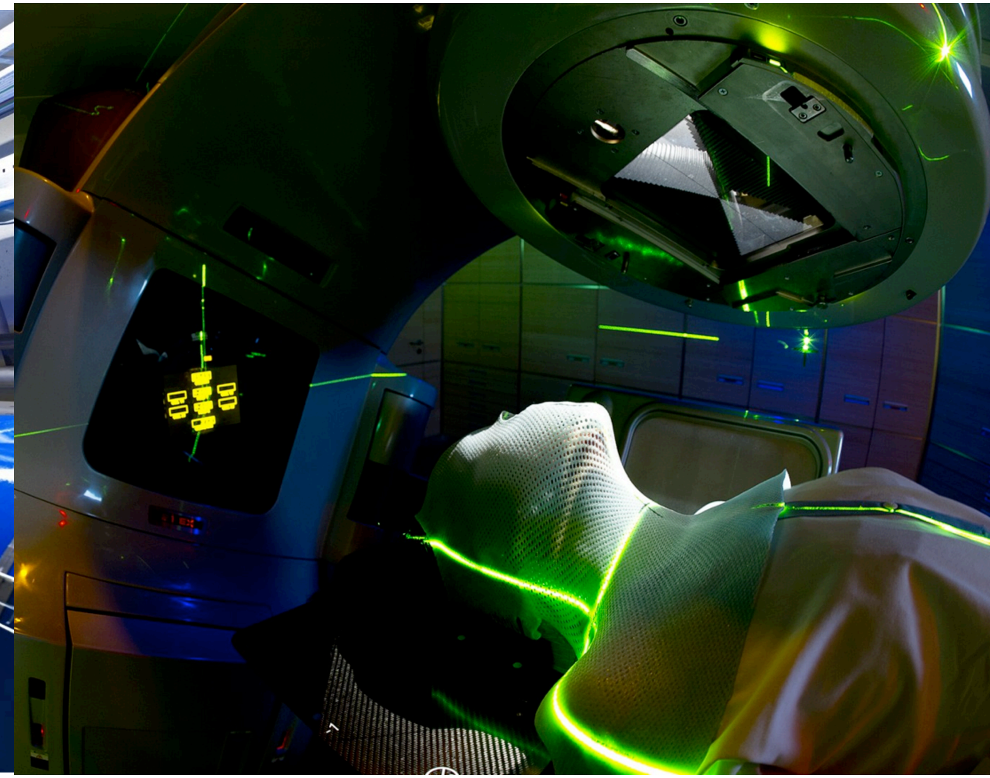
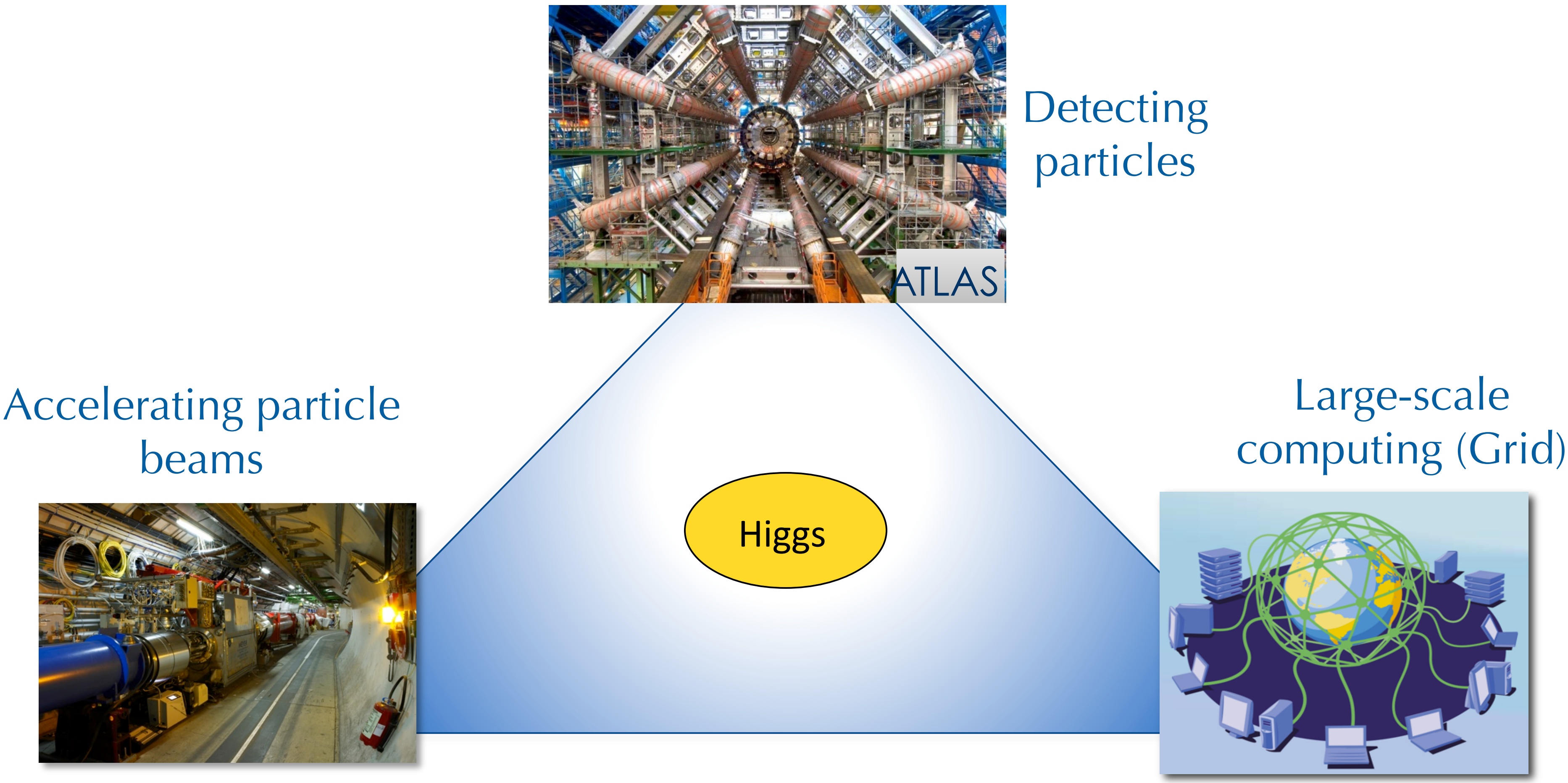
Medical Applications from Physics-1

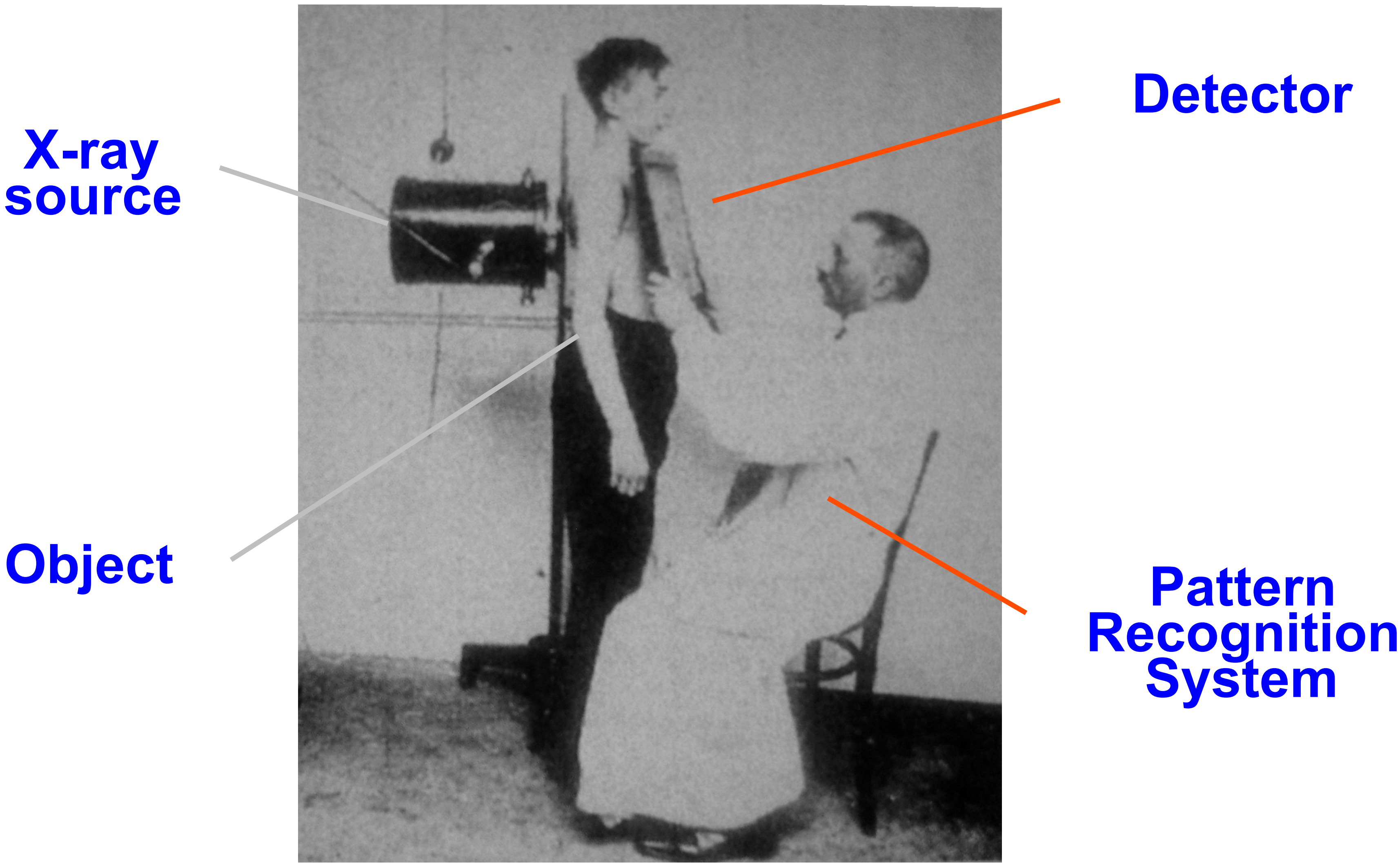


CERN Summer School Student Lectures, 2018

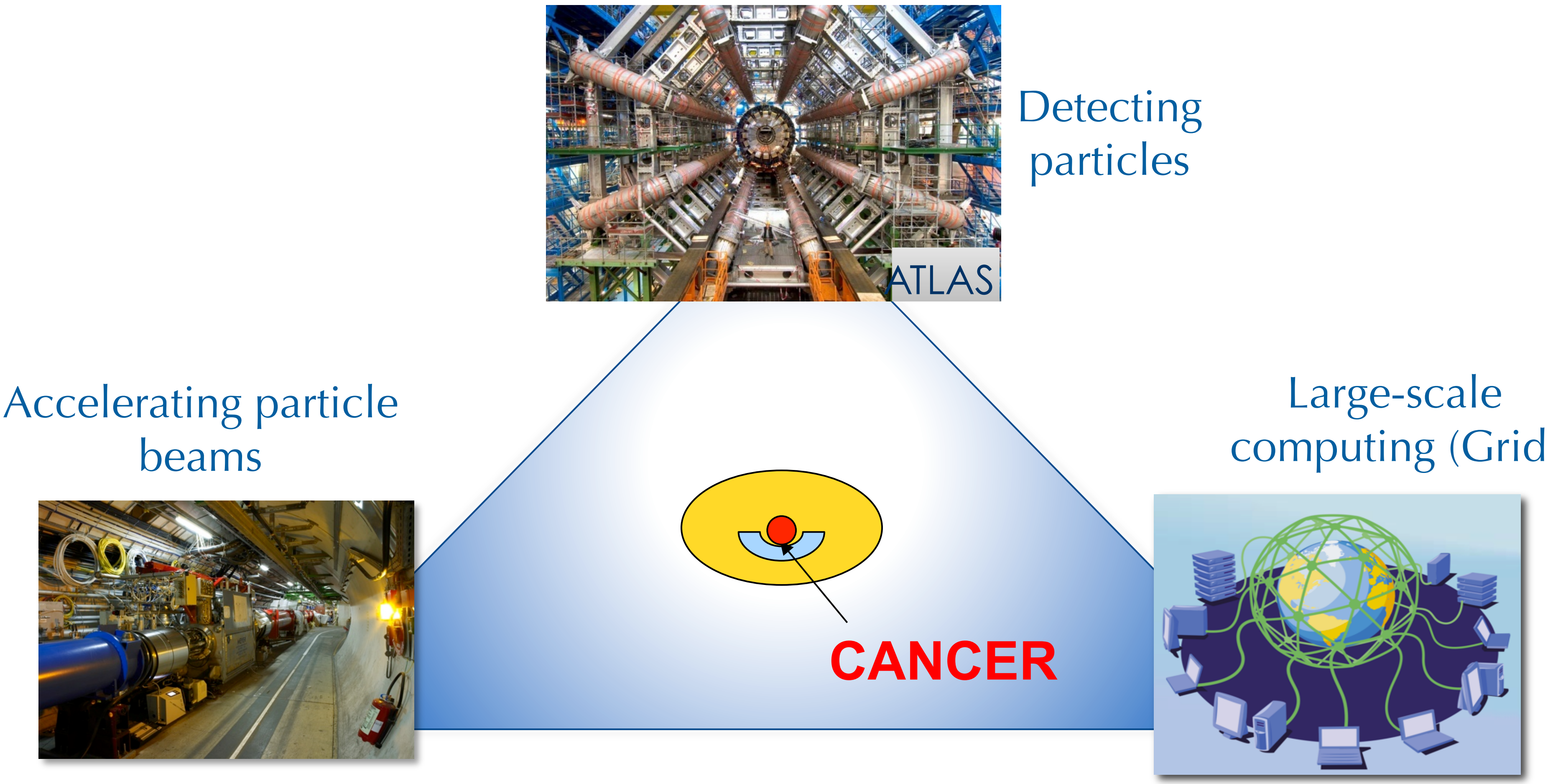
Manjit Dosanjh, CERN
manjit.dosanjh@cern.ch

Physics Technologies




X-ray
source
Detector
Object
Pattern
Recognition
System

Physics technologies for cancer



Why Cancer and physics technologies?

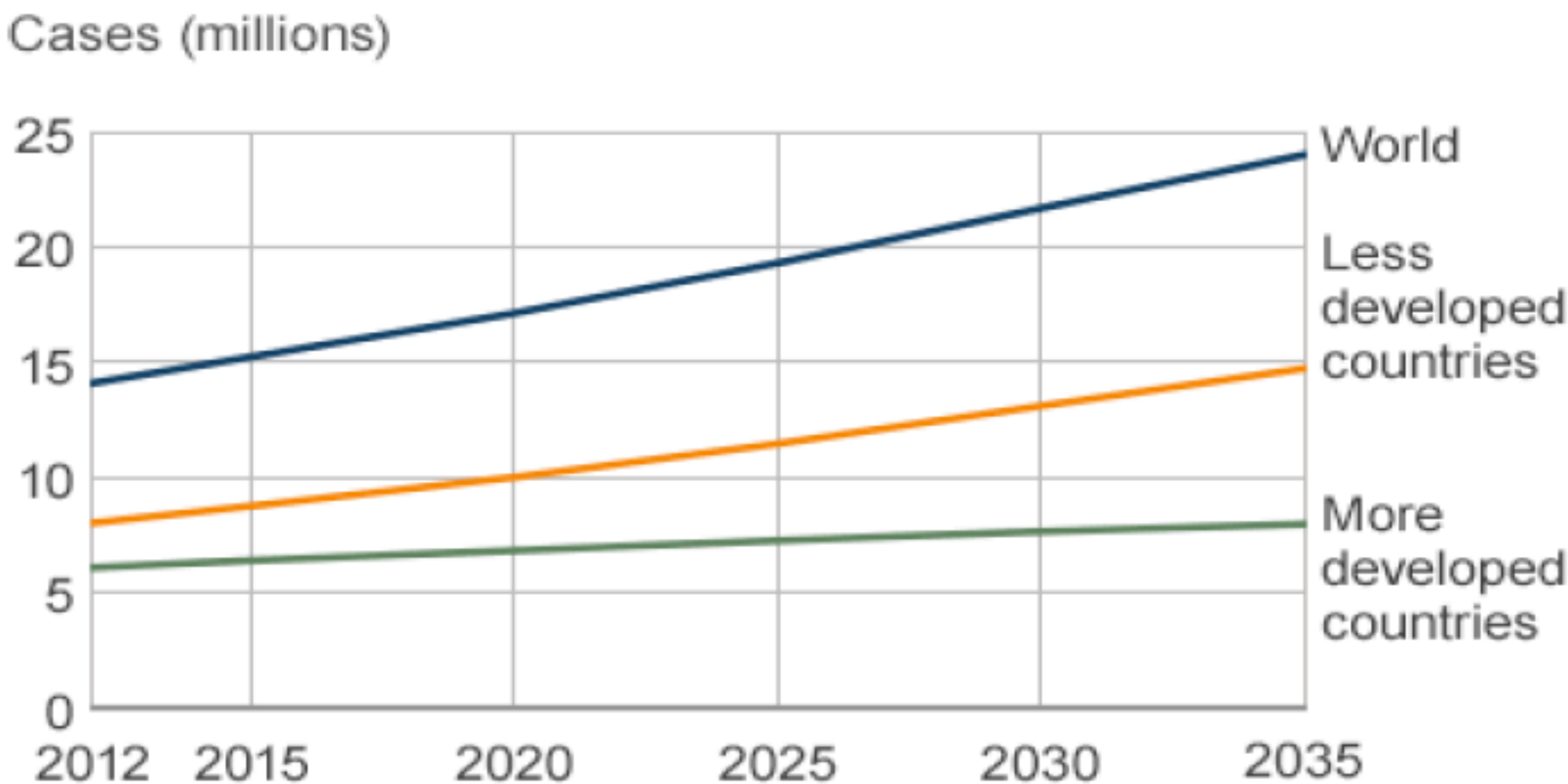
It is a large and a growing societal challenge:

- More than 3 million new cancer cases in Europe in 2015
- Nearly 15 million globally in 2015
- This number will increase to 25 million in 2030
- Currently around 8 million deaths per year

How can physics help?

GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

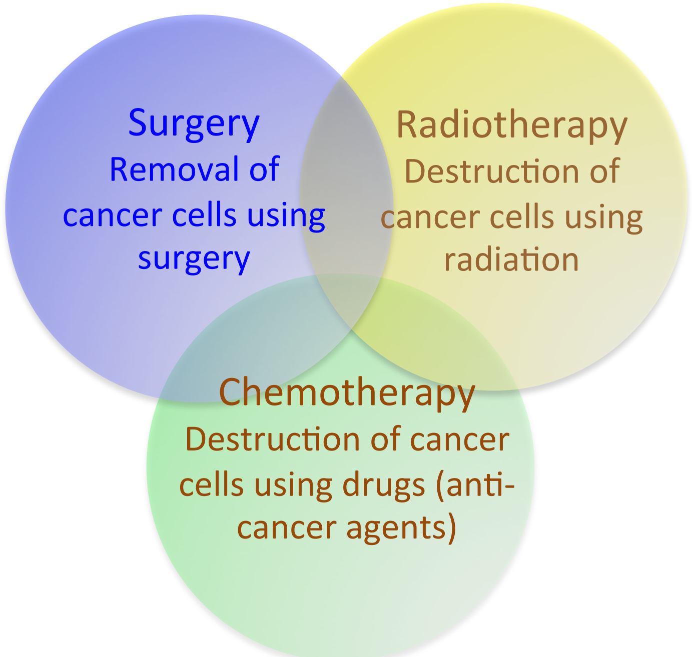
Predicted Global Cancer Cases



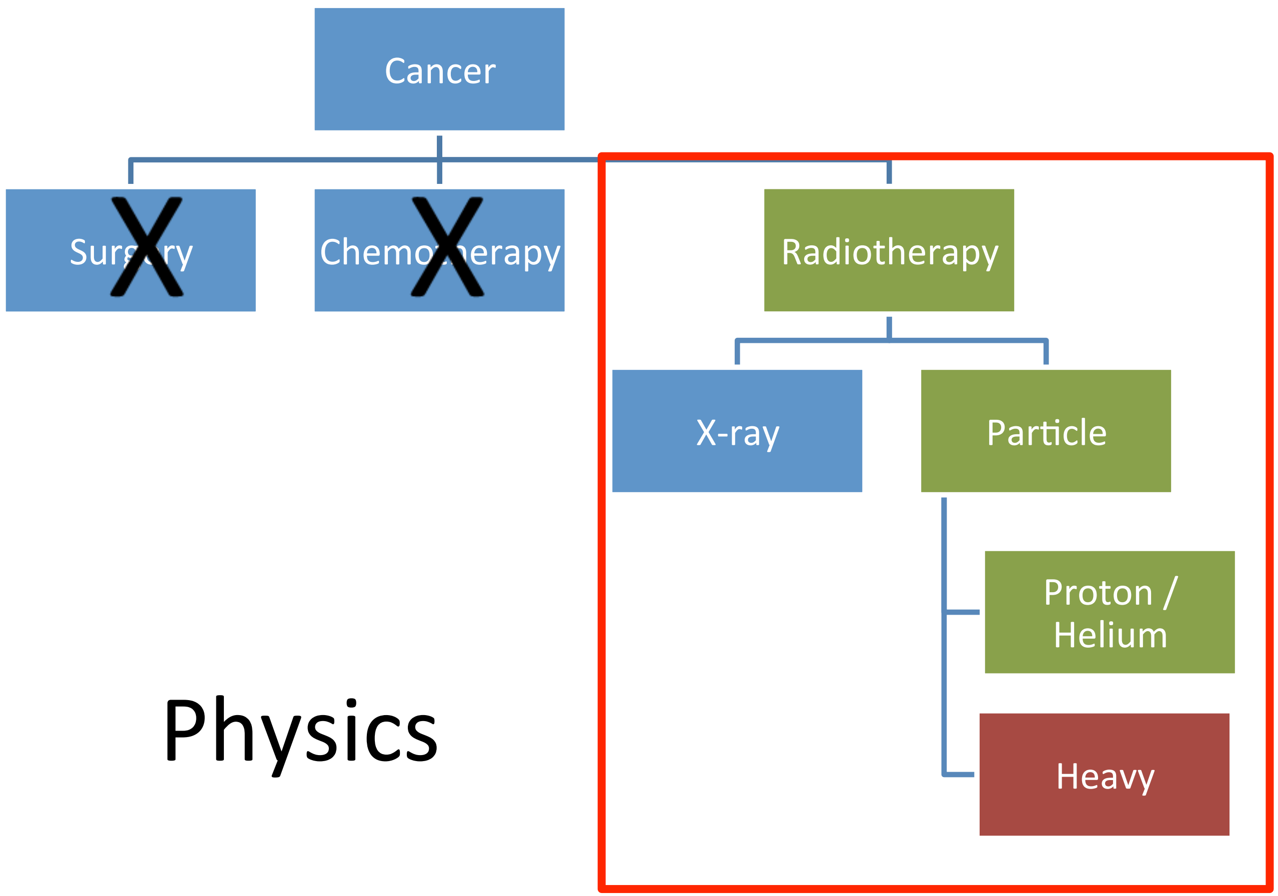
Source: WHO GloboCan

Some facts about Cancer

- Tumour: why?
  - Abnormal growth of cells
  - Malignant: uncontrolled, can spread → cancer
  - Age expectancy
- Treatment: how?
  - Surgery
  - Radiation
  - Chemotherapy



Cancer treatment



The Challenge of Treatment

Ideally one needs to treat:

- The tumour
- The whole tumour
- And nothing BUT the tumour”

Radiotherapy has two equally important goals to destroy the tumour and protect the surrounding normal tissue. Therefore “seeing” in order to know where and precise “delivery” to make sure it goes where it should are key.

