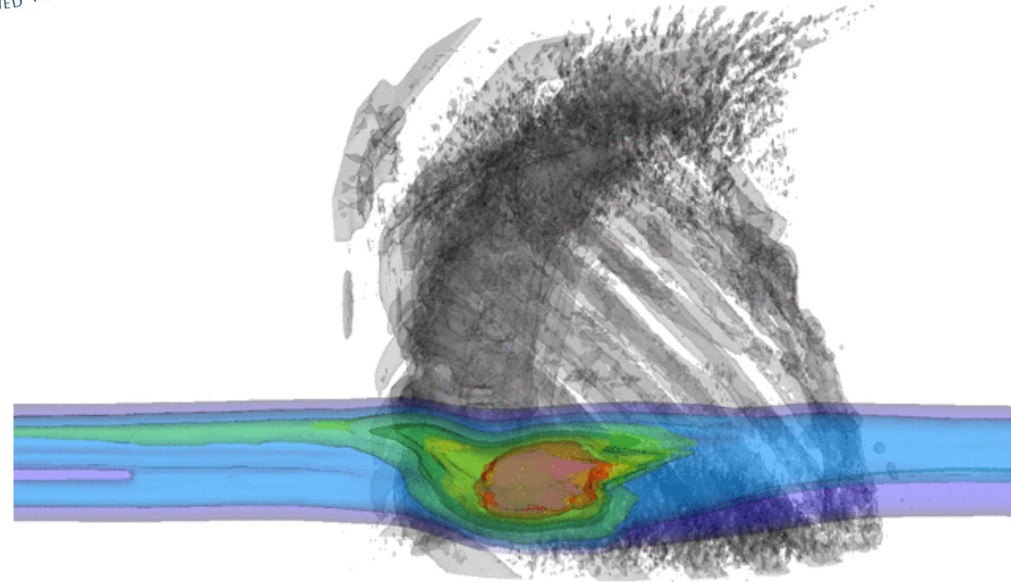
Single fraction, 25 Gy

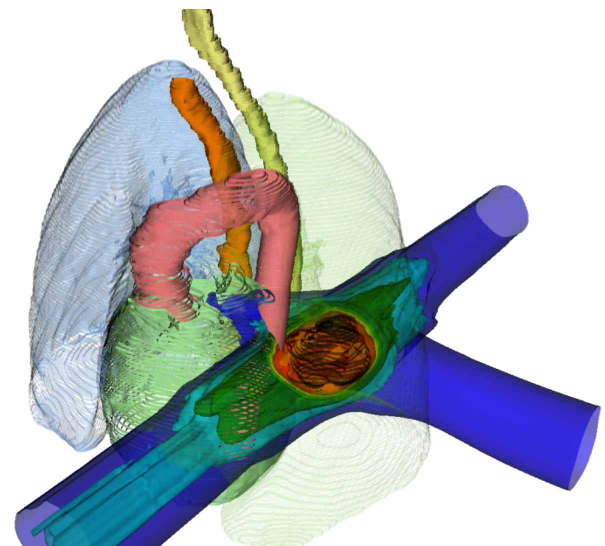
X-rays



C-ions



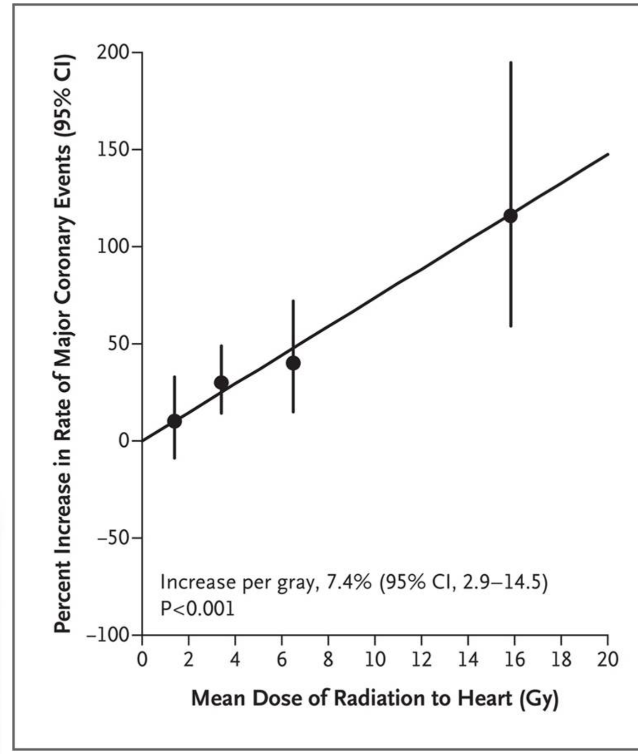


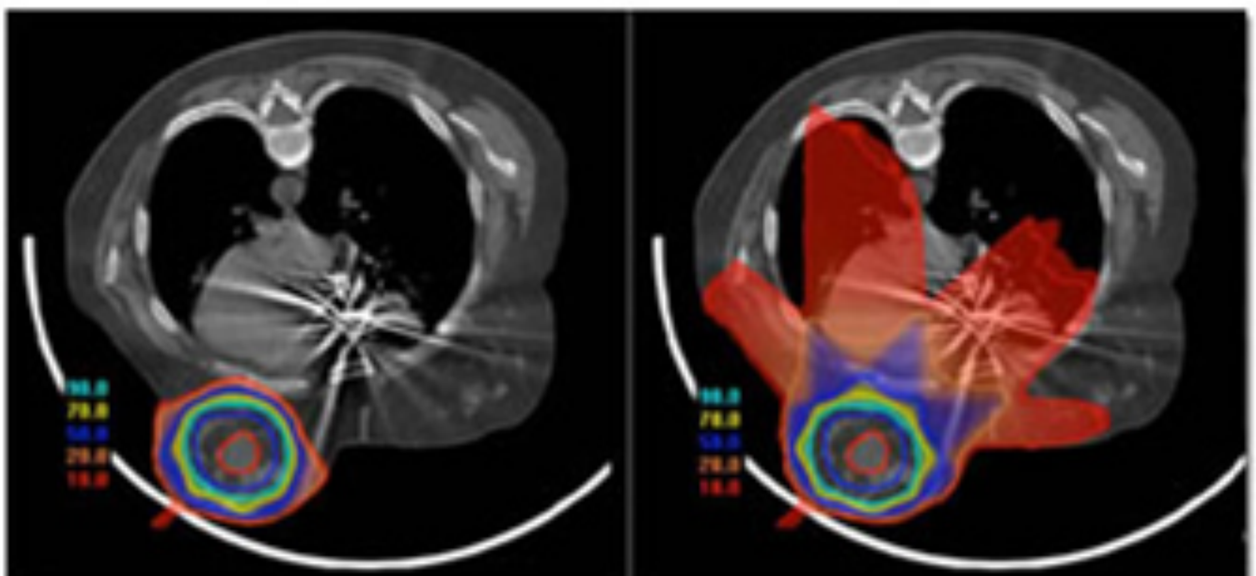


Kristjan Anderle, Ph.D. thesis, TU Darmstadt, 2014

Breast cancer

- 1st cancer in women (1 in 8)
- survival rate 80%
- high risk of late cardiac morbidity





Breast cancer treatment: Proton left, IMRT right

NEJM

14.3.2013

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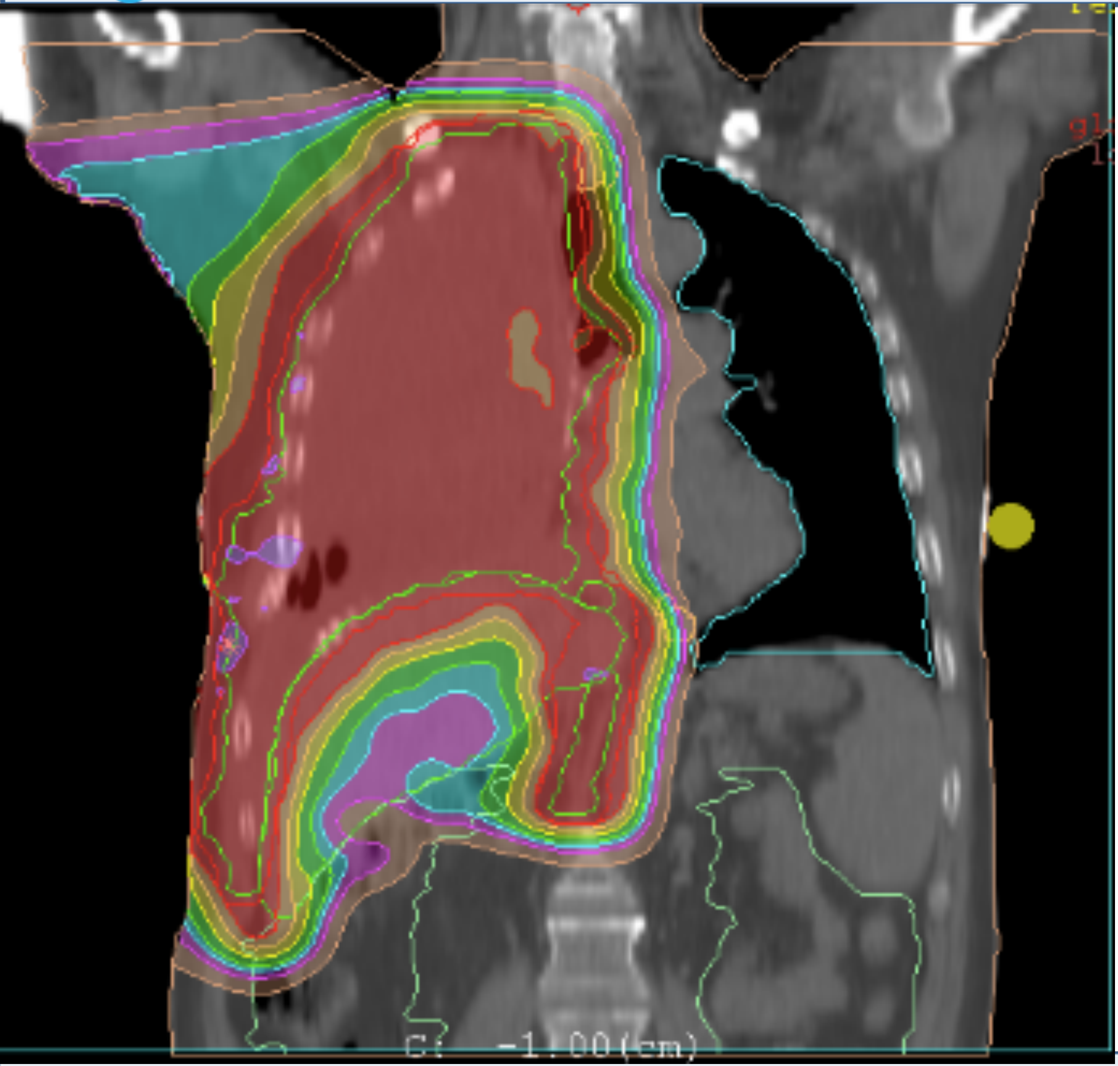
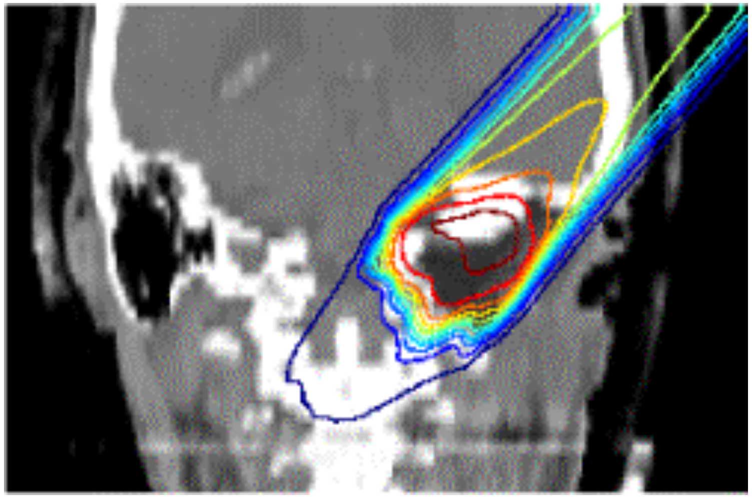


