HITRI*plus*
Heavy Ion Therapy Research Integration

Practical experience of setting up a treatment centre

Sandro Rossi

Director General - CNAO Foundation

HITRI*plus* Coordinator

Workshop - Clinics and Research: consideration to create a novel particle therapy centre

Riga - June 28th, 2023

CNAO
Centro Nazionale di Adroterapia Oncologica

Outline of the presentation

Time, organization and personnel

Technology and authorisations

Patients management, recruitment and networking

Expansion as an option

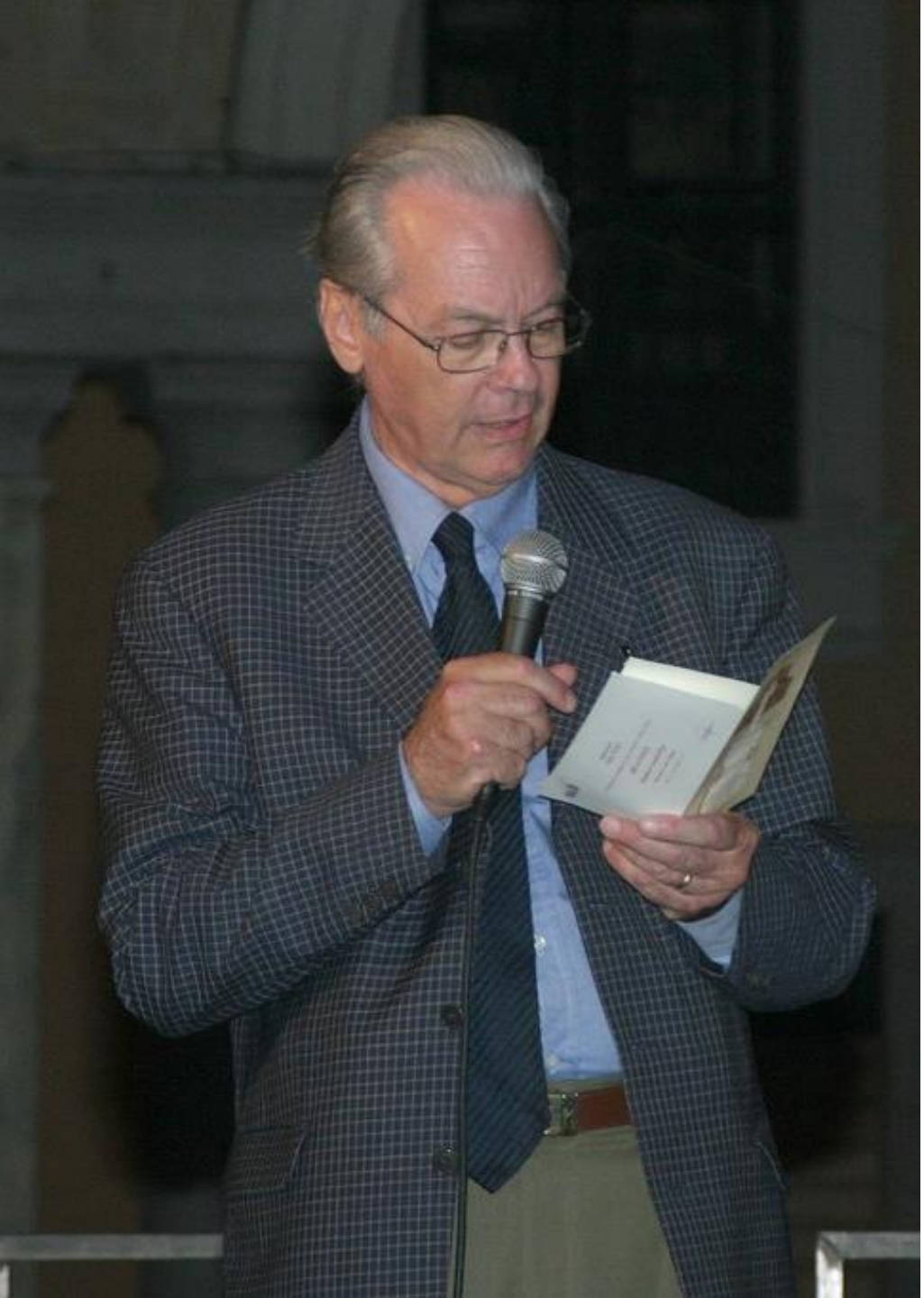
Formation and Research

CNAO = National Centre for Oncological Hadrontherapy

Not-for-profit private Foundation

Created by the Italian Ministry of Health in 2001

with the purpose to build and run a hadrontherapy Centre



Year 1991...

CERN/PPE/UA/eo

25 Maggio 1991

Per un Centro di Teleterapia con Adroni

Ugo Amaldi

CERN e Università di Milano

Giampiero Tosi

Ospedale di Niguarda, Servizio di Fisica Sanitaria,
e Università di Milano

TERA

President: Ugo Amaldi

Phases of CNAO

CNAO Foundation established in 2001

Phase 1: organization → Years: 2002 - 2004

CNAO's Governing Board composition (216 meeting so far)

Founders:

Foundation (hospital) Policlinico Ospedale Maggiore - Milan
Foundation (hospital) Istituto Neurologico C. Besta - Milan
Foundation (hospital) Istituto Nazionale dei Tumori - Milan
European Institute of Oncology - Milan
Foundation (hospital) Policlinico San Matteo - Pavia
TERA Foundation - Novara

Institutional Participants:

National Institute of Nuclear Physics (INFN)
University of Milan
Polytechnic of Milan
University of Pavia
Town of Pavia

Participants:

Cariplo (Bank) Foundation

Ministry of Health

President of the Board
Legal Representative
Erminio Borloni (Manager)
President from 2001-2018
Gianluca Vago since 2019

First crucial decision:
The Site of CNAO - Pavia
Close to Hospitals and Universities