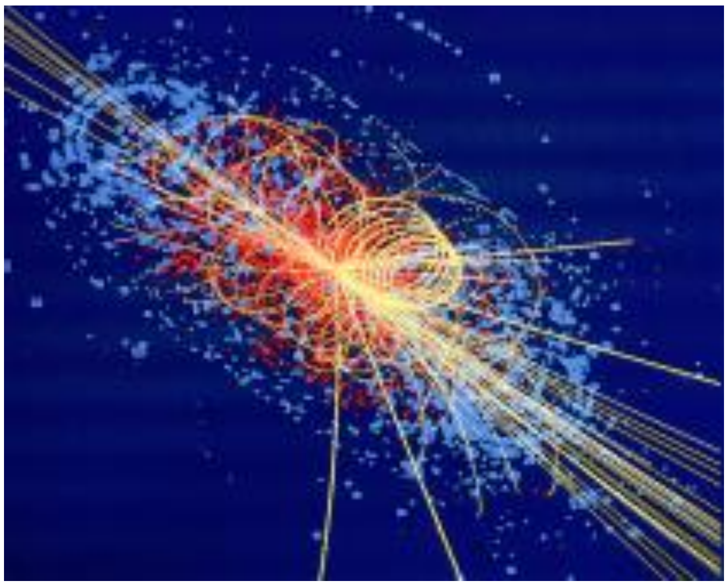
Improving Cancer Outcome

Earlier diagnosis, better tumour control, fewer side-effects

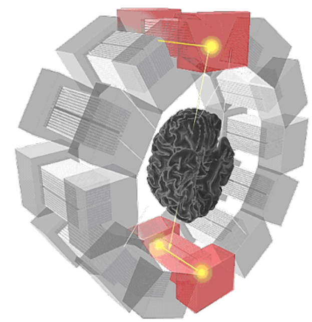
- Imaging: accuracy, multimodality, real-time, organ motion
- Accelerator technologies: higher dose, more localised, real time targeting
- Data: analysis, image fusion/reconstruction, treatment planning, sharing, screening, follow-up patient ….
- Biology: basic research, fractionation, radio-resistance, radio-sensitization, immunotherapy

No treatment without detection!

Particle Detection

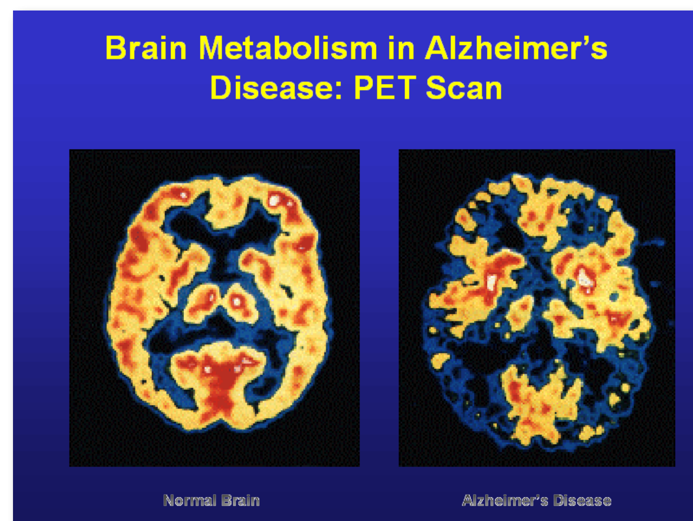


Imaging



PET Scanner

Breast imaging
(ClearPEM)



cds.cern.ch/record/1611721

CERN’s role in detection and imaging…

Continuous development in particle physics:

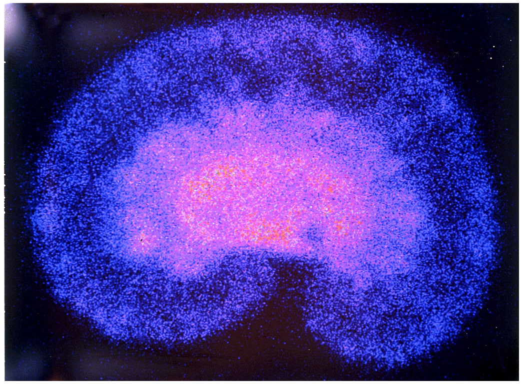
- Scintillating crystals (David Townsend …..)
- Pixel detectors (Medipix collaboration)
- Diamond detectors
- Multi-wire proportional chambers/ GEMS (Charpak…)
- Resistive Plate Chambers for imaging

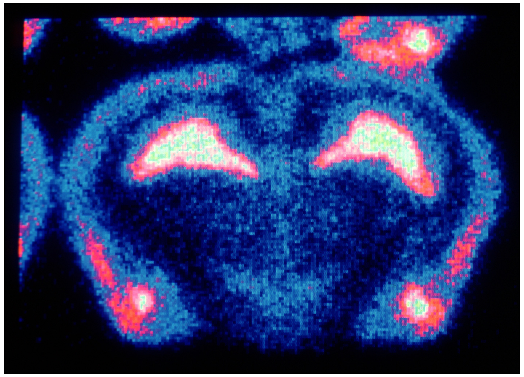
Low dose digital X-Ray Imaging

1968

Physics Nobel Prize 1992

Georges Charpak

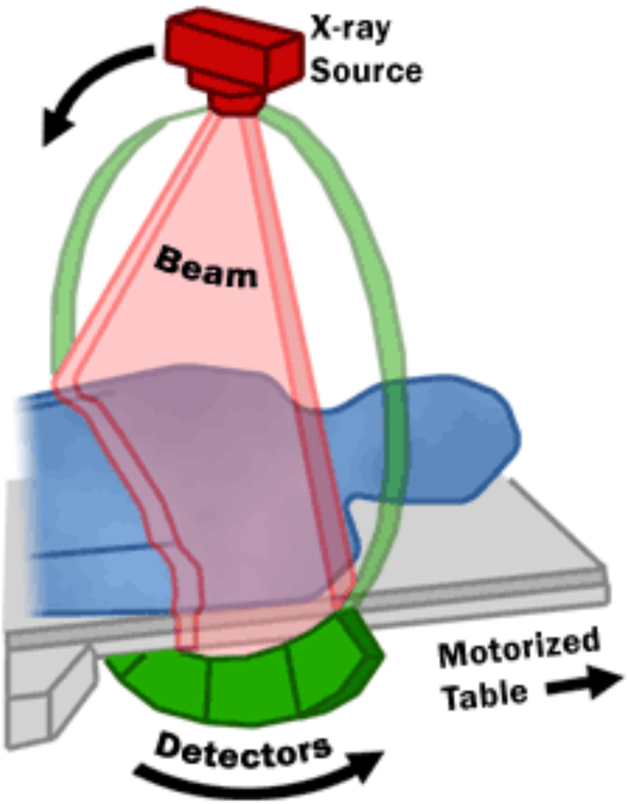




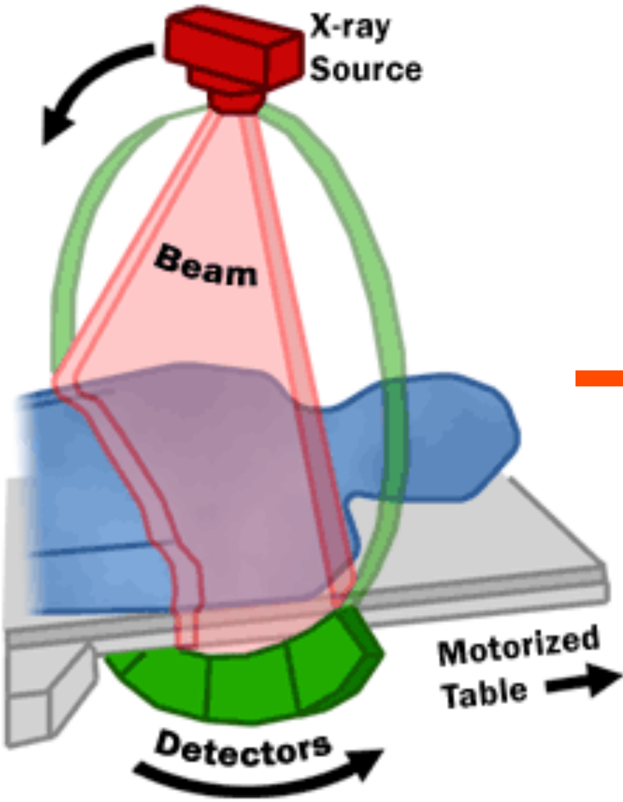
Low dose X-ray image of rat brain and kidney the use of MWPC

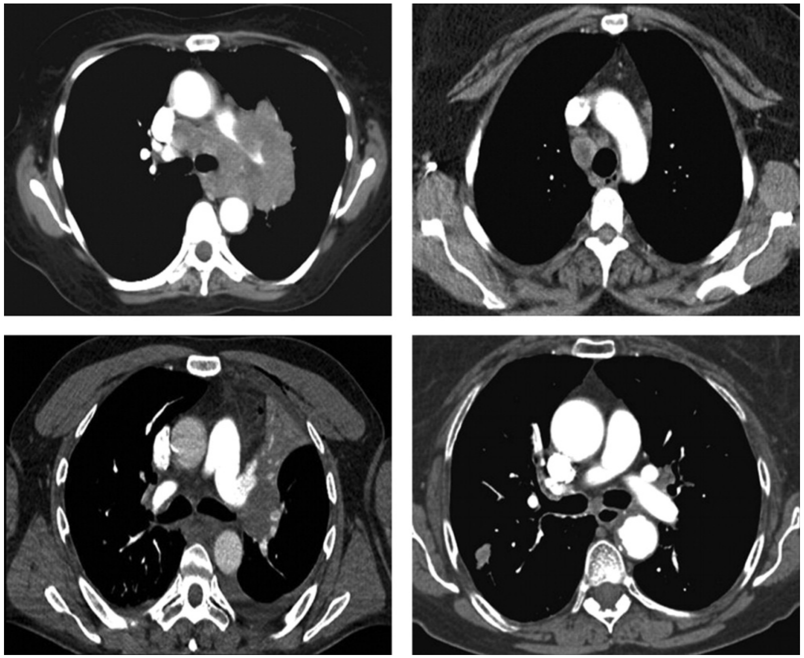
CT – Computed Tomography

"3d X-rays"



CT – Computed Tomography



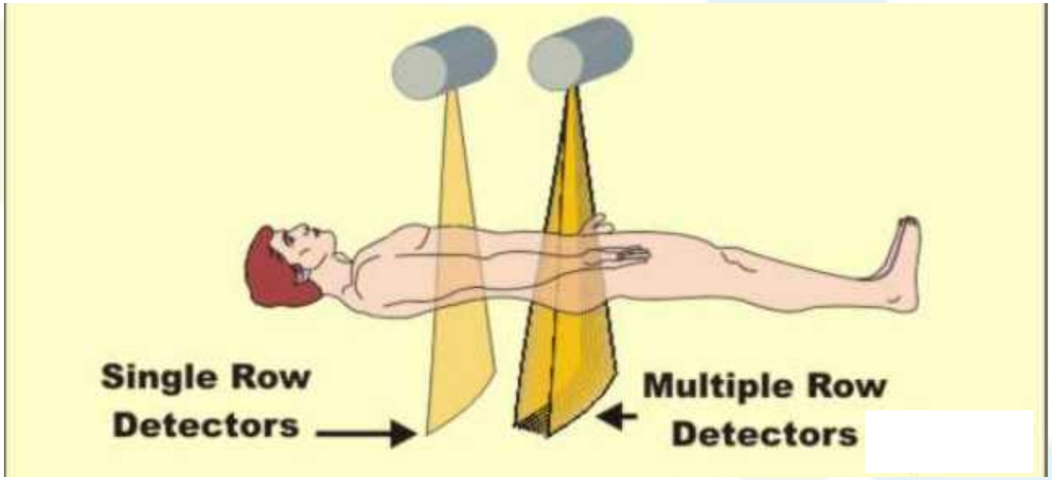


"3D-imaging"

CT is a key driver of changein the medical field

2000-2008 “CT Slice War”

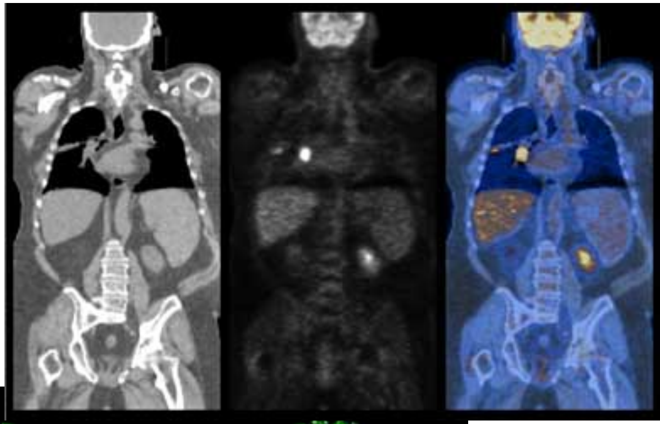
- ***CT became very fast with small voxel / pixels***
  - 2000: acquire a single transverse slice per rotation
  - 2012: acquire up to 64-500 slices per rotation



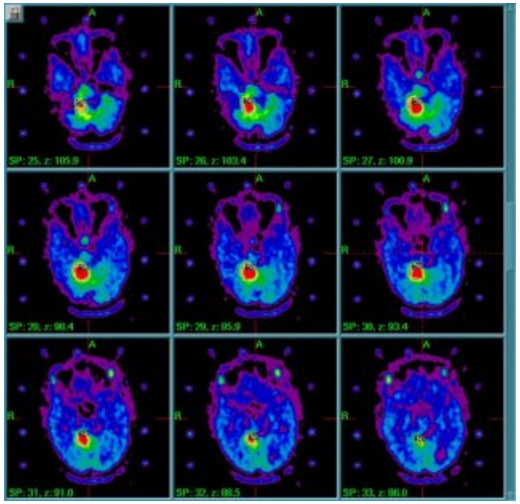
mars

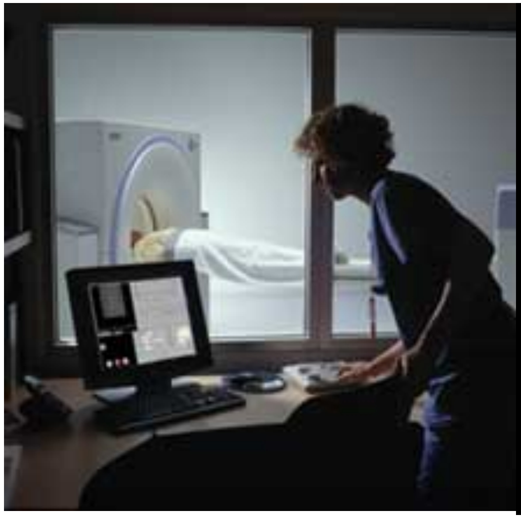
PET: antimatter for clinical use

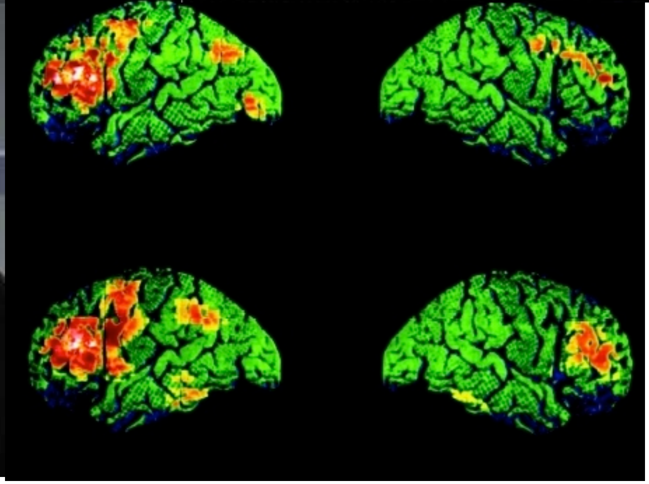
- Not only science-fiction



- Positrons are used in PET:
- PET = Positron Emission Tomography





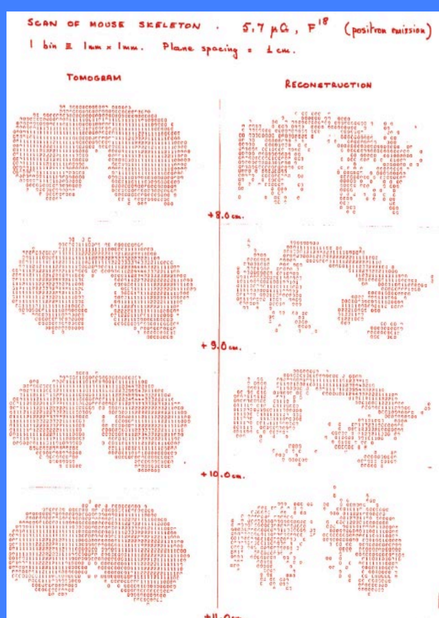


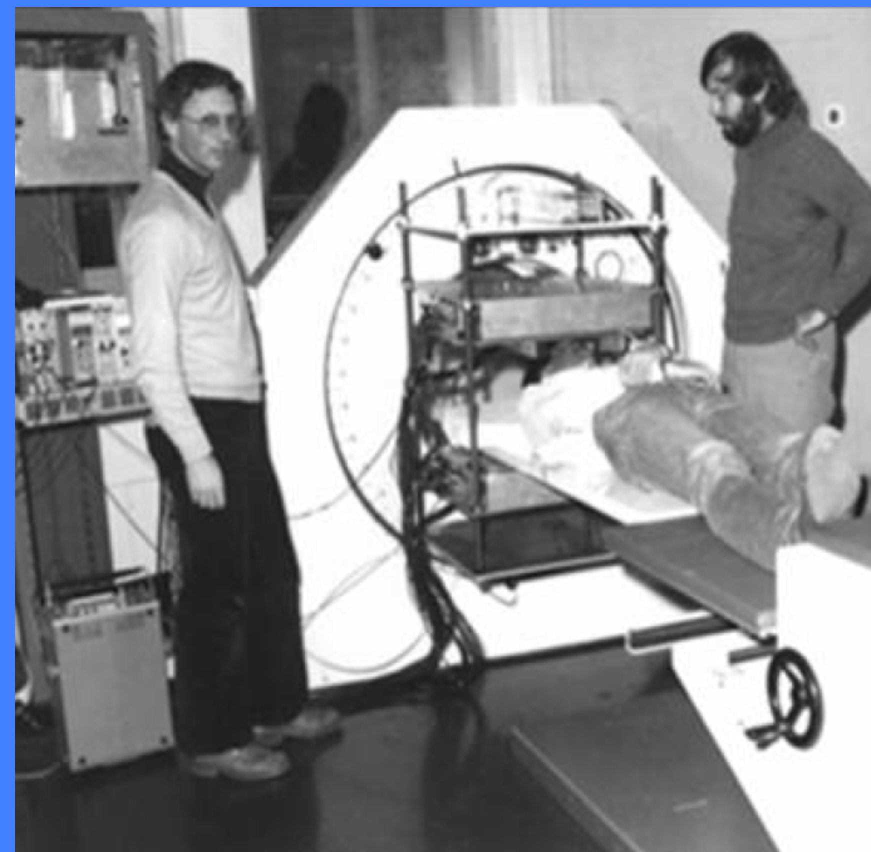
PET Imaging activities at CERN

Alan Jeavons and David Townsend

built and used in Geneva Hospital

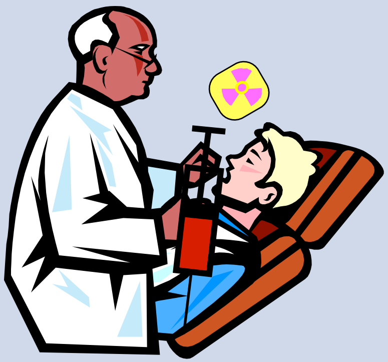
a PET system based on high-density avalanche gas chambers HIDACs

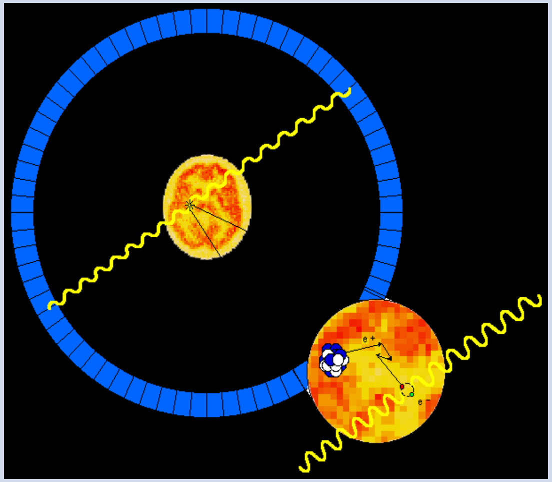




PET Principle

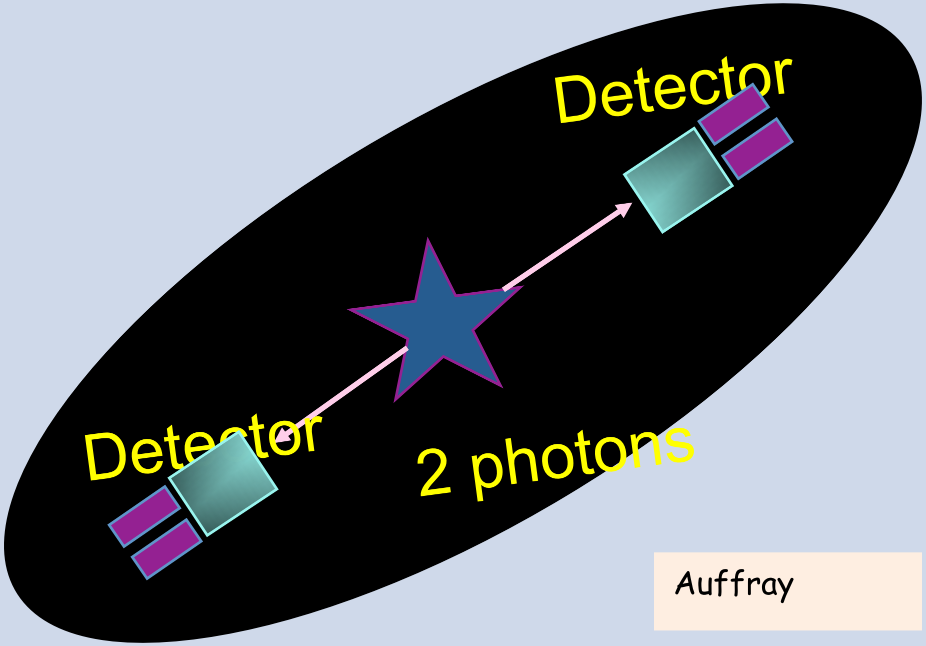
A positron emitting radiopharmaceutical is injected into the patient: the distribution





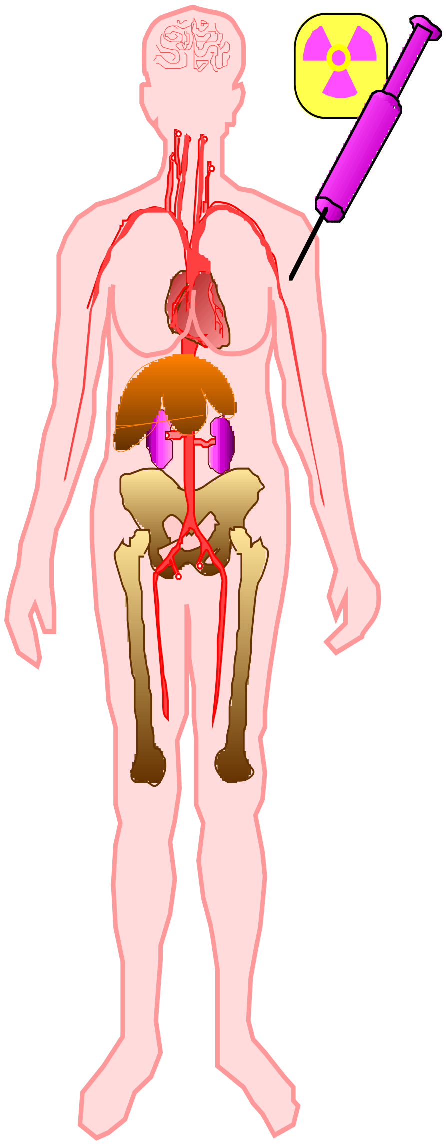
The emitted positrons annihilate with electrons in the tissue producing back-to-back photons detected by scintillating crystals

