ENLIGHT

Particle-Beam Therapy and ENLIGHT

Manjit Dosanjh
CERN and University of Oxford
ENLIGHT Coordinator

LXX International Conference - NUCLEUS2020.

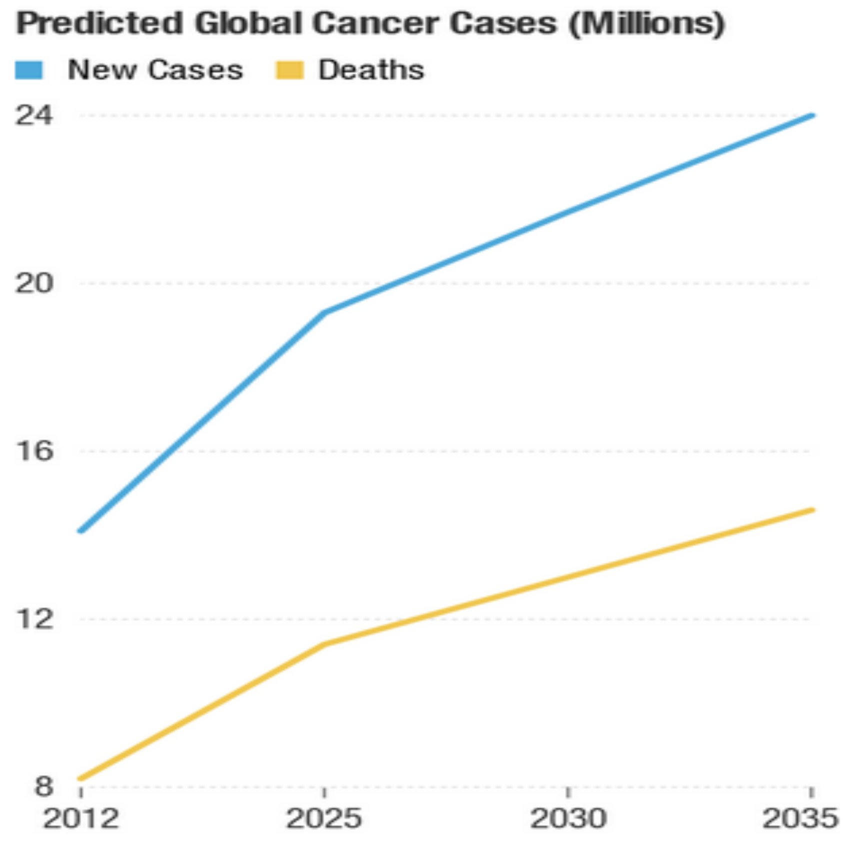
16 October 2020

CERN

UNIVERSITY OF OXFORD

Cancer is growing global challenge

- Globally **18** million new cases per year diagnosed and **9.6** million deaths in **2018**
- This will increase to **27.5** million new cases per year and **16.3** million deaths by **2040**
- **70% of these deaths** will occur in low-and-middle-income countries (LMICs)



Radiation therapy is a key tool for treatment for over 50% patients

Radiotherapy in 21st Century

3 "Cs" of Radiation

Cure (about 50% cancer cases are cured)

Conservative (non-invasive, fewer side effects)

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

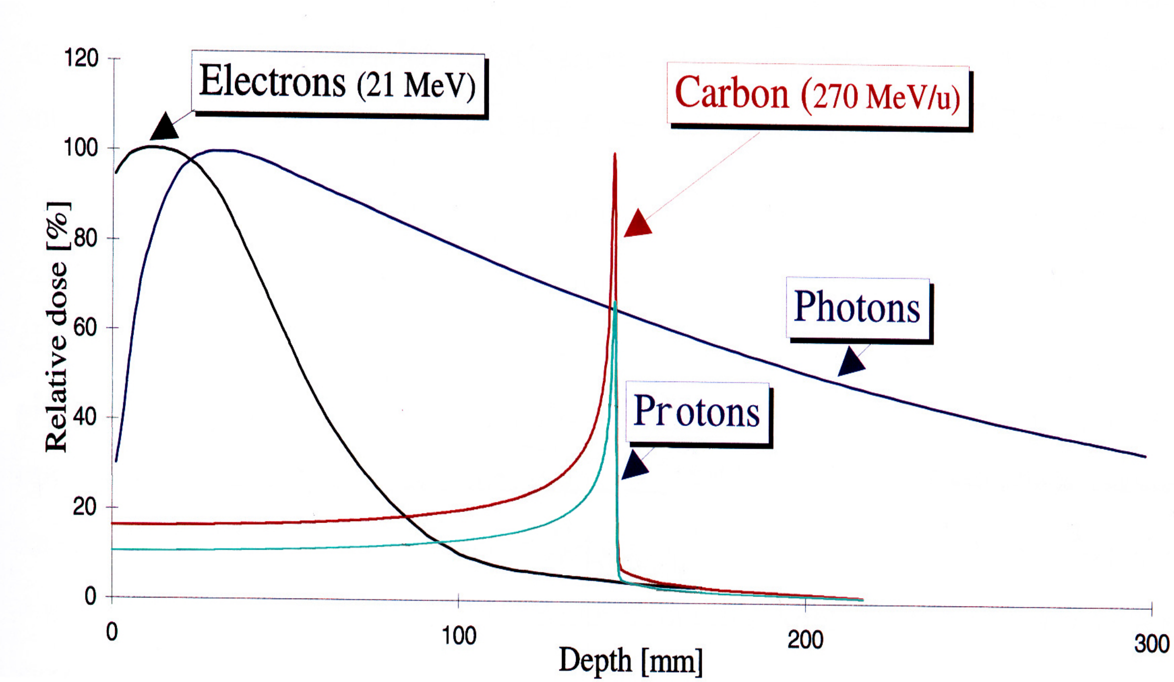
- About 50% patients are treated with RT
- No substitute for RT in the near future
- Number of patients is increasing

Aims of Radiotherapy:

- Irradiate tumour with sufficient dose to **stop cancer growth**
- **Avoid complications** and **minimise** damage to surrounding tissue

Current radiotherapy methods:

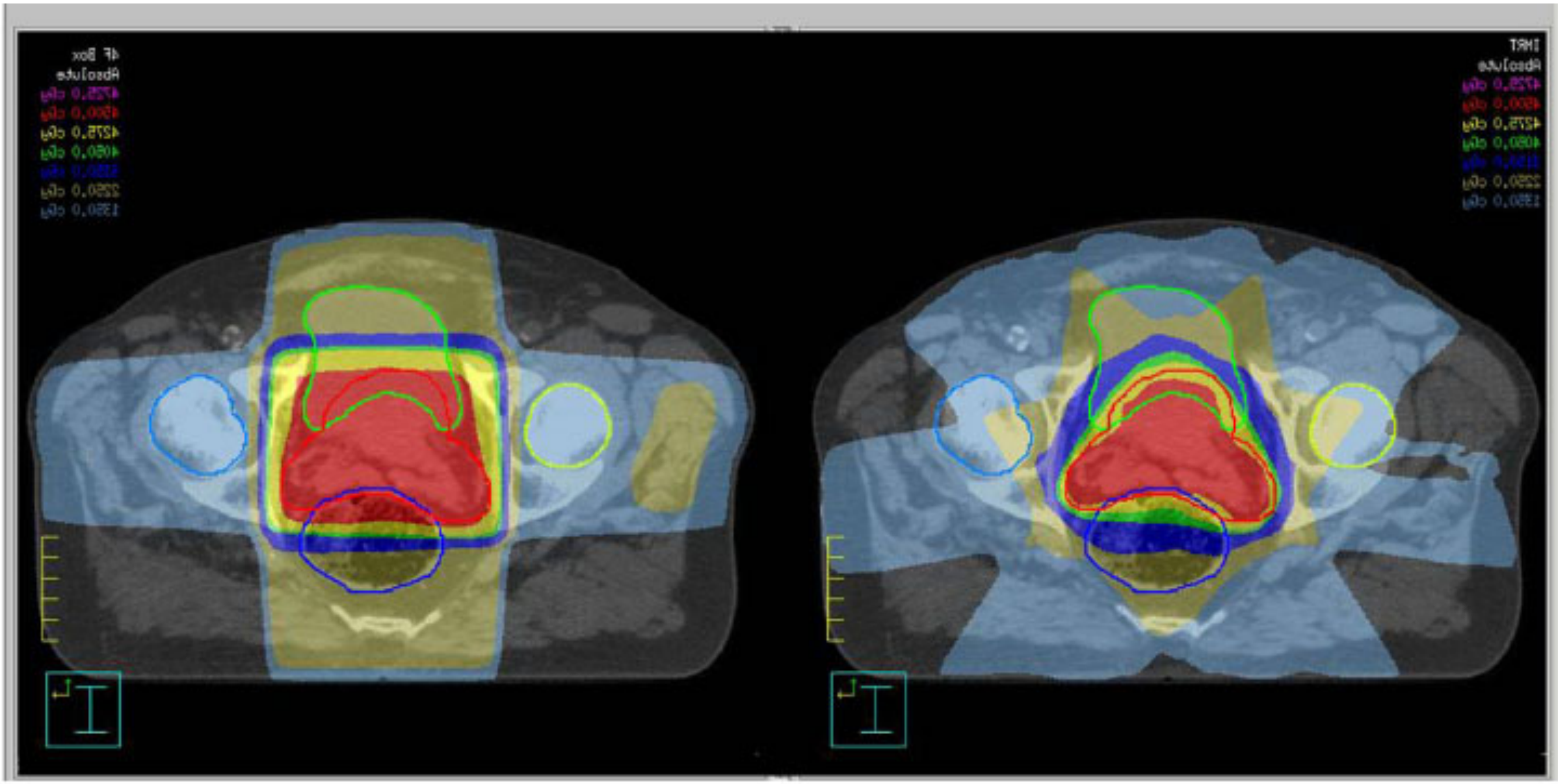
- MV photons
- 5 - 25 MeV electrons
- 50 - 300 MeV/u hadrons



Radiation Therapy Today

- Key radiation therapy delivery systems
  – Cobalt 60 machines
  – Linear accelerators (Linacs)
  – Brachytherapy
  – Image-guided radiotherapy (IGRT);
  – MR-guided linac .
  – Particle therapy (proton and carbon, other ions)
  – FLASH therapy

Improved Delivery

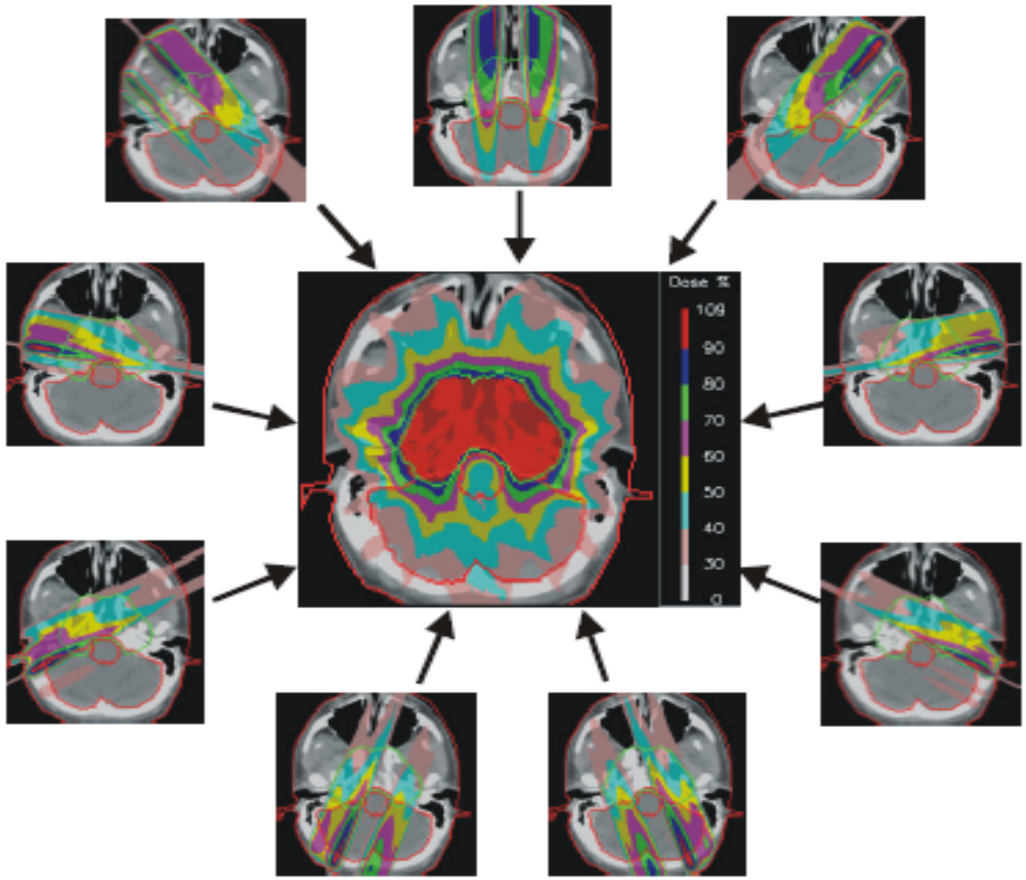


1990s: 4 constant intensity fields

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

60-75 grays (joule/kg) given in 30-35 fractions (6-7weeks)

to allow healthy tissues to repair:

90% of the tumours are radiosensitive

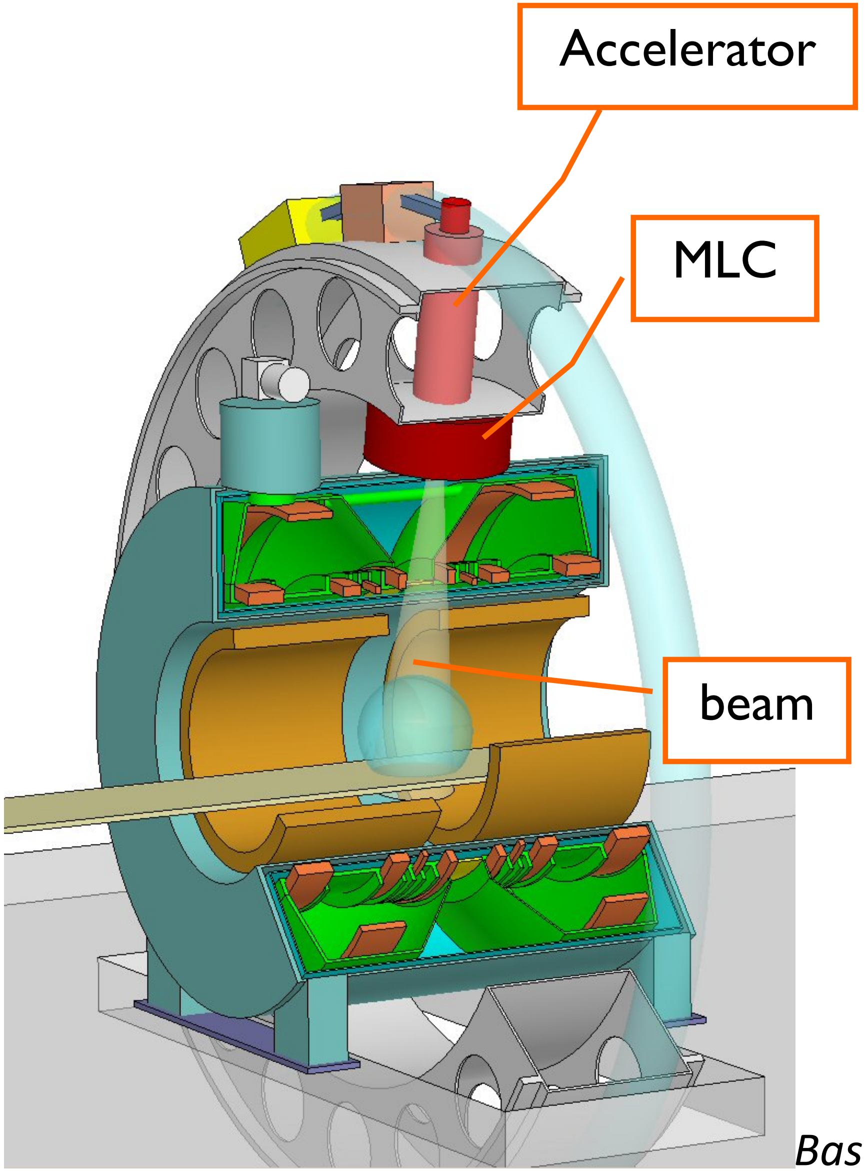
Ugo Amaldi, TERA

Utrecht solution: Integrating a Philips MRI scanner with a Elekta radiotherapy accelerator

1.5T 70 cm bore Philips Ingenia

Lagendijk and Bakker, MRI guided radiotherapy - A MRI based linear accelerator
Radiotherapy and Oncology Volume 56, Supplement 1, September 2000, 220

Concept of MRI guided accelerator



Seeing what you treat at the moment of treatment

Bringing certainty in the actual treatment

Bas Raaymakers, Utrecht, UMC, ENLIGHT

Advances in Radiation Therapy

In the past two decades due to:

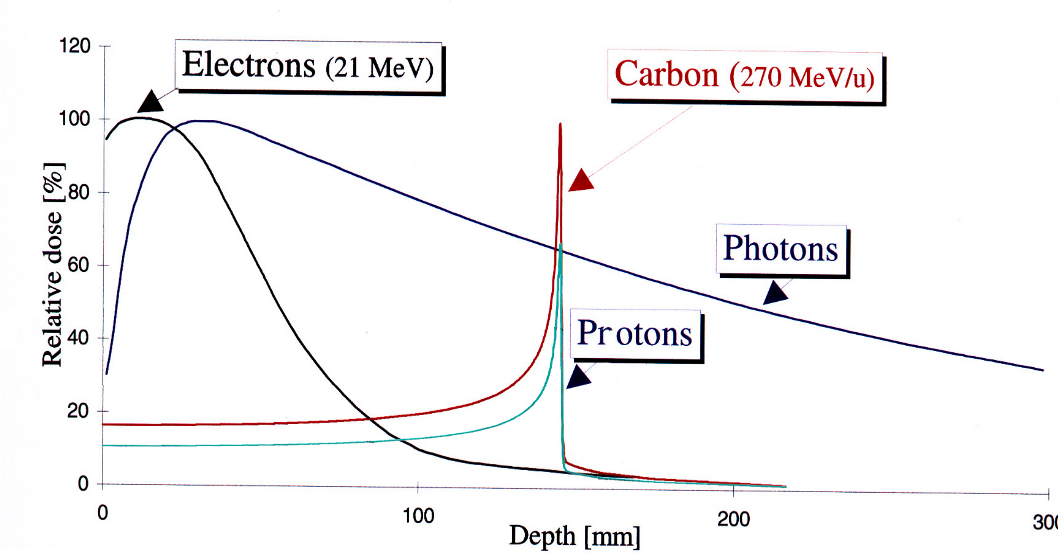
- improvements in imaging modalities,
- powerful computers and software and delivery systems have enabled:
  - Intensity Modulated Radiotherapy (IMRT),
  - Image Guided Radiotherapy (IGRT),
  - Volumetric Arc Therapy (VMAT) and
  - Stereotactic Body Radiotherapy (SBRT)
  - MRI-guided linac therapy
-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

Hadron Therapy

In 1946 Robert Wilson:

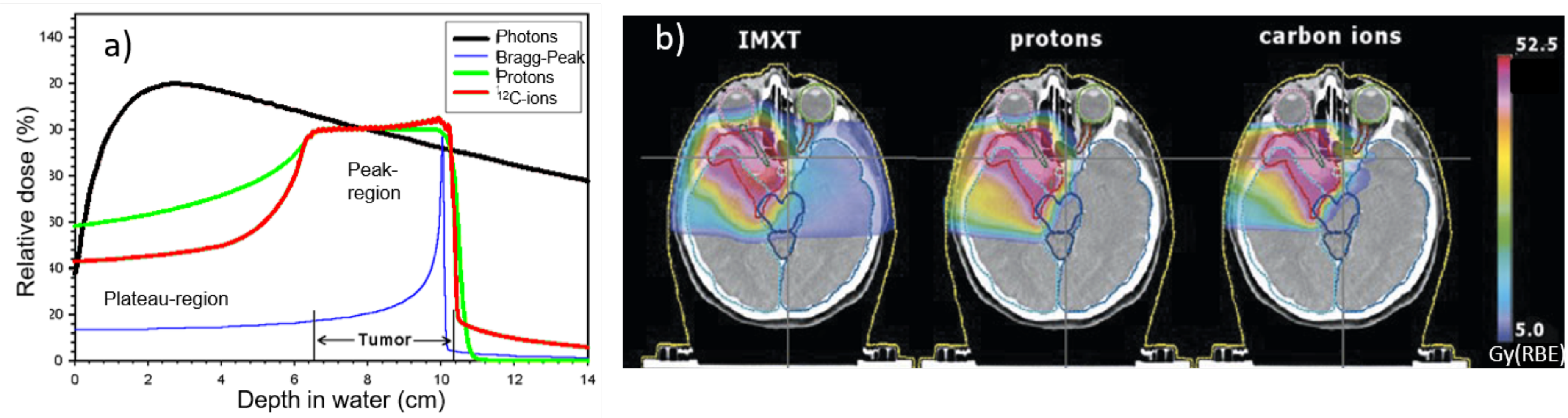
- **Protons can be used clinically**
- **Accelerators are available**
- **Maximum radiation dose can be placed into the tumour**
- **Particle therapy provides sparing of normal tissues**

- Tumours near critical organs
- Tumours in children
- Radio-resistant tumours



Depth in the body (mm)

Why Particle/Hadron Therapy?

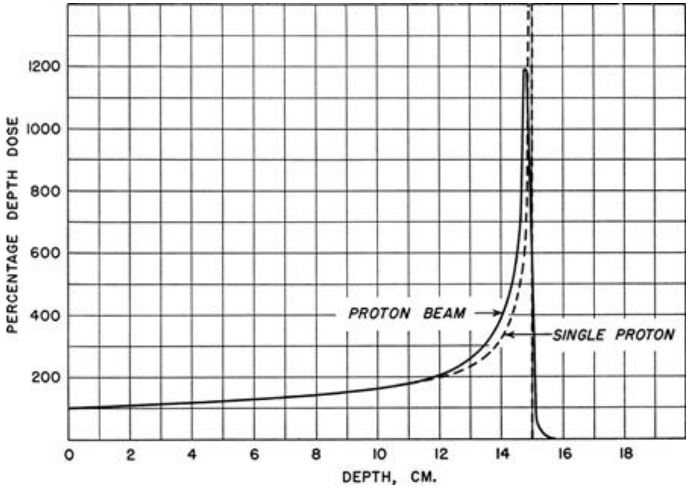


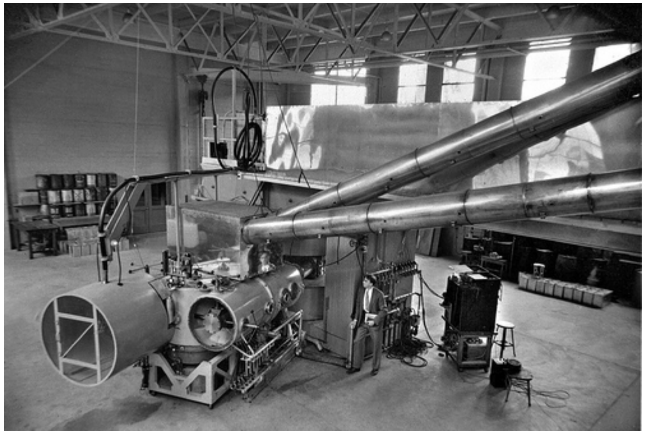
Depth dose profiles in water (a) and treatment plans (b) comparing photons, delivered with the most advanced intensity modulation RT (IMXT), and state-of-the-art scanned protons and ^{12}C ions, showing the increased tumour-dose conformity of ion therapy due to the characteristic Bragg peak (a).