Second crucial decision:
Finalization of CNAO design

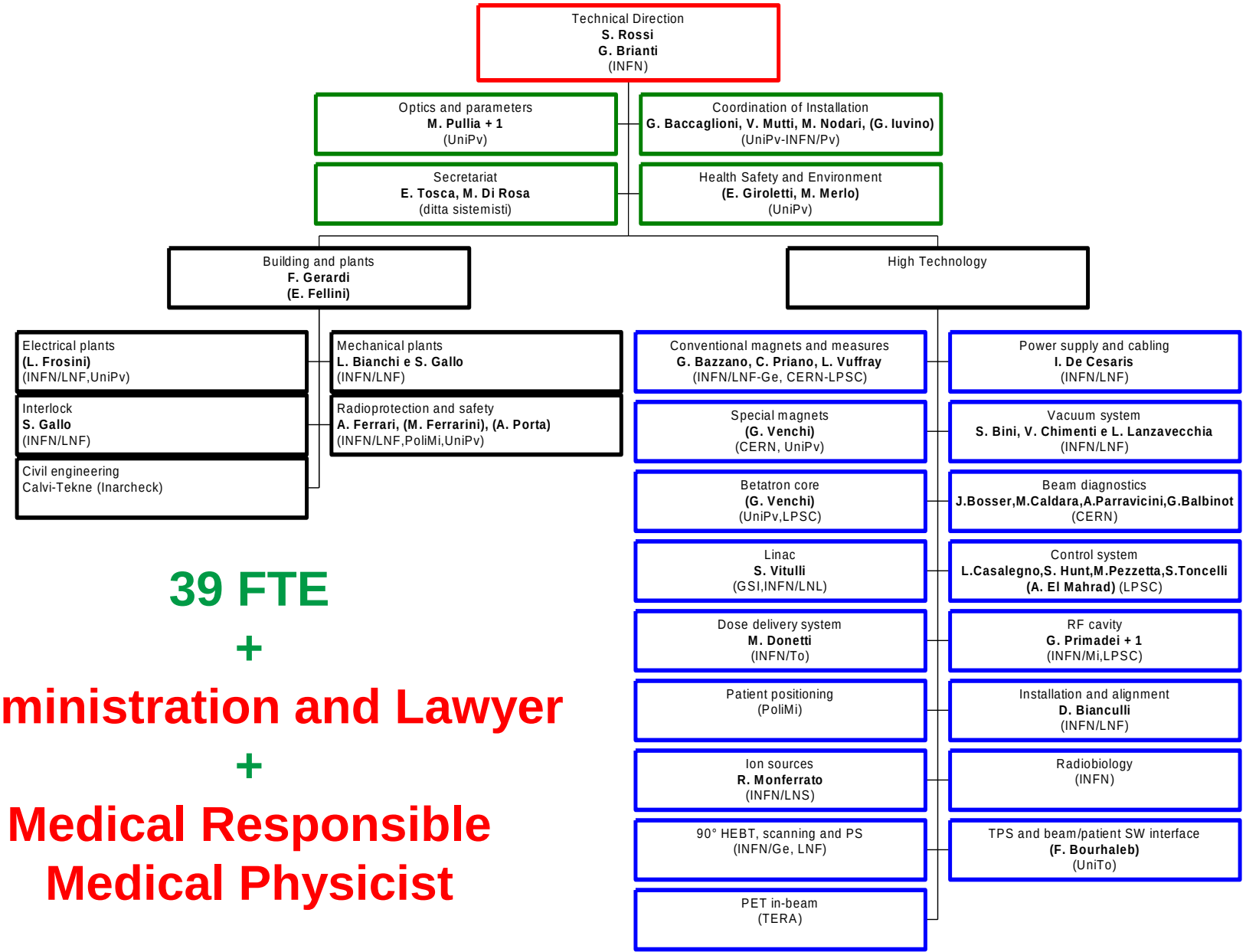
Phases of CNAO

CNAO Foundation established in 2001

Phase 1: organization → Years: 2002 - 2004

Phase 2: construction → Years : 2005 - 2010

Organization Chart in 2006



39 FTE

+

Administration and Lawyer

+

Medical Responsible
Medical Physicist

Collaboration agreements: fundamental contracts for construction and presently for technology R&D