The patient is placed in the imaging scanner



Auffray

PET: how it works

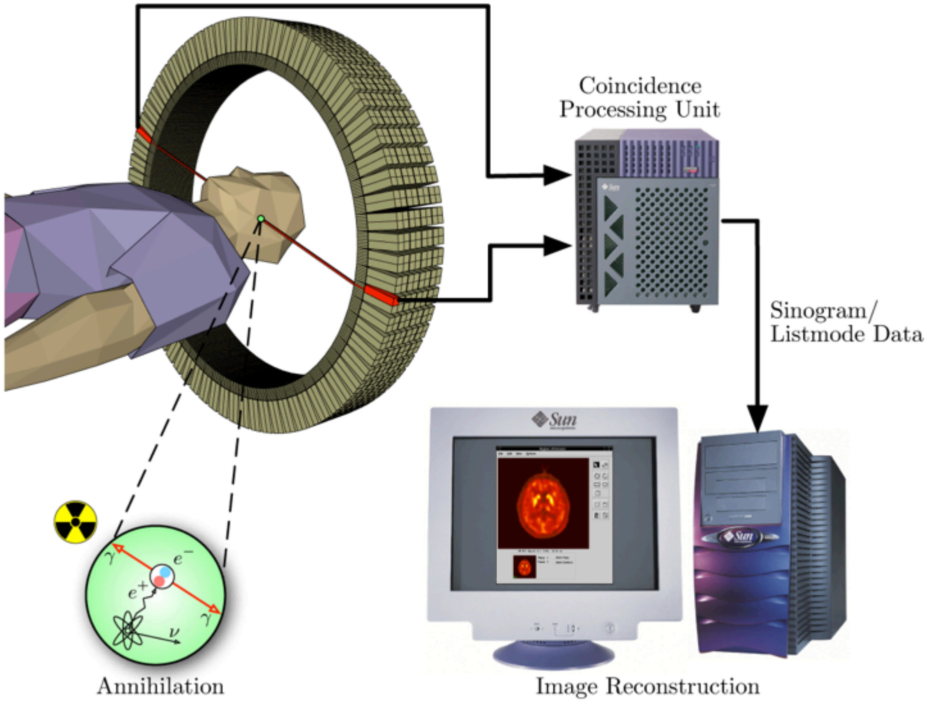


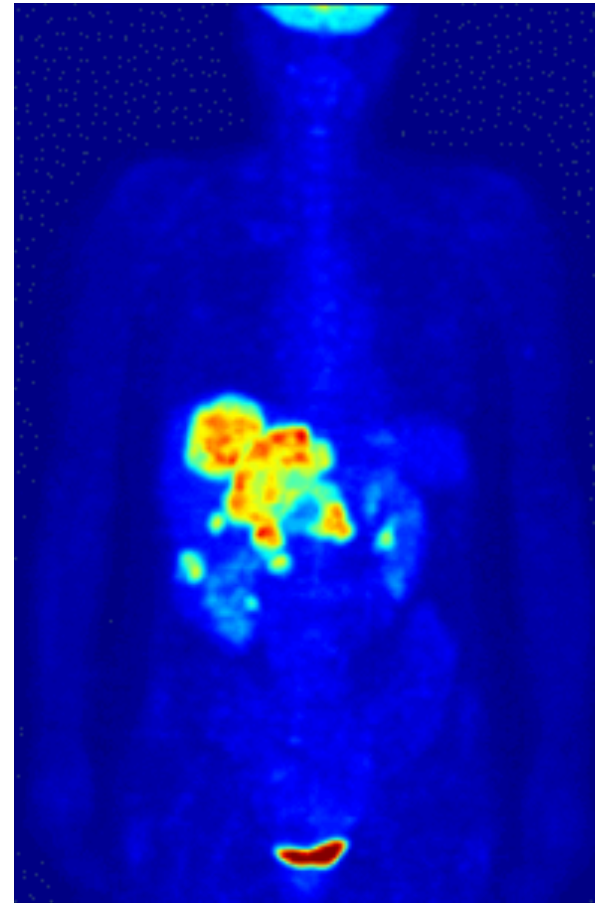
- Drug is labeled with positron (β+) emitting radionuclide.
- Drug localizes in patient according to metabolic properties of that drug.
- Trace (pico-molar) quantities of drug are sufficient.
- Radiation dose fairly small (<1 rem = 0.01 Sv).

PET – How it works

http://www.nymus3d.nl/portfolio/animation/55

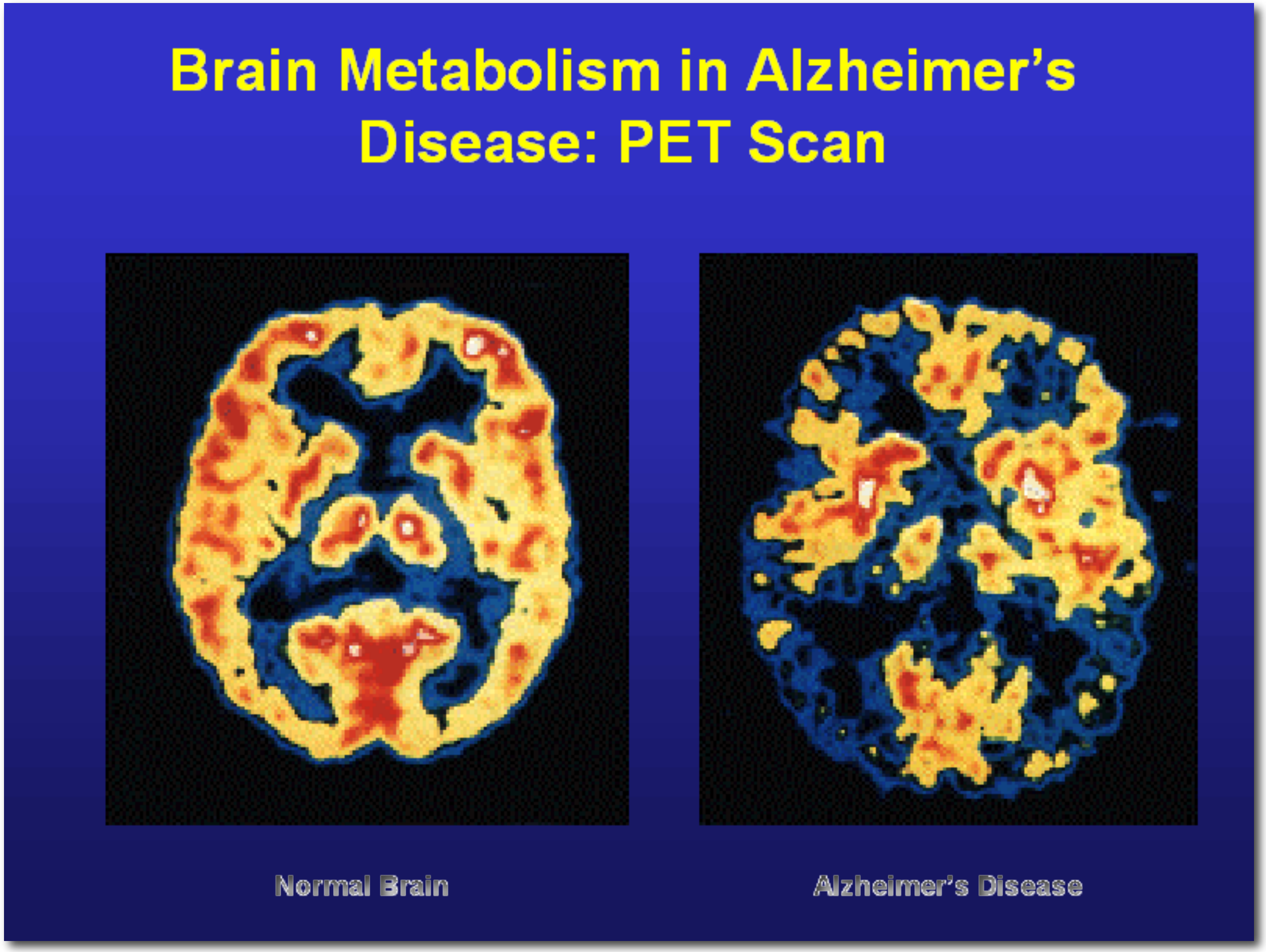
Positron Emission Tomography



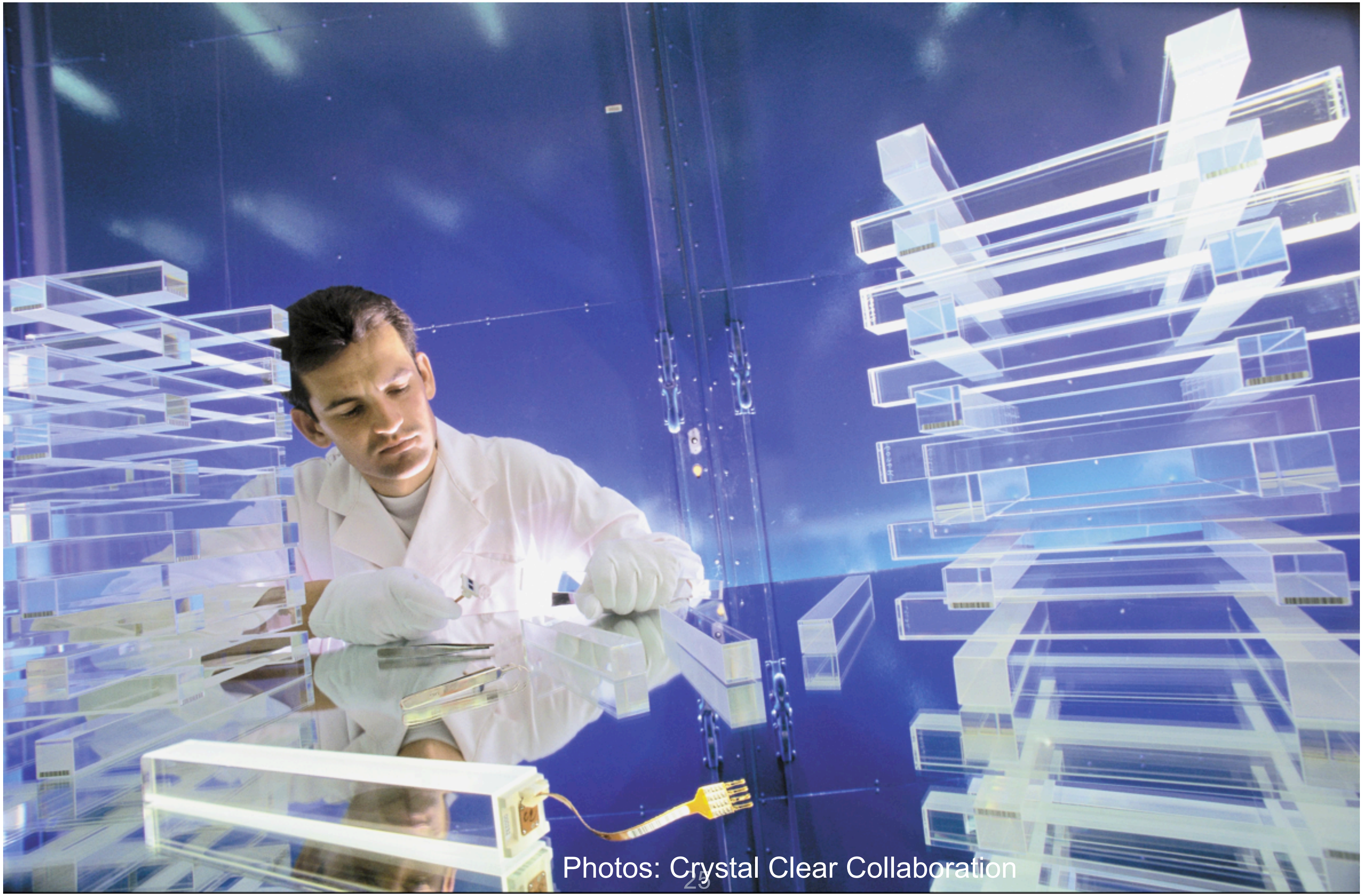


- ^{18}FDG carries the ^{18}F to areas of high metabolic activity
- 90% of PET scans are in clinical oncology
- 3D - image

PET measures tissue activity: can be up or down



Crystal Clear Collaboration

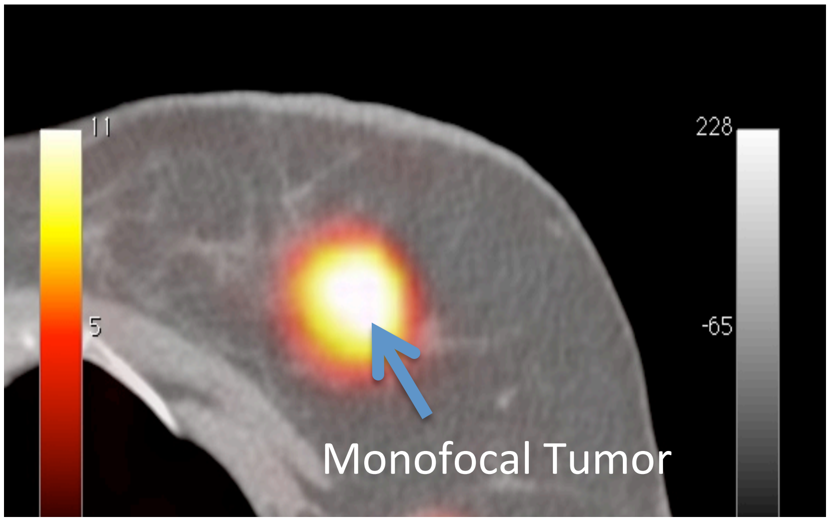


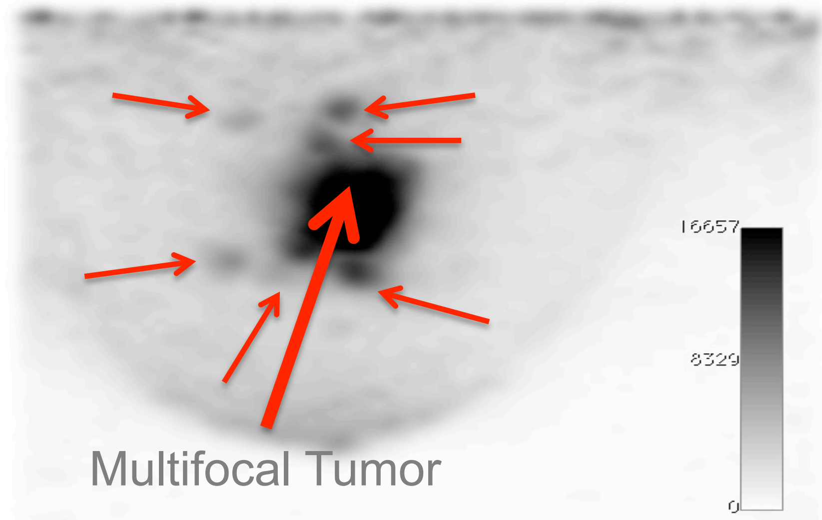
Photos: Crystal Clear Collaboration

ClearPEM

PET for mammography: Crystal Clear Collaboration

Breast Cancer Detection





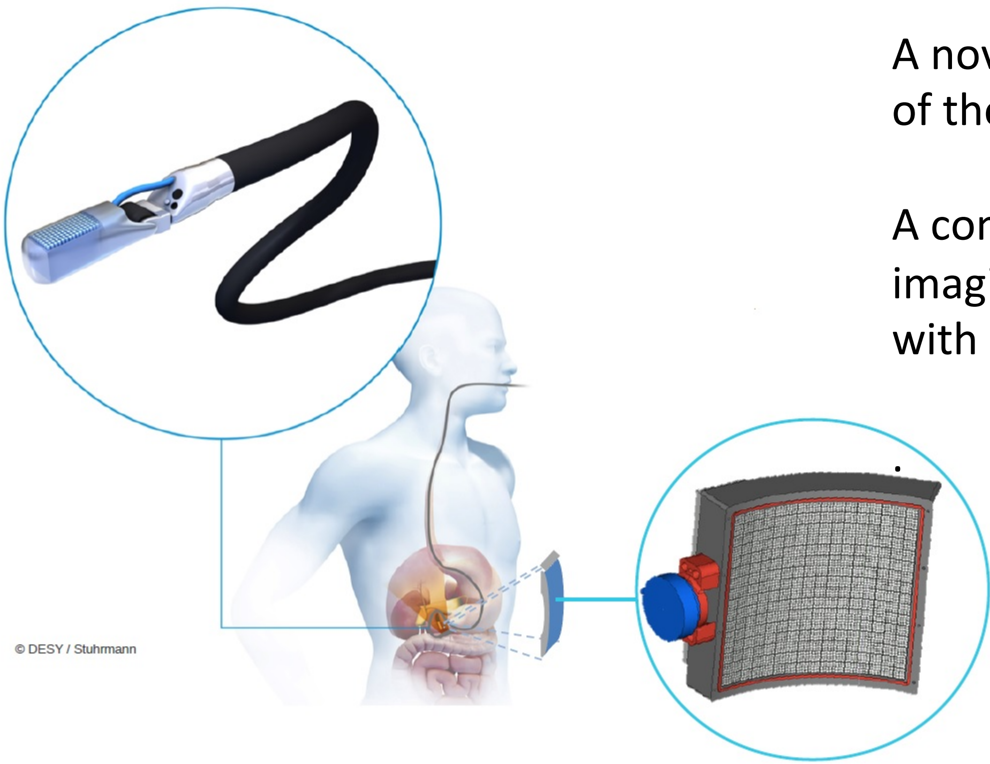
PET Wholebody

ClearPEM dedicated Breast imaging

Courtesy of Paul Lecoq, : Crystal Clear Cololaboration

Endo TOFPET-US

a novel multimodal tool for endoscopy and positron emission tomography



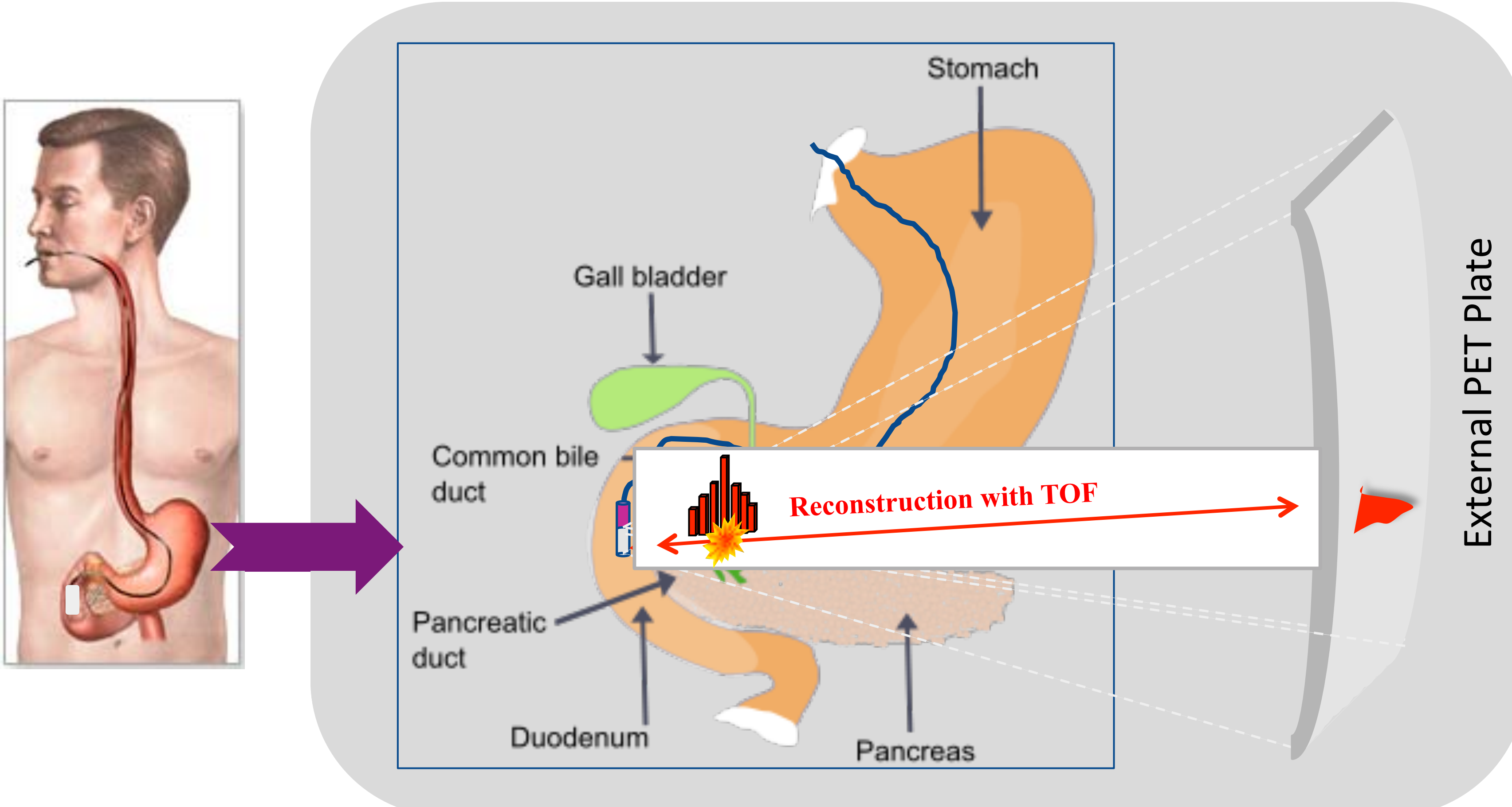
A novel imaging system for endoscopic exams of the pancreas or the prostate.

A combination of high resolution metabolic imaging with TOFPET and anatomical imaging with ultrasound.

Endo = Endoscopic
TOF =Time of Flight PET
US = Ultrasound

Courtesy of Paul Lecoq, : Crystal Clear Collaboration

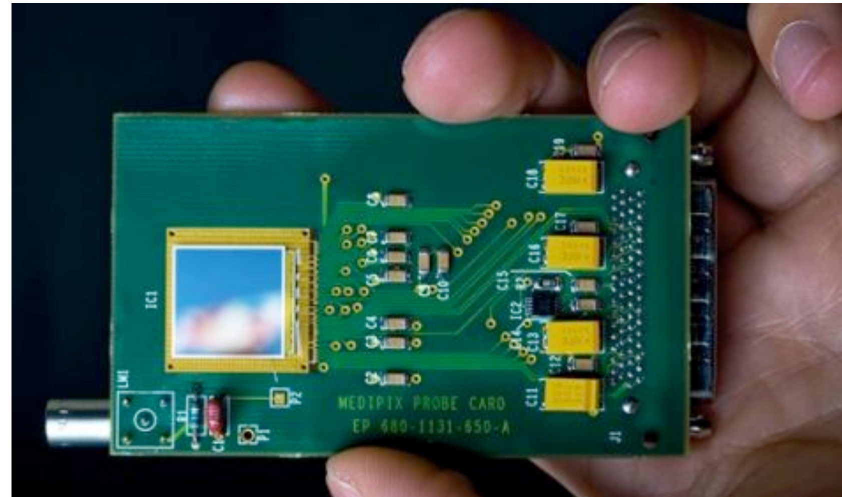
The Principle



Courtesy of Paul Lecoq, Crystal Clear Collaboration

Medipix

- High Energy Physics original development:
  - Particle track detectors
  - Allows counting of single photons in contrast to traditional charge integrating devices like film or CCD
- Main properties:
  - Fully digital device
  - Very high space resolution
  - Very fast photon counting
  - Good conversion efficiency of low energy X-rays



Credits: Simon Procz, University of Freiburg

Anatomical imaging is now really good

Molecular imaging is the future

What is the tissue?

What is its behaviour?

Is the treatment working?