1932 - E. Lawrence First cyclotron

1946 – proton therapy proposed by R. Wilson

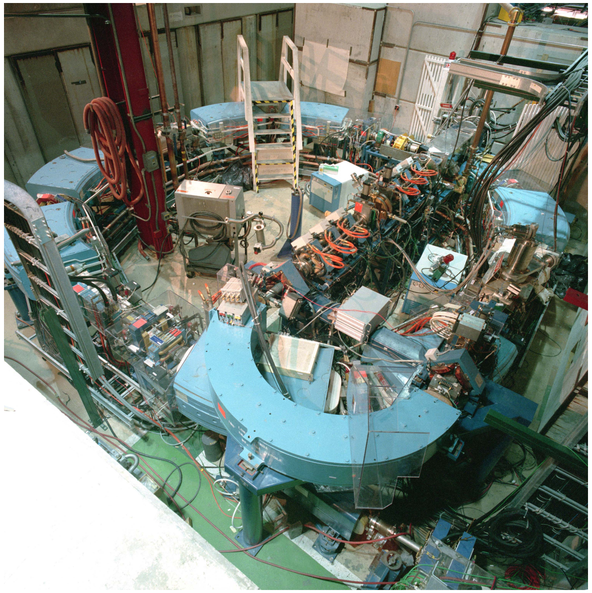
1954 – Berkeley treats the first patient





From physics……..

1993- Loma Linda USA (proton)



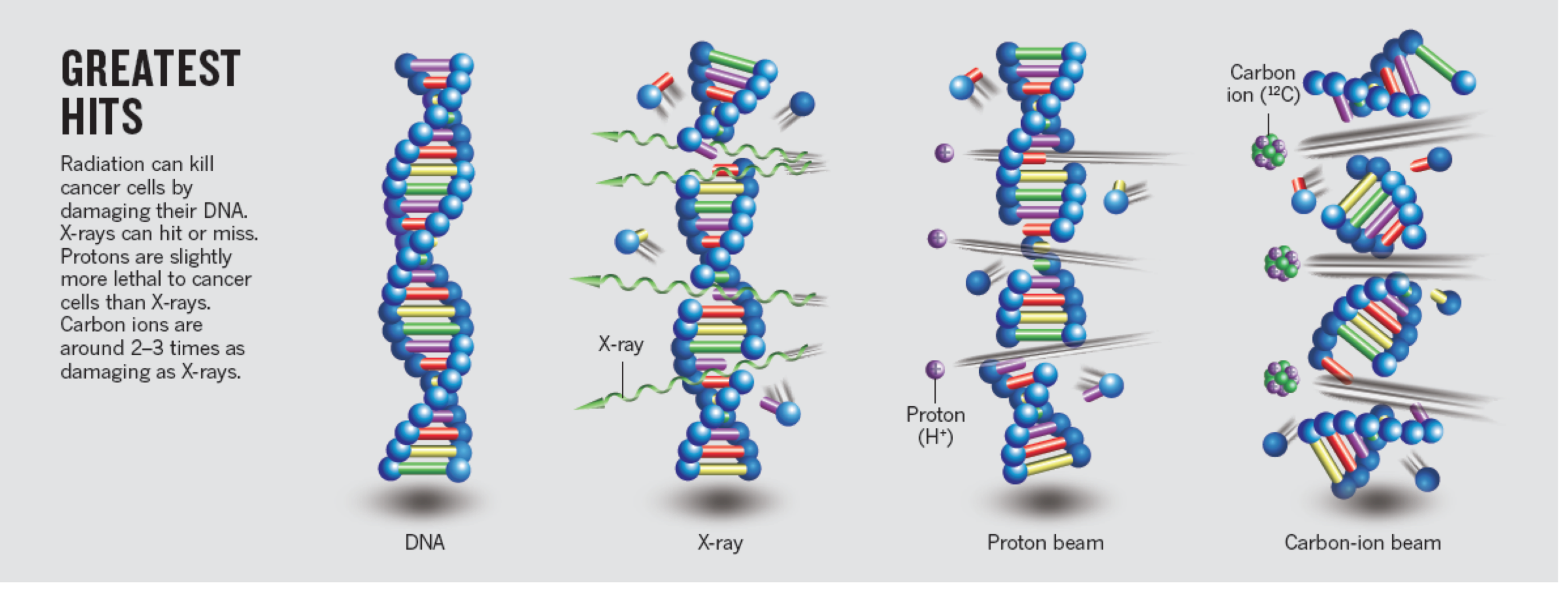
First dedicated clinical facility

1994 – HIMAC/NIRS Japan (carbon)

1997 – GSI Germany (carbon)

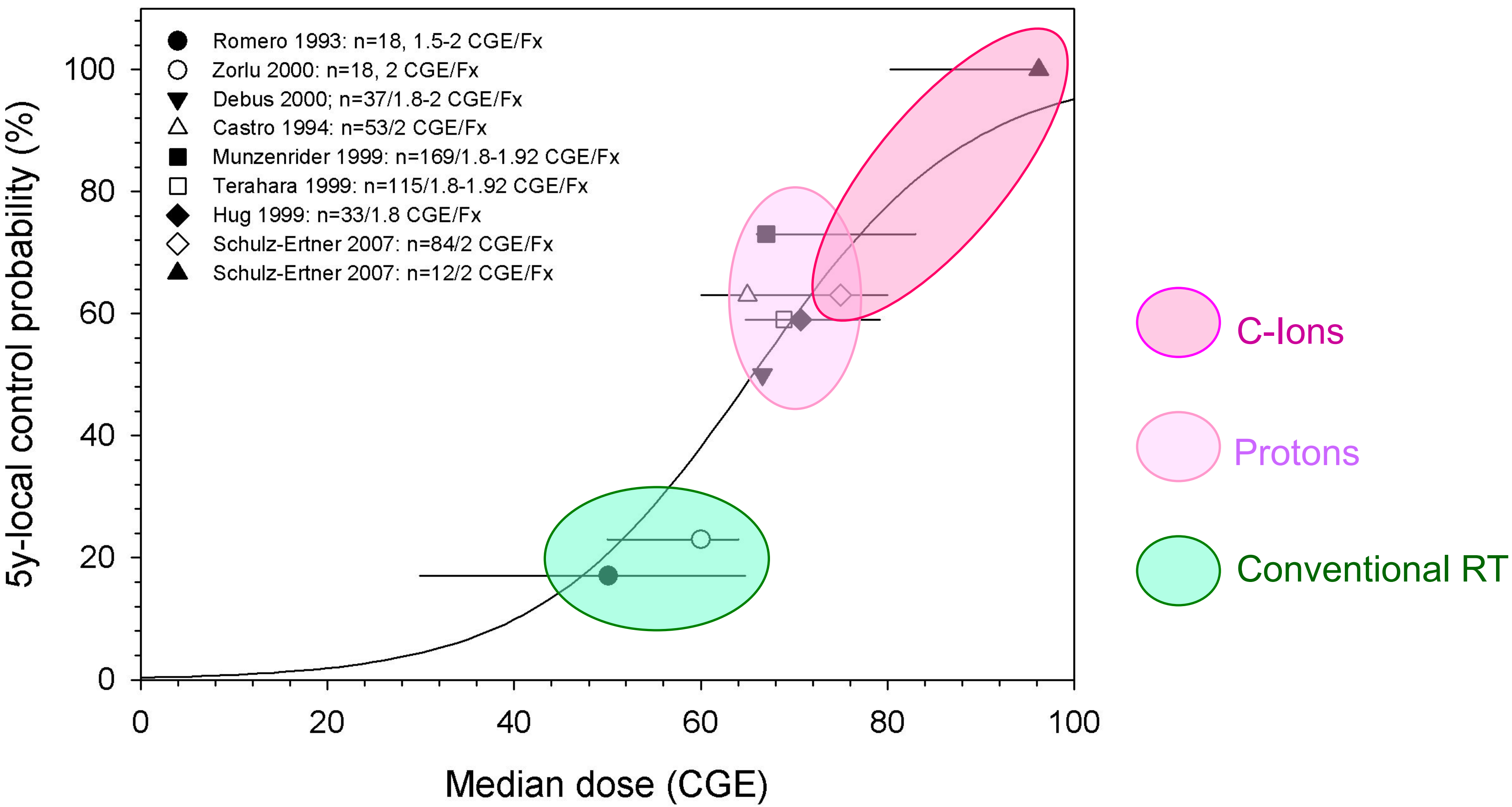
Three crucial years for PT……..to clinics