NATIONAL

TERA Foundation: final design and high tech specifications

INFN: technical issues, radiobiology, research, formation

University of Milan: medical coordination and formation

University of Pavia: technical issues, radiobiology, formation

Polytechnic of Milan: patient positioning, radioprotection, authorisations

INTERNATIONAL

CERN (Geneva): technical tasks, PIMMS

GSI (Darmstadt): linac and special components

LPSC (Grenoble): technical tasks

NIRS (Chiba): medical activities, radiobiology, formation

Phases of CNAO

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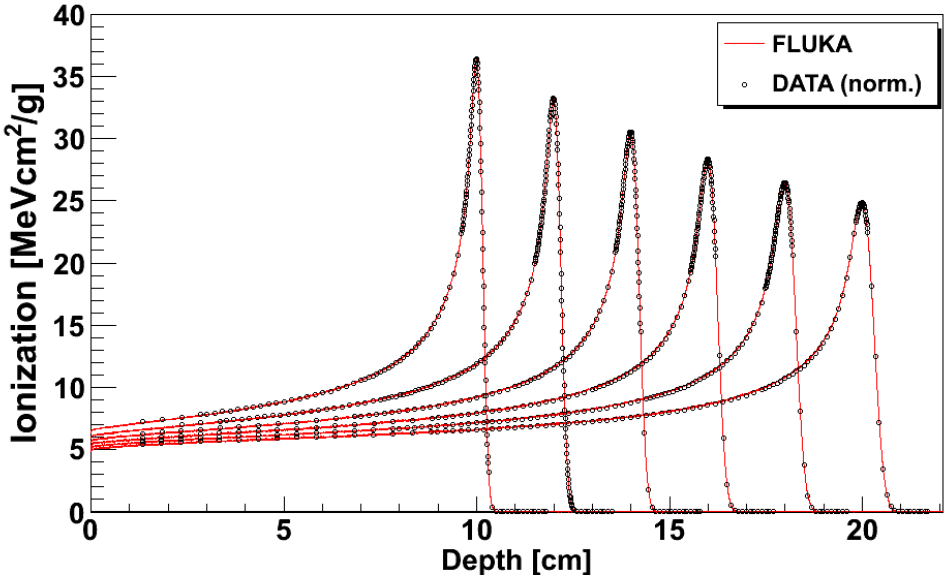
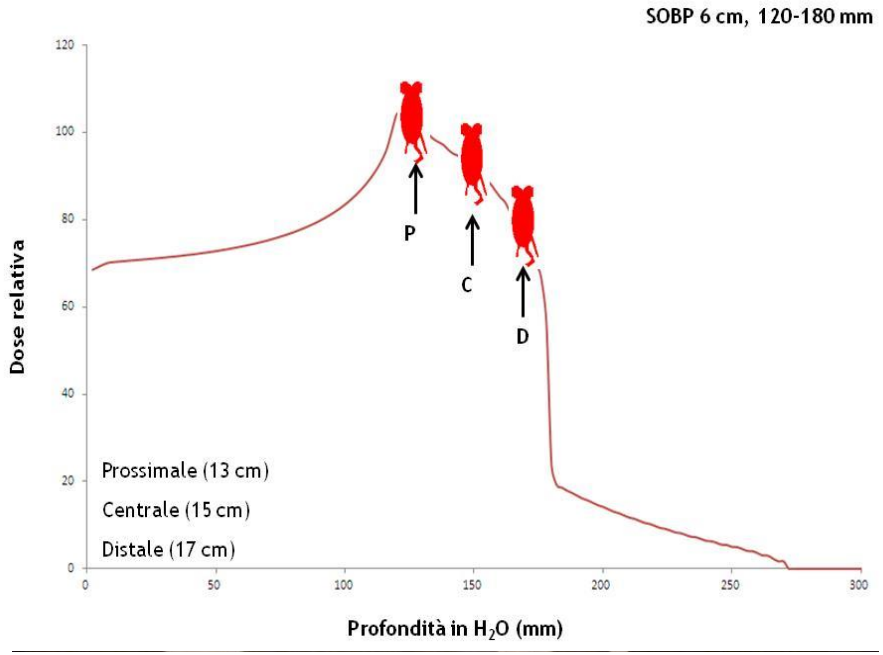
Phase 1: organization → Years: 2002 - 2004