(not just size, shape, location)

What the researcher wants to know

- *Constituents (fat, water, calcium, iron)*
- *Cancer and pathogen labels*
- *Physiological markers*
- *etc*

Anatomical imaging is now really good

Molecular imaging is the future

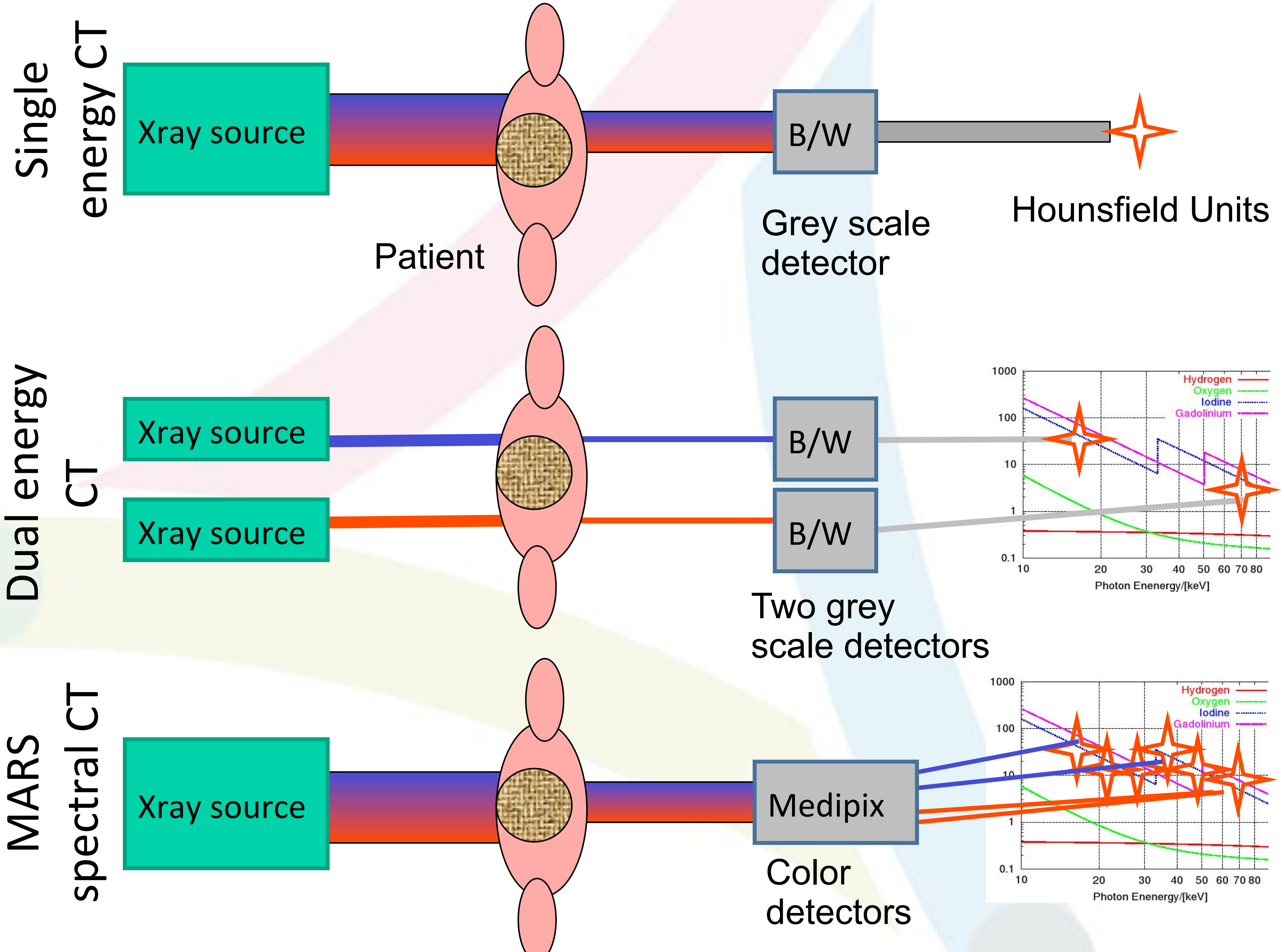
What is the tissue?

What is its behaviour?

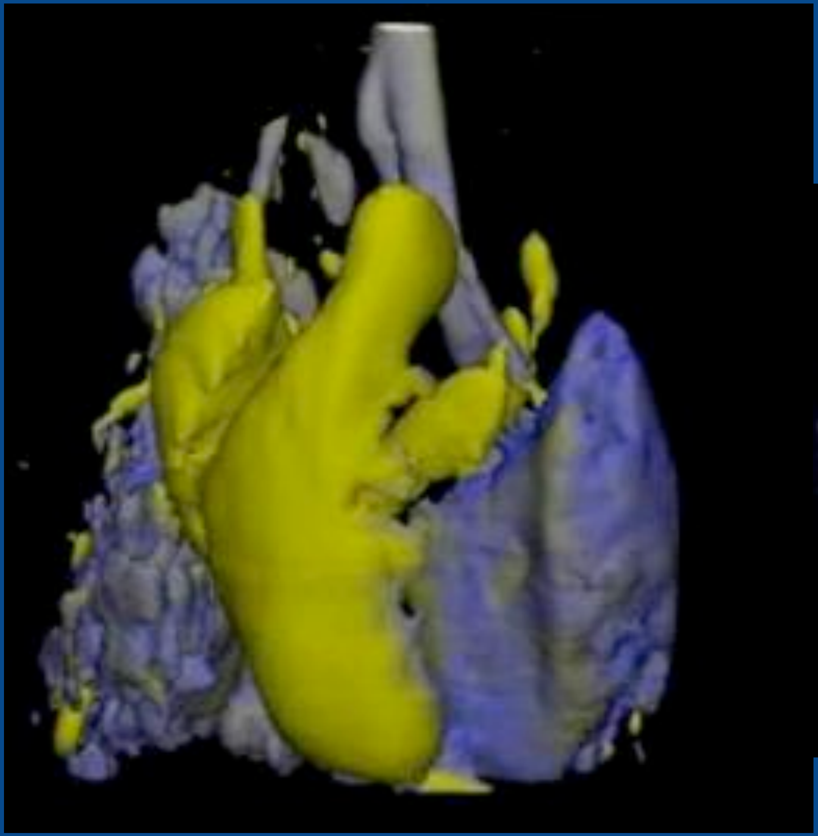
We need a fundamental change in the information provided by x-rays

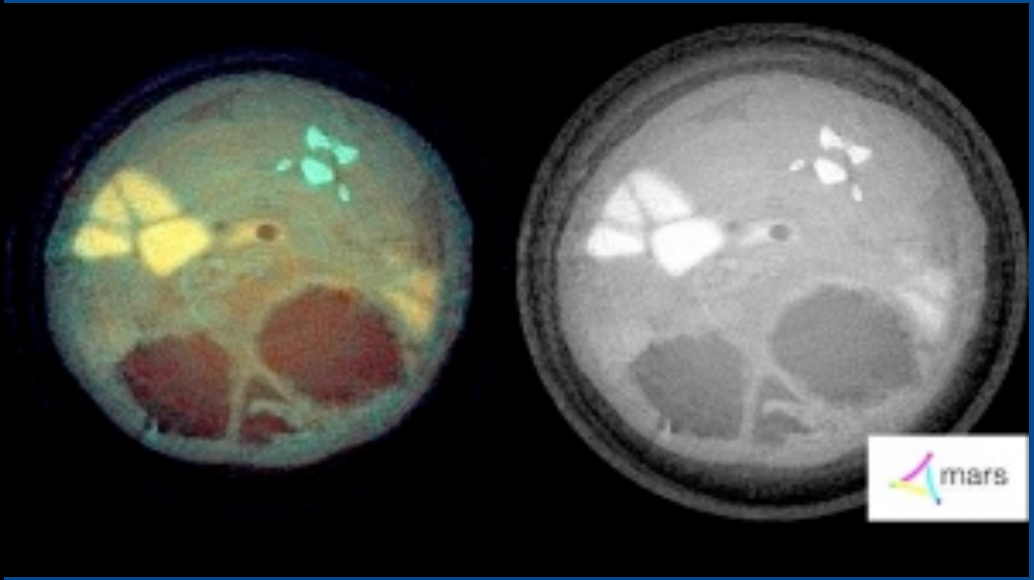
- *Constituents (fat, water, calcium, iron)*
- *Cancer and pathogen labels*
- *Physiological markers*
- *etc*

Single- , dual-, and spectral CT



MARS – MEDIPIX ALL RESOLUTION SYSTEM

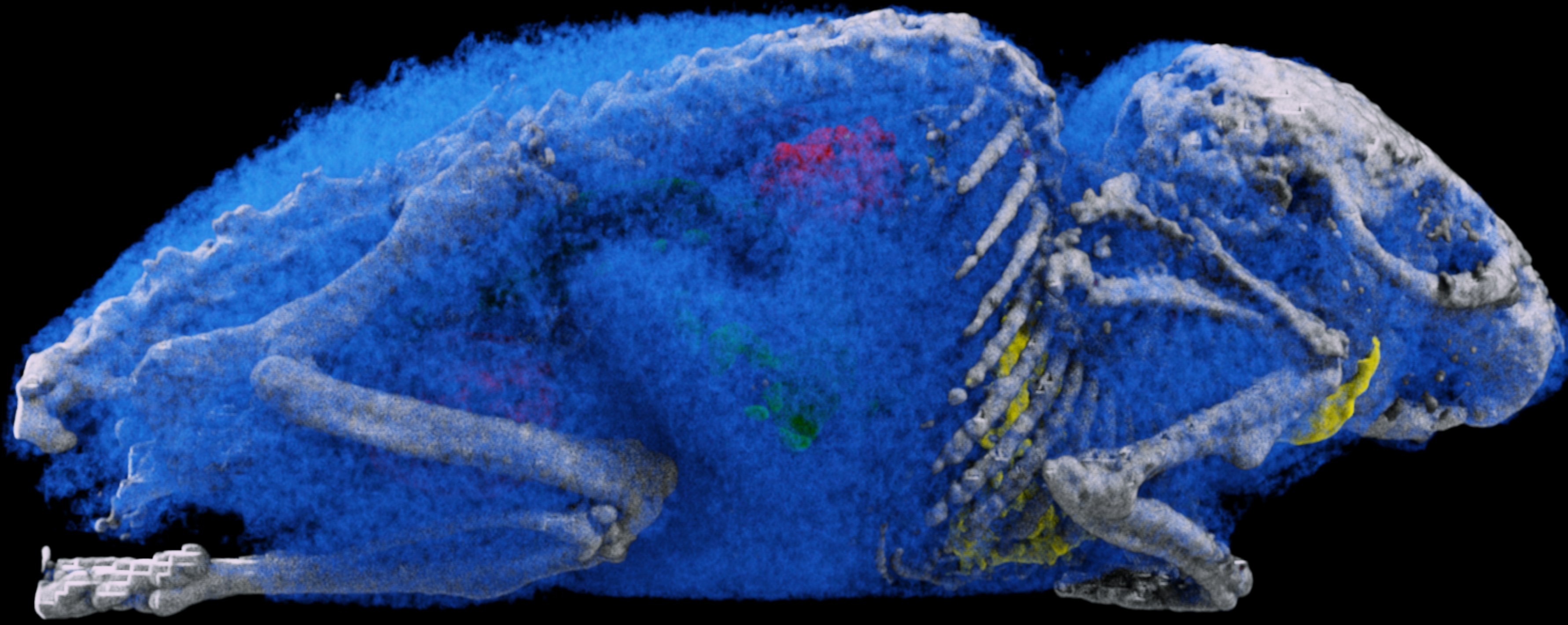




courtesy of MARS Bioimaging Ltd)

Greyscale to Material Imaging

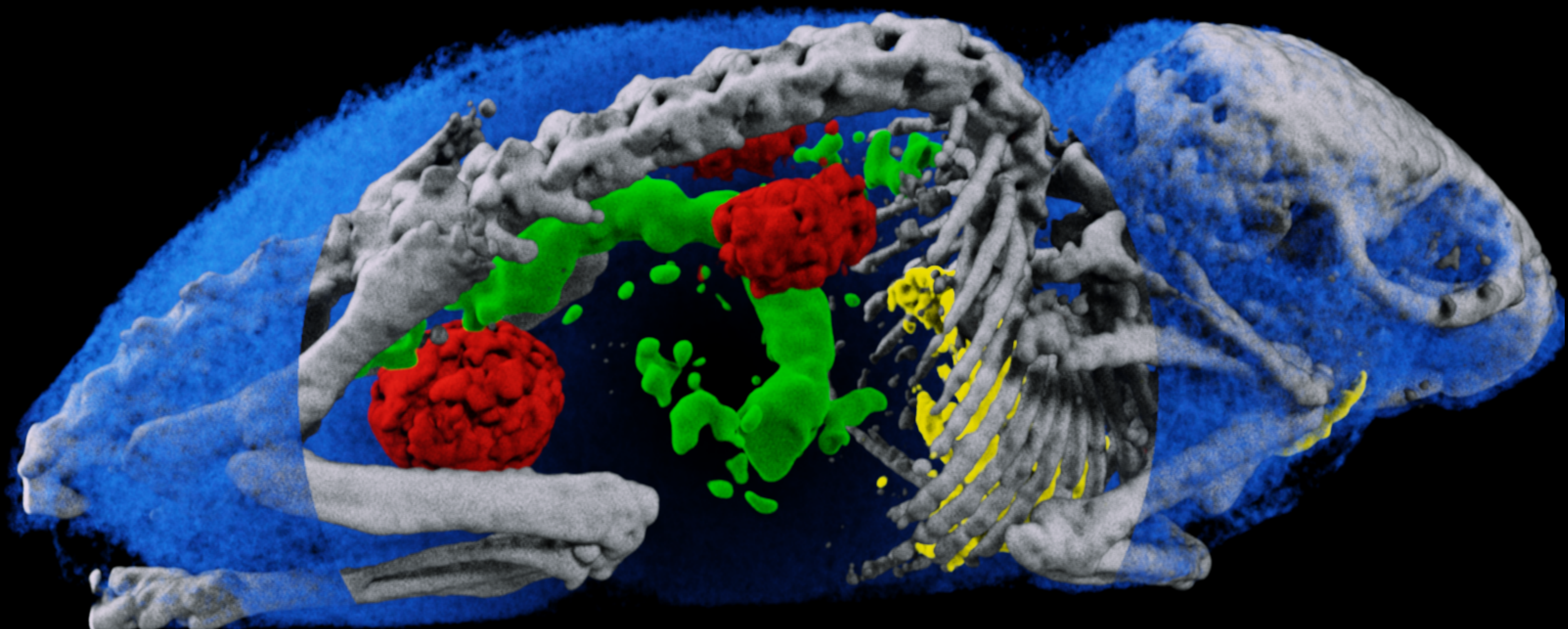
A mouse containing, gold, gadolinium, and iodine



All materials are shown in this image

Images presented and the European Congress of Radiology, Vienna, March 2017. MARS BioImaging Ltd

Greyscale to Material Imaging



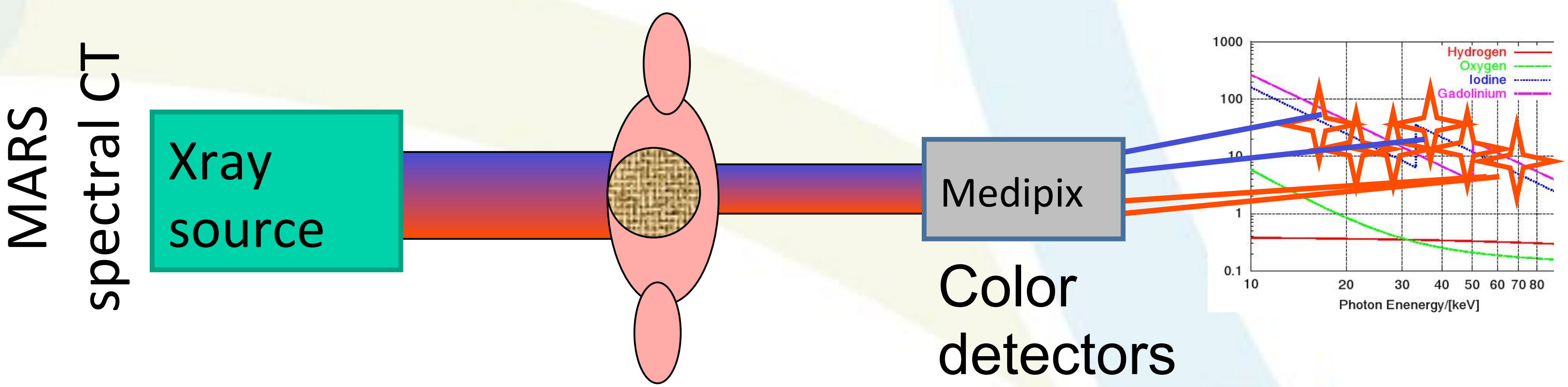
The water has been partly cut away to reveal the bone, gold, gadolinium and iodine

Images presented and the European Congress of Radiology, Vienna, March 2017. MARS BioImaging Ltd

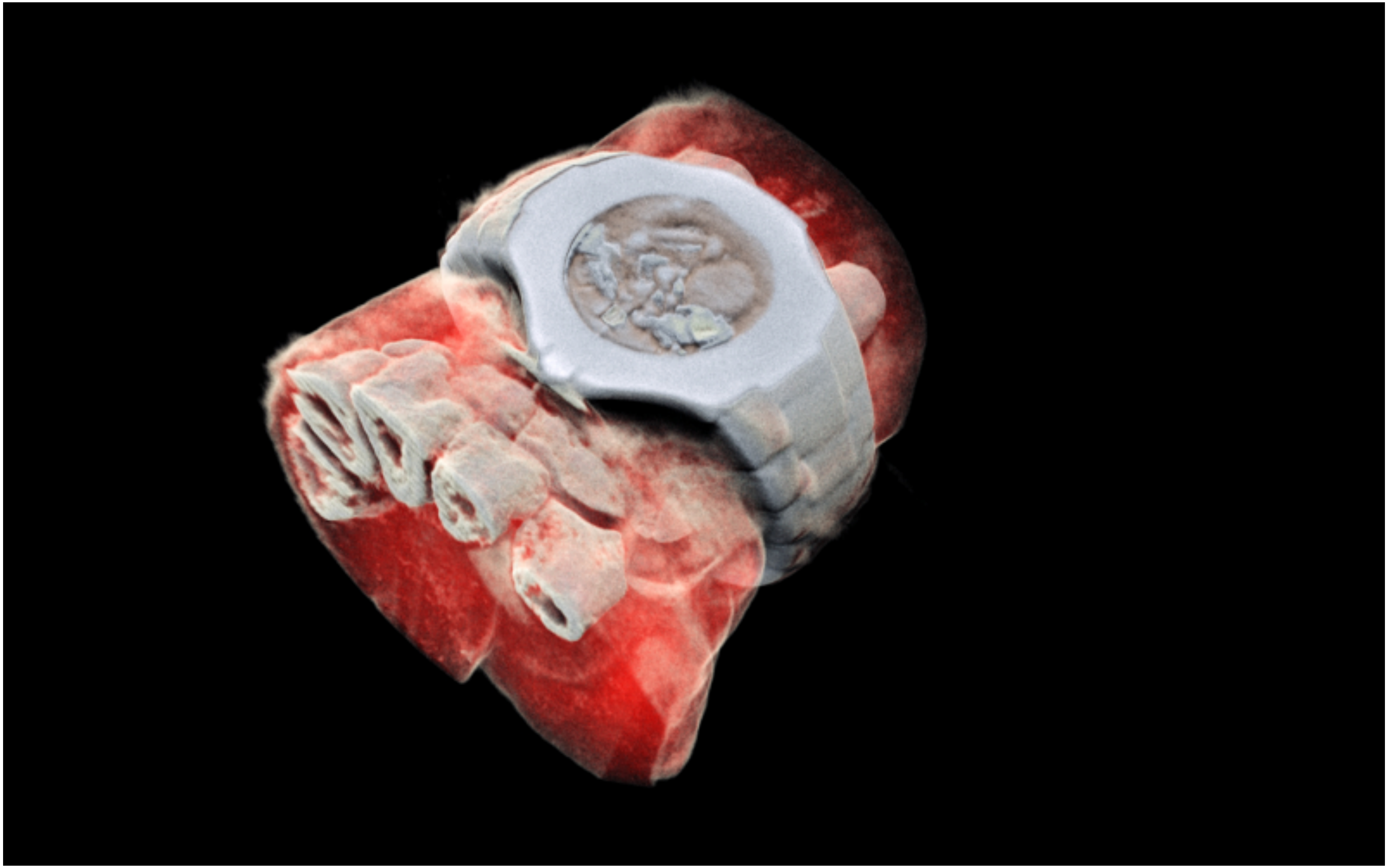
Spectral CT is now possible

Medipix **A**ll **R**esolution **S**ystem

- **Energy resolution**
- Spatial resolution
- Temporal resolution



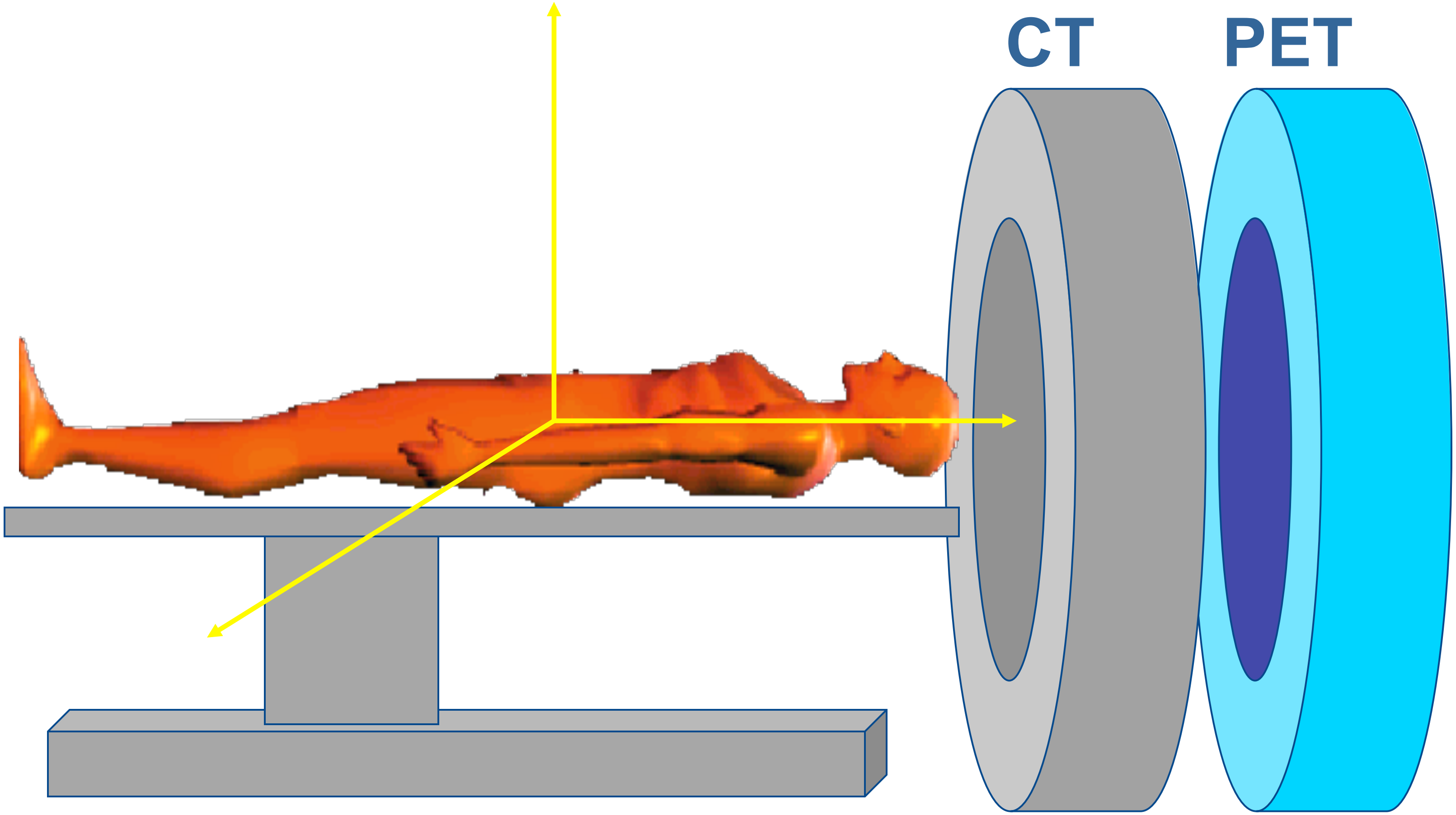
First 3D colour x-ray image of human



A 3D image of a wrist with a watch showing part of the finger bones in white and soft tissue in red. couples the spectroscopic information generated by the Medipix3 with powerful algorithms to generate 3D images (Image: MARS Bioimaging Ltd)