DNA **X-rays** **Protons** **Carbon ions**



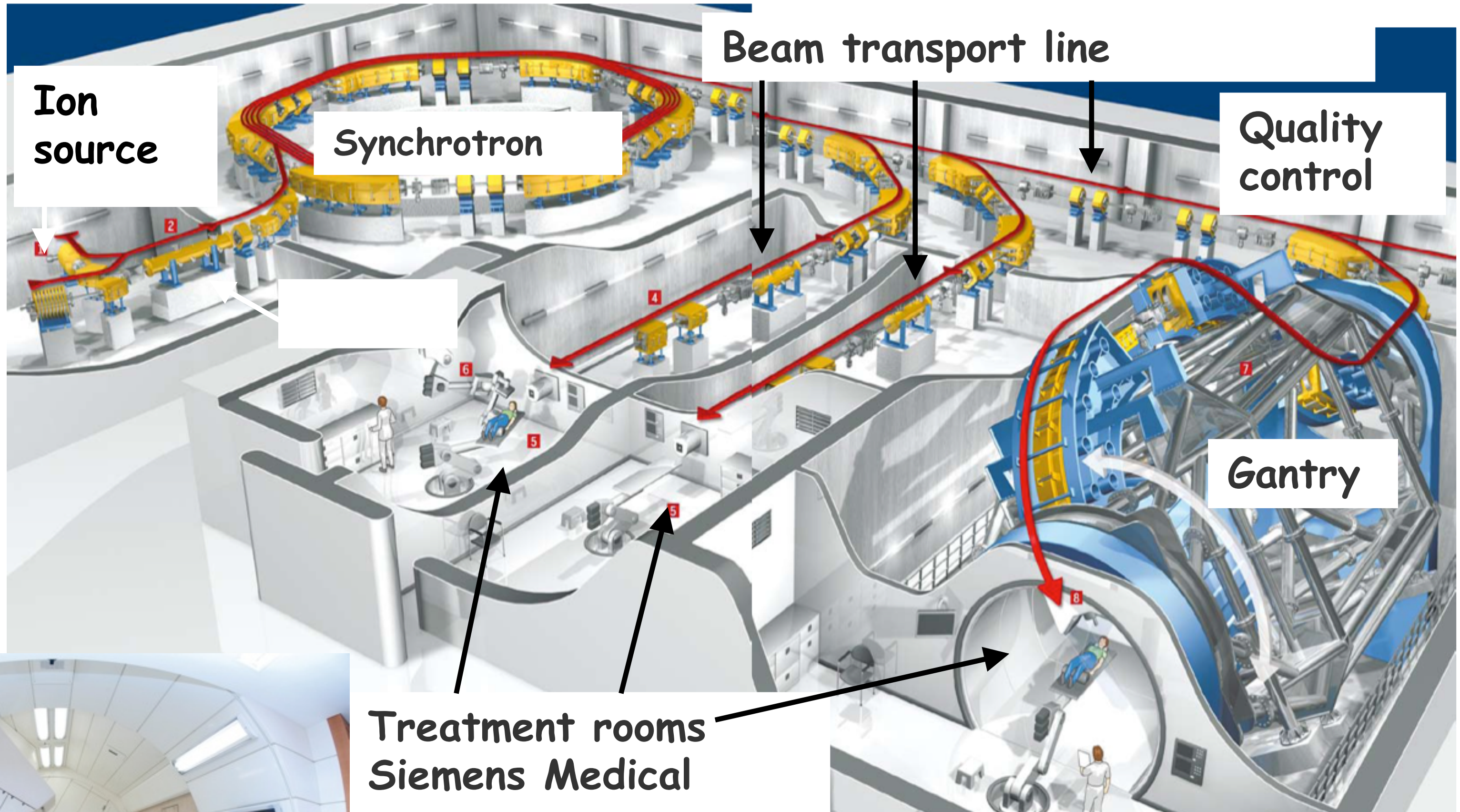
Marx, Nature, 2014

Tumour Control Rate: Chordomas



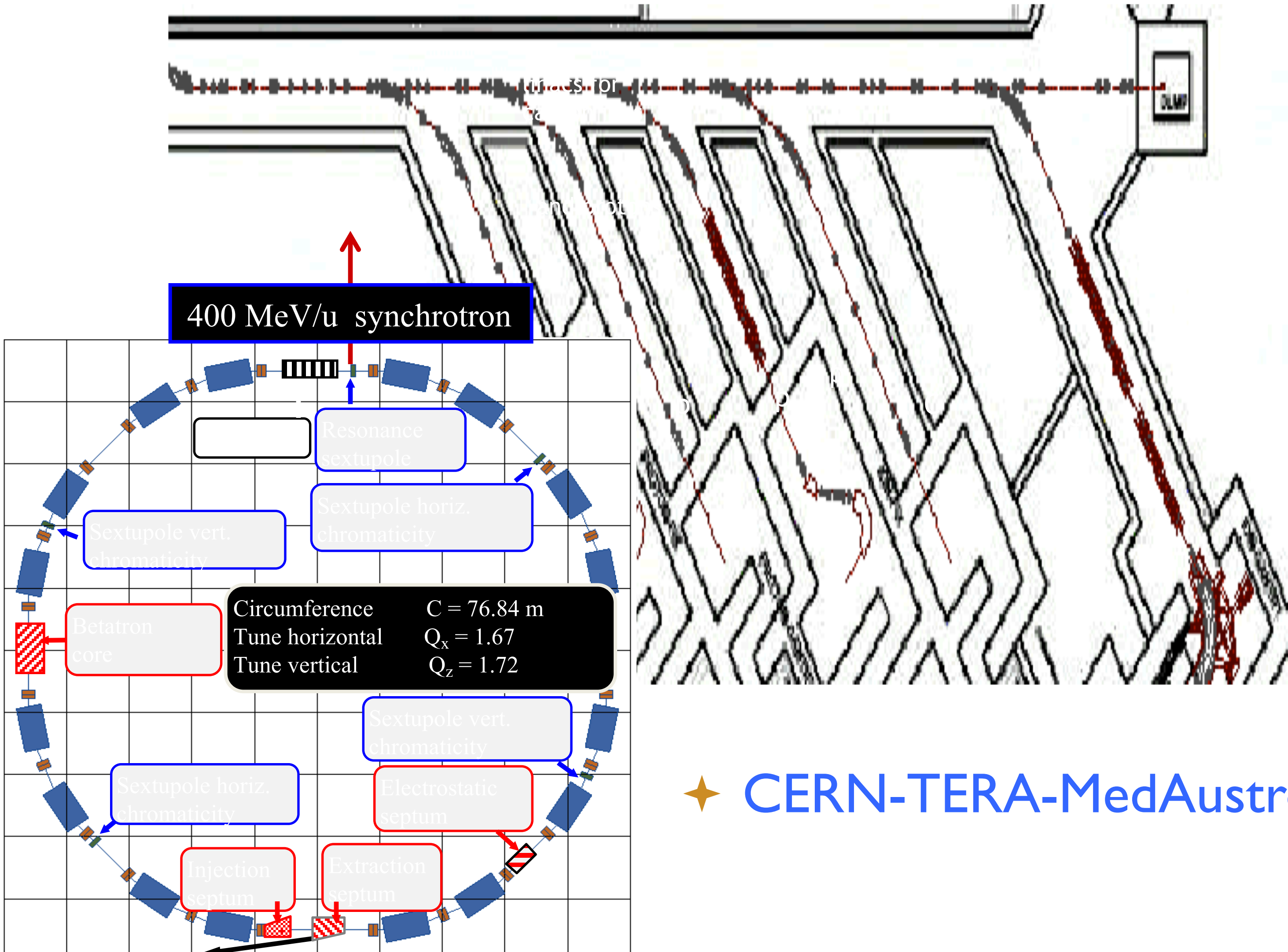
Schulz-Ertner, IJROBP 2007

HIT - Heidelberg



Carbon facilities in Europe: first was HIT in Heidelberg – started treating patients in 2009

PIMMS at CERN (1996-2000)



✦ CERN-TERA-MedAustron

The beginnings of ENLIGHT

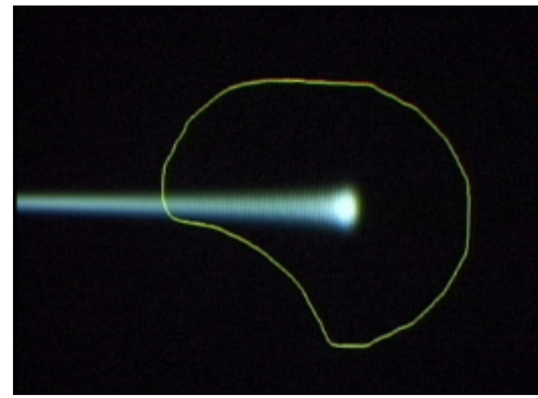
- The idea germinated in 2001 after ESTRO- Med-AUSTRON meeting
- In October 2001 the proposal for a Thematic Network was submitted to EC
- ENLIGHT was launched In February 2002 at CERN
- Funded: 1 million Euros in 2002

Driving Force:
Ugo Amaldi
Jean Pierre Gerard
Germane Heeren

Organisation:
Hans Hoffmann
Manjit Dosanjh

European Network for Light Ion Hadron Therapy

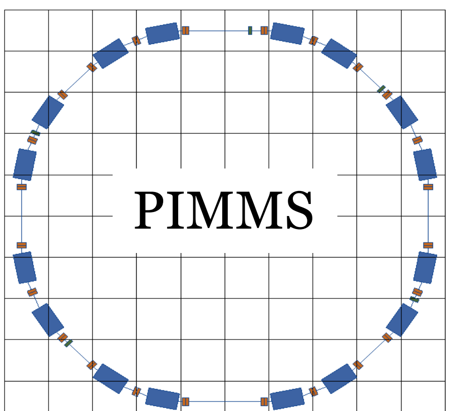
- Launched at CERN in 2002, following PIMMS study
- Common **multidisciplinary platform**
- Cancer treatment
- Identify **challenges**
- Share **knowledge** and best practices
- Harmonise data
- Provide **training**, education
- **Innovate** to improve
- Lobby for funding



PIMMS study at CERN (1996-2000)

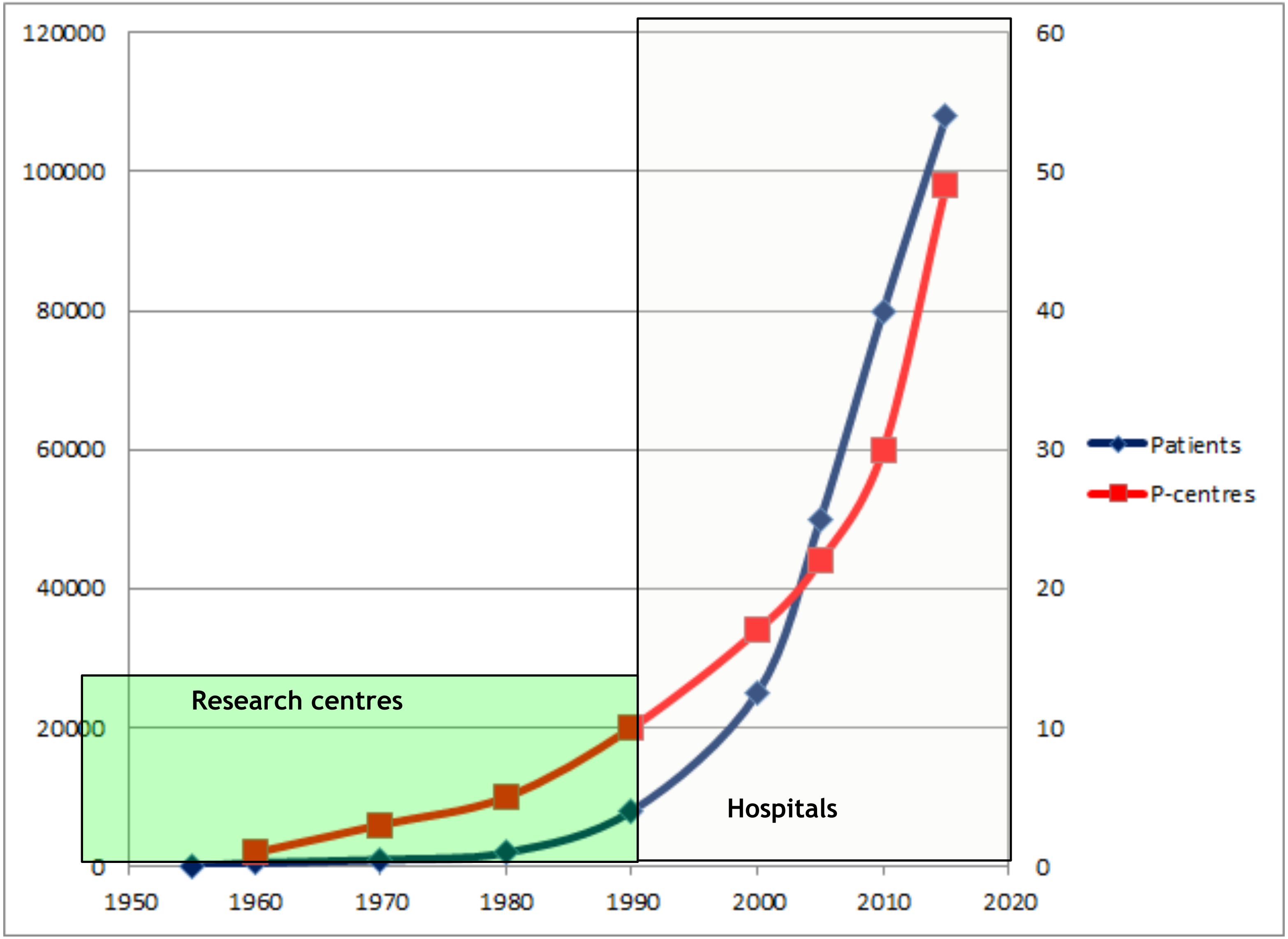
Treatment , CNAO, Italy
2011

1996-2000
PIMMS study



MedAustron, Austria 2016

[Data from www.ptcog.ch]