Treatment plan with protons: pleural mesothelioma

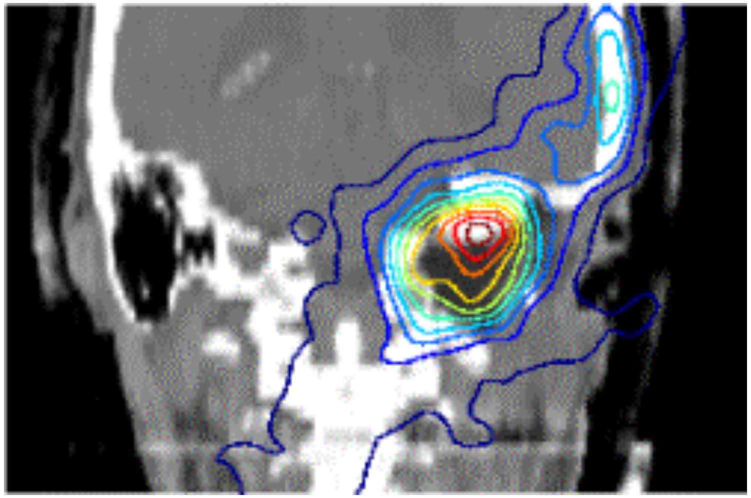
Courtesy of Marco Schwarz, AtrEP, Trento, Italy

Range uncertainty: protons stop, but where?

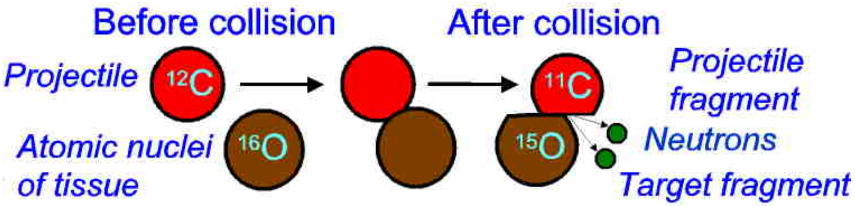
In situ control with PET

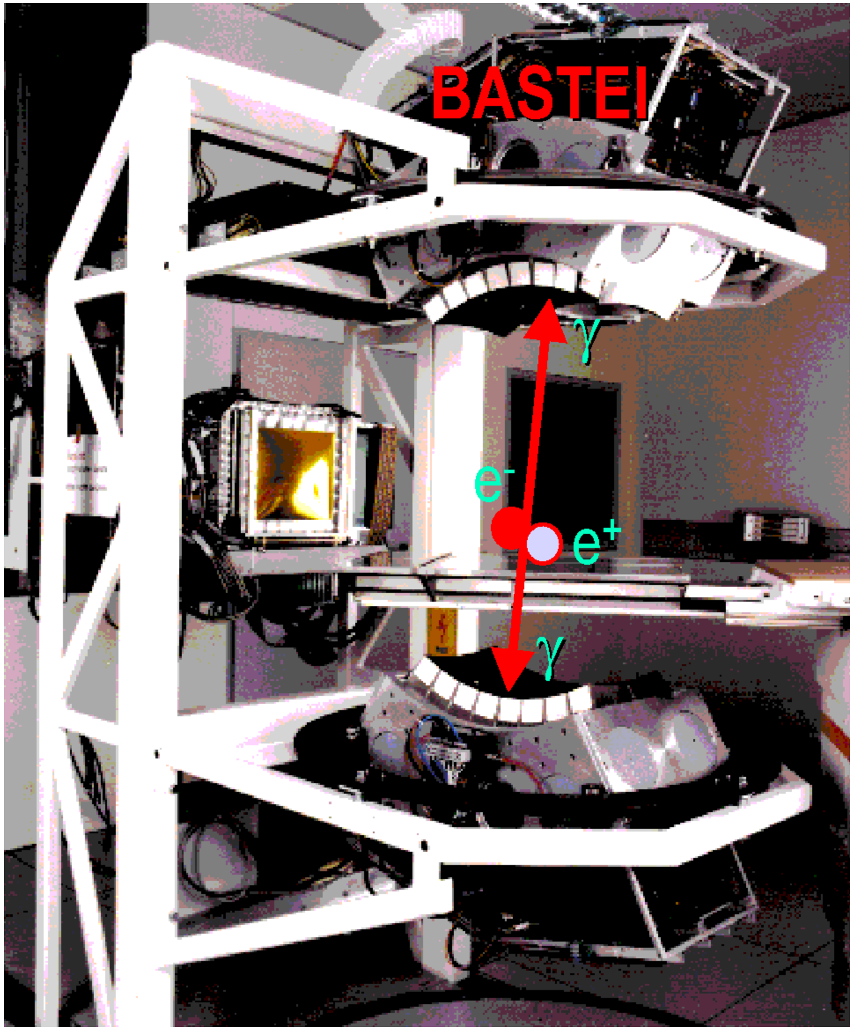


dose plan



measured

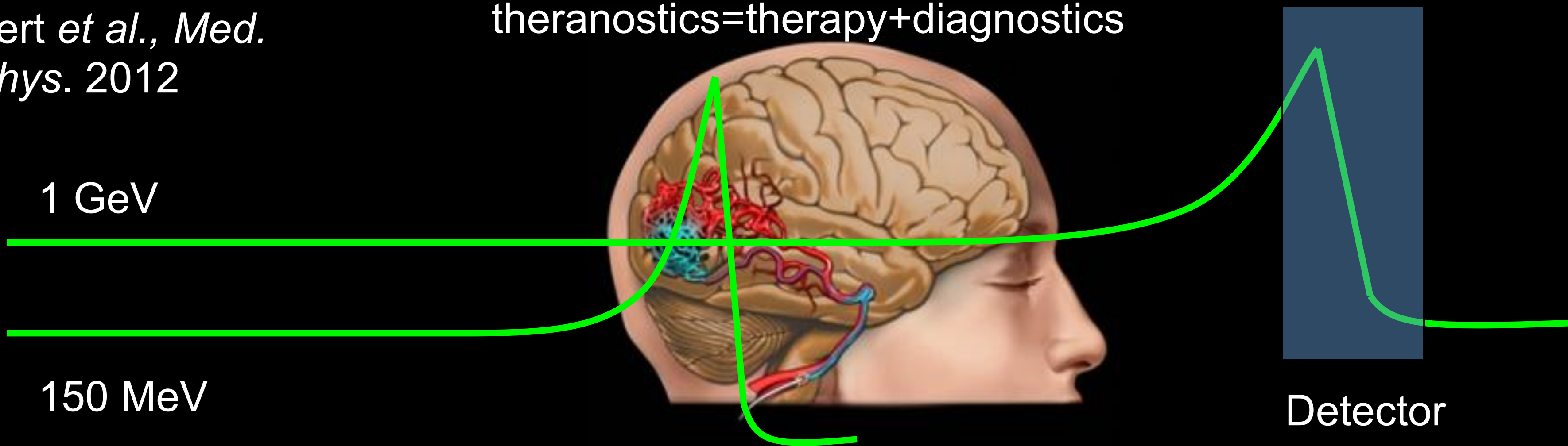




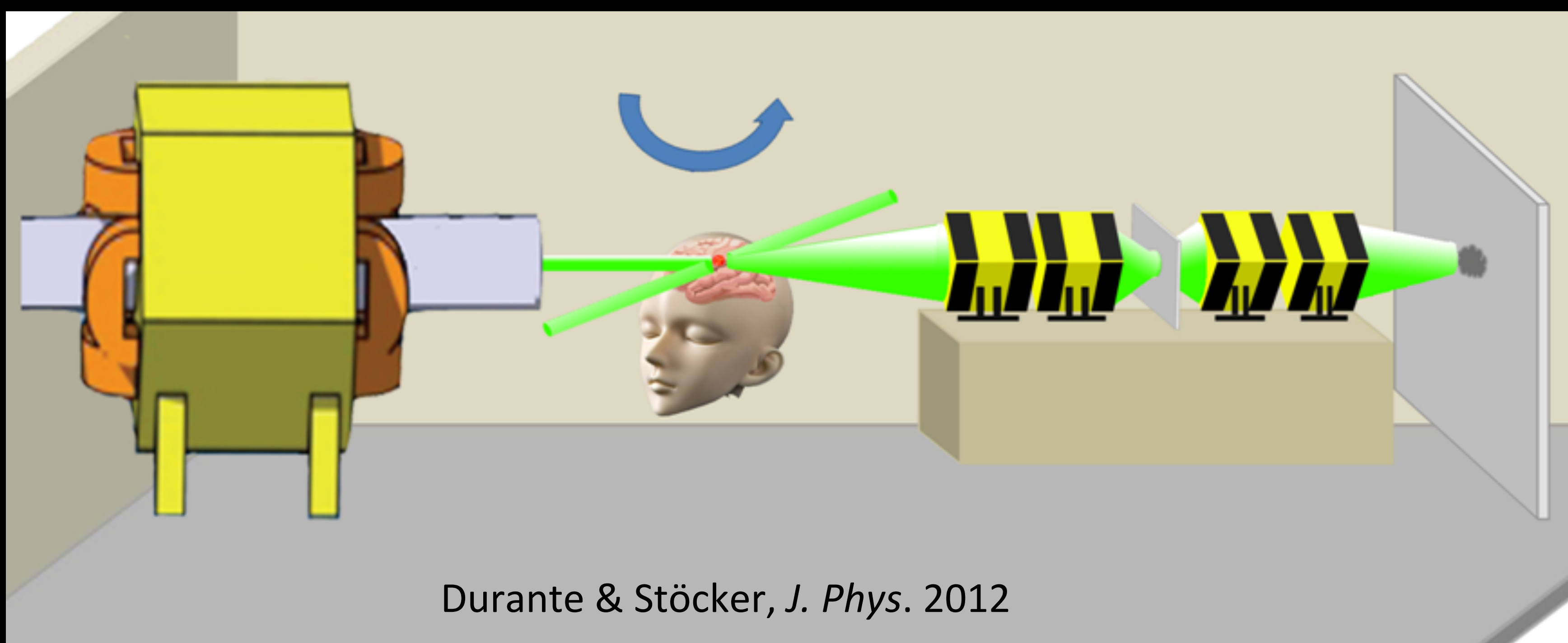
Courtesy of Wolfgang Enghardt, HZDR, Dresden

Bert *et al.*, *Med. Phys*. 2012

theranostics=therapy+diagnostics



Relativistic plateau (non-Bragg-peak) protons for image-guided stereotactic particle radiosurgery (IGSpRS)