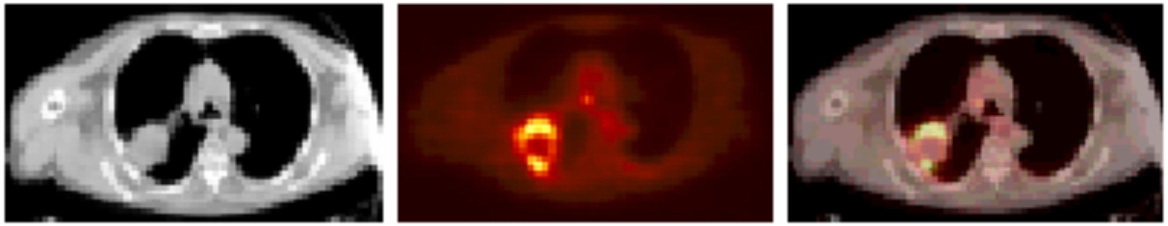
Concept of PET-CT

David Townsend



Multi-modality imaging

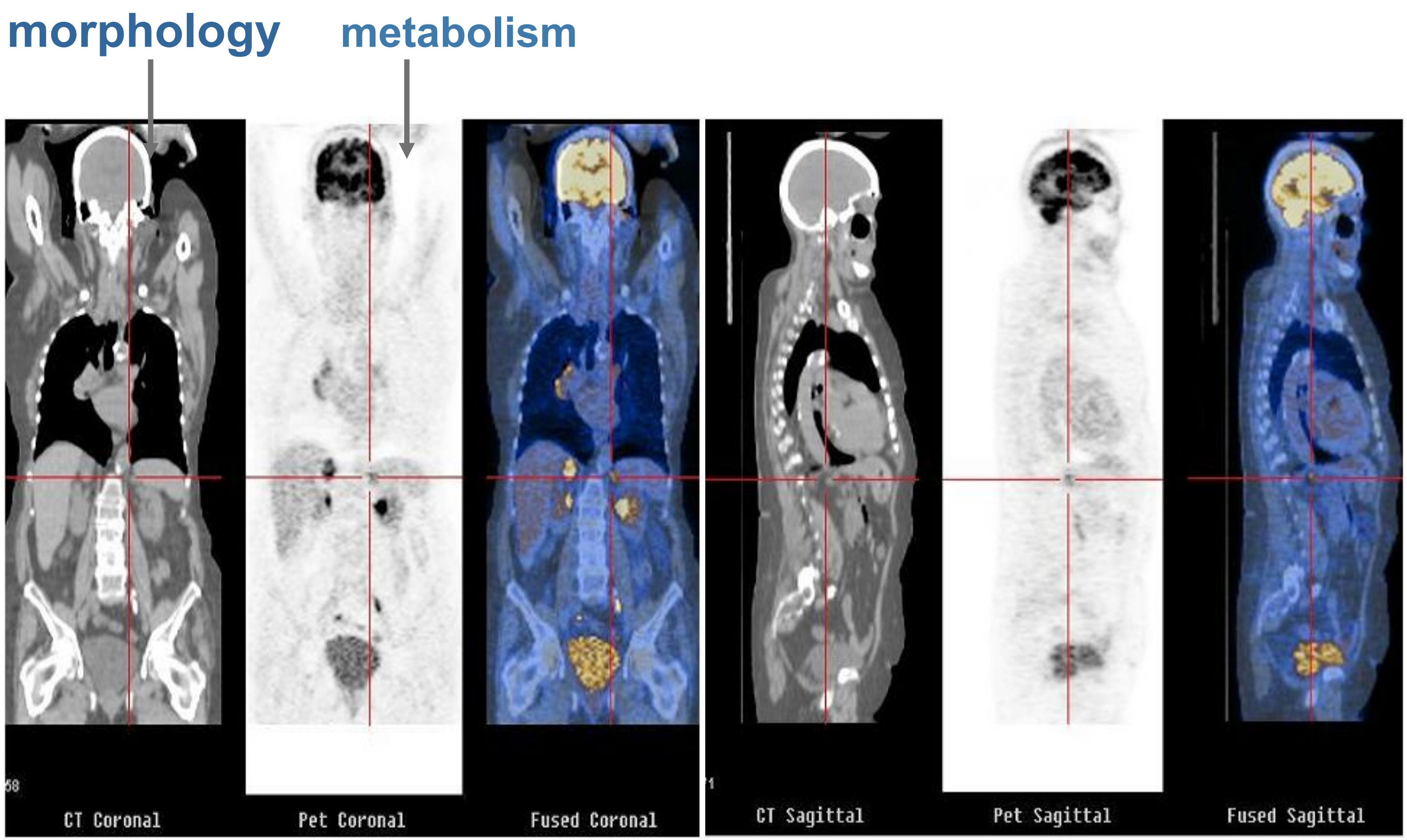
Primary lung cancer imaged with the Dual/Commercial scanner. A large lung tumor, which appears on CT as a uniformly attenuating hypodense mass, has a rim of FDG activity and a necrotic center revealed by PET.



Courtesy of David Townsend

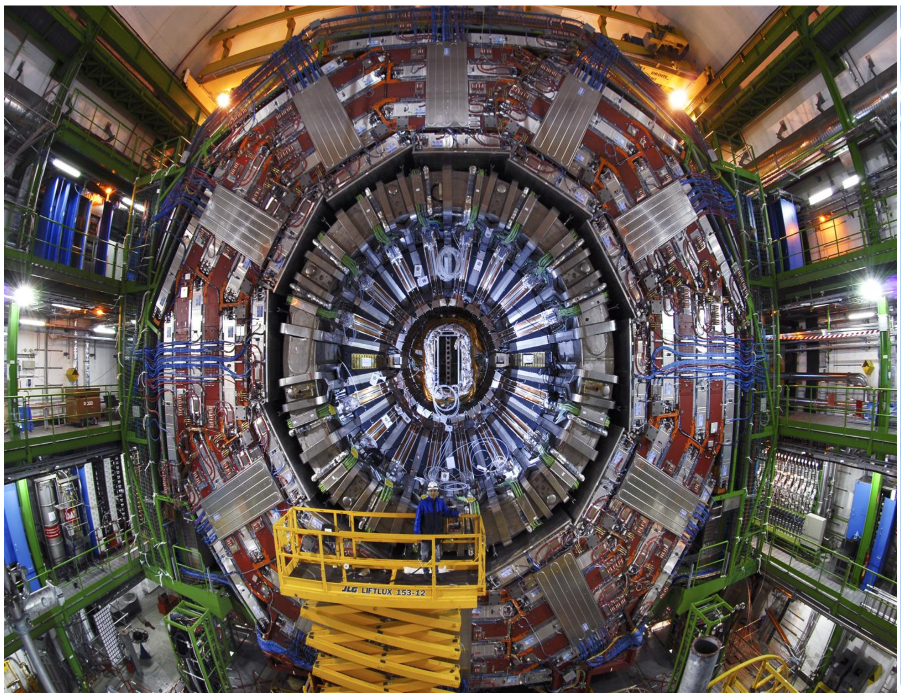
Multimodality imaging: CT with PET

Combining anatomic and functional imaging



David Townsend, Former CERN Physicist

The next challenge: PET + MRI




Detectors in magnetic field

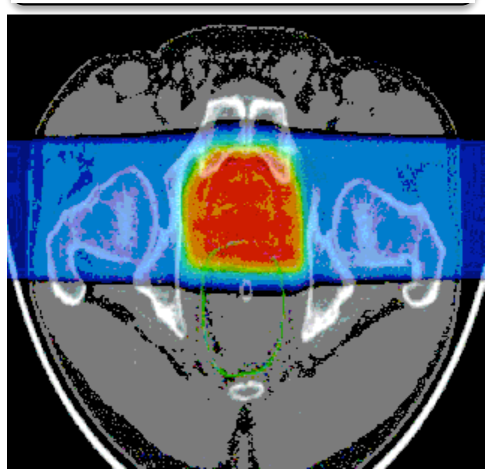
The Challenge of Treatment

- The tumour
- The whole tumour
- And nothing BUT the tumour

Treatment options

Surgery

Radiotherapy



X-ray, IMRT, Brachytherapy, Hadrontherapy

Chemotherapy (+ others)

Hormones; Immunotherapy;
Cell therapy; Genetic treatments; Novel specific targets (genetics..)

AIM:
Survival, Quality of life

Radiotherapy in 21st Century

3 "Cs" of Radiation

Cure (40-50% cancer cases are cured)

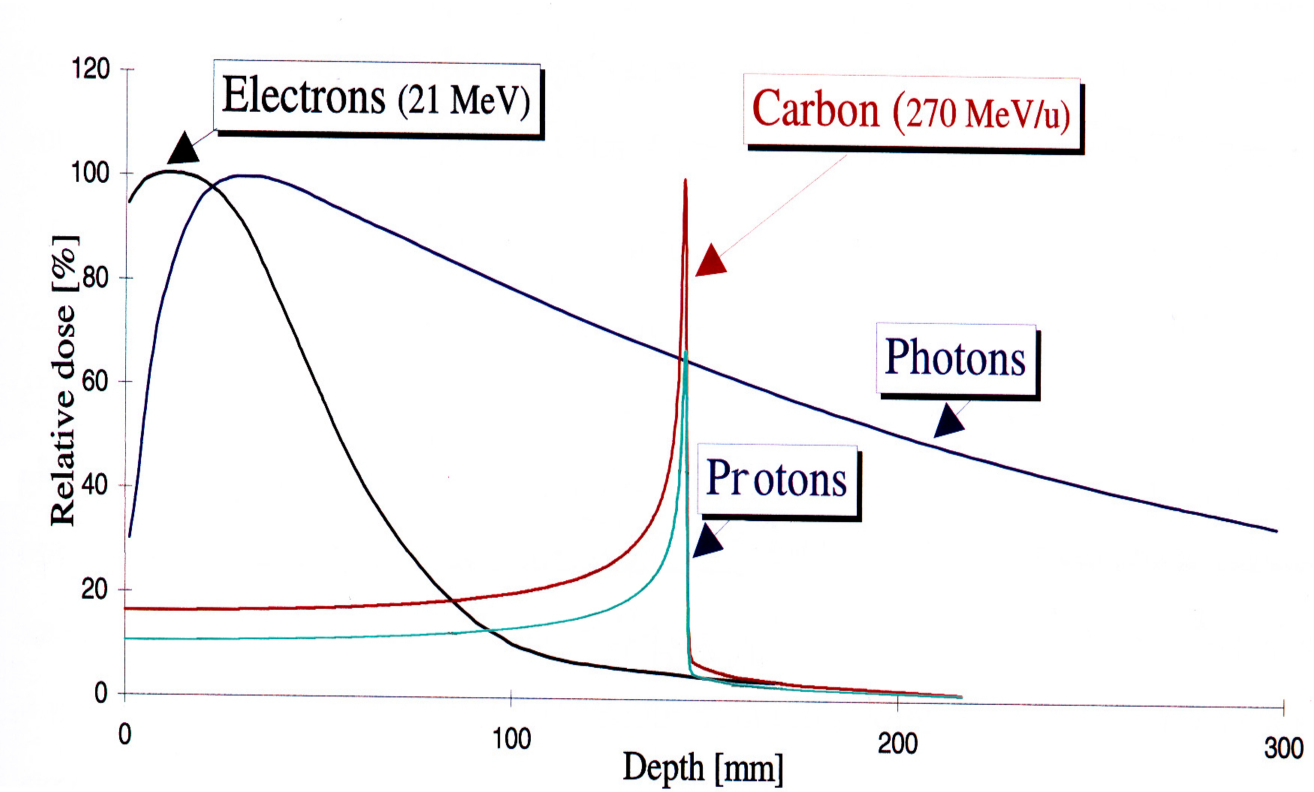
Conservative (non-invasive, fewer side effects)

Cheap (about 10% of total cost of cancer on radiation)

(J.P.Gérard)

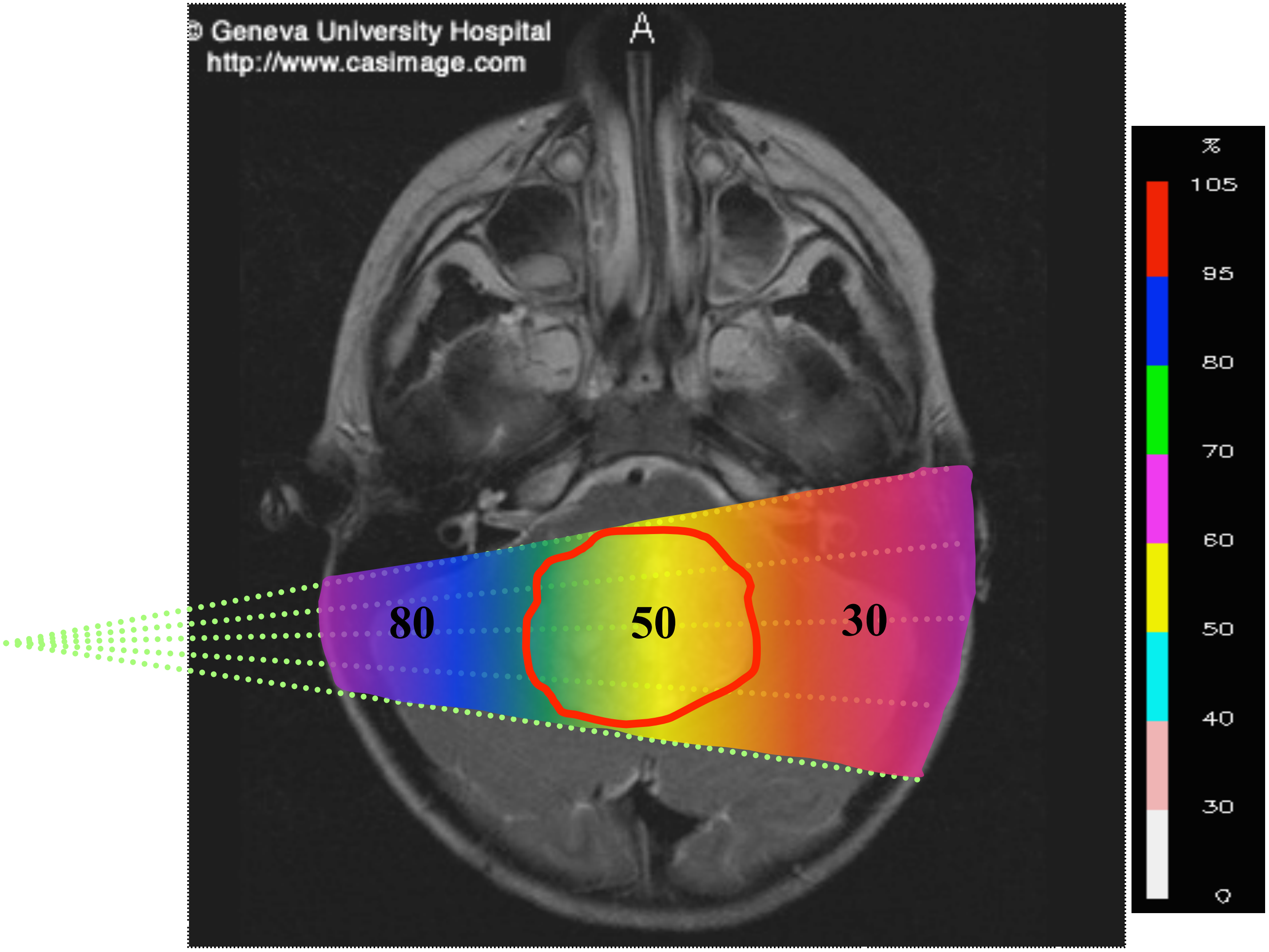
- About 50% patients are treated with RT
- No substitute for RT in the near future
- No of patients is increasing

Radiation therapy

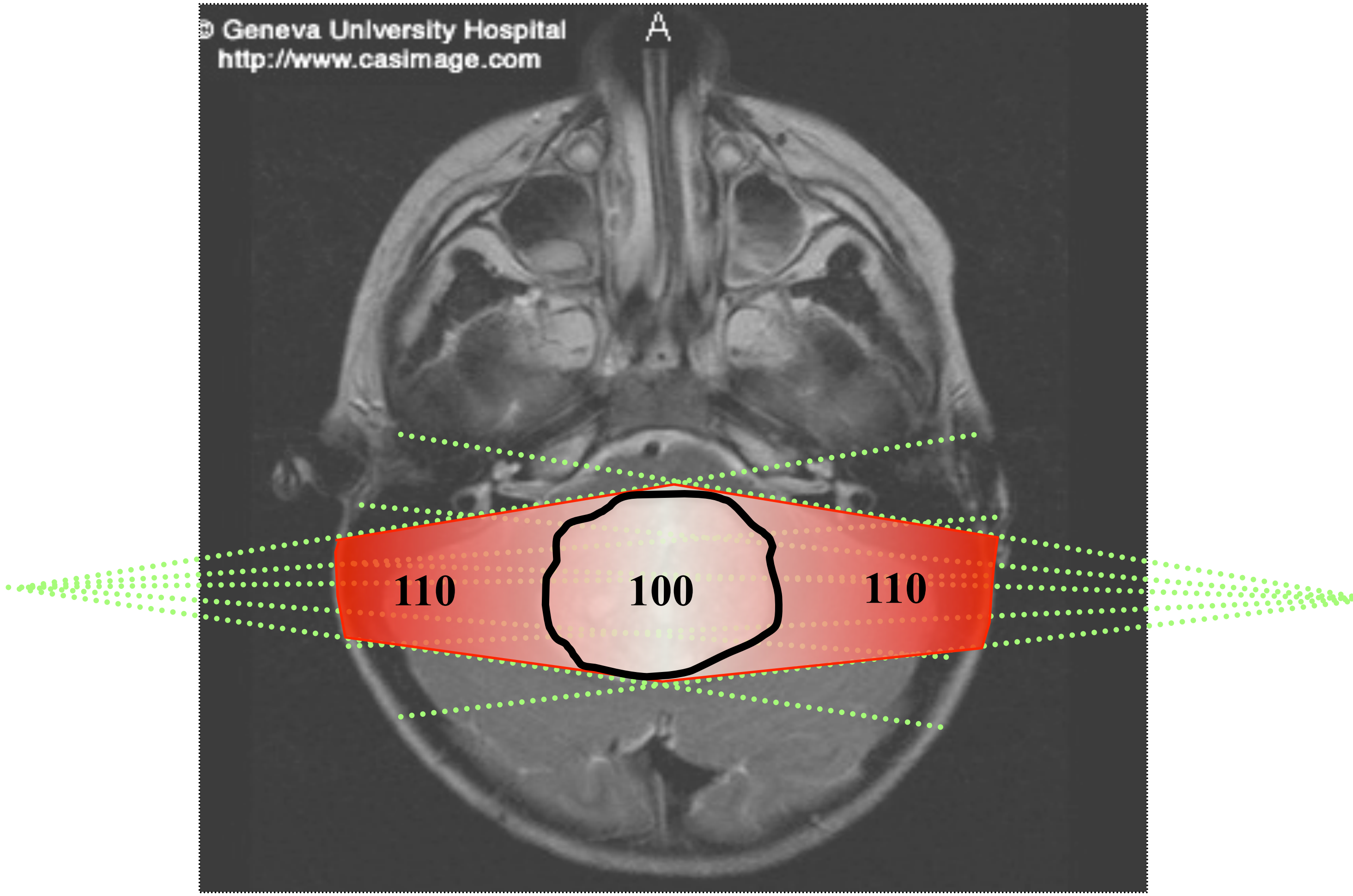


Depth in the body (mm)

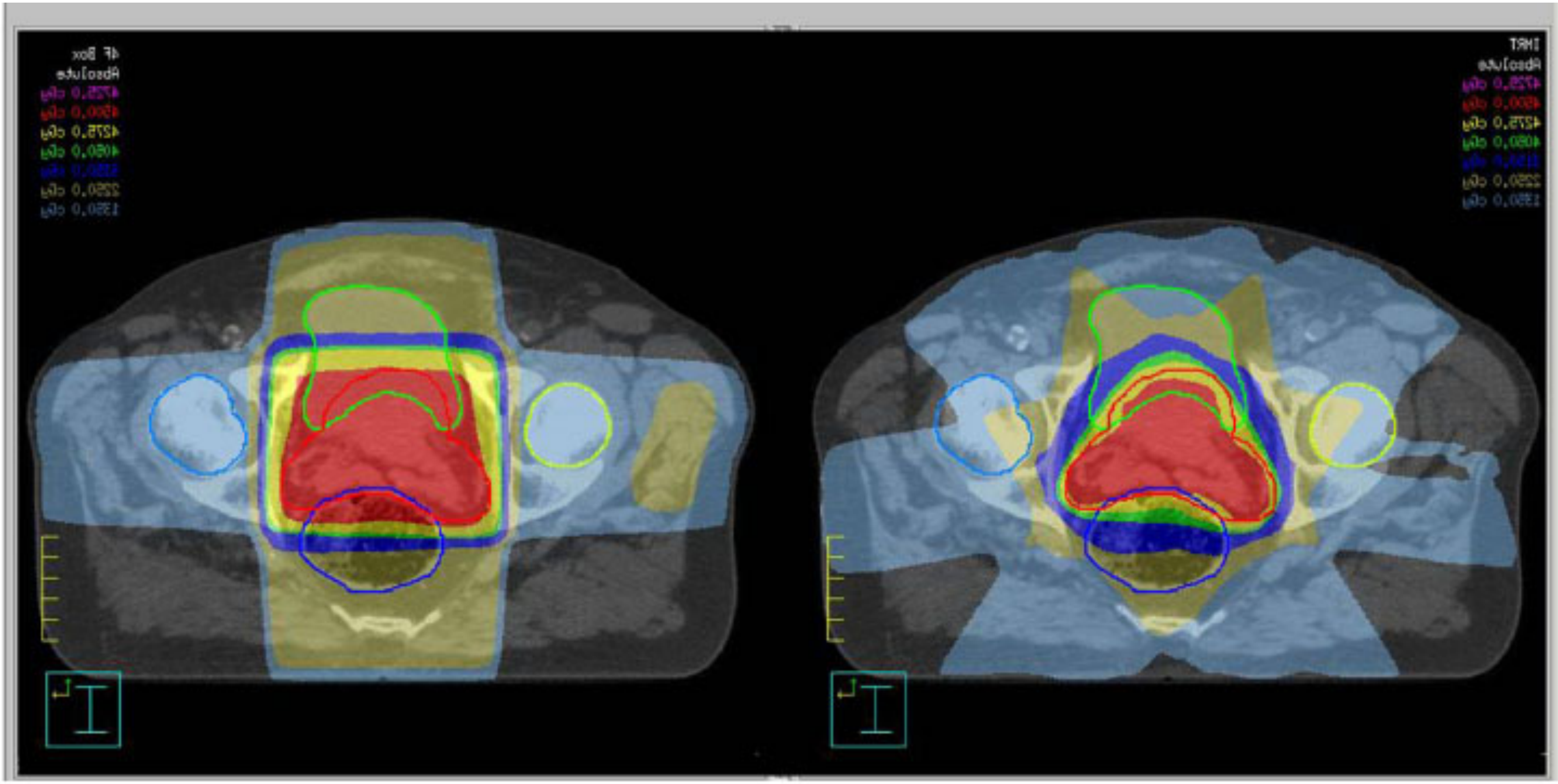
Single beam of photons



2 opposite photon beams



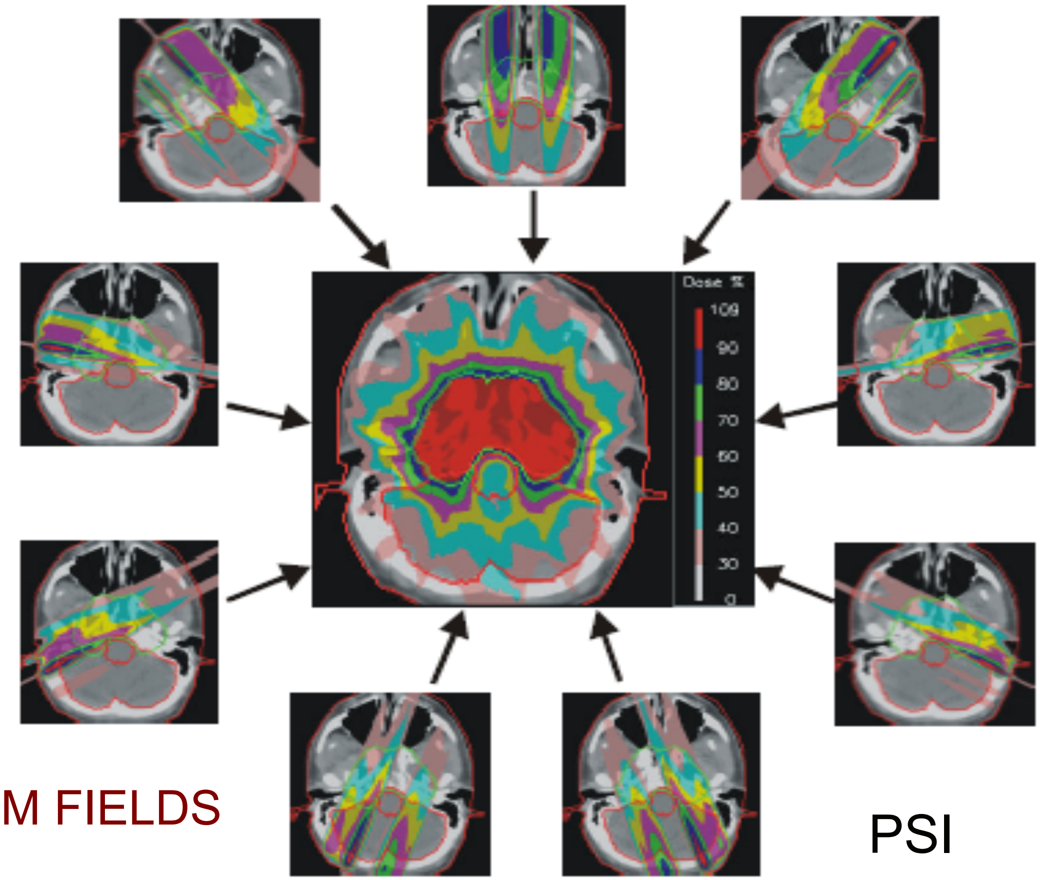
Improved Delivery



1990s: 4 constant intensity fields

Current state of RT: Intensity Modulated Radiotherapy (IMRT) – Multiple converging field with planar (2D) intensity variations