Facilities in operation in Europe 2020

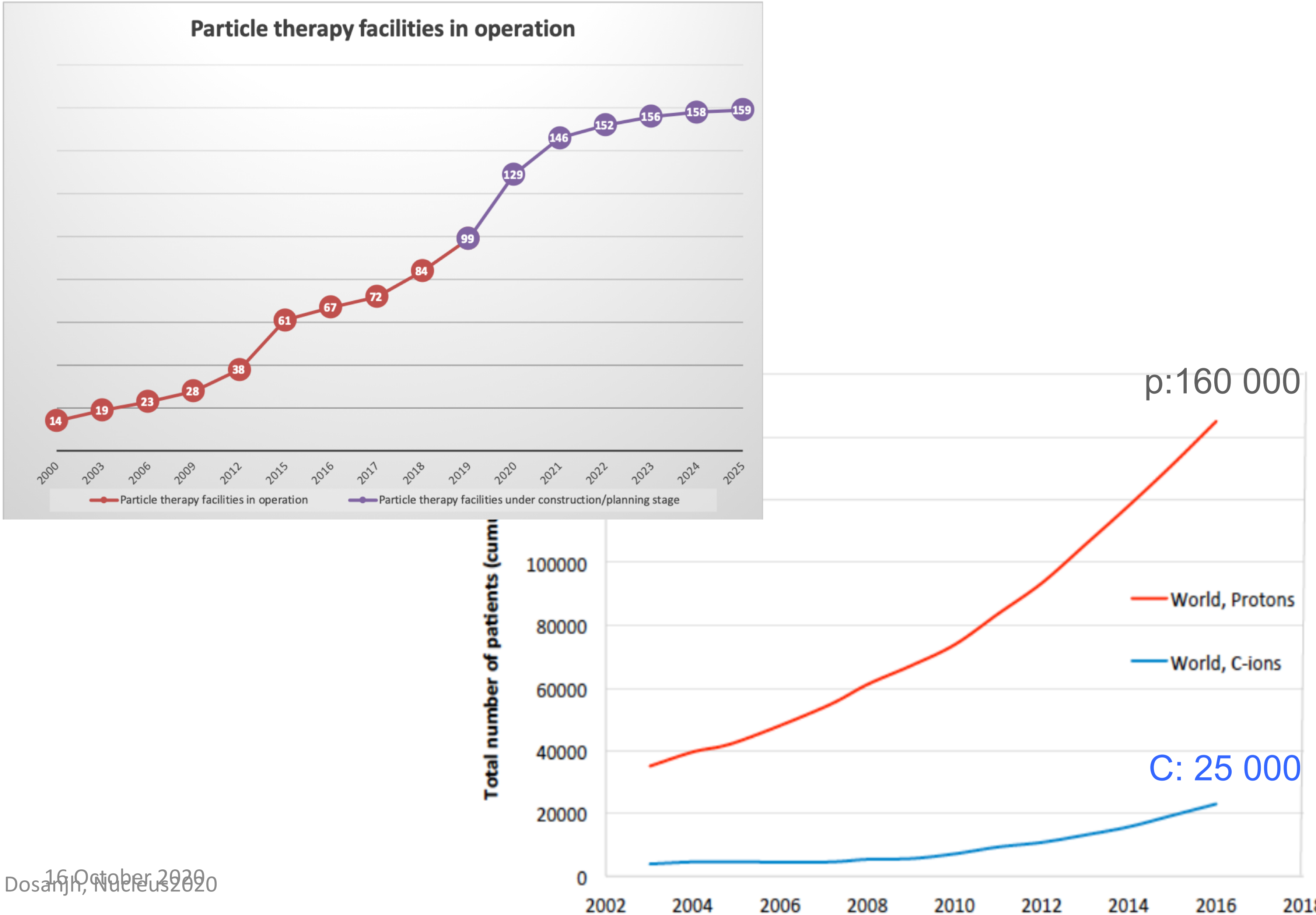
Manjit Dosanjh, Nucleus2020

Current status of Proton centres in East Europe

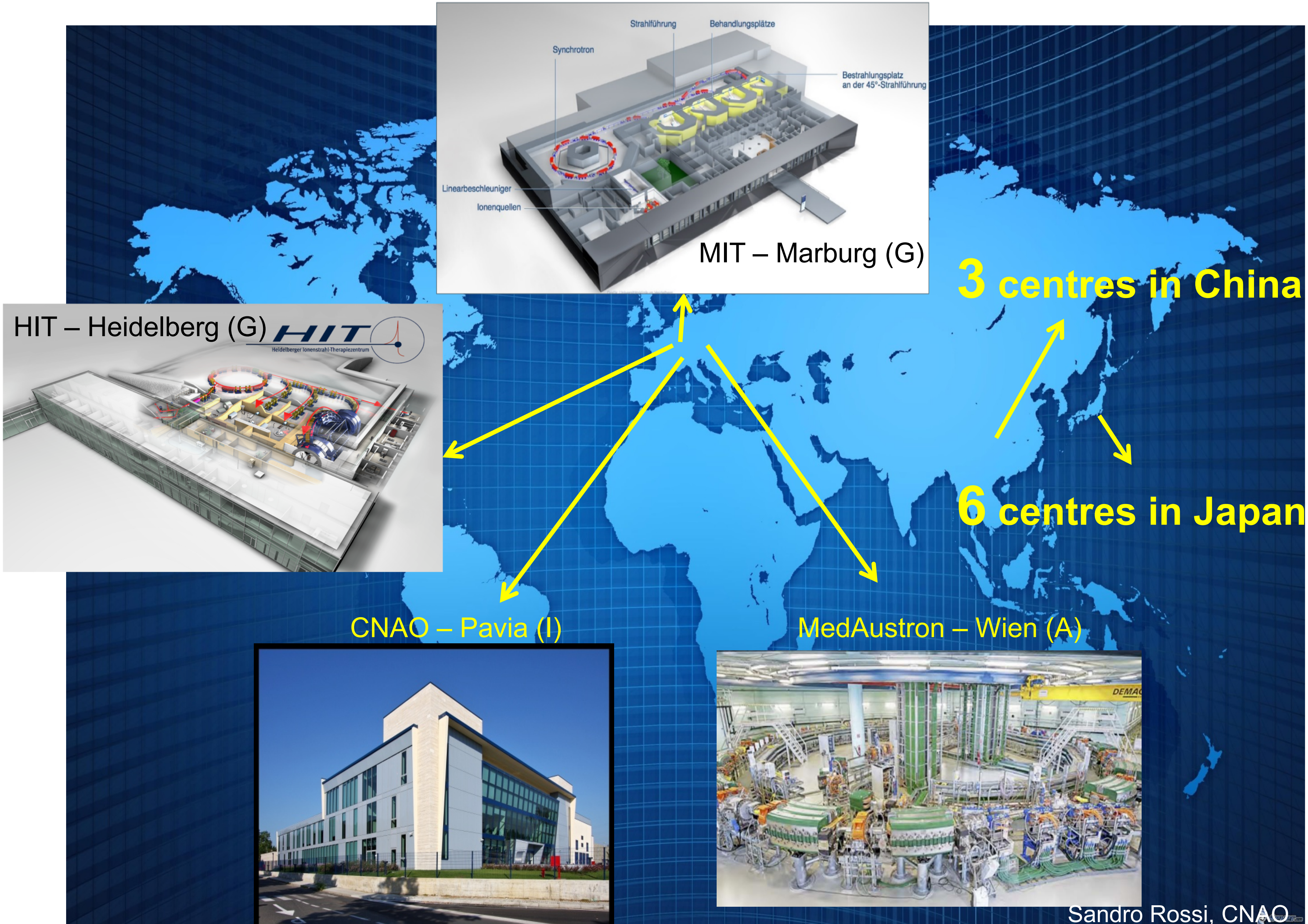
- In clinical operation
- Under construction
- In planning stage

@ENLIGHTNetwork 2020

Centres and patients worldwide



Multi-ions clinical facilities in the World



Much more still needs to be done

- Treat the tumour and only the tumour
  - ⇒ Imaging and dose delivery: control and monitor the ideal dose to the tumour
  - ⇒ Minimal collateral radiation “outside” the tumour
  - ⇒ Minimal radiation to nearby critical organs
  - ➢ Even if the tumour is moving
- Compact: Fit into a large hospital
  - ⇒ Accelerator: smaller, simpler, cheaper
  - ⇒ Gantry: compact, cheaper, energy efficient
- Be affordable
  - ✓ Capital cost ?
  - ✓ Operating costs ?
  - ✓ Increased number of treated patients per year ?
- Wish list from community
  - ✓ Improve patient through-put
  - ✓ Increase effectiveness
  - ✓ Decrease cost
- New ideas being explored

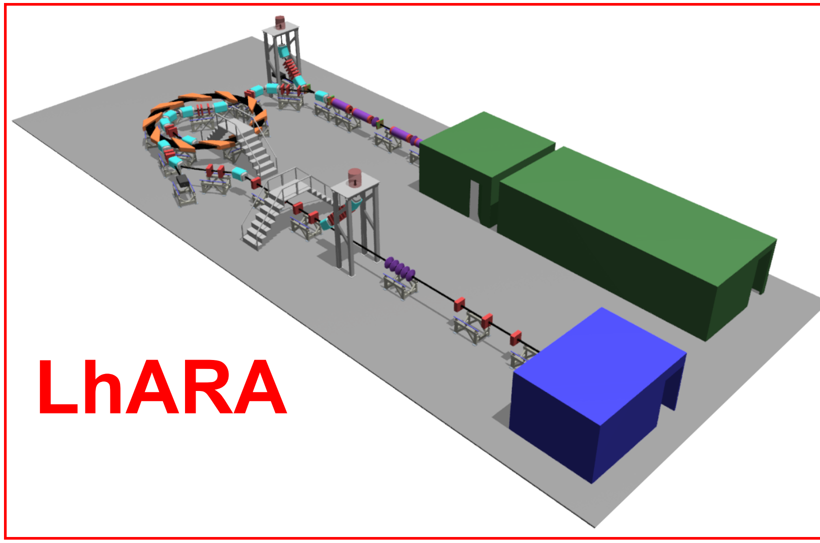
LhARA: Laser-hybrid Accelerator for Radiobiological Applications (K.Long, ICL)

Pre-CDR: CCAP-TN-01; arXiv:2006.00493; submitted to Frontiers in Nuclear Physics, Medical Physics and Imaging

A novel, hybrid, approach:

- **High-flux, laser-driven proton/ion source:**
  - Overcome instantaneous dose-rate limitation
- **Delivers protons or ions in very short pulses:**
  - Pulse length 10 – 40 ns
- **Arbitrary pulse structure**
- **Novel plasma-lens capture & focusing**
- **Fast, flexible, efficient acceleration using FFA:**
  - Protons up to 127 MeV p;
  - Ions up to ~33 MeV/u

→ **compact, uniquely flexible facility**



The LhARA consortium

University partners: Imperial College London, CCAP, University of Liverpool, Department of Physics, Manchester 1824 The University of Manchester, University of Strathclyde Science, Royal Holloway University of London, Queen's University Belfast

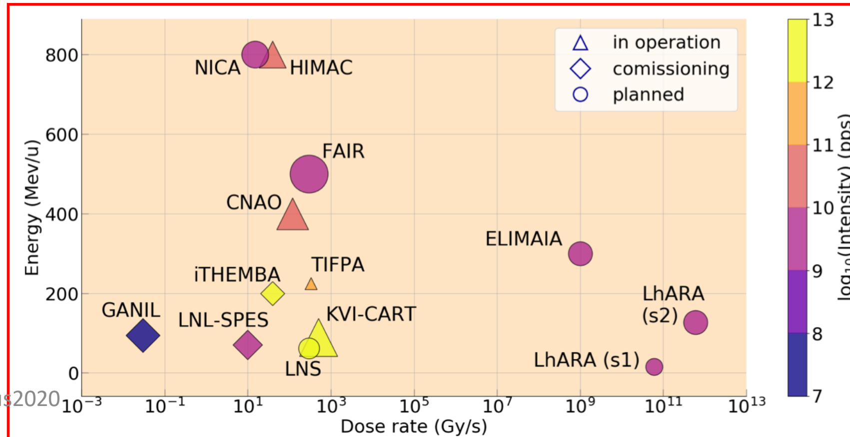
Accelerator institute partners: Science & Technology Facilities Council ASTeC, JAI John Adams Institute for Accelerator Science, The Cockcroft Institute of Accelerator Science and Technology

Laboratory partners: Science & Technology Facilities Council Particle Physics Department, Science & Technology Facilities Council Central Laser Facility, Science & Technology Facilities Council ASTeC, Science & Technology Facilities Council ISIS Neutron and Muon Source

Clinical partners: Oncologists, medical/biophysics, providers — Imperial College Healthcare NHS Trust, 70 Years of the NHS 1948 - 2018, The Clatterbridge Cancer Centre NHS Foundation Trust