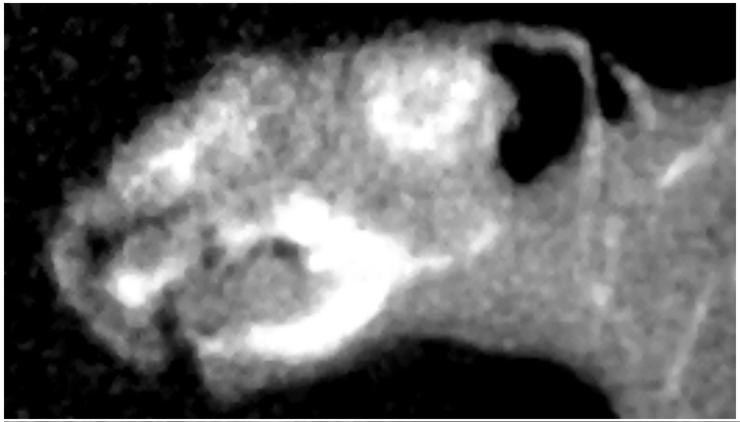


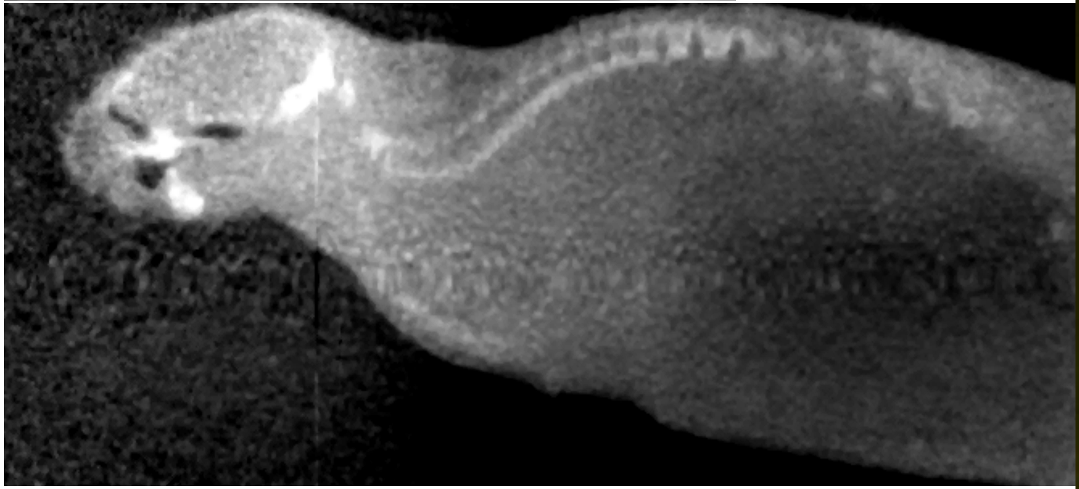
Durante & Stöcker, *J. Phys*. 2012

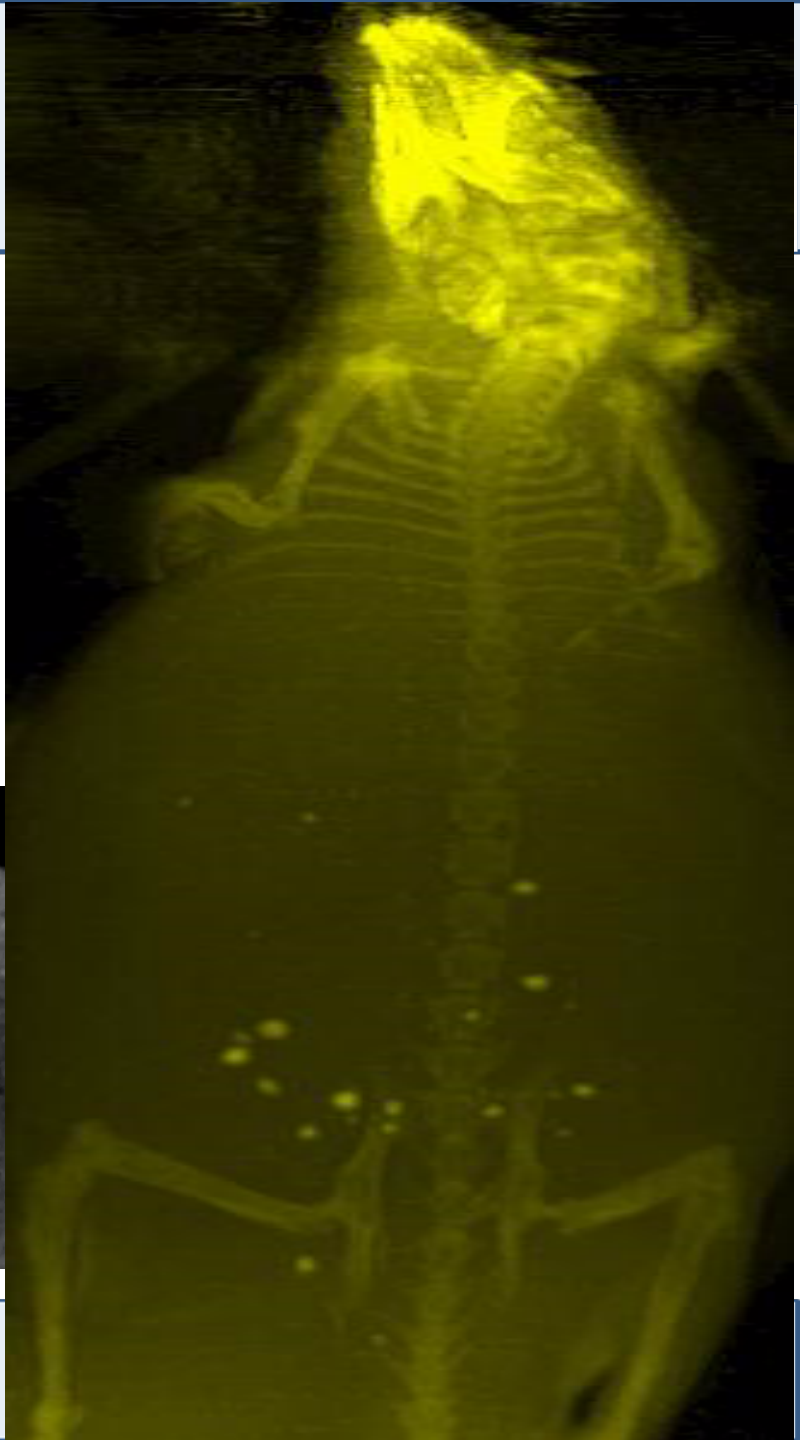
Mouse Proton Tomography

Trento Institute for Fundamental Physics and Applications

800 MeV proton beam at LANL







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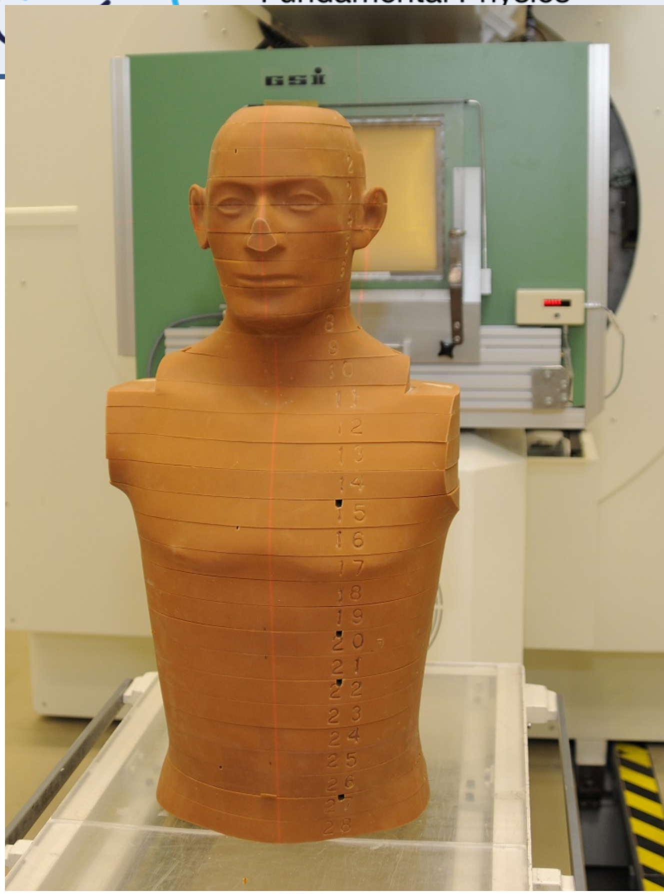
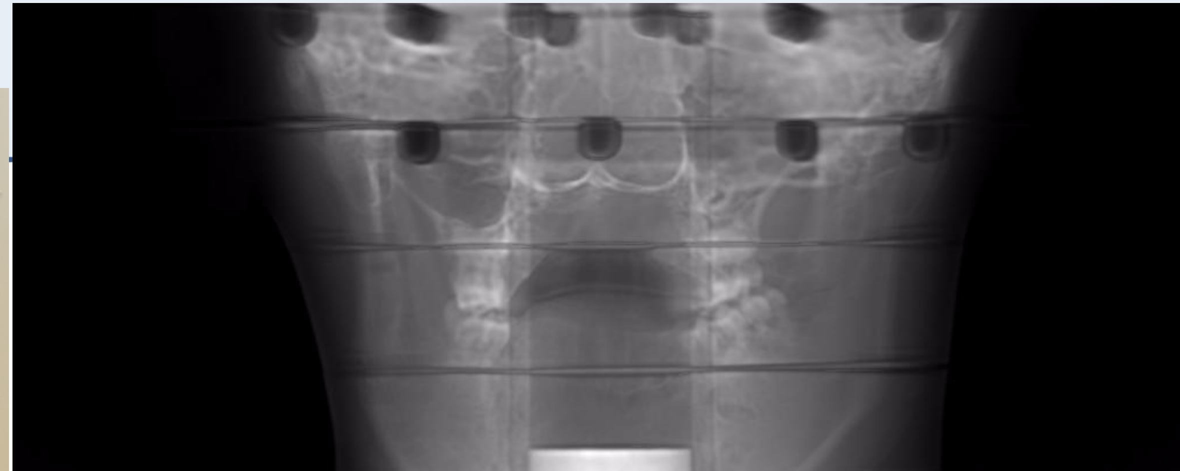
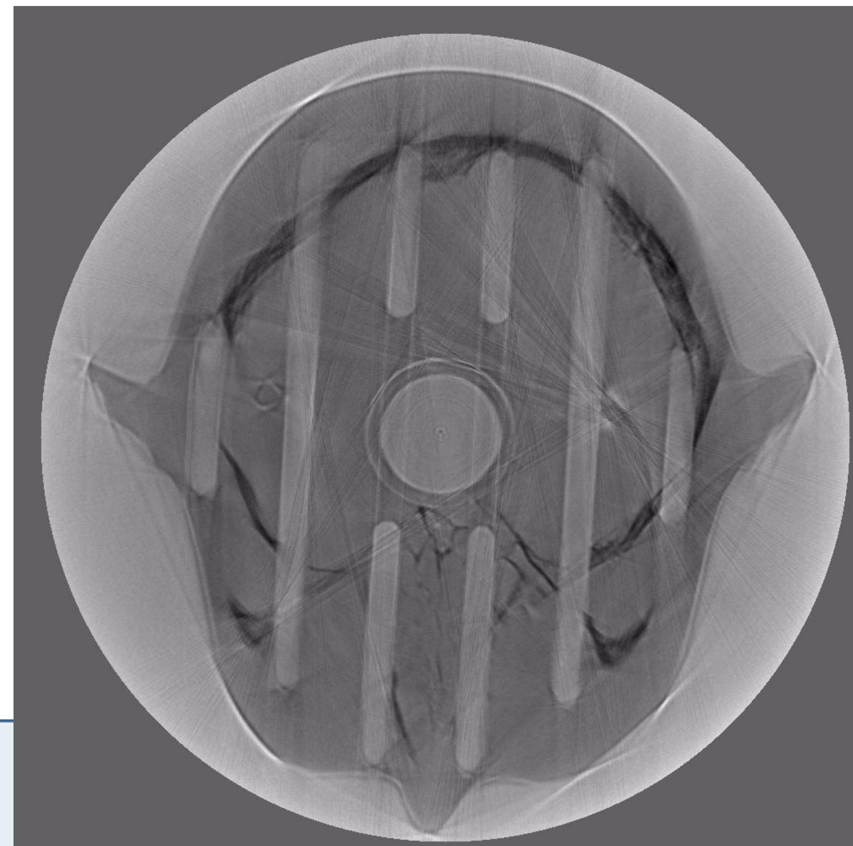
Human phantom Tomography – 800 MeV