Phase 2: construction → Years : 2005 - 2010





First patient treatment (compassionate): September 2011

Phases of CNAO

CNAO Foundation established in 2001

Phase 1: organization → Years: 2002 - 2004

Phase 2: construction → Years : 2005 - 2010

First patient treatment: September 2011

Phase 3: clinical trials → Years: 2010 - 2013

150 patients enrolled in clinical trials

CE marking and approval in NHS

Phases of CNAO

CNAO Foundation established in 2001

Phase 1: organization → Years: 2002 - 2004

Phase 2: construction → Years : 2005 - 2010

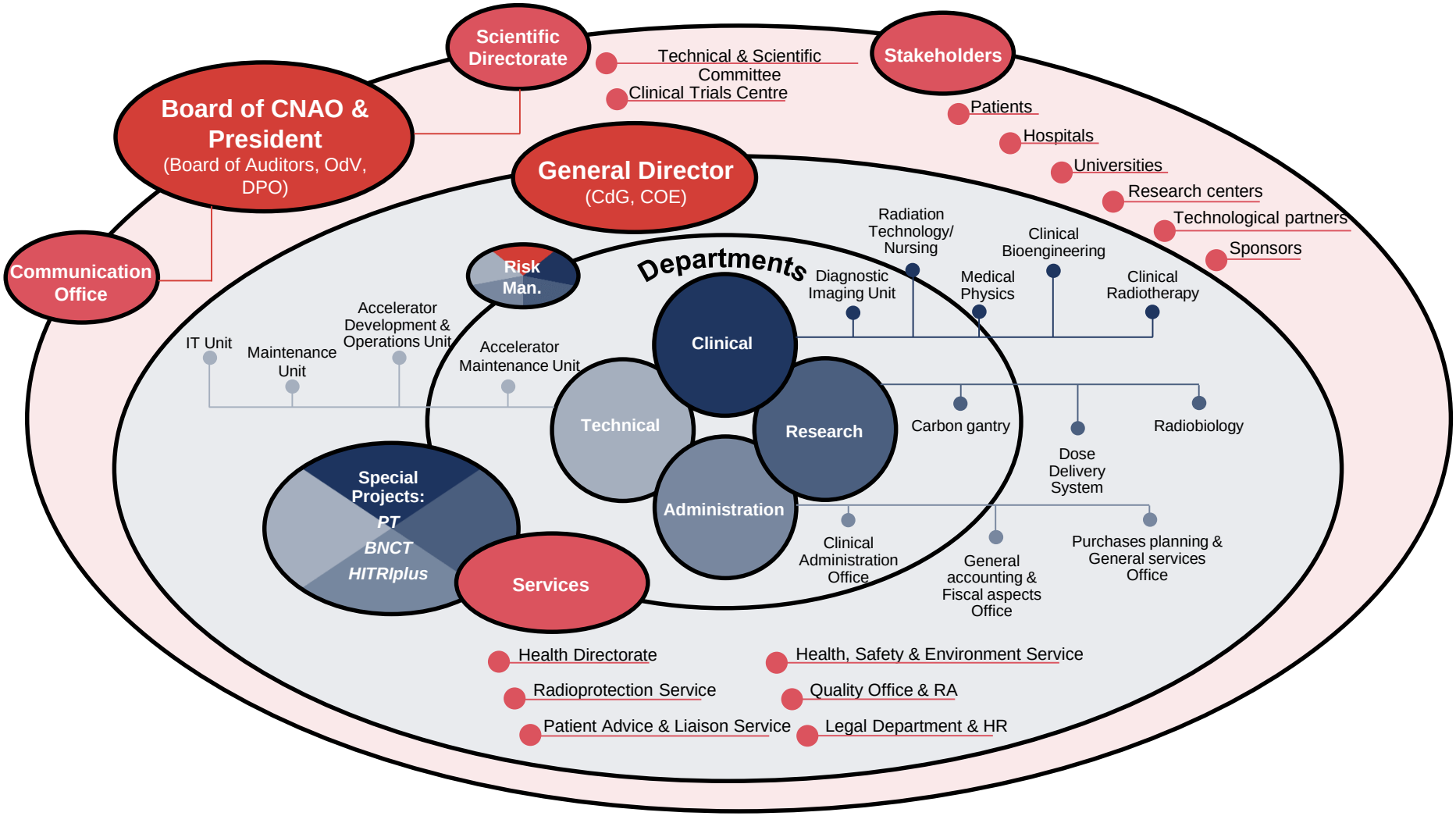
First patient treatment: September 2011

Phase 3: clinical trials → Years: 2010 - 2013

CE marking and approval in NHS

Phase 4: running → Years: 2014 - …

Organization Chart 2023



CNAO Personnel beginning 2023

Total number: 155

Women: 88

Men: 67

Mean age: 39

Graduates: 79% (37% PhD)

Positions: 20

Disciplines: 17

January 2023	#
Director General and Services	19
Scientific Directorate and Clinical Trial Centre	5
Clinical Department	70
Administration and Finance Department	16
Technical Department	39
R&D Department	6
Total	**155**