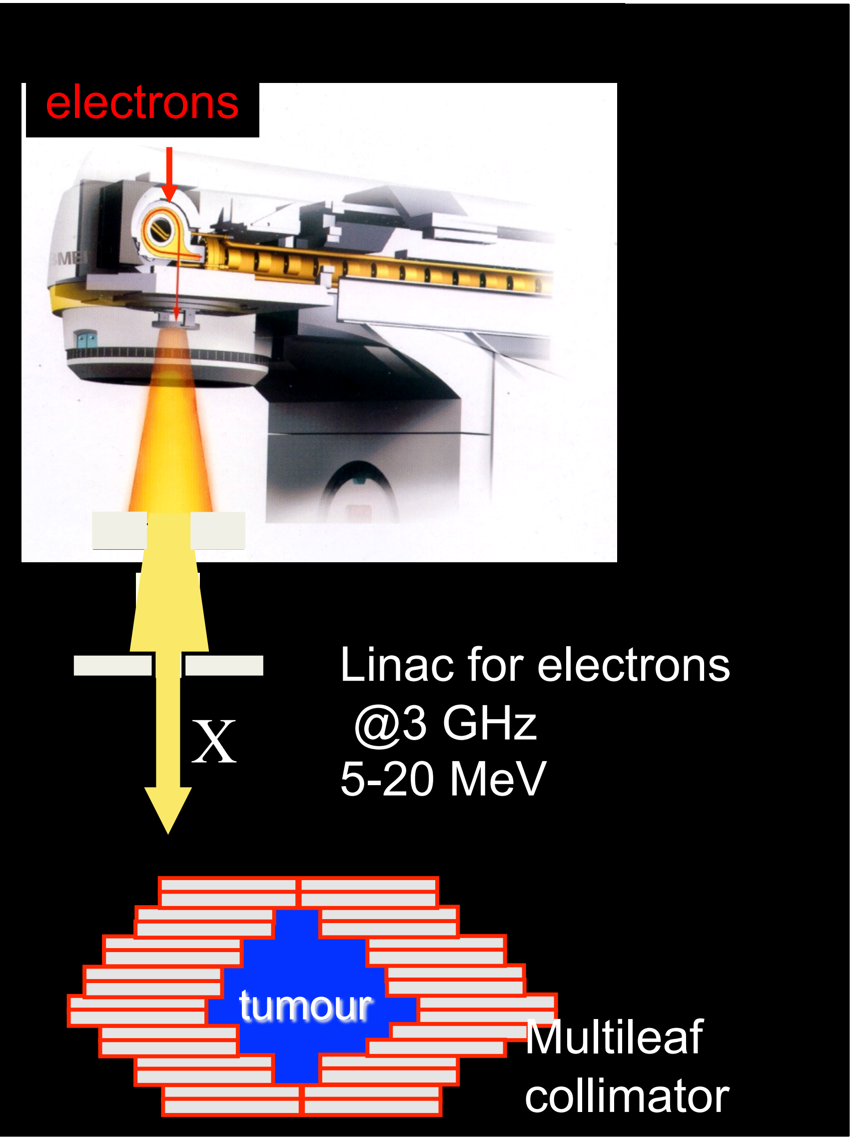
Intensity Modulated Radiation Therapy



9 NON-UNIFORM FIELDS

PSI

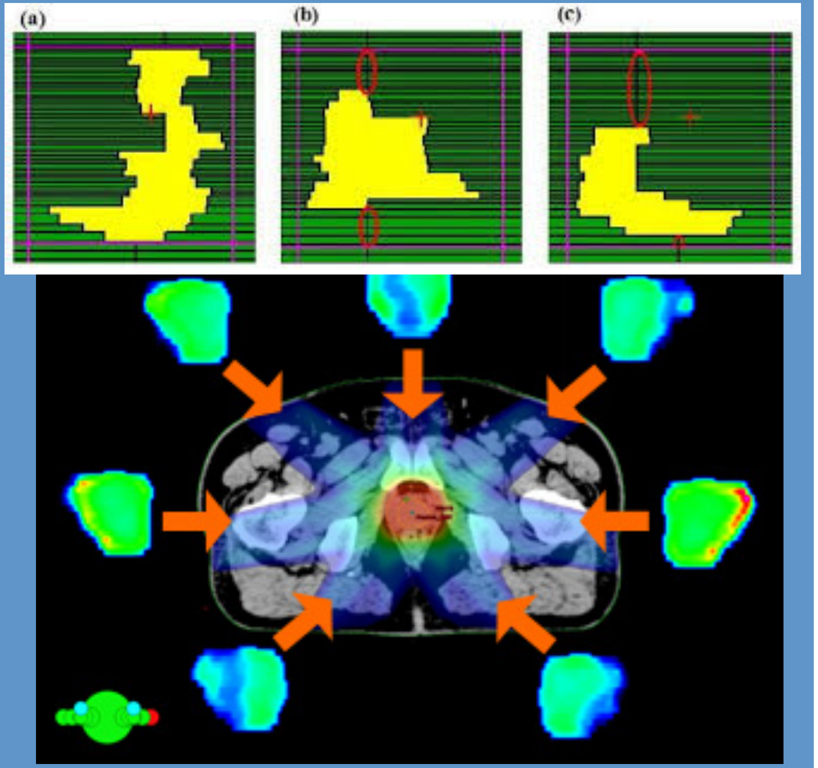
‘Conventional’ radiotherapy: LINACS (linear accelerators) dominate



Courtesy of Elekta

5 linacs for 1 million inhabitants needed

Modern Conventional Therapy



Current accelerator system with gantry, patient positioner and X-ray panels to acquire CBCT and planar X-rays.
Intensity modulation is achieved by changing the multi-leaf collimator (MLC) patterns (right), gantry rotation and dose rate. Thus, intensity modulation is achieved through mechanical (slow) means.

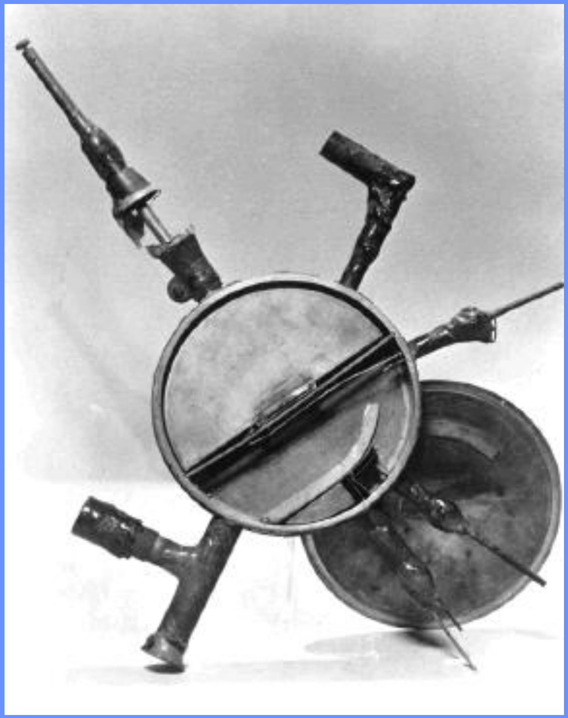
Advances in Radiation Therapy

In the past two decades due to:

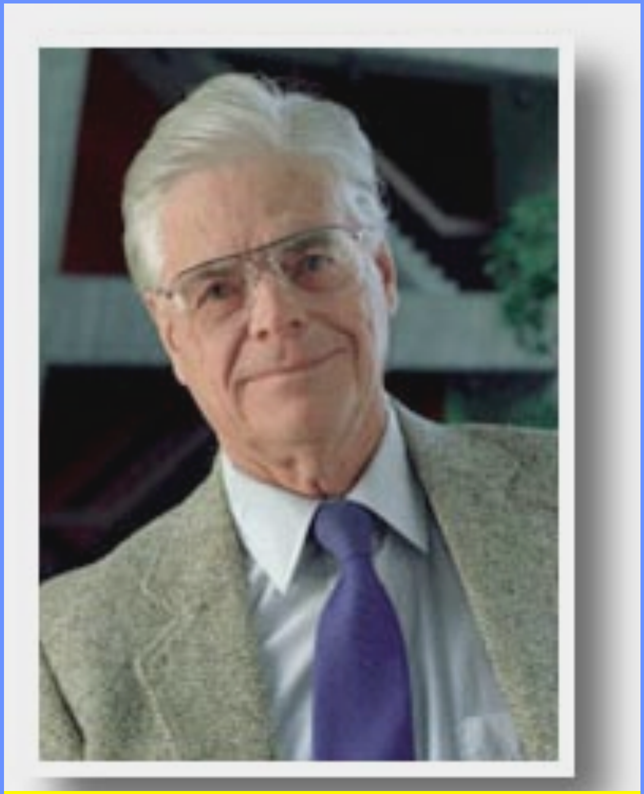
- improvements in imaging modalities,
- powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
- Is Particle Therapy the future since the physics of X-rays cannot be changed?

Beginnings of HT

Lawrence, Nobel Prize 1939



First Cyclotron



Founder and first director of Fermilab - 1990

1946: Wilson proposes the use of Bragg Peak

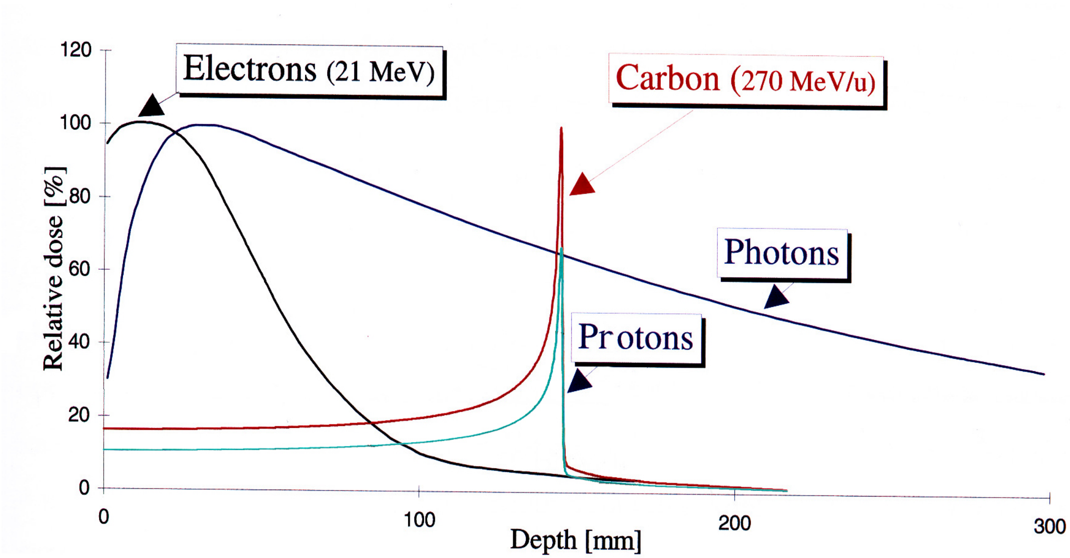
Eleanor Blakely, LBL

Hadron Therapy

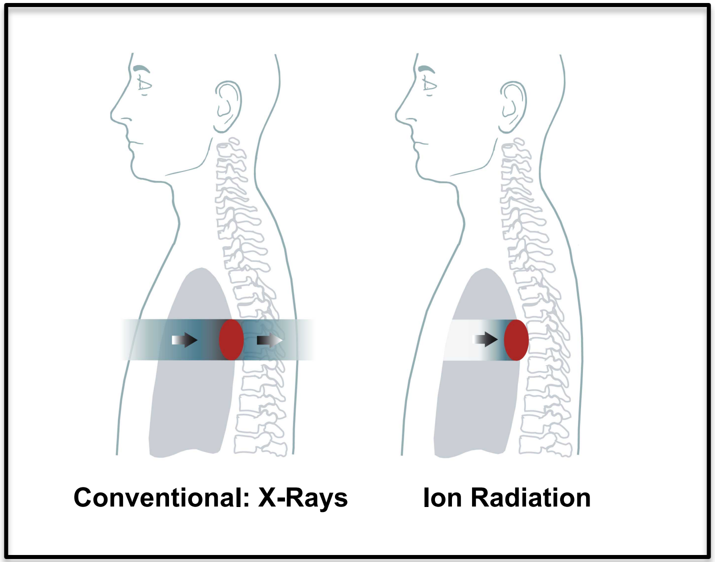
In 1946 Robert Wilson:

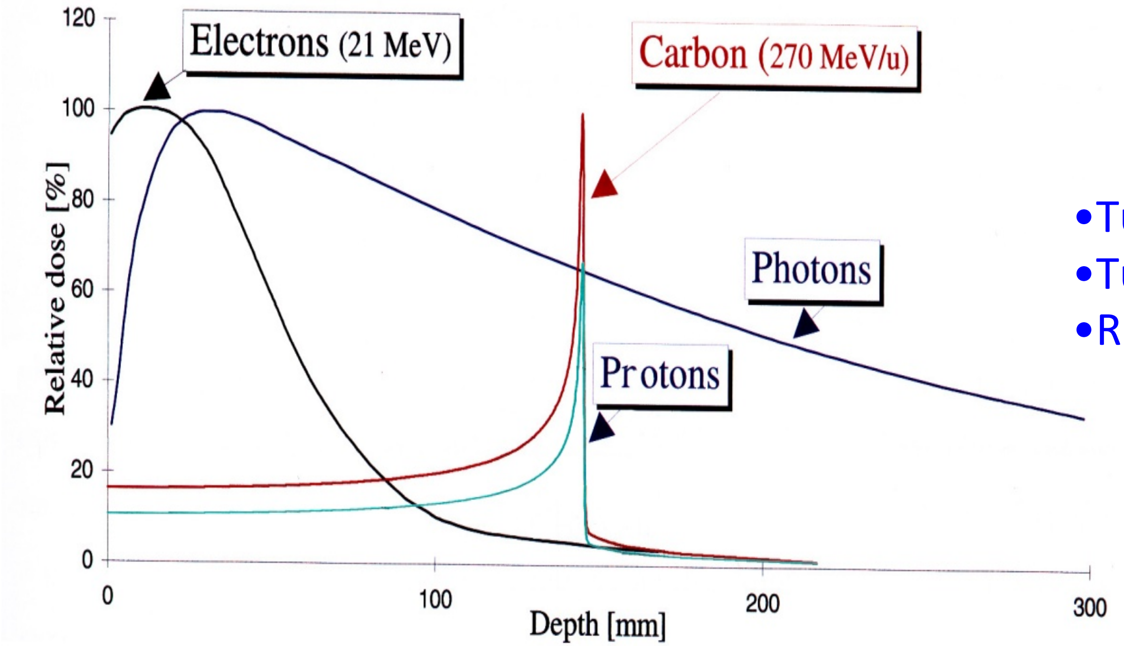
- **Hadrons can be used clinically**
- **Accelerators are available**
- **Maximum radiation dose can be placed into the tumour**
- **Particle therapy provides sparing of normal tissues**

- Tumours close to critical organs
- Tumours in children
- Radio-resistant tumours



Depth in the body (mm)





- Tumours close to critical organs
- Tumours in children
- Radio-resistant tumours

Energy deposition

Photons and Electrons vs. Hadrons

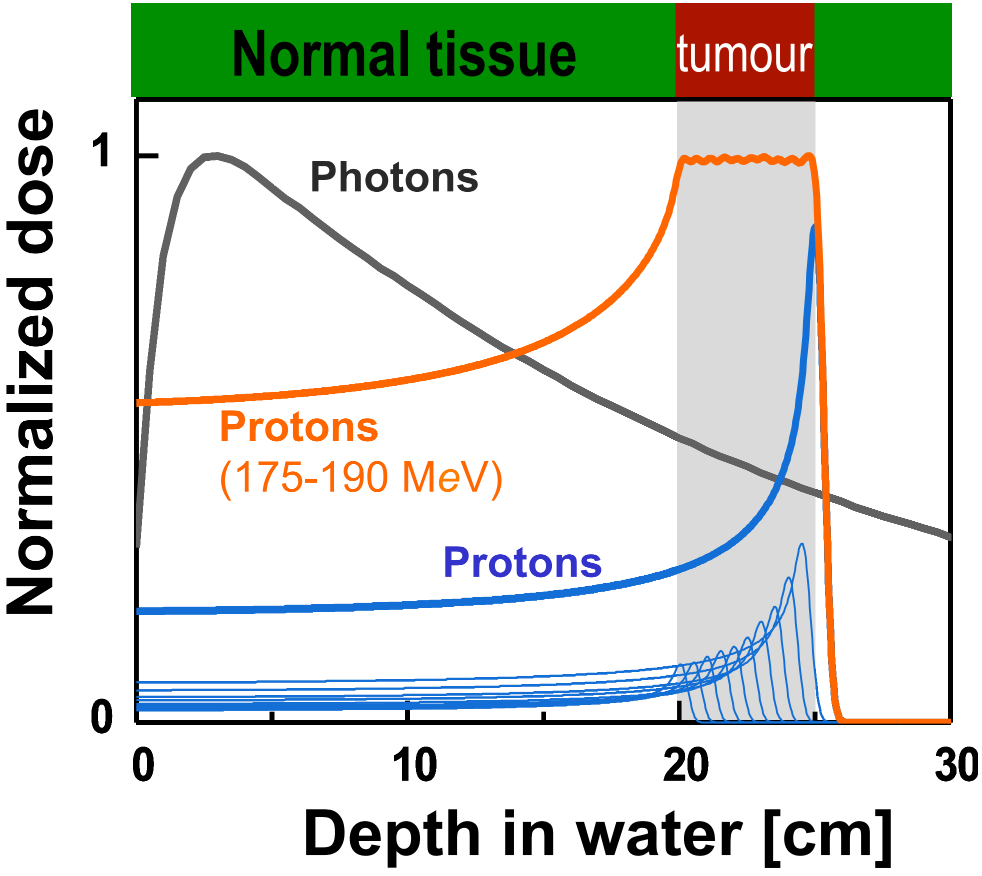
Photons and Electrons

- Physical dose high near surface
- DNA damage easily repaired
- Biological effect lower
- Need presence of oxygen
- Effect not localised

Hadrons

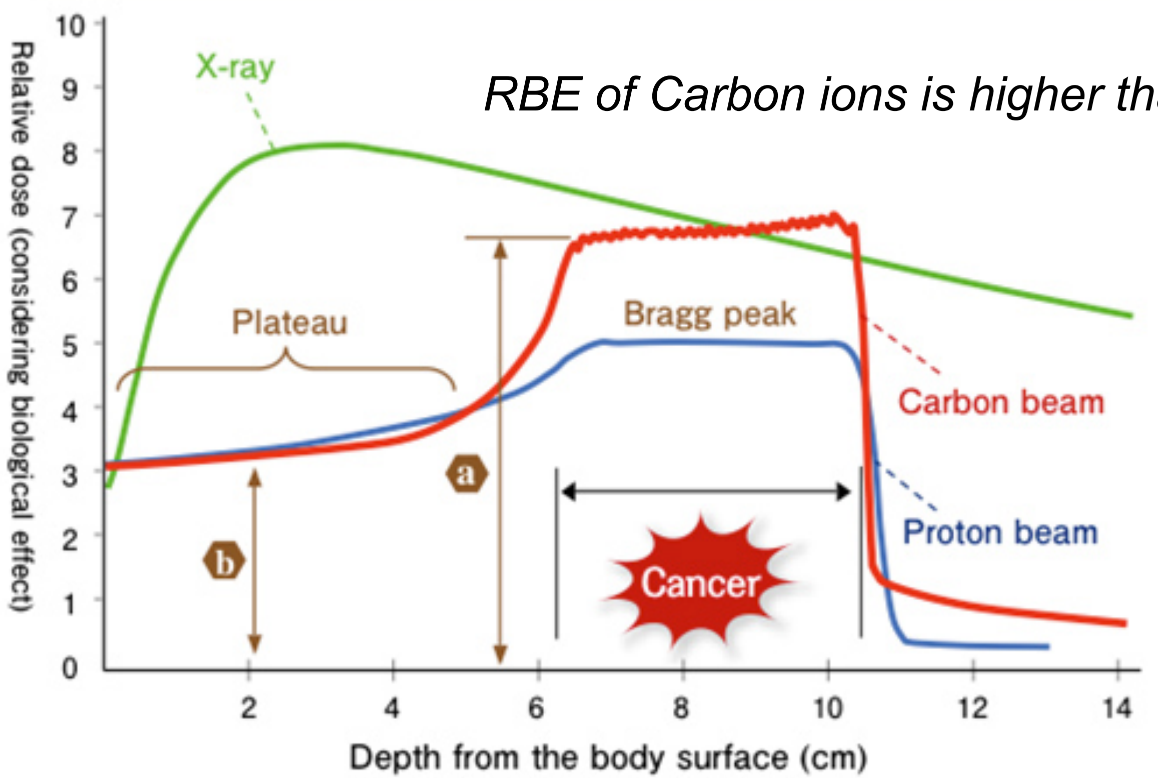
- Dose highest at Bragg Peak
- DNA damage not repaired
- Biological effect high
- Do not need oxygen
- Effect is localised

Physical basis

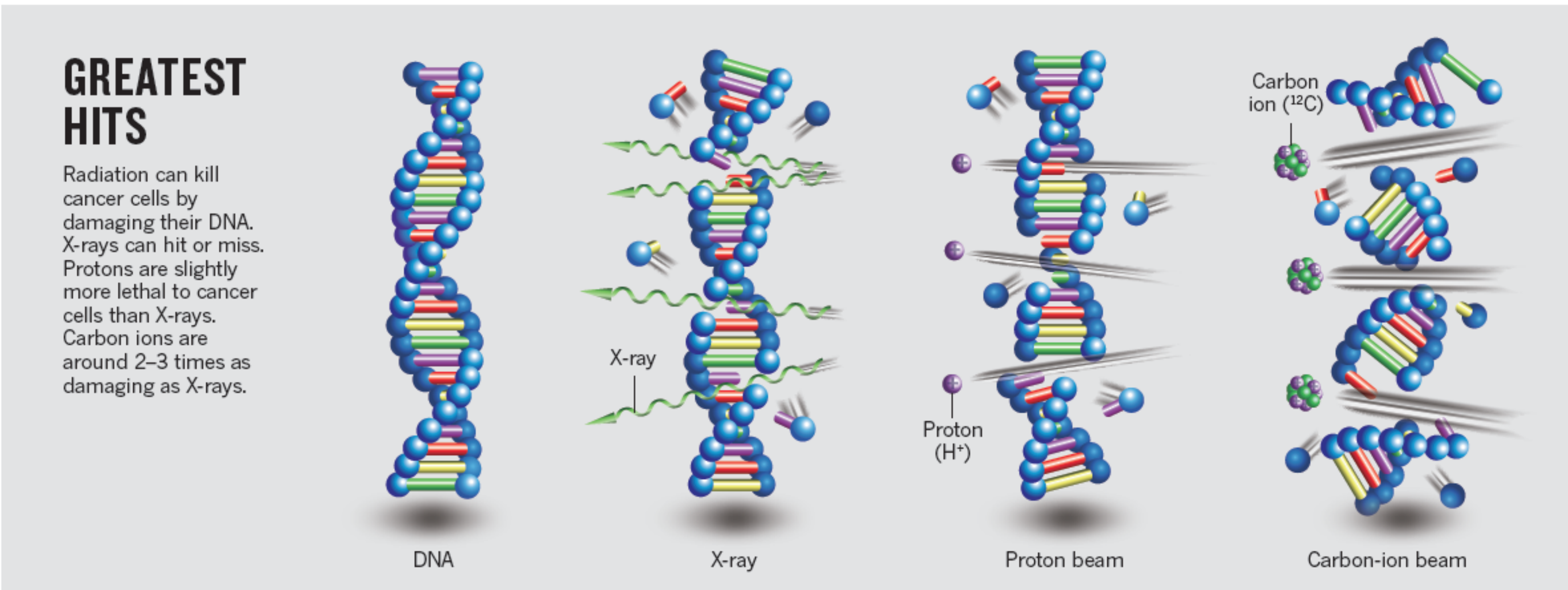


Why carbon ions?