TIFPA
Trento Institute for
Fundamental Physics







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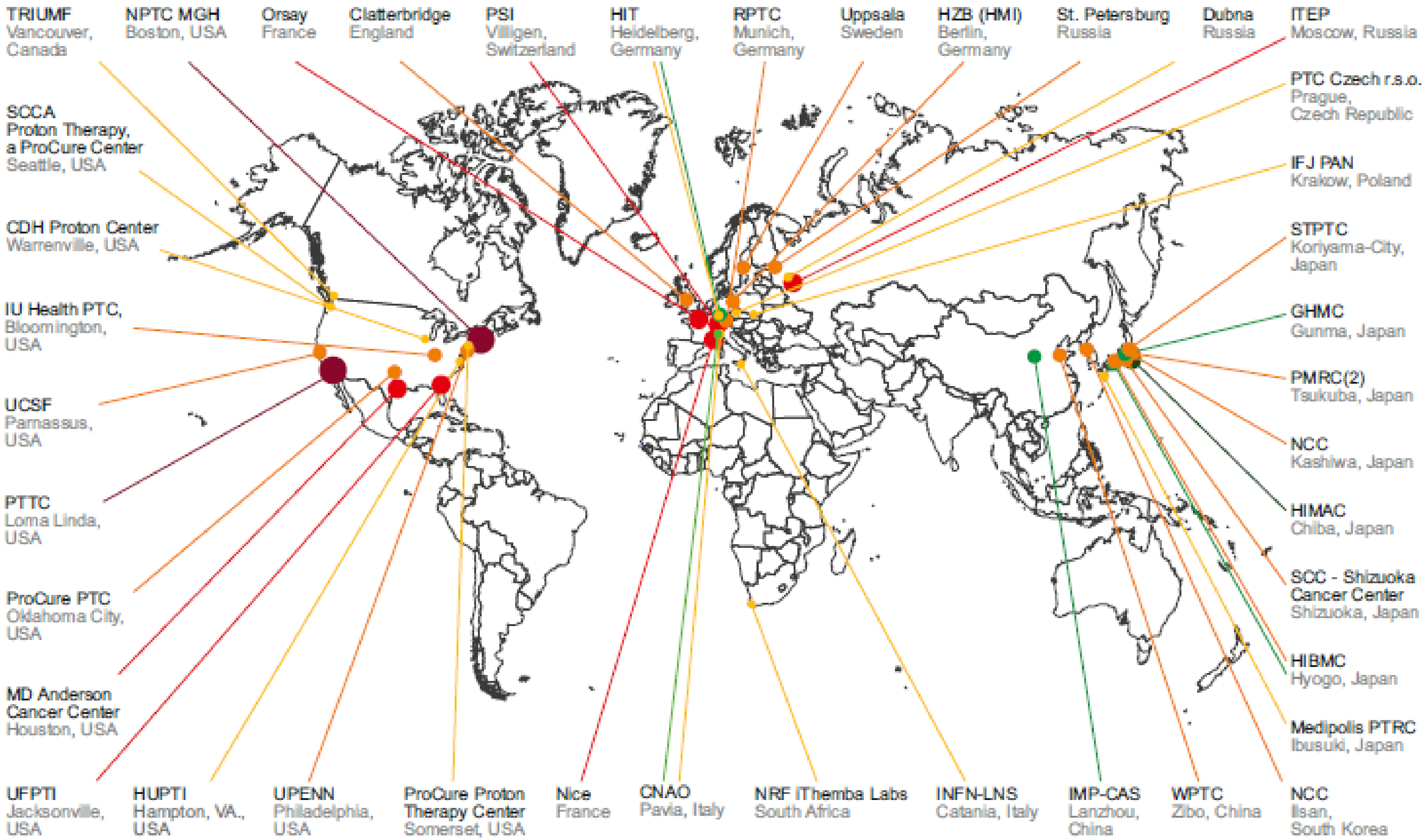
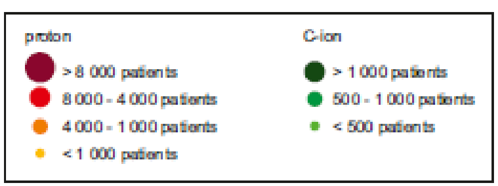
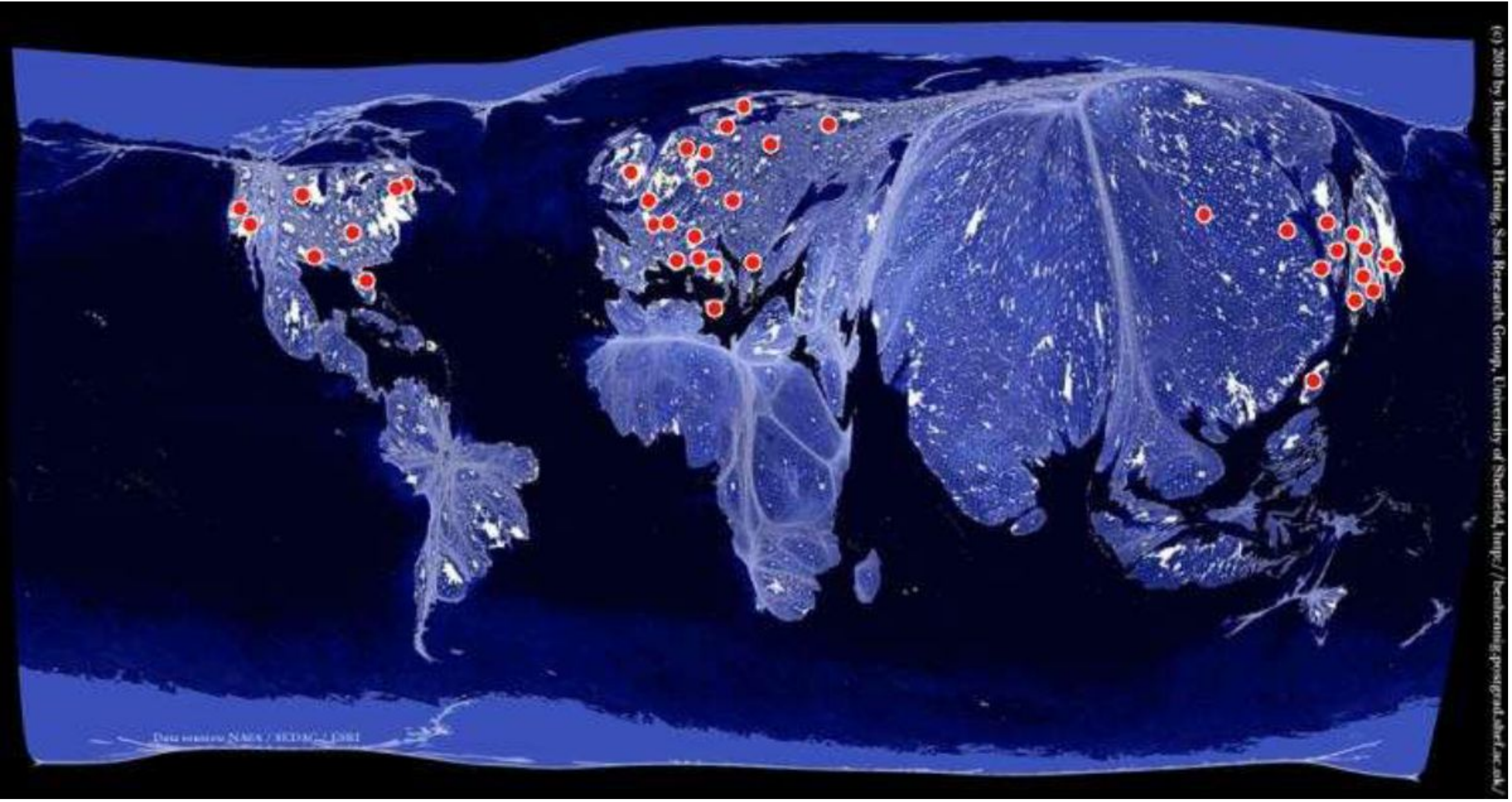
FAIR



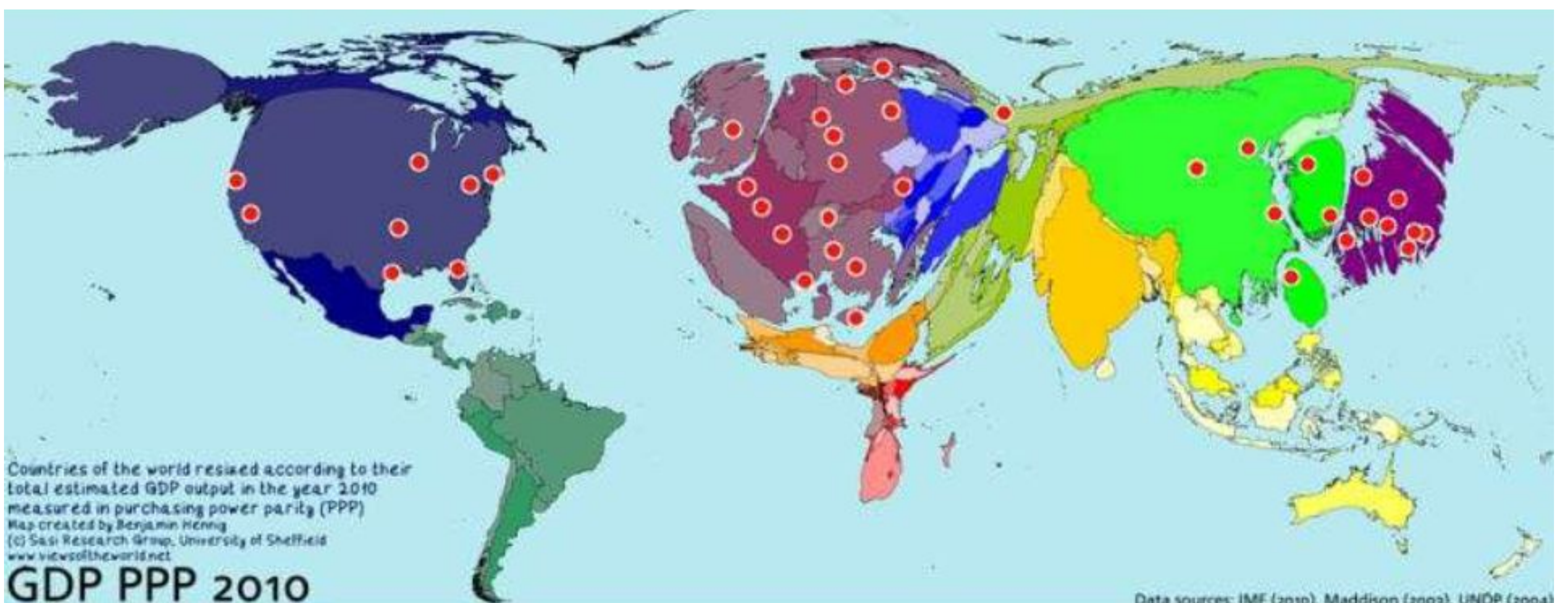


March 2014: 44 proton/7 heavy ion centers
Under construction: 25 proton/ 4 heavy ion centers
Only in USA, 27 new centers expected by 2017