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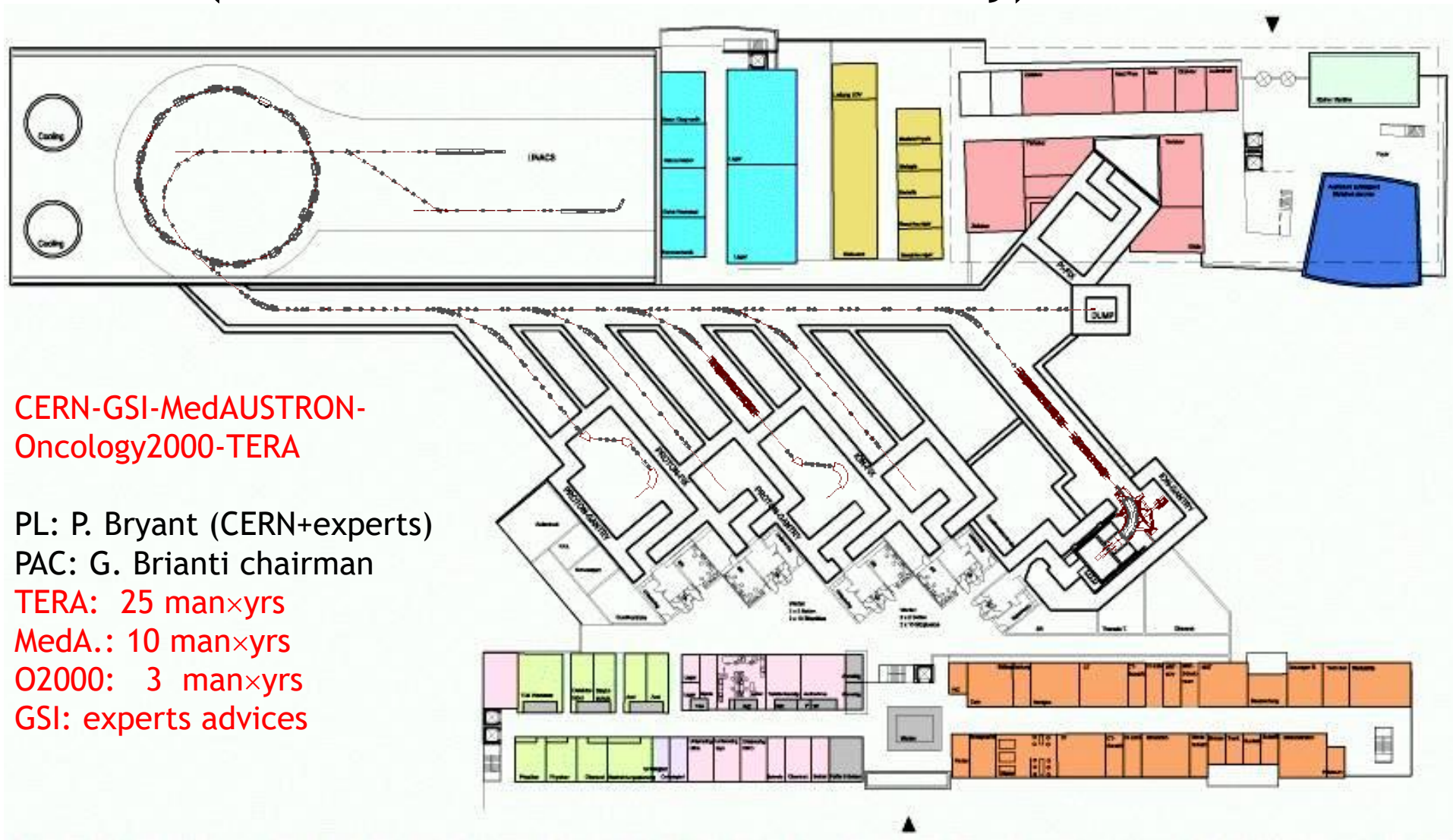
Formation and Research

From 1996 to 1999 at CERN

PIMMS (Proton-Ions Medical Machine Study)



CERN-GSI-MedAUSTRON-
Oncology2000-TERA

PL: P. Bryant (CERN+experts)
PAC: G. Brianti chairman
TERA: 25 man×yrs
MedA.: 10 man×yrs
O2000: 3 man×yrs
GSI: experts advices