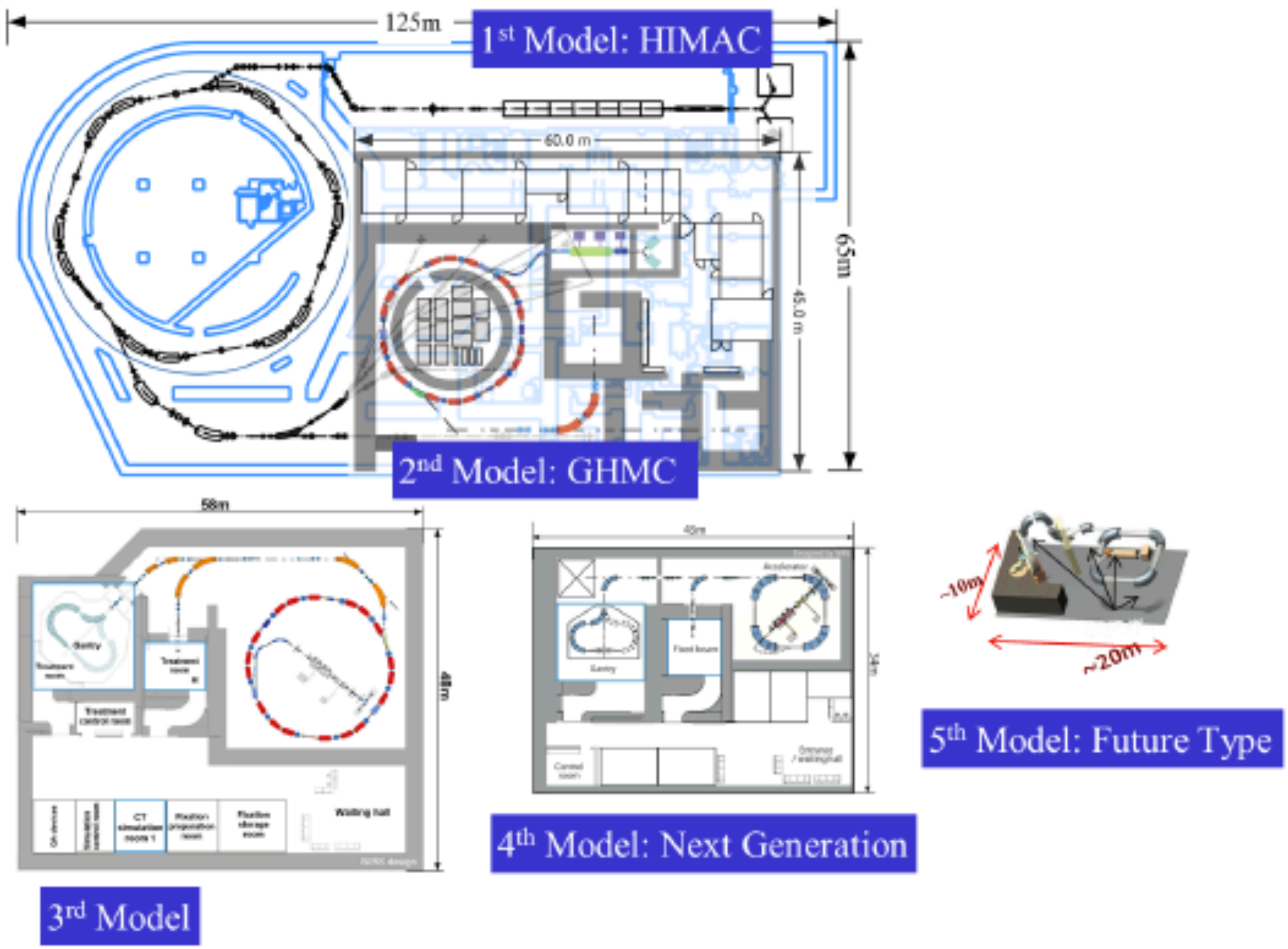
Industrial partners: Maxeler Technologies Maximum Performance Computing, Corerain 鲲云科技, LEO Cancer Care

+ Brm (Phys, Hosp, Cyclotron), NPL, Surrey, Institut Curie



Future Plan

Plan of Miniaturizing Machine



Courtesy of Dr. Kojii Noda

CERN: Beyond PIMMS to NIMMS

A new accelerator design

Requirements of the ion therapy community, expressed at the Archamps Workshop, June 2018

1. Concentrate on heavy ions (Carbon but also Helium, Oxygen, etc.) because proton therapy is now commercial (4 companies offer turn-key facilities) while ions have higher potential for treatment but lower diffusion.

2. A next generation ion research and therapy accelerator must have:

- ❑ Lower cost, compared to present;
- ❑ Reduced footprint;
- ❑ Lower running costs;
- ❑ Faster dose delivery with higher beam intensity or pulse rate;
- ❑ A rotating ion gantry;
- ❑ Operation with multiple ions (for therapy and research).

An innovative design:

- Can attract a wide support from the scientific community;
- Can increase the exchange SEE-WE and inside SEE thanks to stronger collaboration on scientific and technical issues;
- Can bring modern high technology to the region, with new opportunities for local industry and scientific institutions.

+ Specific requirements for SEEIIST:

- ❑ Easy Industrialization
- ❑ Reliability
- ❑ Simple operation
- ❑ Reduced risk
- ❑ Acceptable time to development

Current Hot topics: FLASH, VHEE……….

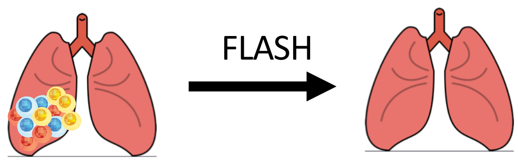
FLASH radiotherapy is based on the observation that healthy tissue is less damaged if treatment occurs very fast

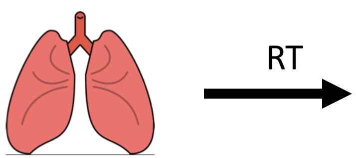
RESEARCH ARTICLE

RADIATION TOXICITY

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

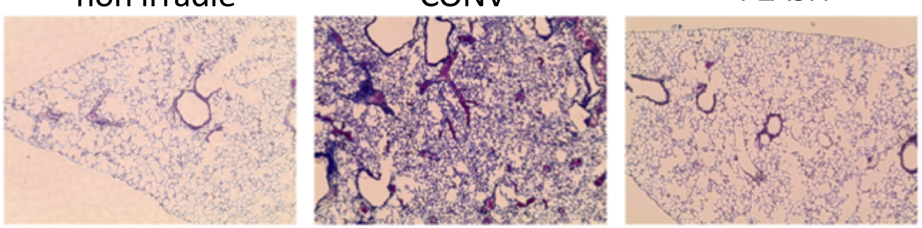
Vincent Favaudon,[1,2*] Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2||] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]





Toxicity evaluation

Contrôle non irradié	17 Gy CONV	17 Gy FLASH



HEALTHY	FIBROTIC	HEALTHY

Anti-tumor efficacy

↓

FLASH EFFECT

↑

Absence of radiation-induced toxicity in the Normal lung

FLASH THERAPY

What are the underlaying mechanisms in FLASH effect?

The role of the oxygen

Playing with the oxygen tension = modify ROS production

1 – Make mice breathe 95% of oxygen (before and during IR)

2 – Increase oxygen tension in the brain

3 – Deliver FLASH or conventional dose-rate irradiation

4 – Evaluate memory

CONV | CONV OXYGEN | FLASH | FLASH OXYGEN

Memory Loss | Memory Loss | Memory OK | Memory Loss

Increase in O2 tension reverses the FLASH effect

Less ROS produced by FLASH-RT ?

Montay-Gruel et al (in revision)

Treatment of a first patient with FLASH-radiotherapy

Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com
ELSEVIER

Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland

5.6 MeV linac adapted for accelerating electrons in FLASH mode

15 Gy with 10 pulses **in 90 ms**

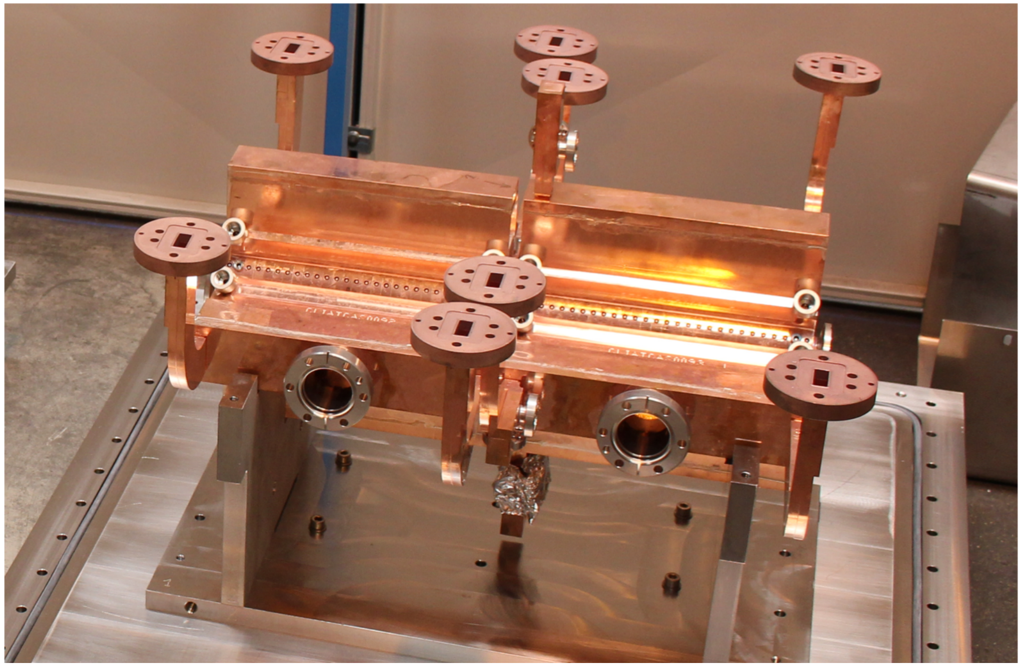
3.5 cm diameter tumour, multiresistant cutaneous

Appears that instantaneous dose Induces a massive oxygen consumption and a transient protective hypoxia in normal issues

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

New State of the art?

With recent High-Gradient linac technology developments,
Very High Energy Electrons (VHEE) in the range 100–250 MeV
offer the promise to be a cost-effective option for Radiation Therapy