uPECC report „Nuclear Physics in Medicine“, 2014
vailable online www.nupecc.org



Population – scaled

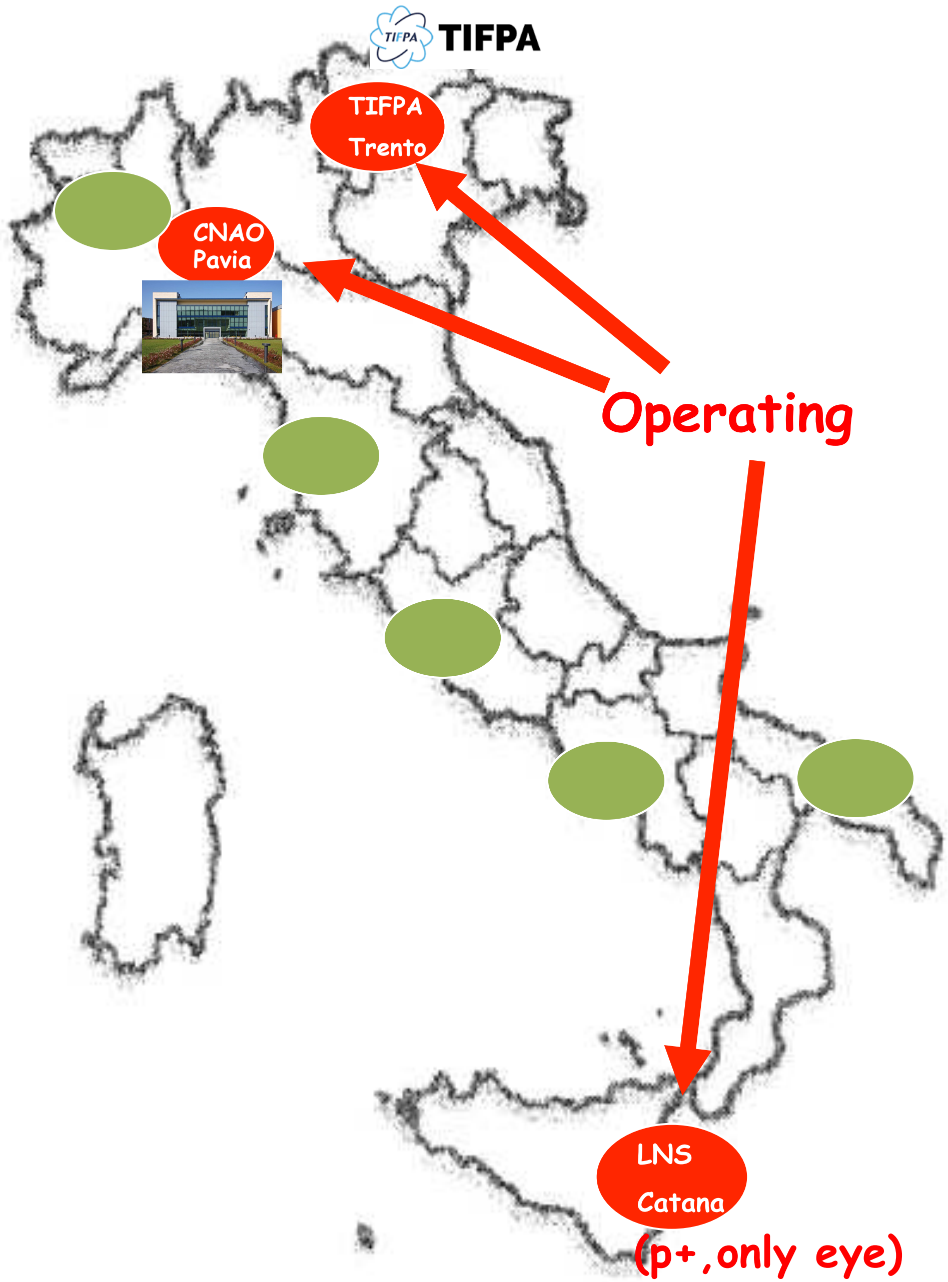


GPD-scaled

ITALIAN NETWORK FOR HADRONTHERAPY

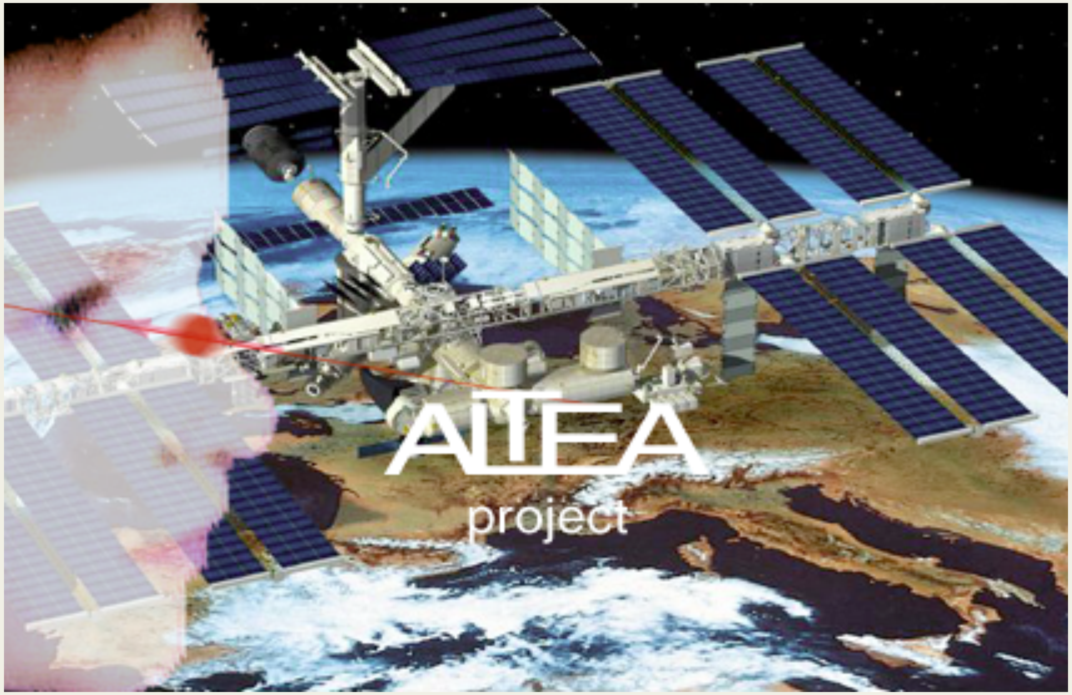
EXISTING CENTRES

INTEREST FOR PROTONS



1. Particle therapy contributing to space research

Heavy ion effects on the Central Nervous System: ground and space investigations: the ALTEA program

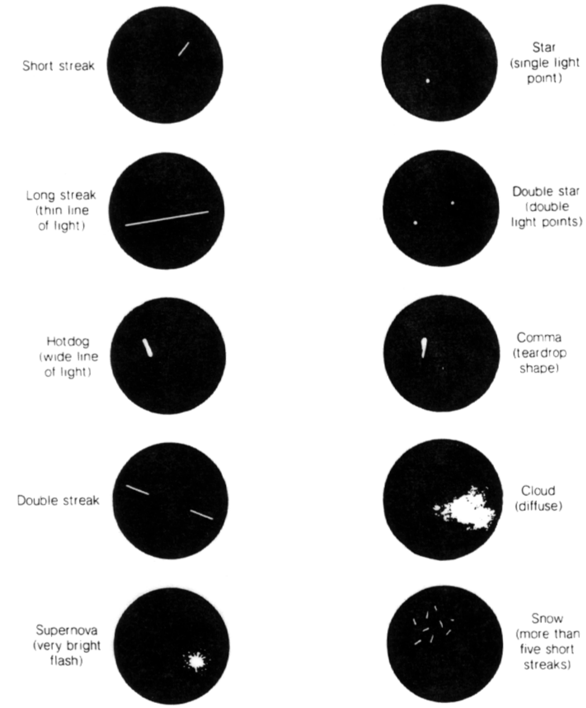


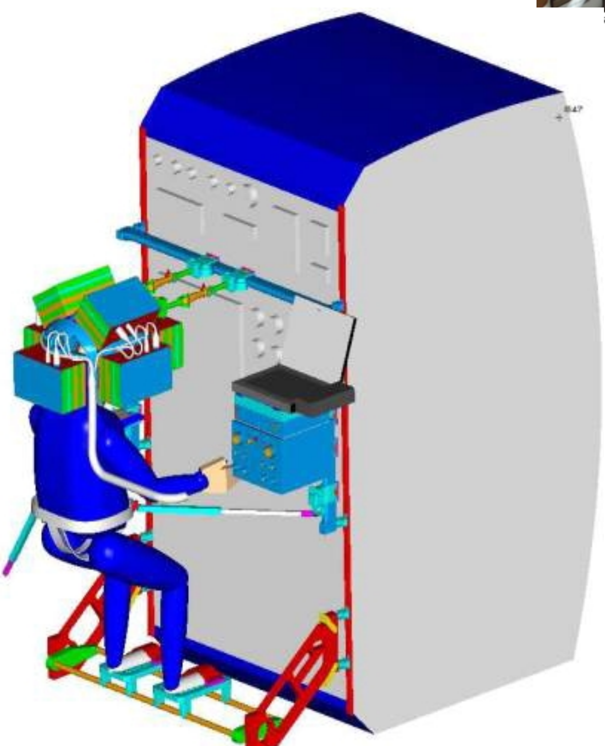
University of Rome
“Tor Vergata”

PI: Livio Narici
Department of Physics, University of Rome and INFN
‘Tor Vergata’ Rome, Italy

ALTEA - space: the launch and set up

STS121: July 4, 2006



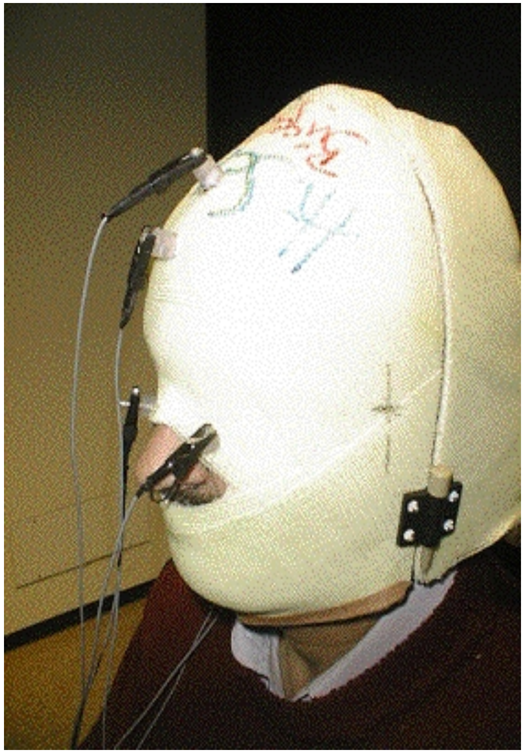


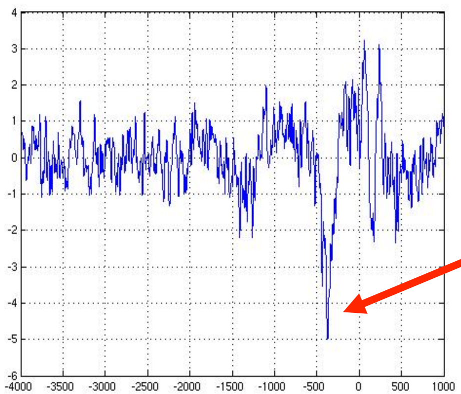
Light flashes seen by astronauts in space