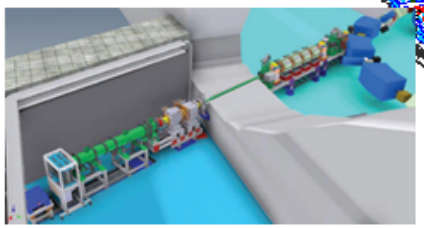
Objective: define the optimal hadrontherapy centre without constraints

The CNAO system: for treatments and research

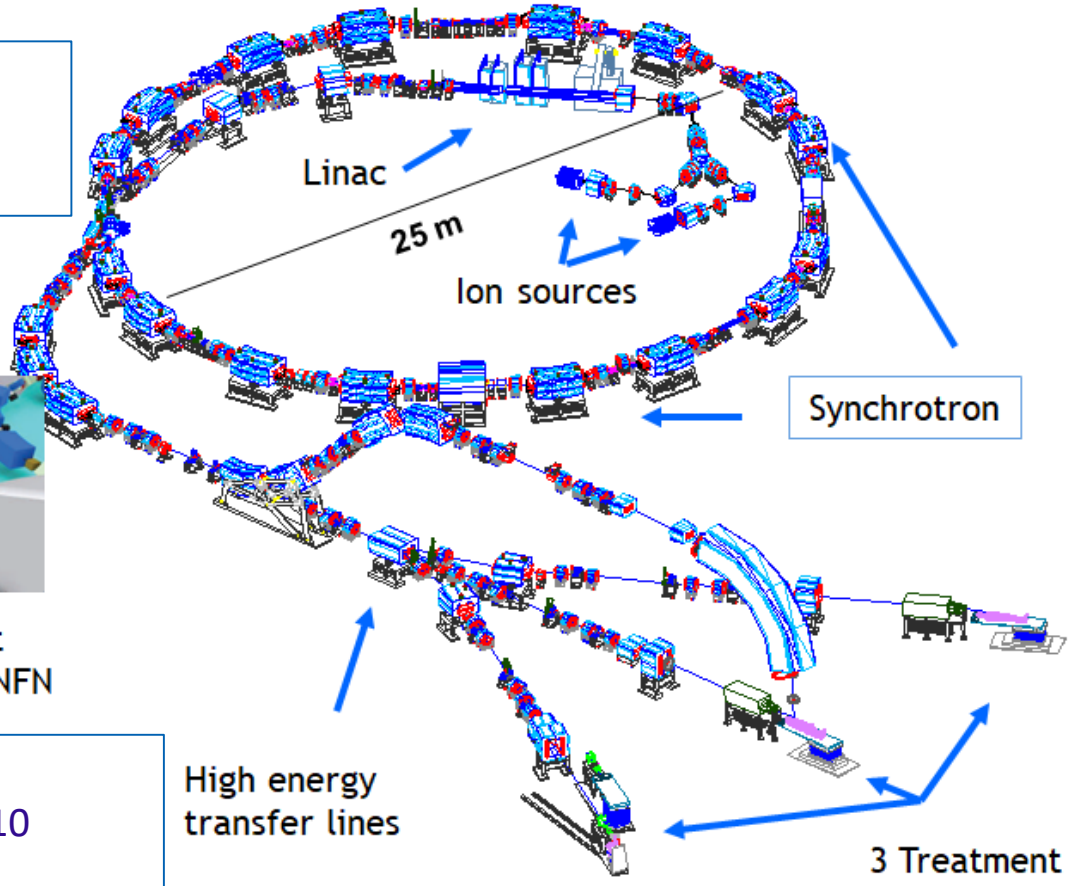
Intellectual property shared by CNAO – INFN - CERN

Accelerated ion	p, C, He …
Energy range (MeV/u)	60-225 (p) (30-320mm)
	120-400 (C) (30-270mm)