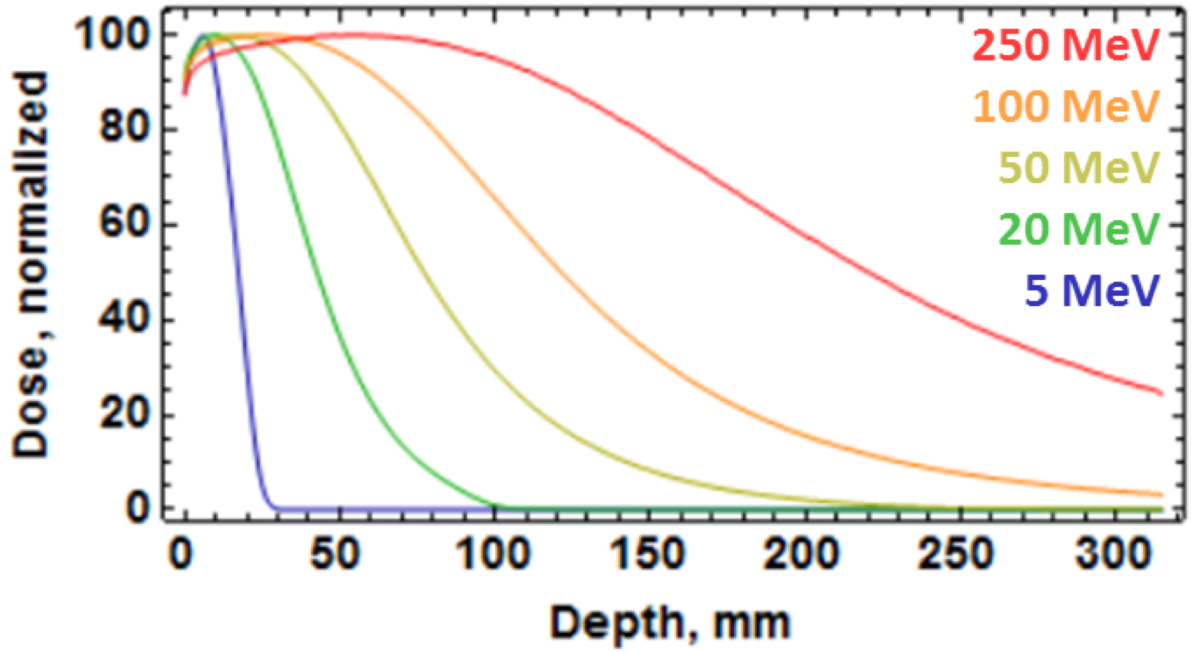


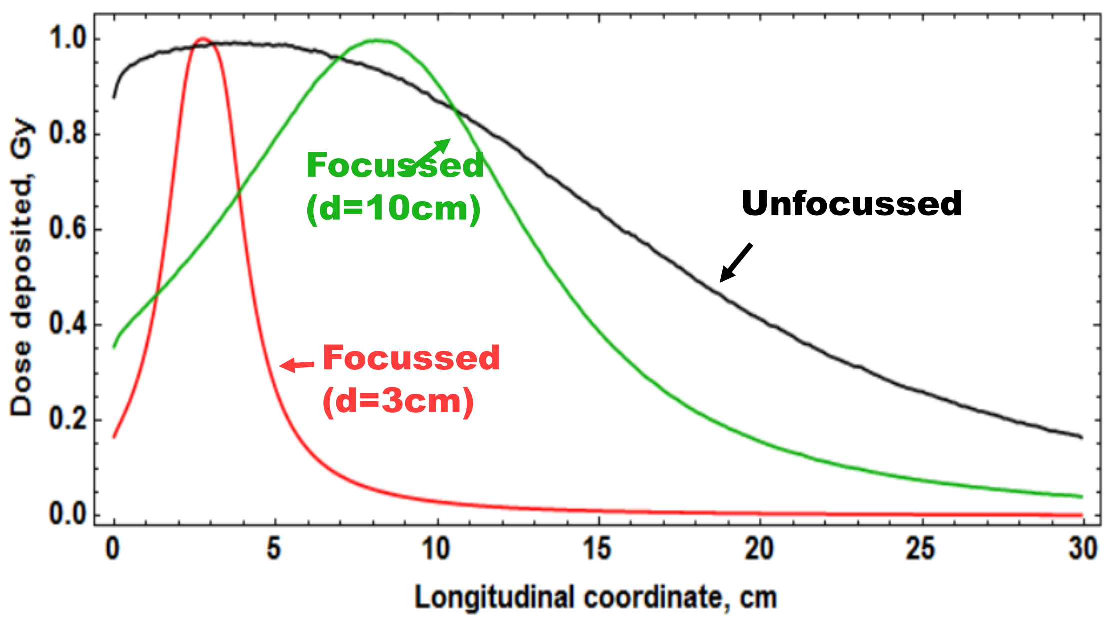
CLIC RF X-band cavity prototype (12 Ghz, 100 MV/m)

Compact Linear Collider

$\sigma = 5$ mm, various energies

A. Lagzda





Where are we going?
Which experiments/facilities are needed?

Dr. A. Faus-Golfe
Dr. M. Dosanjh

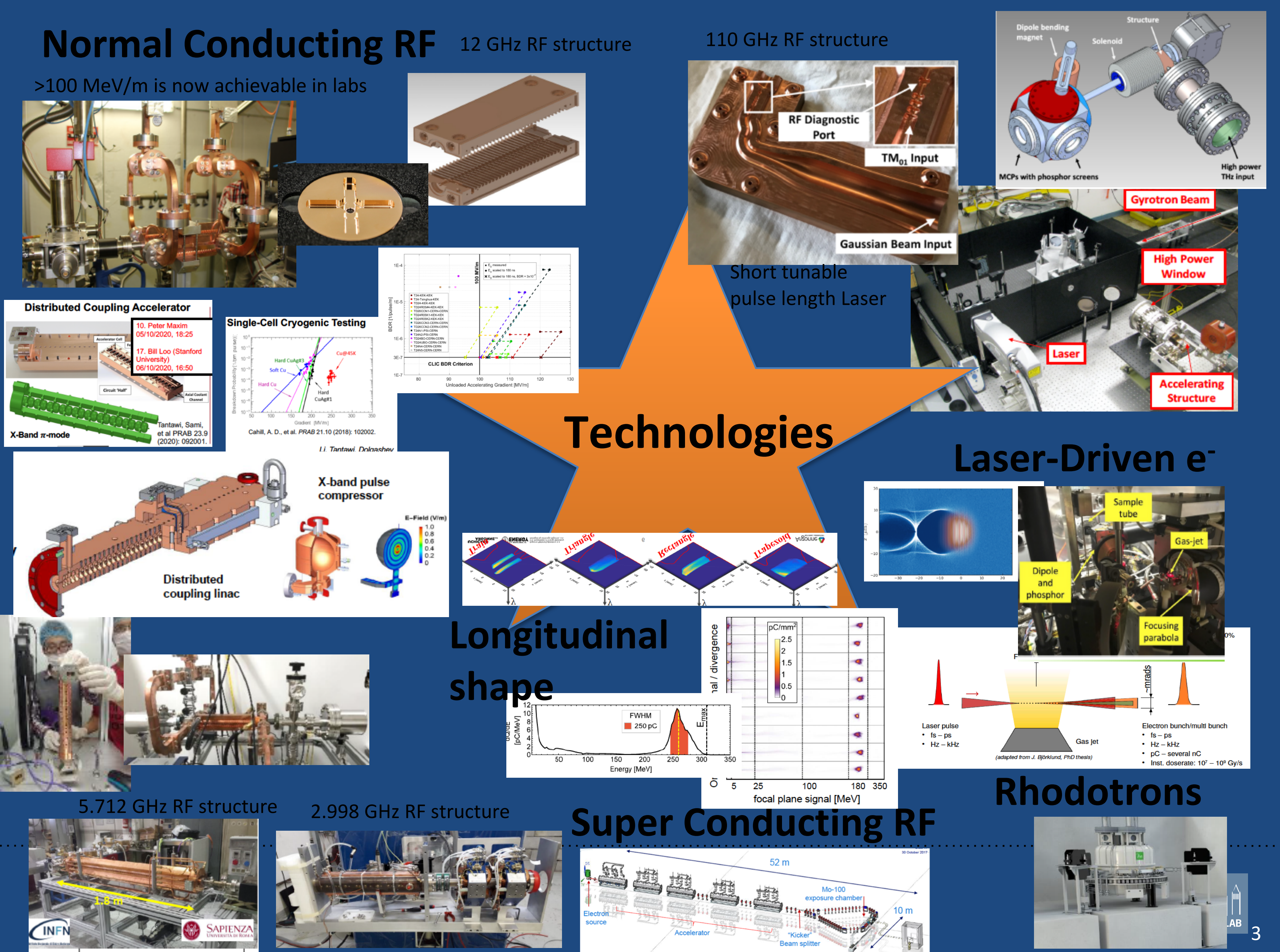
Accelerators and Technologies

Accelerators to enables:

- ➢ More **COMPACT** accelerators, using **HIGH-GRADIENT**, **SC** and **NOVEL** acceleration Techniques (**laser-driven**)
- ➢ Enabling **NEW DELIVERY DOSE** techniques: **FLASH**, mini-beams, pencil beam scanning….
  - ➢ ***FASTER*** High-Repetition Rates
  - ➢ **HIGH-INTENSITY**

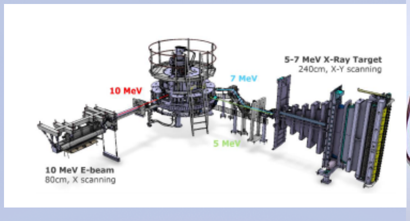
Furthermore:

- ➢ Combined **IRRADIATION** and **IMAGING**
- ➢ Combined **IRRADIATION** and **DOSIMETRY**
- ➢ **SIMPLER** cost-effective designs, more **EFFICIENT**, **ROBUST** and **RELIABLE**, **CHEAPER** to run



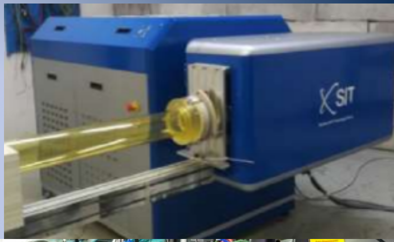
Normal Conducting RF
12 GHz RF structure
>100 MeV/m is now achievable in labs
110 GHz RF structure
RF Diagnostic Port
TM_{01} Input
Gaussian Beam Input
Dipole bending magnet
Structure
Solenoid
MCPs with phosphor screens
High power THz input
Gyrotron Beam
High Power Window
Laser
Accelerating Structure
Short tunable pulse length Laser
Distributed Coupling Accelerator
10. Peter Maxim 05/10/2020, 18:25
17. Bill Loo (Stanford University) 06/10/2020, 16:50
X-Band π-mode
Tantawi, Sami, et al PRAB 23.9 (2020): 092001.
Single-Cell Cryogenic Testing
Cahill, A. D., et al. PRAB 21.10 (2018): 102002.
CLIC BDR Criterion
Unloaded Accelerating Gradient [MV/m]
X-band pulse compressor
Distributed coupling linac
E-Field (V/m)
Technologies
Laser-Driven e⁻
Sample tube
Gas-jet
Dipole and phosphor
Focusing parabola
Longitudinal shape
Triangle
Rectangle
Doorstep
FWHM
250 pC
Energy [MeV]
focal plane signal [MeV]
Laser pulse
fs – ps
Hz – kHz
Gas jet
Electron bunch/multi bunch
fs – ps
Hz – kHz
pC – several nC
Inst. doserate: 10^7 – 10^9 Gy/s
(adapted from J. Björklund, PhD thesis)
Rhodotrons
5.712 GHz RF structure
1.8 m
INFN
SAPIENZA Università di Roma
2.998 GHz RF structure
Super Conducting RF
52 m
Mo-100 exposure chamber
10 m
Electron source
Accelerator
"Kicker" Beam splitter