A controlled approach on patients at GSI

ALTEA-HIT

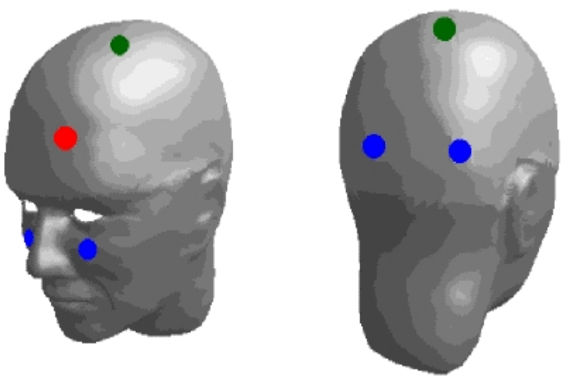
- LF perceived by several patients during the therapy
- Use the high precision in beam time/site localisation to search for the interaction site
- Electrophysiology during the treatment

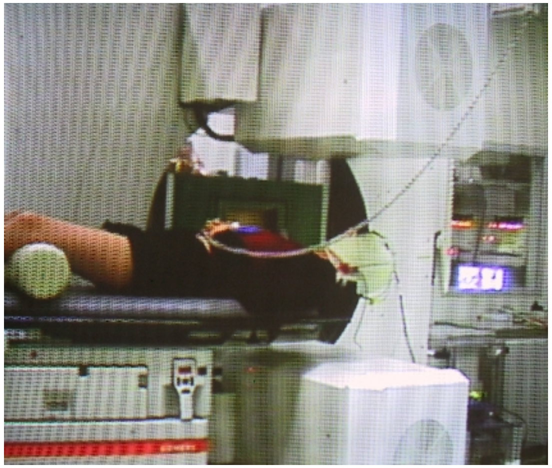




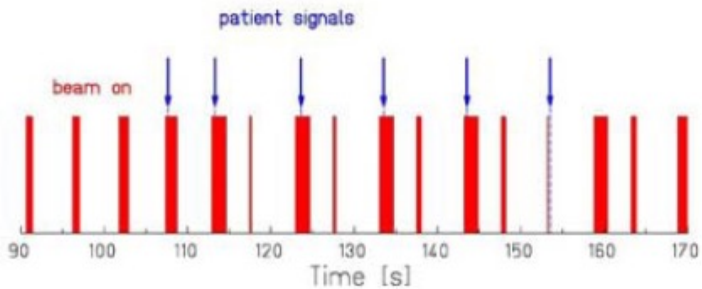
- Particle Evoked Responses?

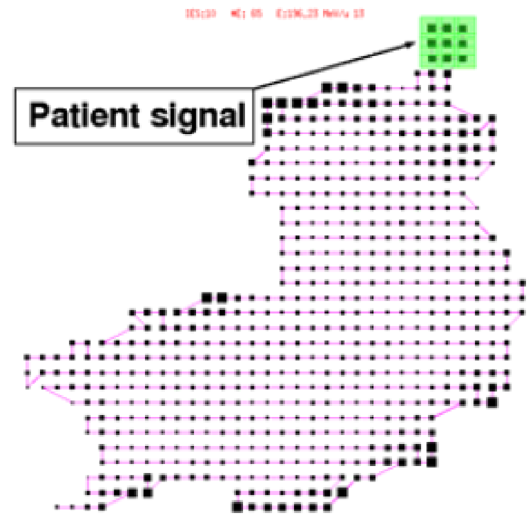
A candidate for an electrophys. averaged ion response

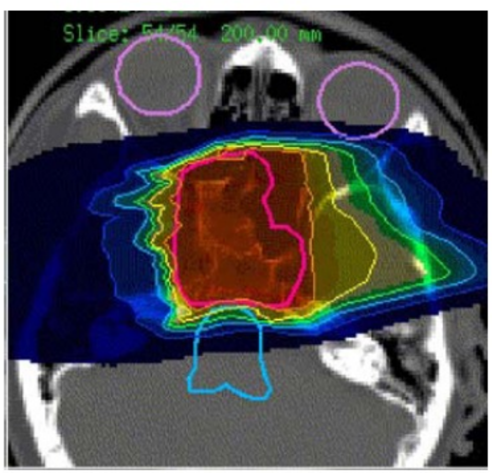




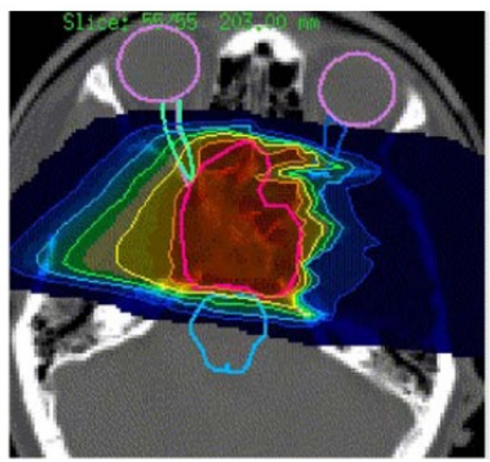
Patients' experiments at GSI







Phosphene

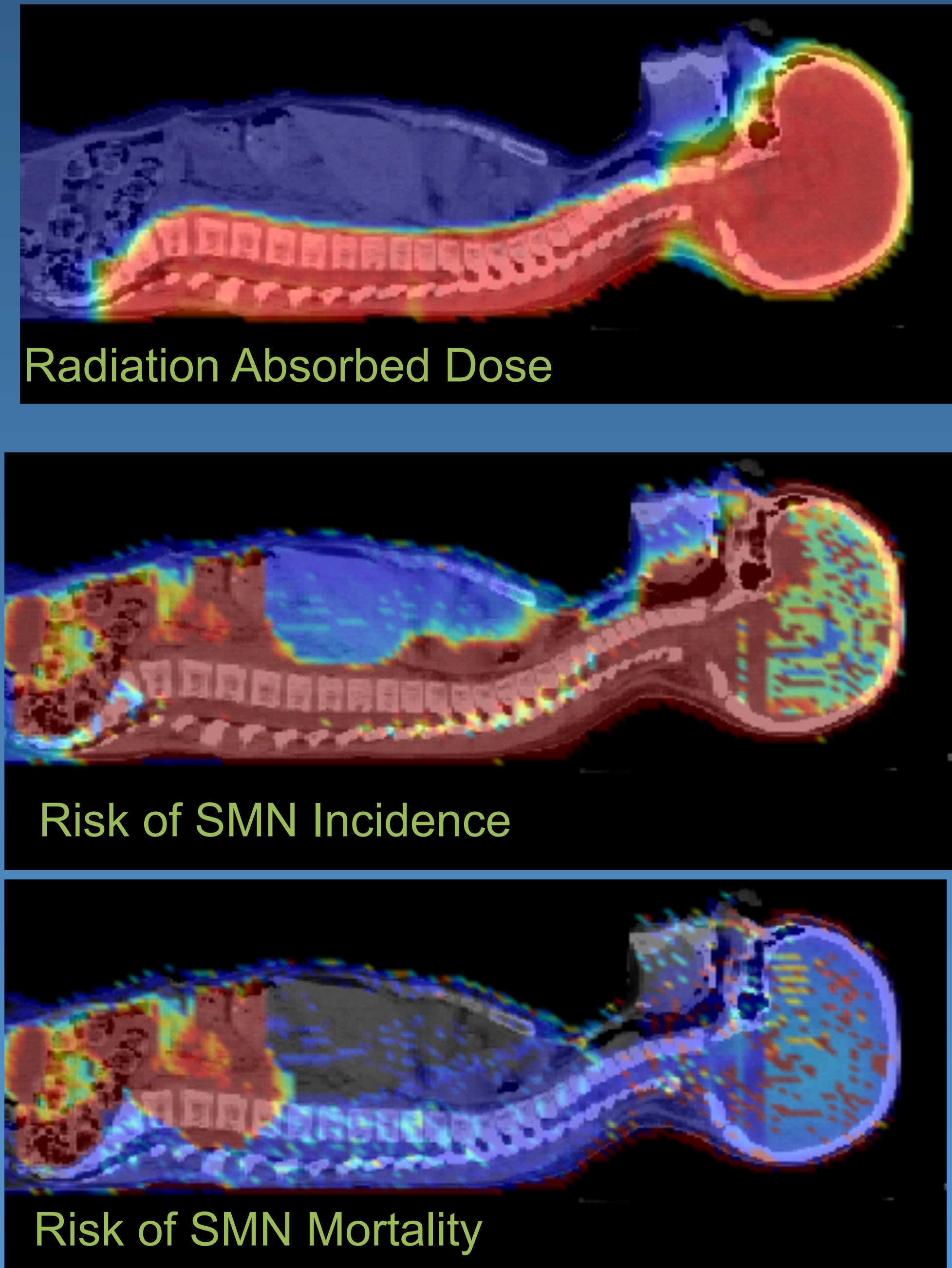


No phosphene

Phosphenes are correlated to dose deposition within the eye

Schardt *et al.*, *Brain Stimul.* 2012

2. Space research contributing to particle therapy



Secondary Malignant Neoplasms (SMN) in particle therapy

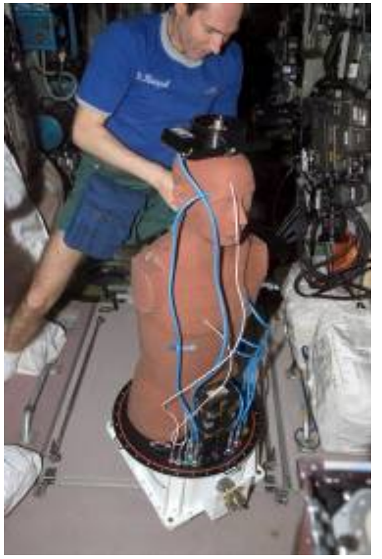
Comparison of relative radiation dose distribution with the corresponding relative risk distribution for radiogenic second cancer incidence and mortality. This 9-year old girl received craniospinal irradiation for medulloblastoma using passively scattered proton beams. The color scale illustrates the difference for absorbed dose, incidence and mortality cancer risk in different organs.

THE UNIVERSITY OF TEXAS
MD Anderson
~~Cancer~~ Center
Making Cancer History®

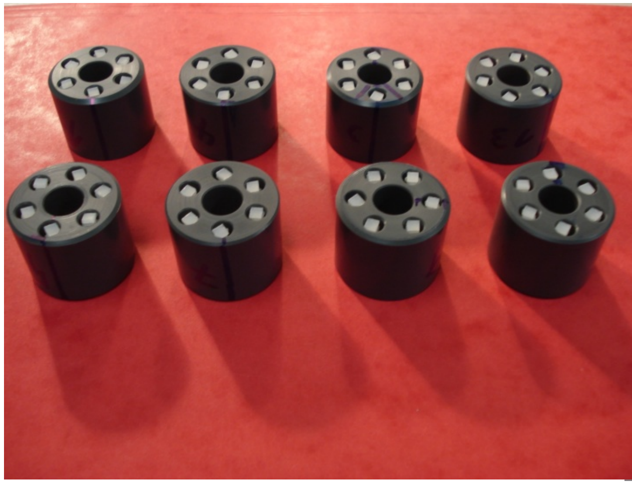
Newhauser & Durante, *Nat. Rev. Cancer* 2011