RBE of Carbon ions is higher than for protons



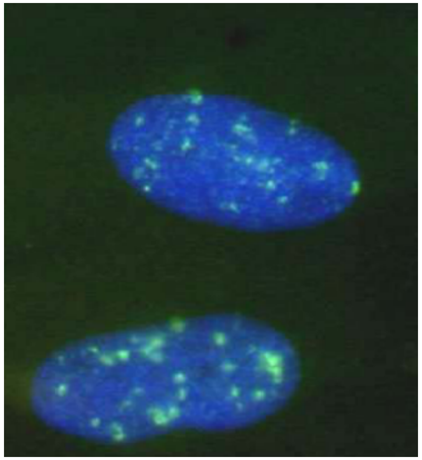
DNA X-rays Protons Carbon ions



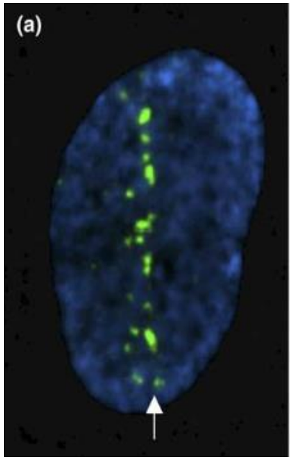
Marx, Nature, 2014

Dose, LET and RBE

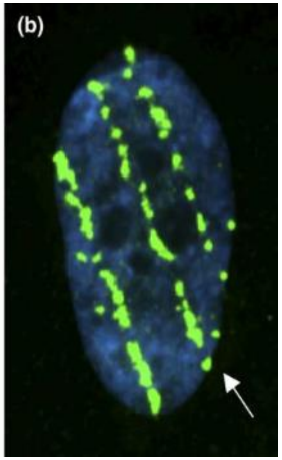
- Cellular response is determined by the level and quality of DNA damage, which reflects the energy deposition pattern.



X-rays



54 keV/μm Si ions



174 keV/μm Fe ions

- Severity of DNA damage depends on lesion proximity and repairability, hence it is not a constant value but depends on physical (particle type, LET, dose) and biological (cell type, oxygenation status, repair capacity) parameters.

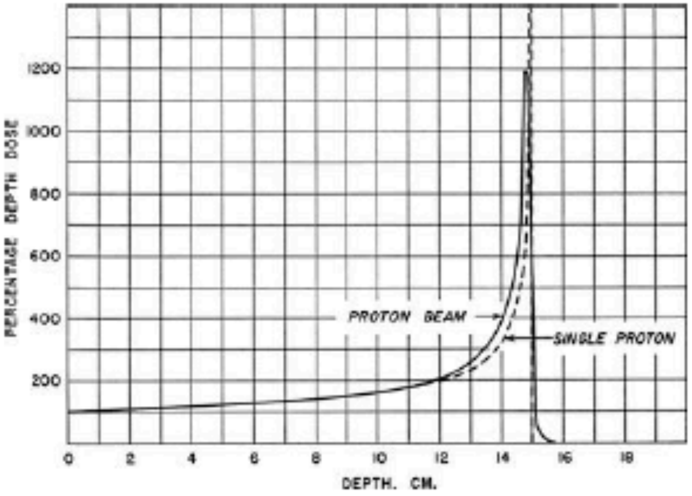
- RBE varies with the particle energy and the change of the beam composition (SOBP and nuclear fragmentations): its distribution is not homogenous across a treatment field.

Kevin Prise, ENLIGHT 2017

CCRCB

1932 - E. Lawrence
First cyclotron

1946 – proton therapy
proposed by R. Wilson



1954 – Berkeley treats
the first patient

From physics…

Knowledge
Transfer

3 Landmark Years for Hadron Therapy

In the years 1992-1994 the rate of progress changed:

- 1992 at Loma Linda first proton patient
- 1993 MGH (Boston) orders the first commercial protontherapy centre
- 1993 GSI starts the carbon ion 'pilot project'
- 1994 HIMAC, NIRS, Chiba first carbon ion patient

Key Milestones of Hadron Therapy

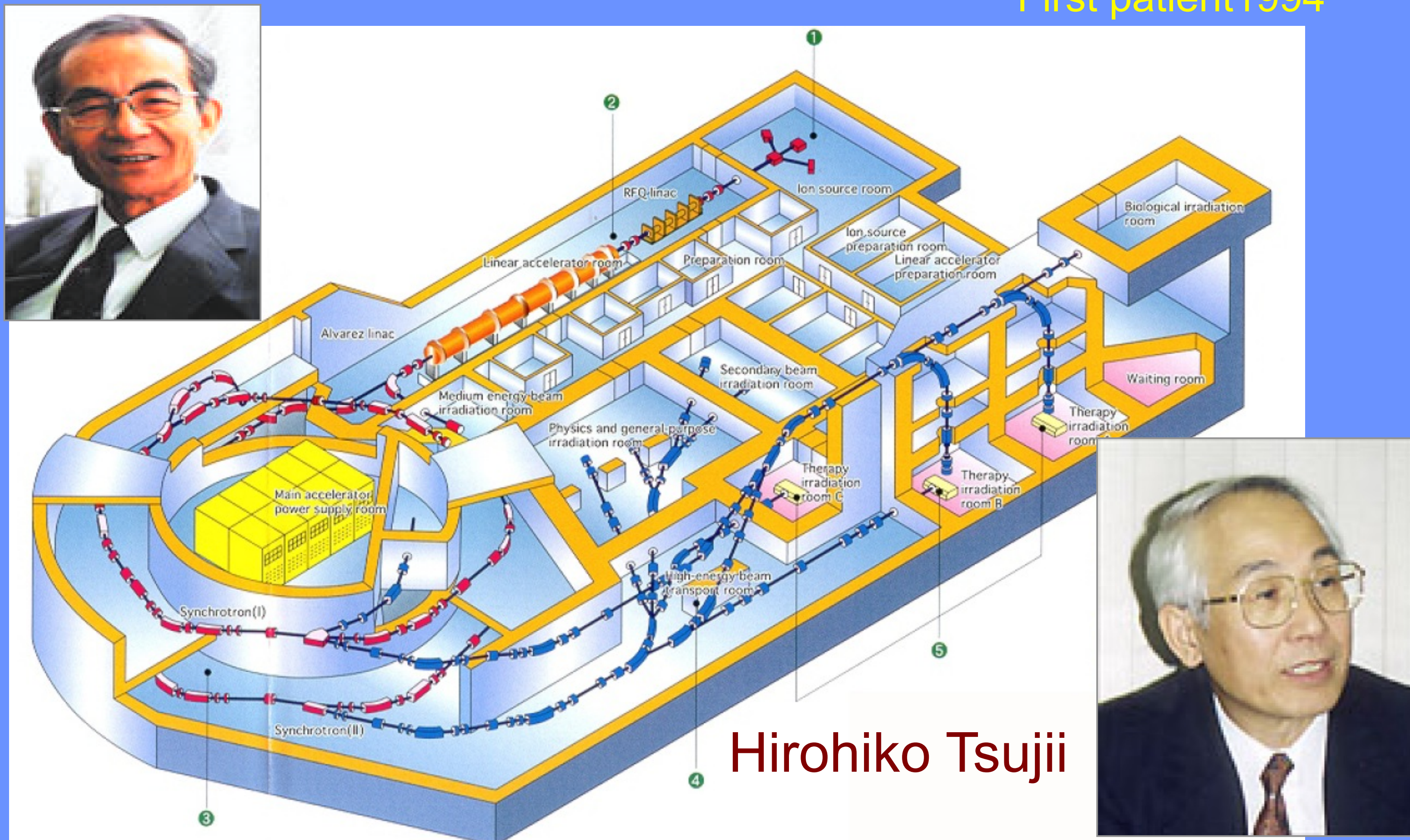
1991 — First hospital based *Proton* facility
Loma Linda University Medical Center, CA, USA

360^0 Gantry

HIMAC, Chiba is the pioneer of carbon therapy (1994)

Yasuo Hirao

First patient1994



Since the cells do not repair. less fractions are possible

HIMAC: reduced fractions! Even single fraction

The Darmstadt GSI 'pilot project' (1997-2008)

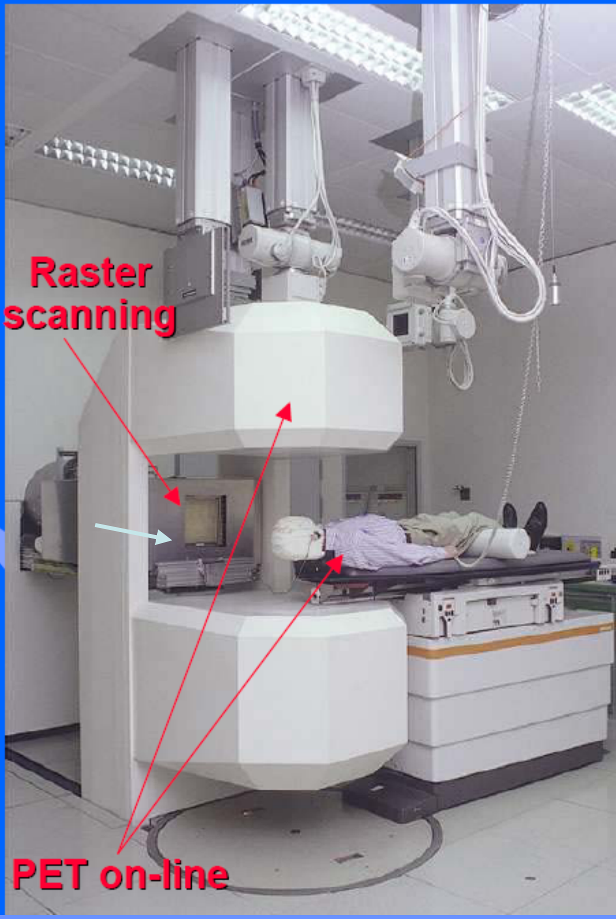
G. Kraft

J. Debus

G. Kraft

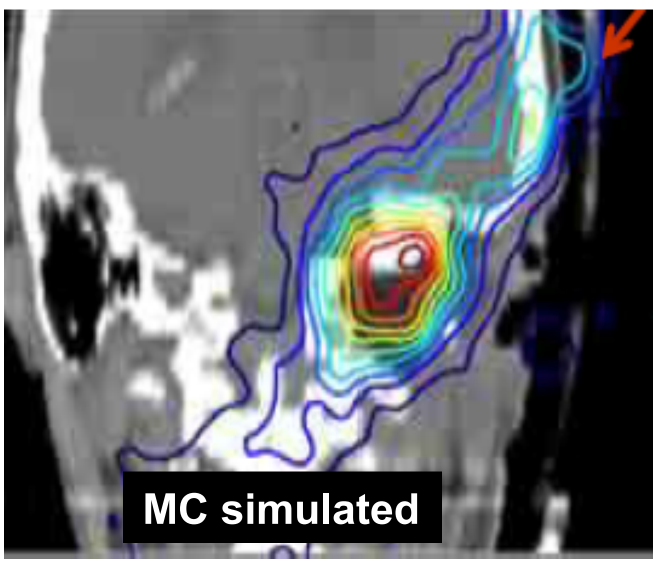
450 patients treated with carbon ions

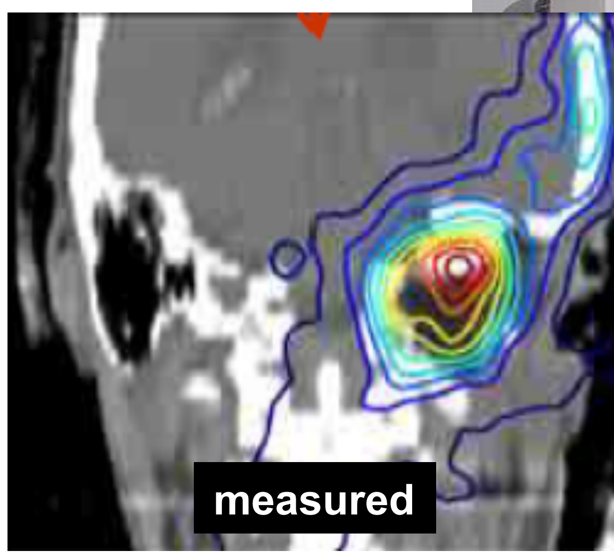
J. Debus (Heidelberg Univ.)