CLEAR CERN



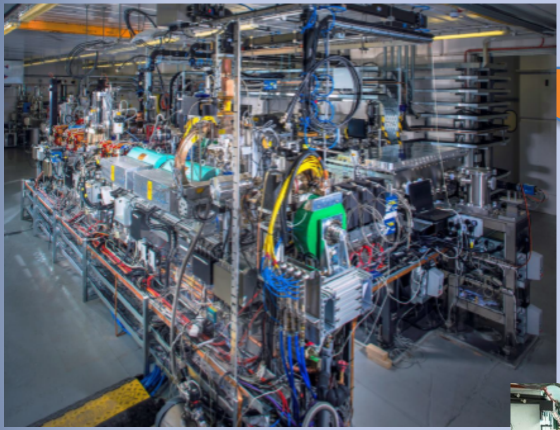
AERIAL

ORIATRON CH

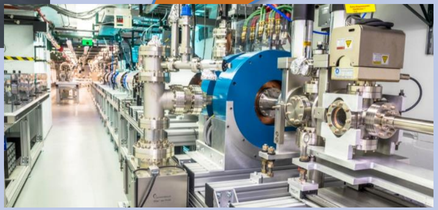


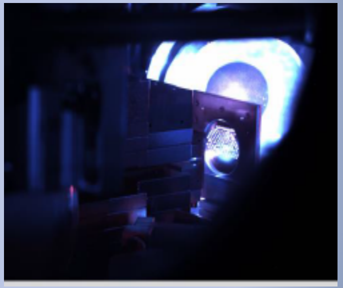
ELBE HZDR

Facilities

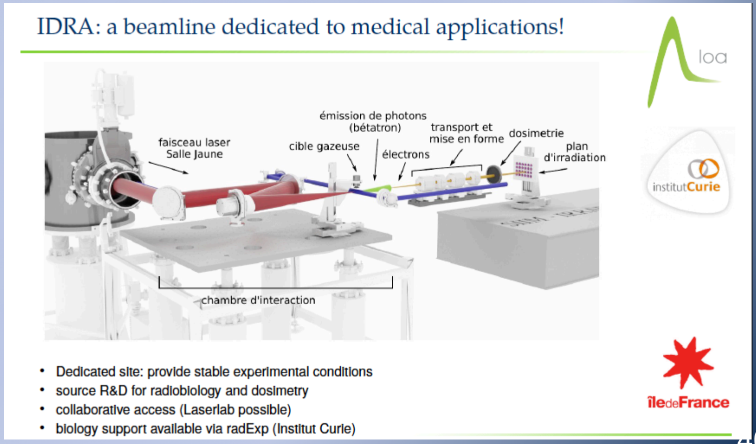


CLARA STFC CI



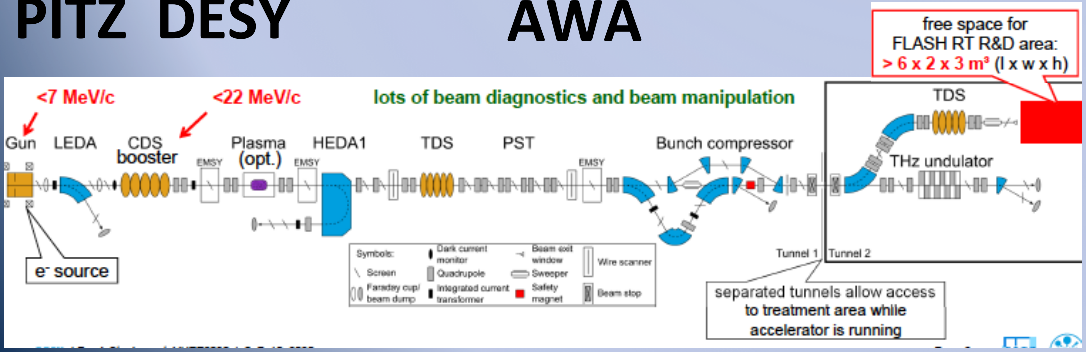


IDRA LOA



PITZ DESY

AWA



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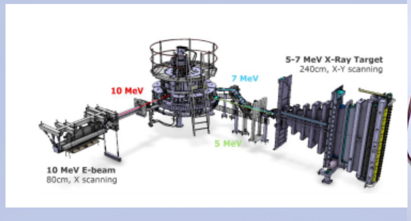

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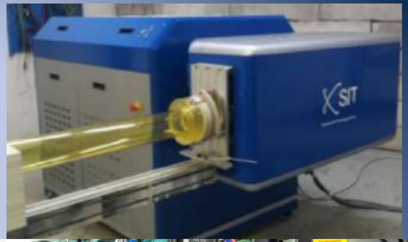
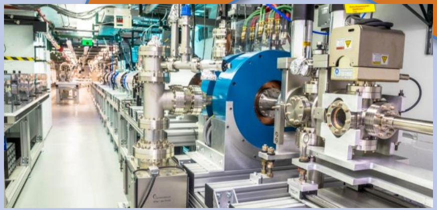


ORIATRON CH

ELBE HZDR

It is time for experiments !!!!!

CLARA STFC CI



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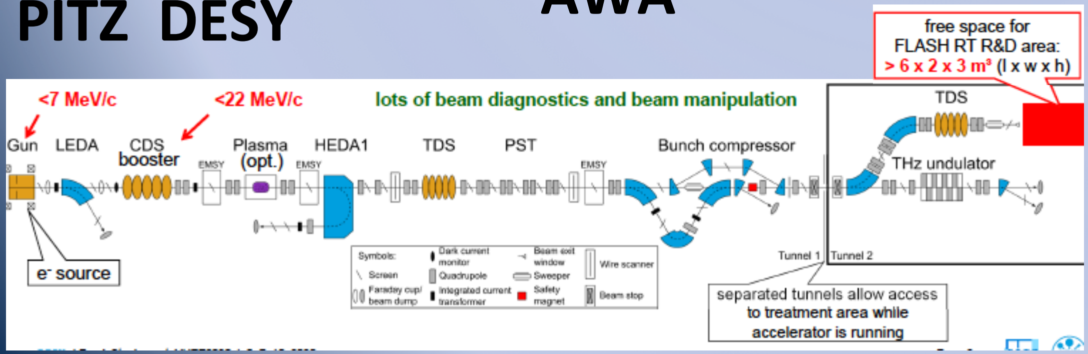
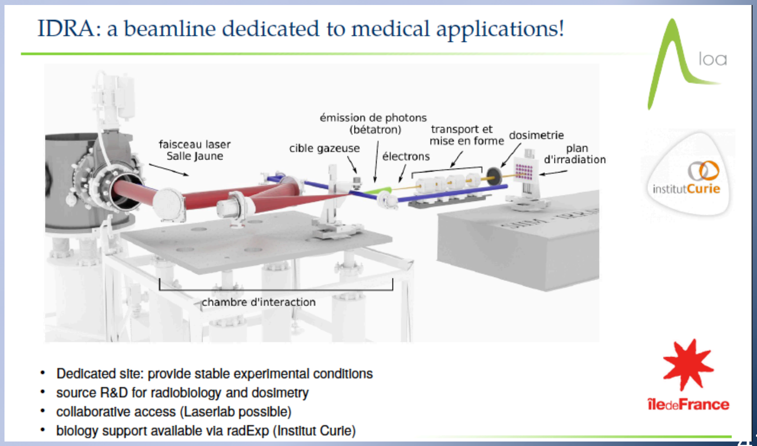


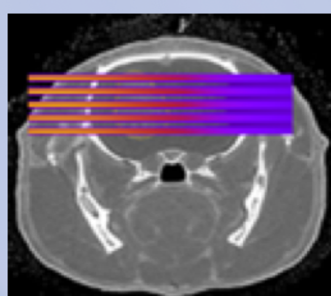


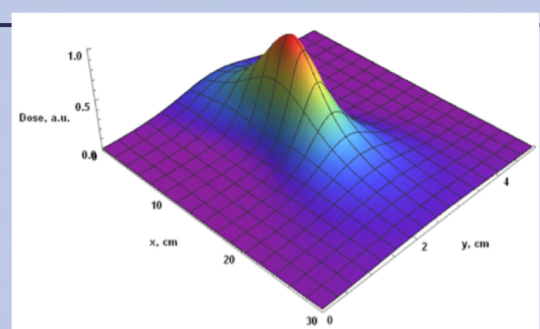
VHEE Open questions:

- ➢ What High-Energy ?
- ➢ Field sizes?
- ➢ Inhomogenities??
- ➢ Scanning small beams ?
- ➢ Focusing and Shaping?
- ➢ In vivo experiments for validate FLASH RT?
- ➢ Pulse structure impact in FLASH RT?

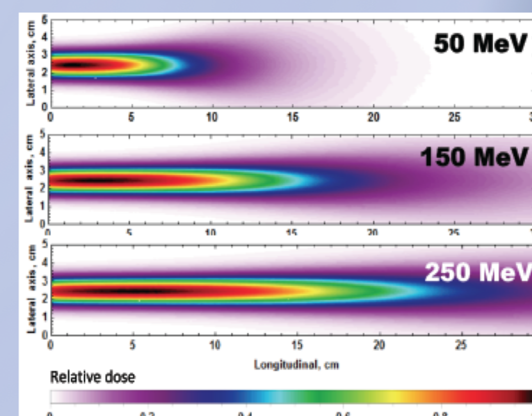
FLASH RT

Mini-beams





Focusing

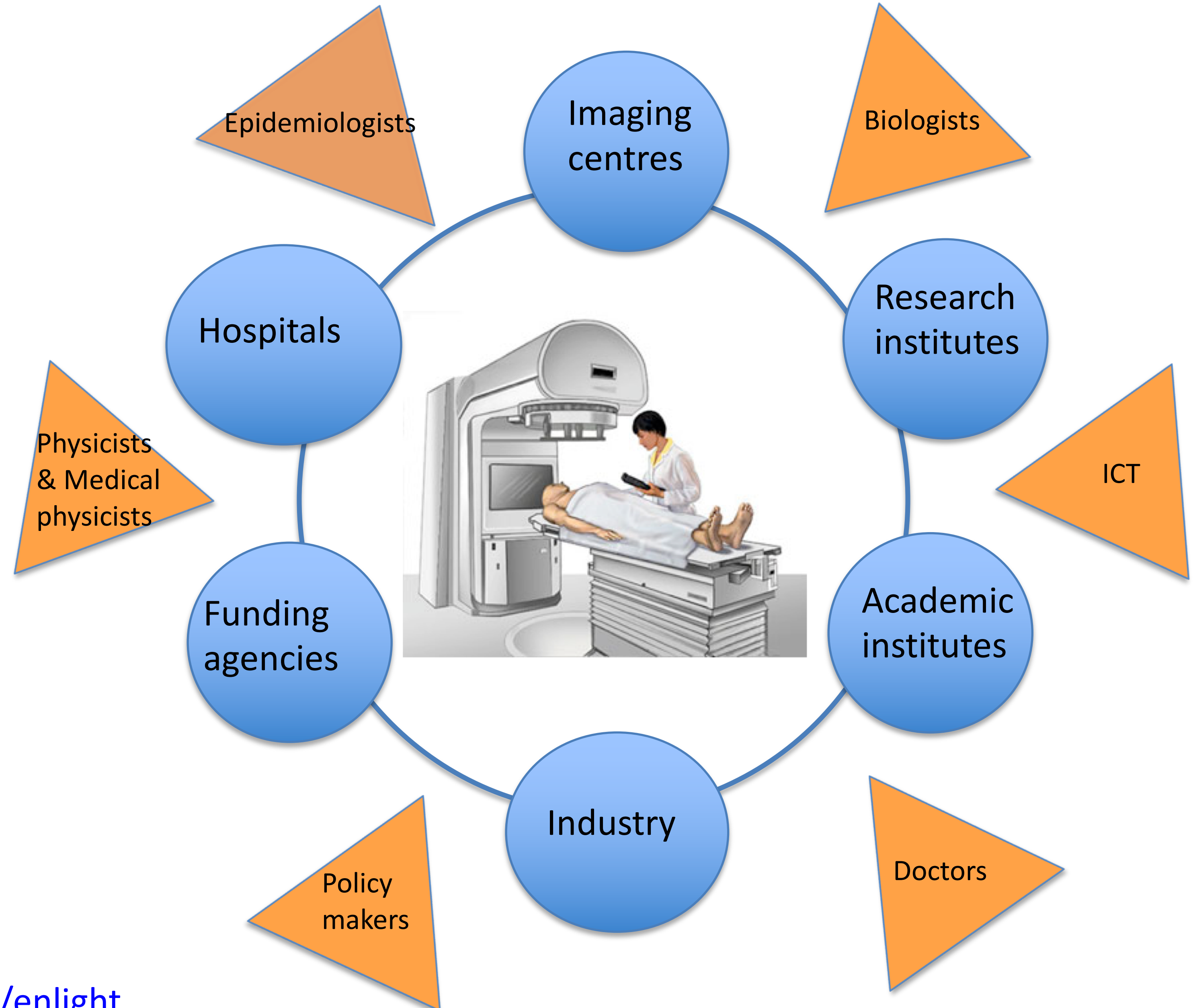


Dose maps of 50, 150 and 250 MeV VHEE beams in water

- ***Annual meeting***, open, free
- Latest developments in the field
- Oral presentation for winning posters
- Networking
- Collaboration
- Exchanges
- Education and training at CERN
- Sharing and building bridges
- Raising awareness at international level
- Special day dedicated to training
- Biannual Magazine – ***Highlights***
- **@ENLIGHTNETWORK**

www.cern.ch/enlight

Thank you for listening and to ENLIGHT



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