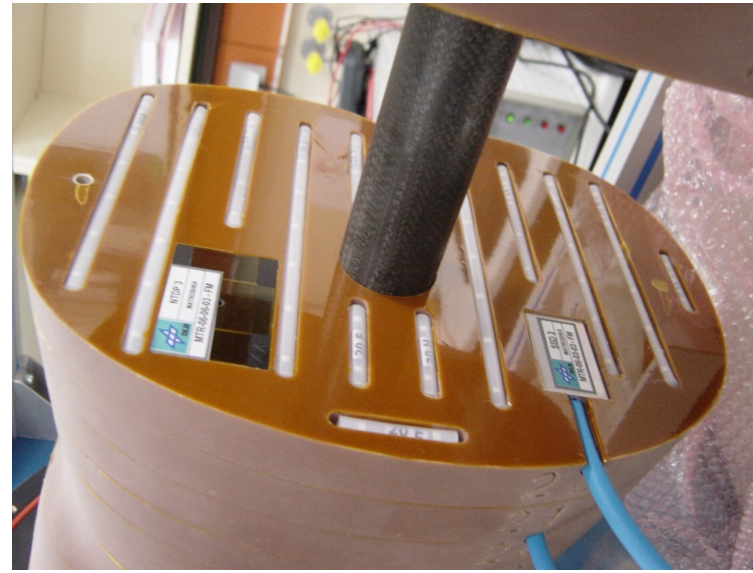
The MATROSHKA facility

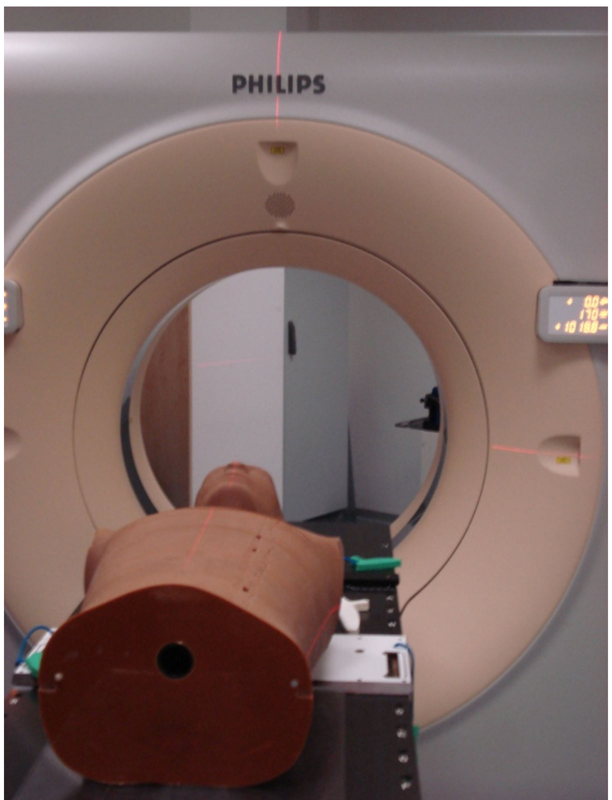
- Standard RANDO phantom of property of DLR (German Aerospace center)
- 850 mm high divided into 34 slices
- Holders for detectors in several slices
- Currently used for space radiation dosimetry inside the ISS

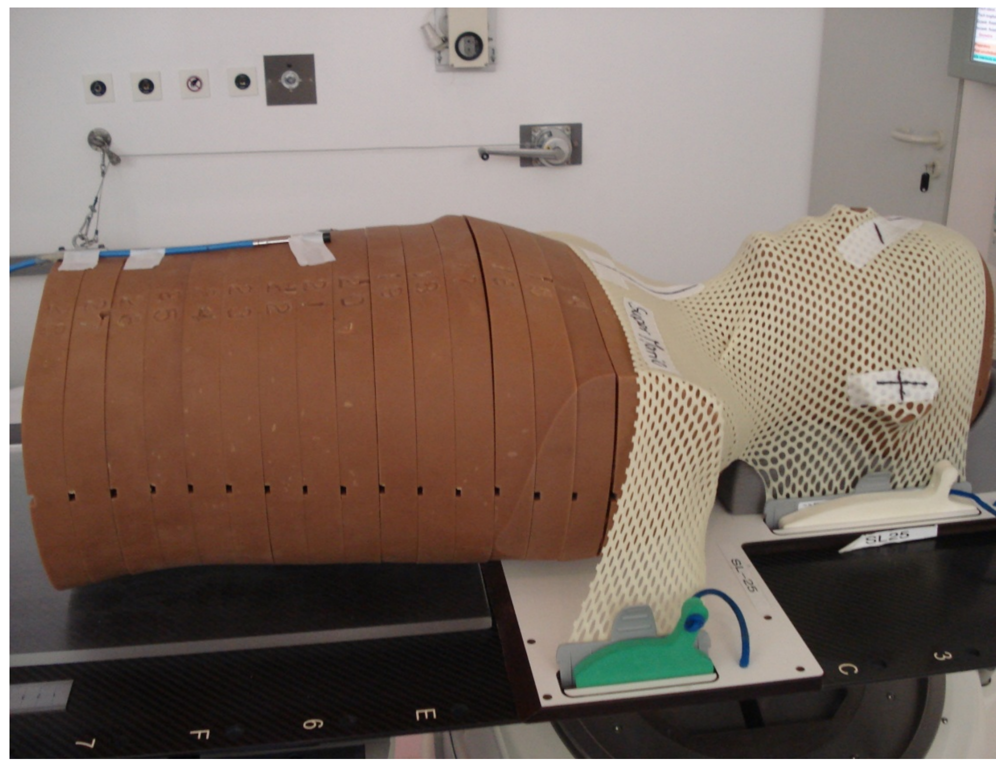


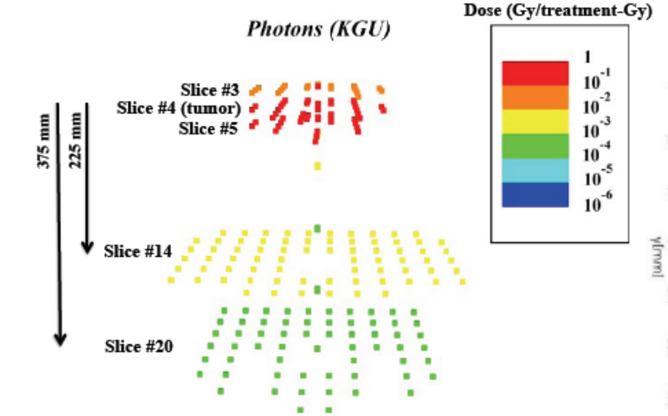
In collaboration with G. Reitz, T. Berger et al. (DLR)

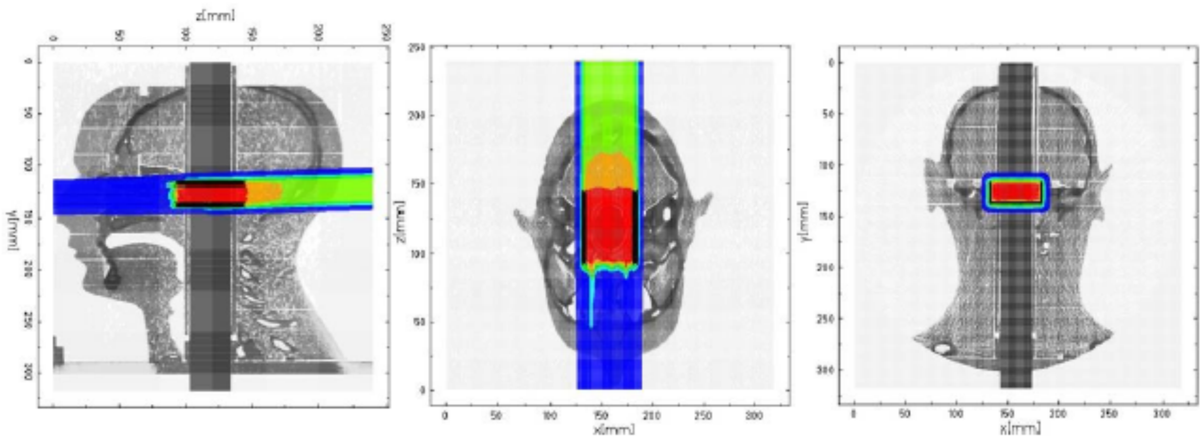


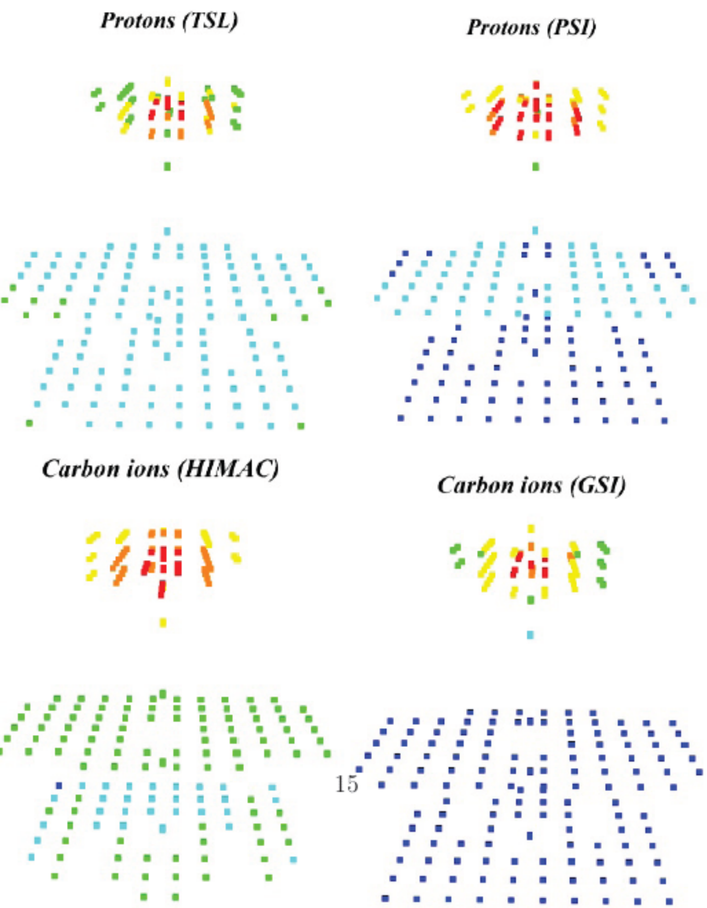


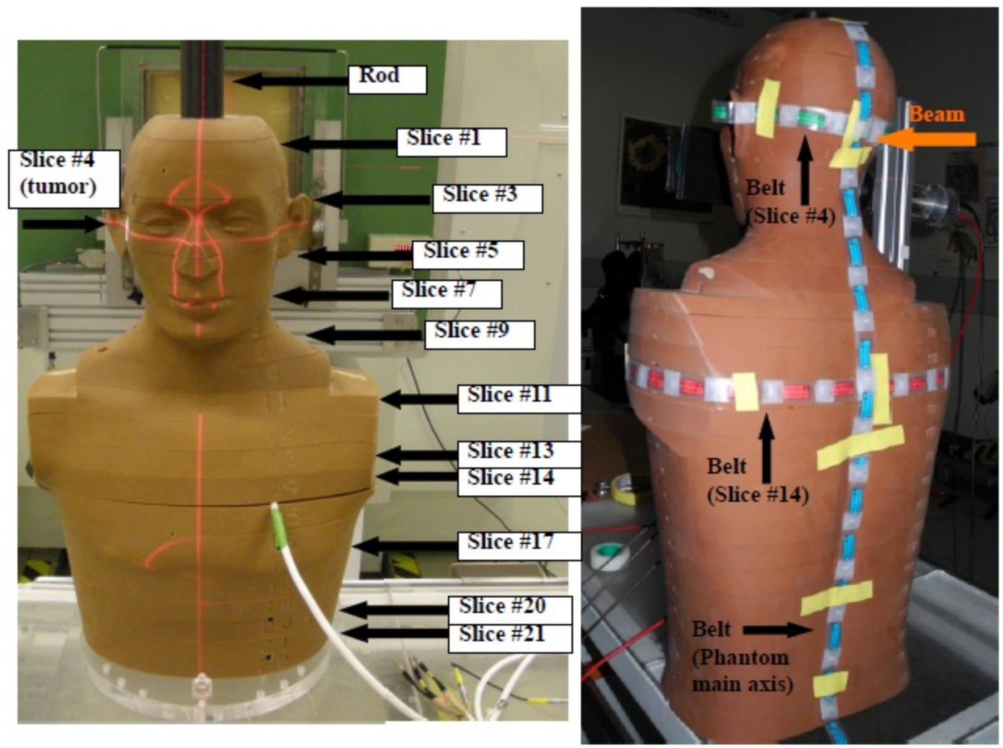

PHILIPS




Photons (KGU)
Dose (Gy/treatment-Gy)
1
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
Slice #3
Slice #4 (tumor)
Slice #5
375 mm
225 mm
Slice #14
Slice #20