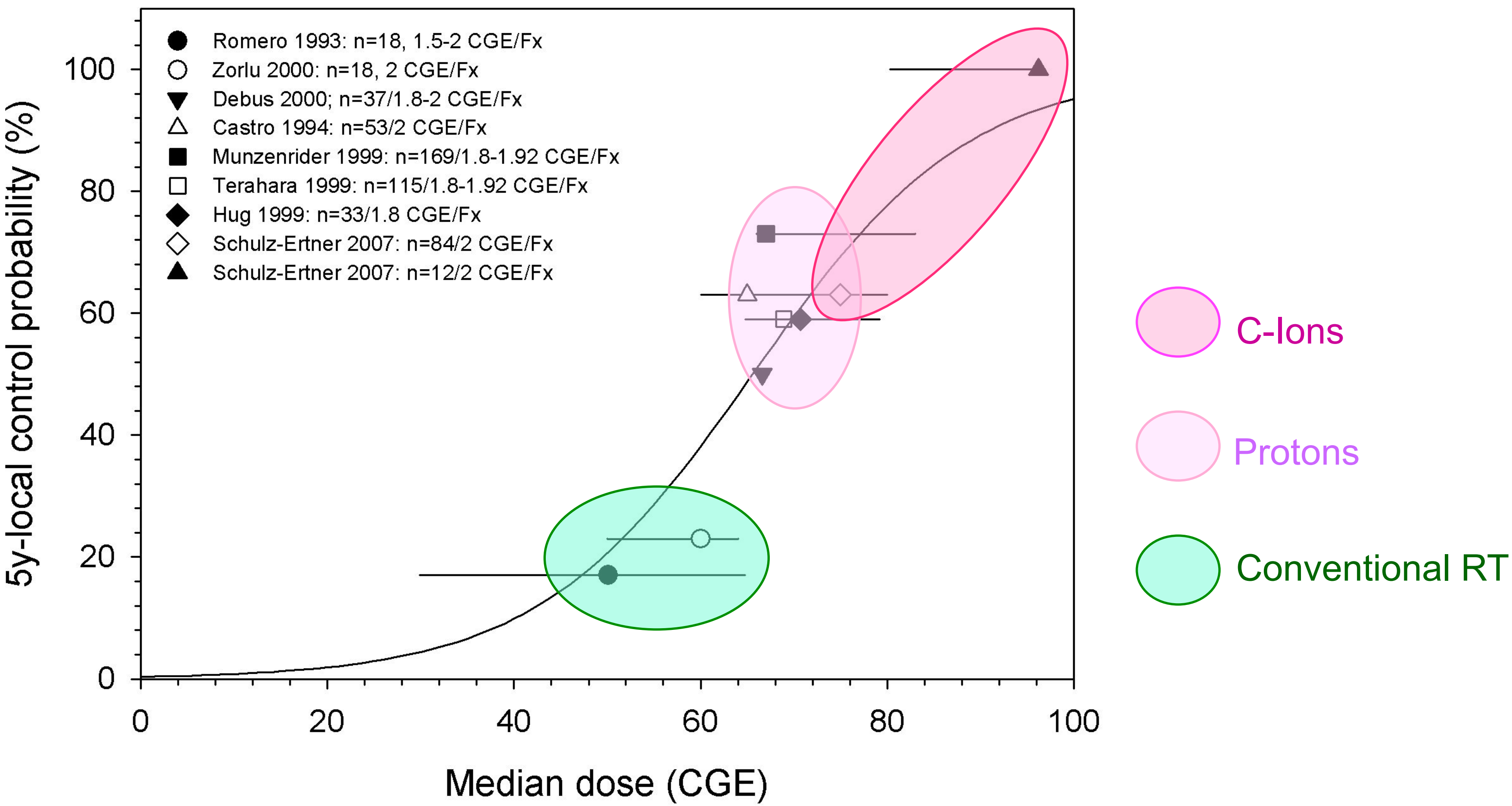
Real-time monitoring

- In-beam PET @ GSI (Germany)
- MonteCarlo simulations
- Organ motion





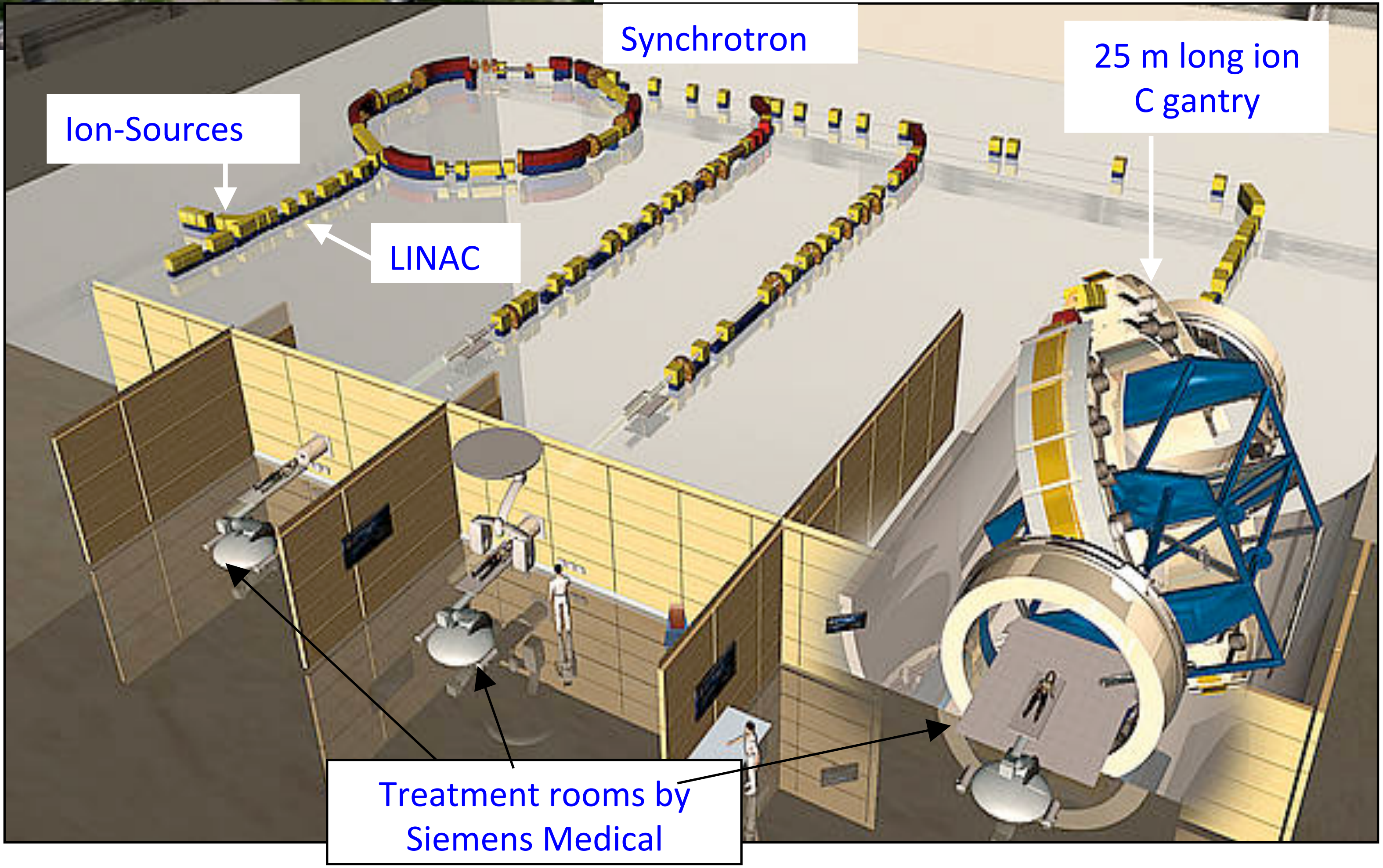
Tumour Control Rate: Chordomas



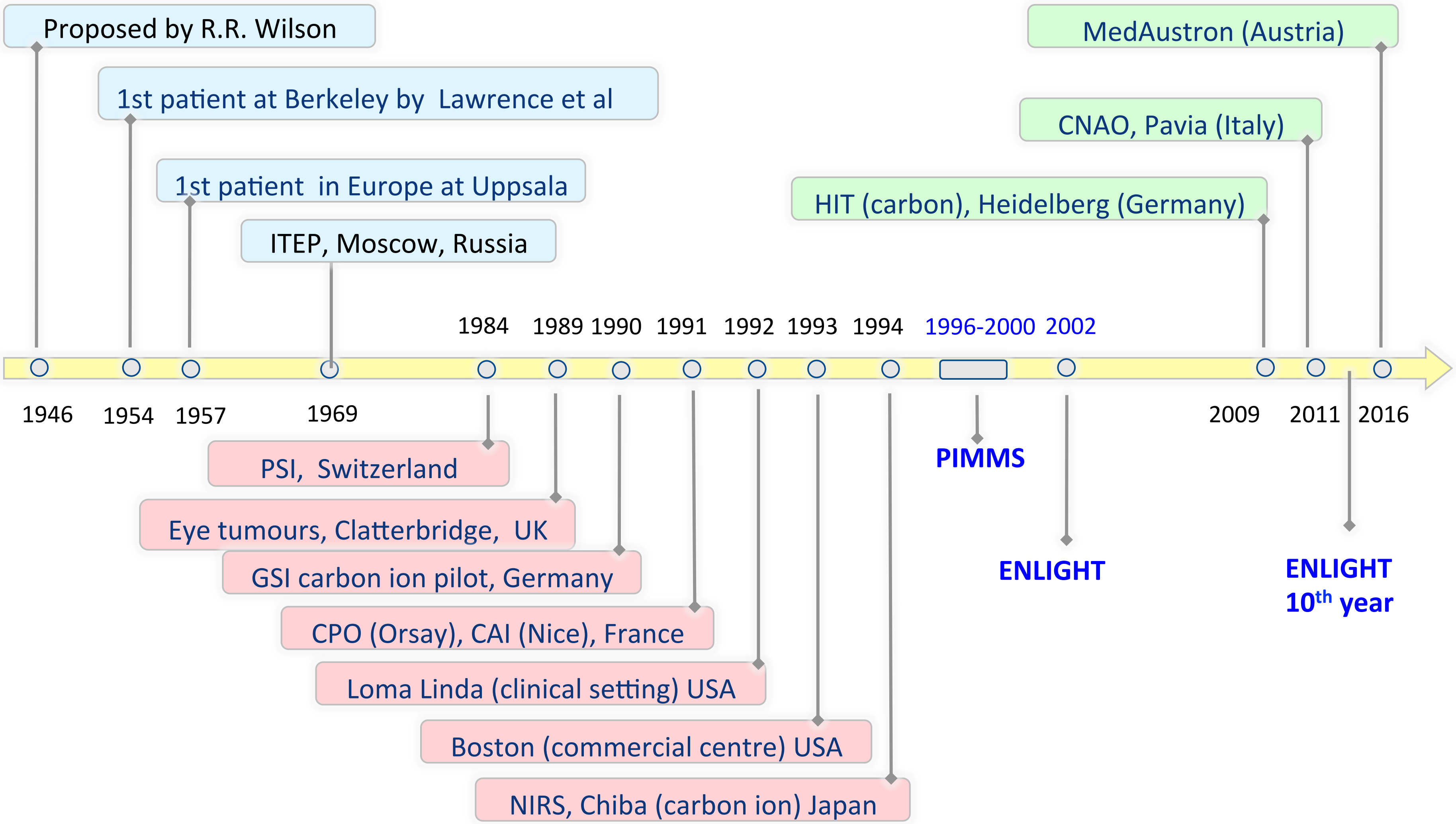
Schulz-Ertner, IJROBP 2007

HIT at Heidelberg

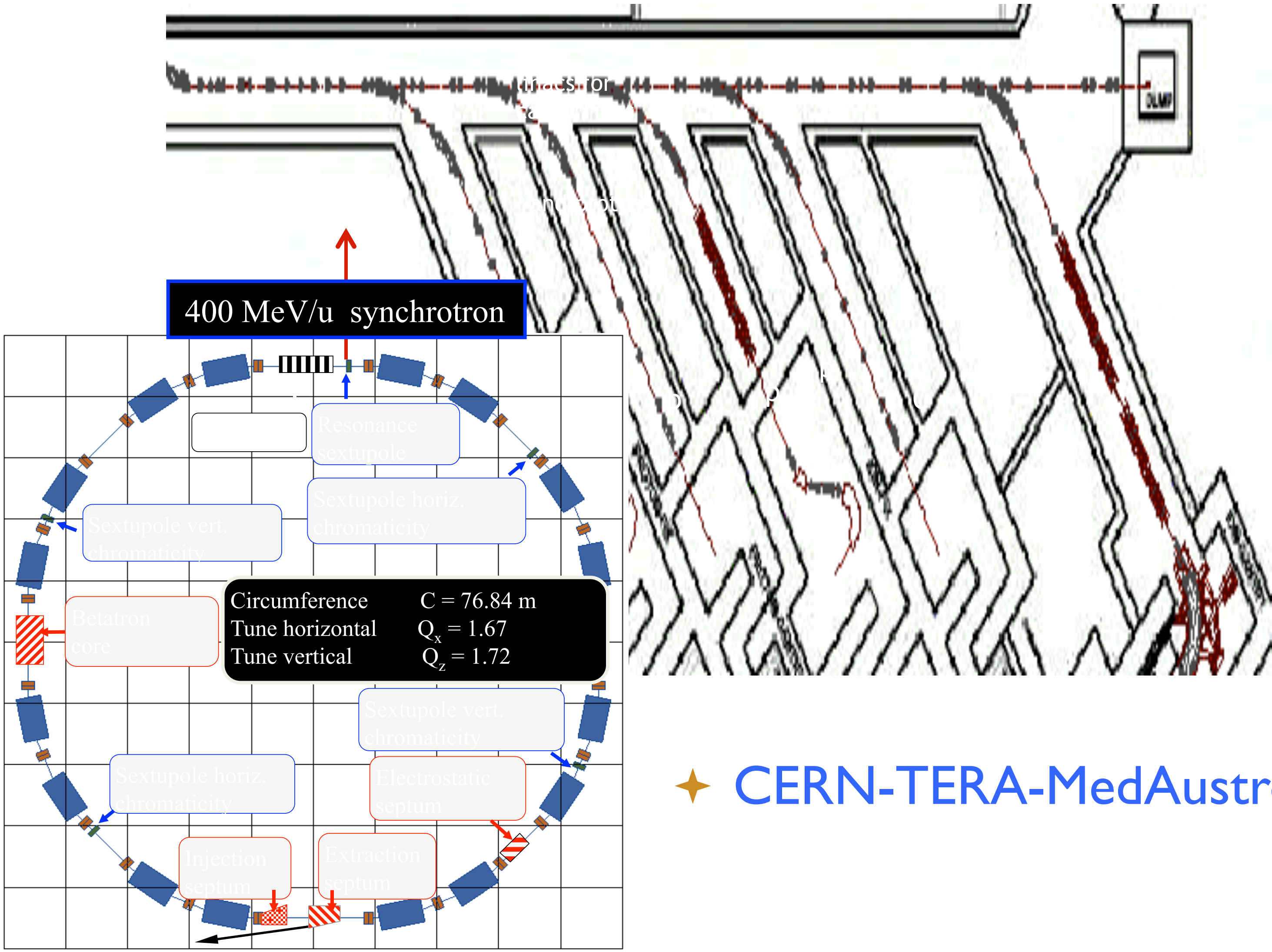
First patient: September 2009



Particle therapy: a short history



PIMMS at CERN (1996-2000)



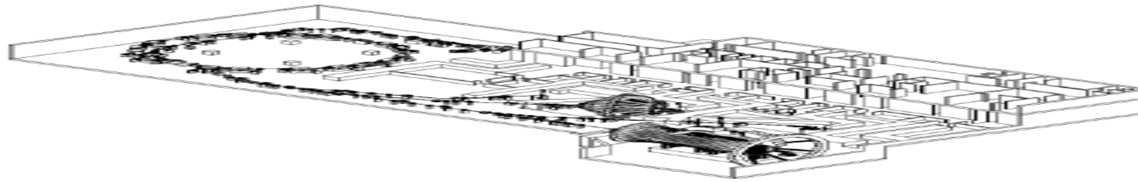
- CERN-TERA-MedAustron

Facilities in operation then – Europe (2002)

Source: PTCOG

Accelerator Technologies

PIMMS 2000
(coordinated by
CERN) has led to:



TERA
Fondazione per Adroterapia Oncologica

fondazione CNAO

Treatment centre in Pavia, Italy.

First patient treated with in 2011

ebg MedAustron

Treatment centre in Wiener Neustadt, Austria,
foundation stone in 2011, installation moved to
MedAustron at beginning of 2012, first patient treated
in 2016

From PIMMS study to clinical reality

TERA

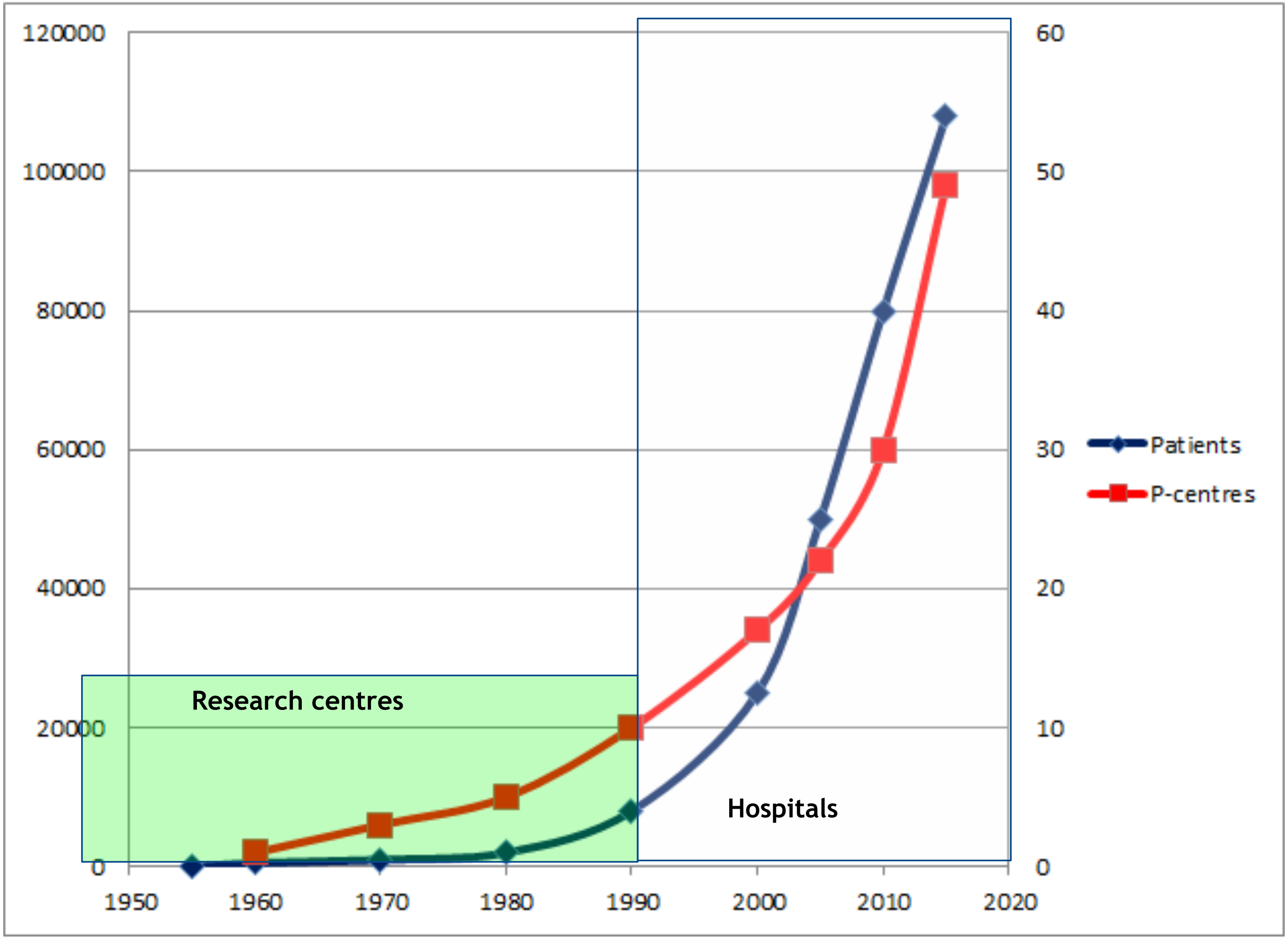
fondazione CNAO

ebg MedAustron

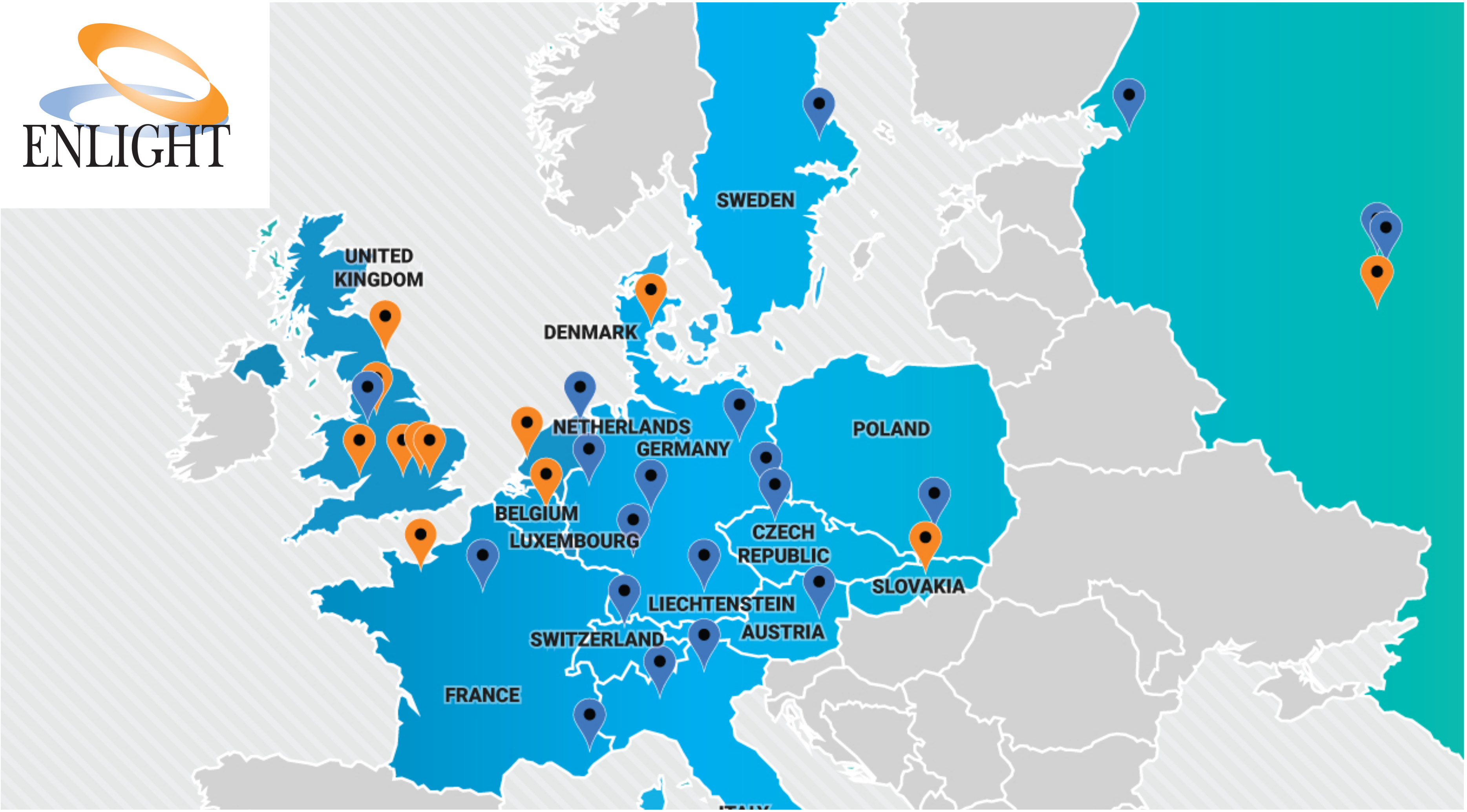
First patient with carbon ions Nov 2012

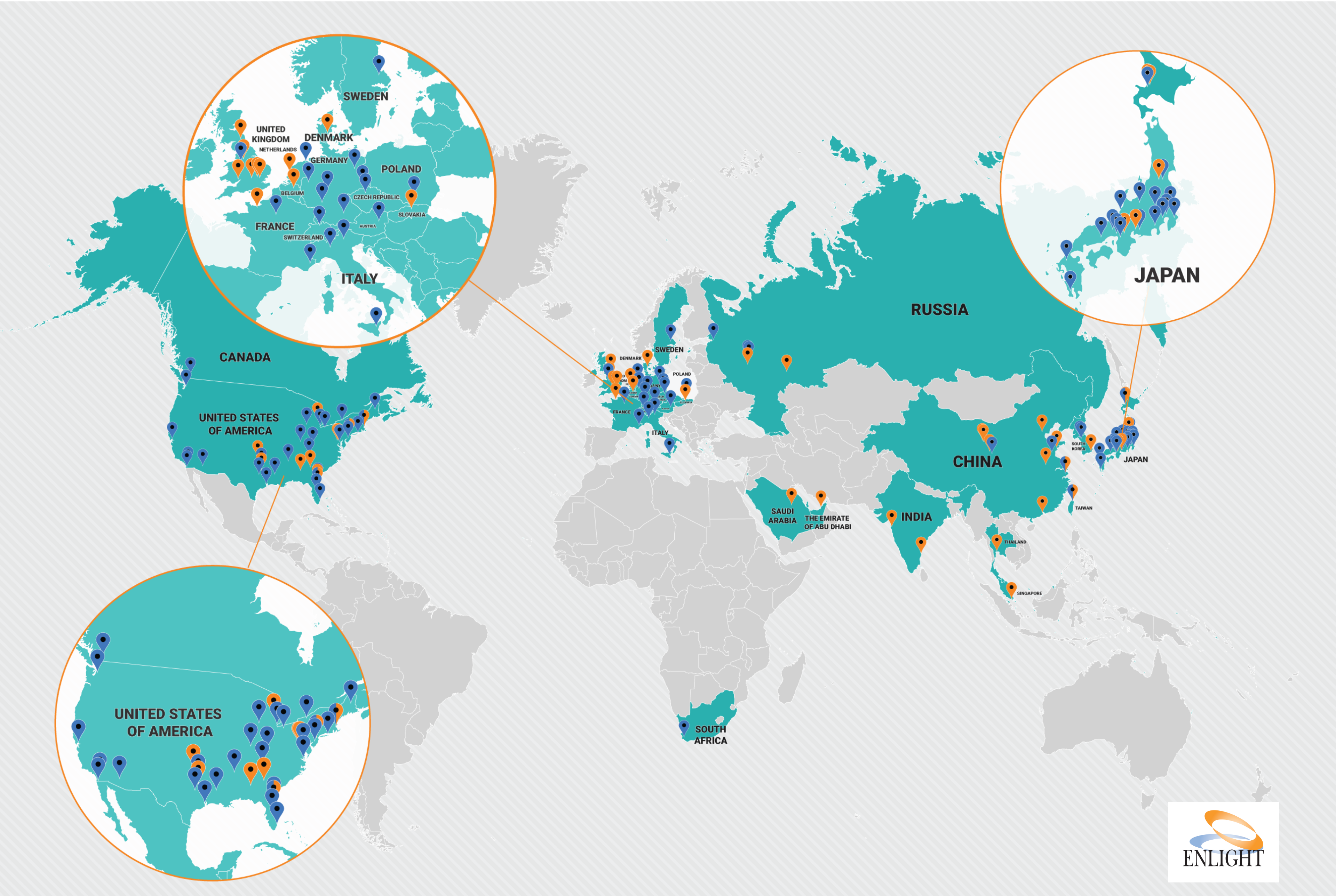
Treatment started in 2016

[Data from www.ptcog.ch]



Facilities in operation now – Europe (2018)





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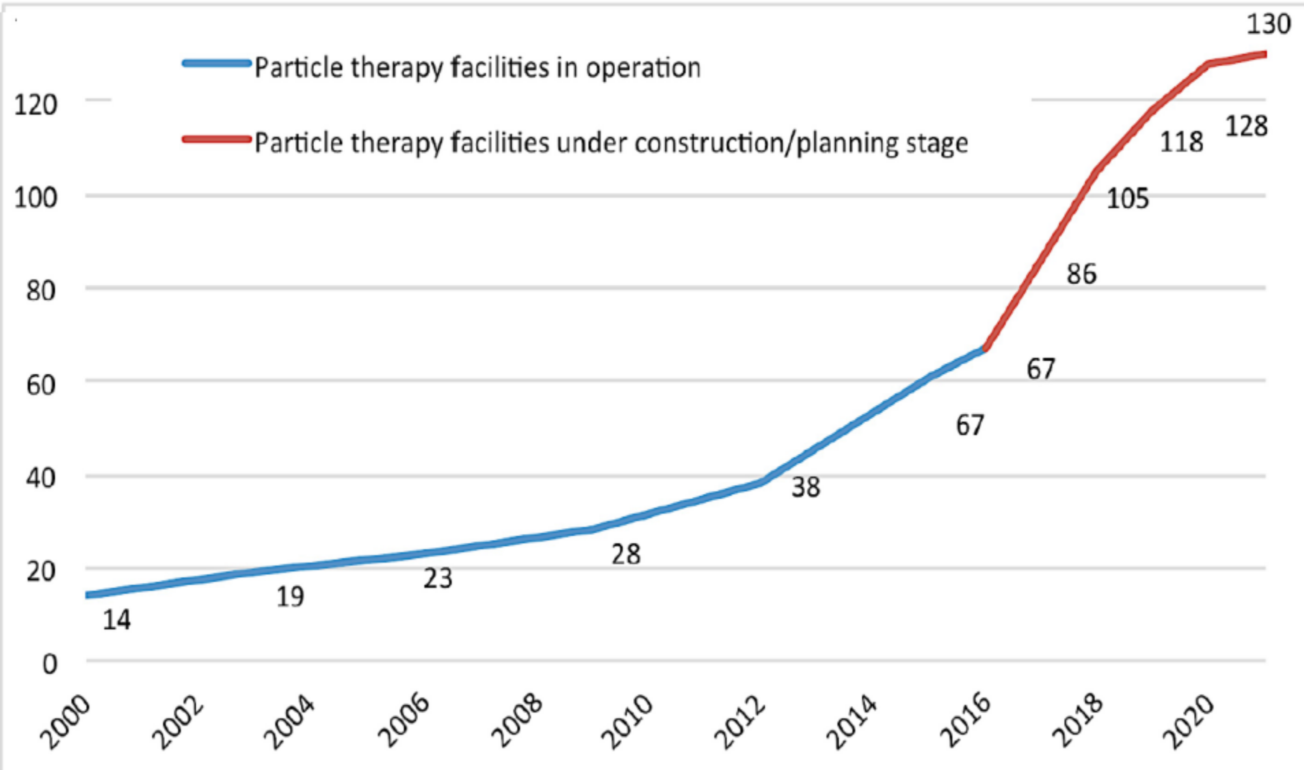
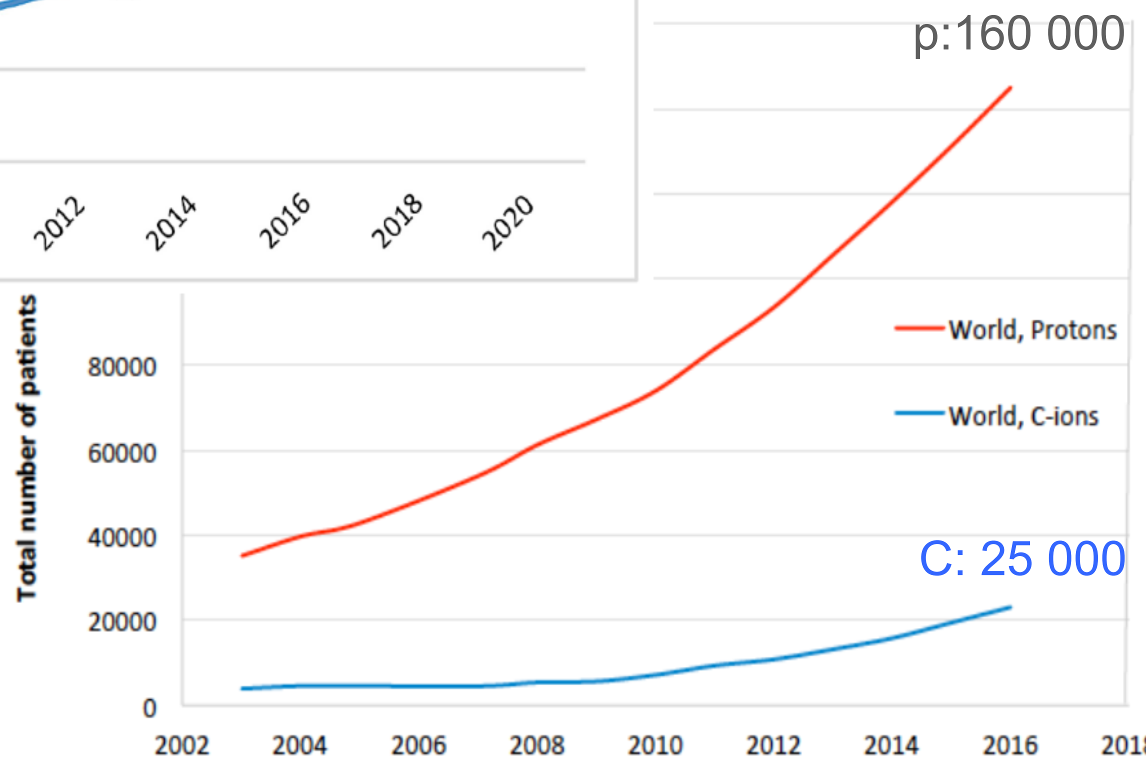
FUNCTIONAL CENTERS UNDER CONSTRUCTION

Centres and patients worldwide





cern.ch/virtual-hadron-therapy-centre

Many thanks to:

- U. Amaldi, CERN &TERA
- E. Blakely, LBNL, USA
- M Durante, GSI, Germany
- HIT, CNAO, MedAustro, PSI and ENLIGHT colleagues
- MARS BioImaging Ltd

Useful links

- *cern.ch/crystalclear*
- *cern.ch/enlight*
- *cern.ch/virtual-hadron-therapy-centre*
- *http://cds.cern.ch/record/1611721*
- *cern.ch/knowledgetransfer*
- *cern.ch/medipix*
- *cern.ch/twiki/bin/view/AXIALPET*
- *cern.ch/medaustron*
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