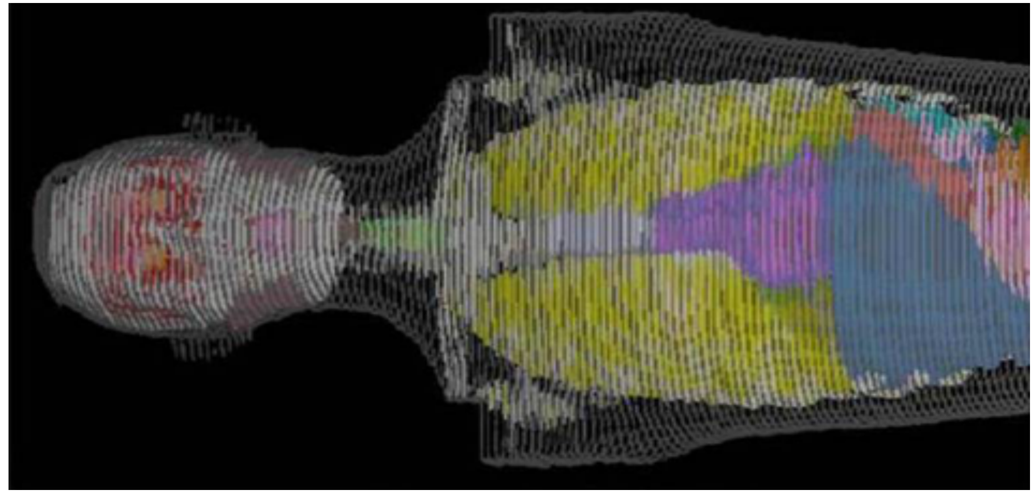

z[mm]
y[mm]
z[mm]
x[mm]
y[mm]
x[mm]


Protons (TSL)
Protons (PSI)
Carbon ions (HIMAC)
Carbon ions (GSI)

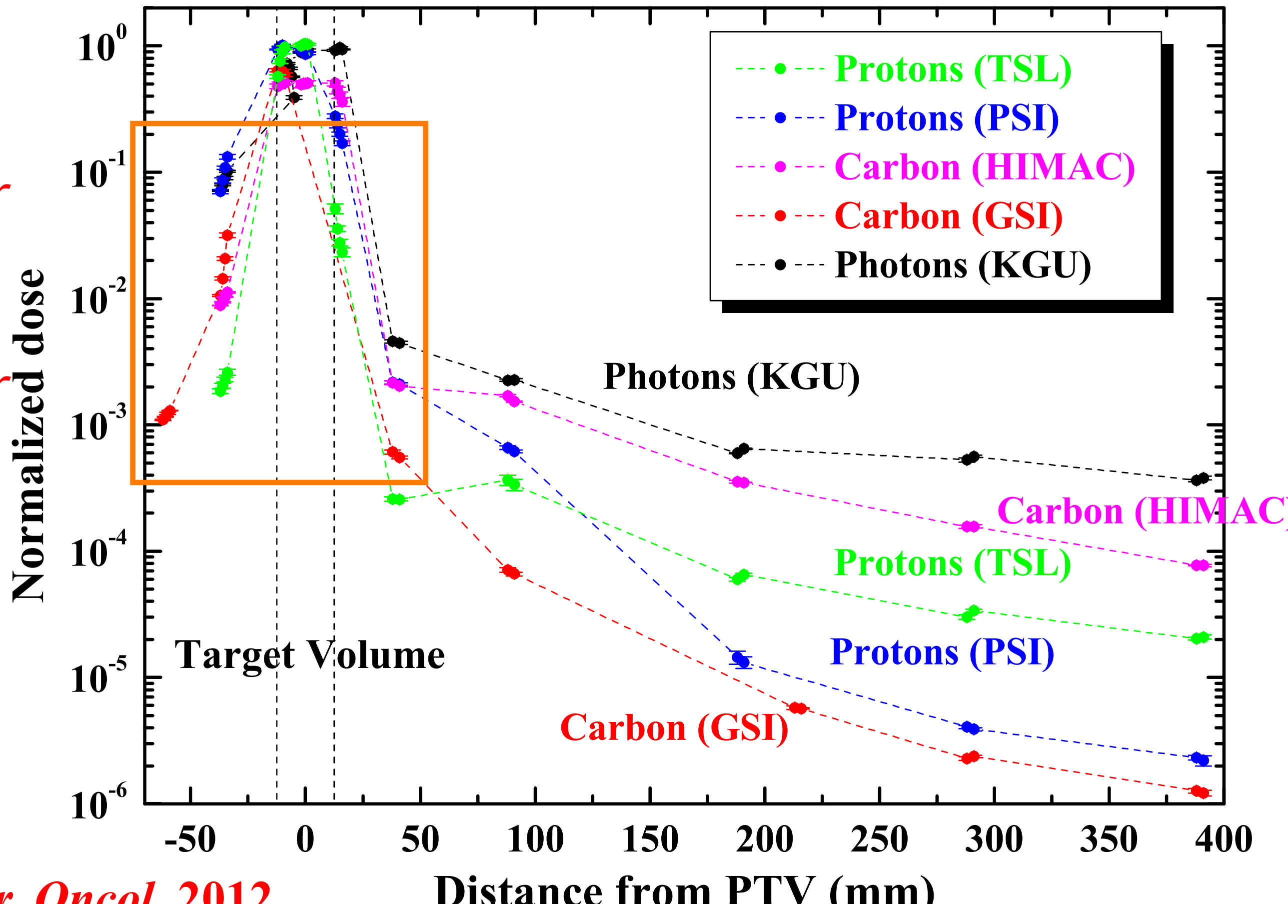

Rod
Slice #1
Slice #4
(tumor)
Slice #3
Slice #5
Slice #7
Slice #9
Slice #11
Slice #13
Slice #14
Slice #17
Slice #20
Slice #21
Beam
Belt
(Slice #4)
Belt
(Slice #14)
Belt
(Phantom
main axis)

Inner dose

TLD 700



- Highest out-of-field dose for photons
- Higher lateral dose for passive modulation than scanning delivery
- Higher lateral dose for protons than carbon ions
- Collimator produces sharper field edges



La Tessa *et al.*, *Radiother. Oncol.* 2012

In patient dosimetry
(uterus dose for a pregnant woman)

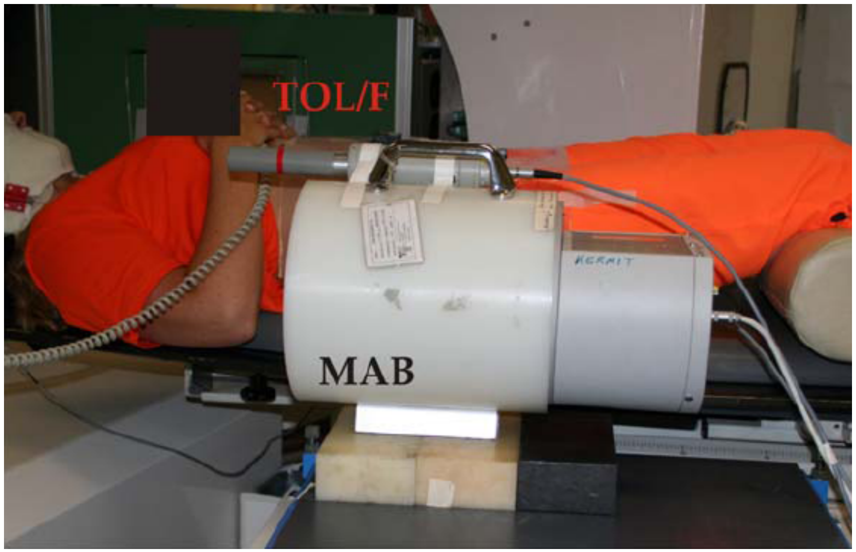


TABLE 1

Measured doses in the pelvic region during the treatment.

	Photon dose (μSv/fraction)	Neutron dose (μSv/fraction)	No. of fractions	Total dose (μSv)
Normal field	3.0[a]	1.4	15	66
Boost field	2.2[b]	1.0	5	16
Total treatment			20	82

[a] Calculated assuming a factor of 1.4 between normal and boost fields as in neutron dose.
[b] Measured by the TOL/F gamma dose rate meter. The passive thermoluminescence dosimeter films did not measure any significant dose above the normal background.

Münter. Heavy ion radiotherapy during pregnancy. Fertil Steril 2010.

Total dose < 0.3 mSv

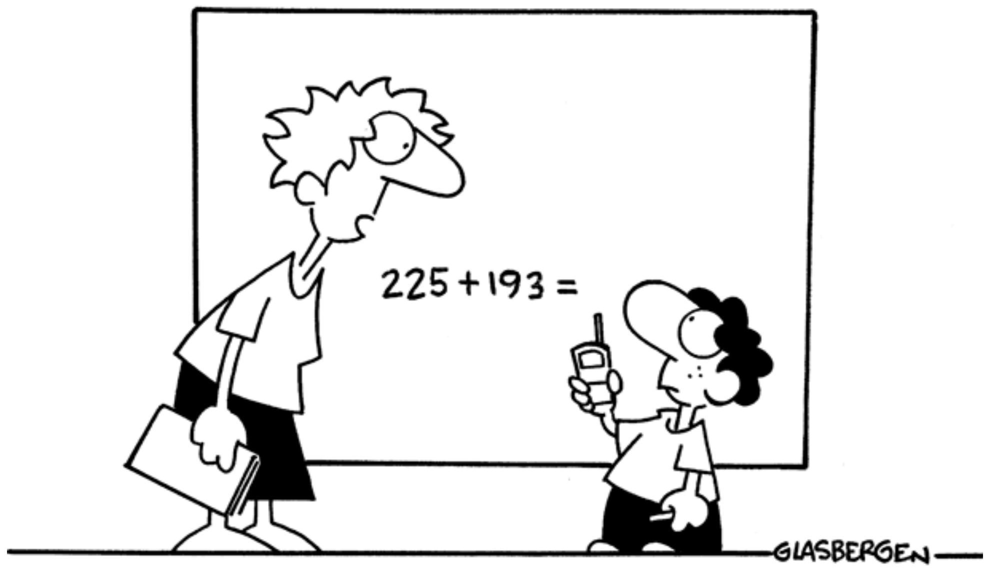
Very low stray radiation reduced risk of secondary cancers or teratogen effects

Münter *et al., Fertil Steril.* 2010

Conclusions

- Heavy ions are different in many facets from X-rays and other genotoxic agents
- Their „special“ radiobiological properties make them very effective in radiotherapy, but potentially dangerous for late effects, and therefore a major hazard in human space exploration
- The biological effects depend on many different factors, and can drastically change for different endpoints. Notwithstanding many years of research in the field, the uncertainty is still high
- Accelerator-based research in radiobiology is essential for improving radiotherapy and ensure protection in space: it should be increased, and can serve both medical and space research communities

Thank you for attention!



"You have to solve this problem by yourself. You can't call tech support."