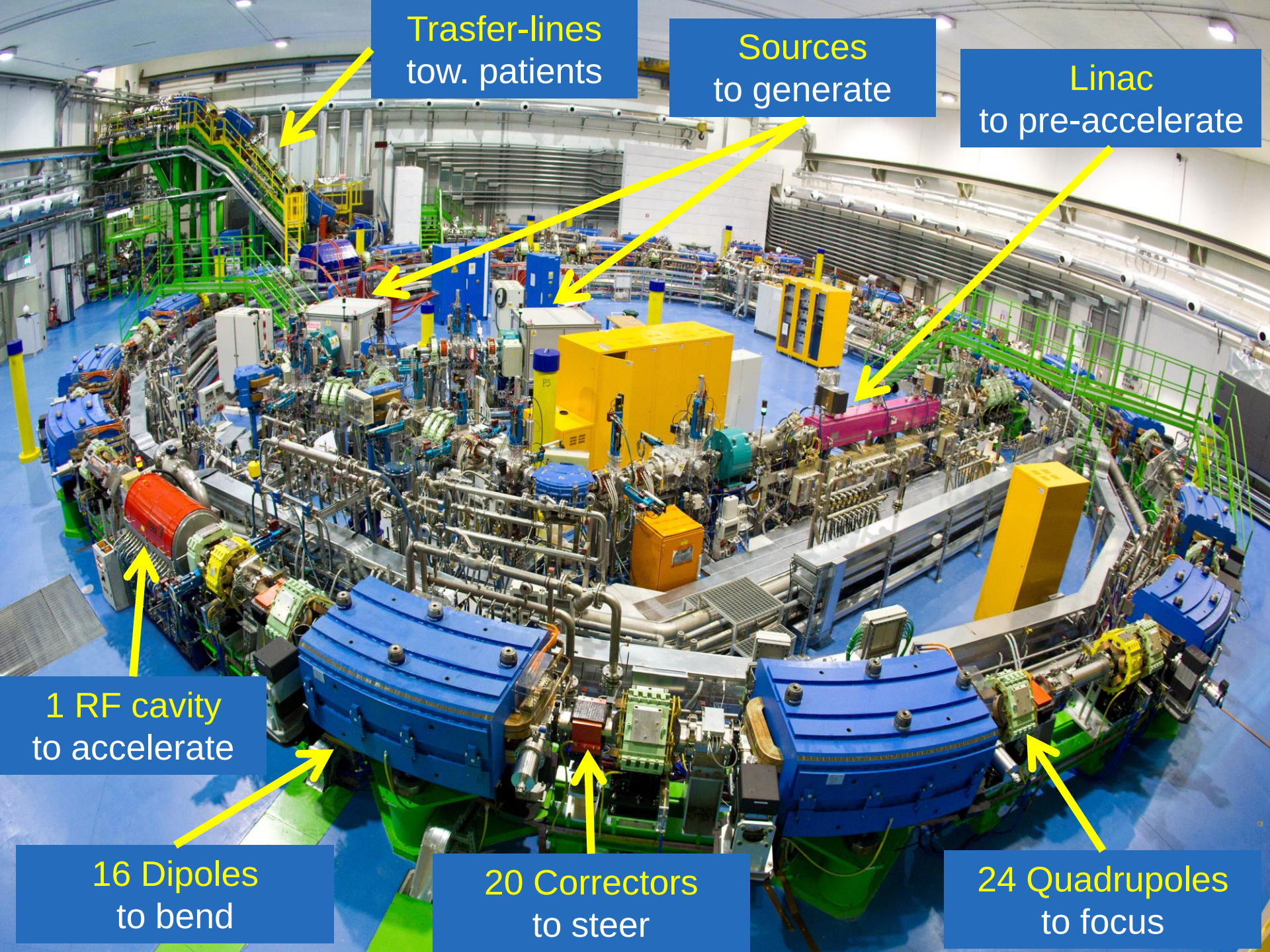
Extraction	Slow - scanning
Dose uniformity	± 2.5%
Average dose rate	2 Gy/min/liter



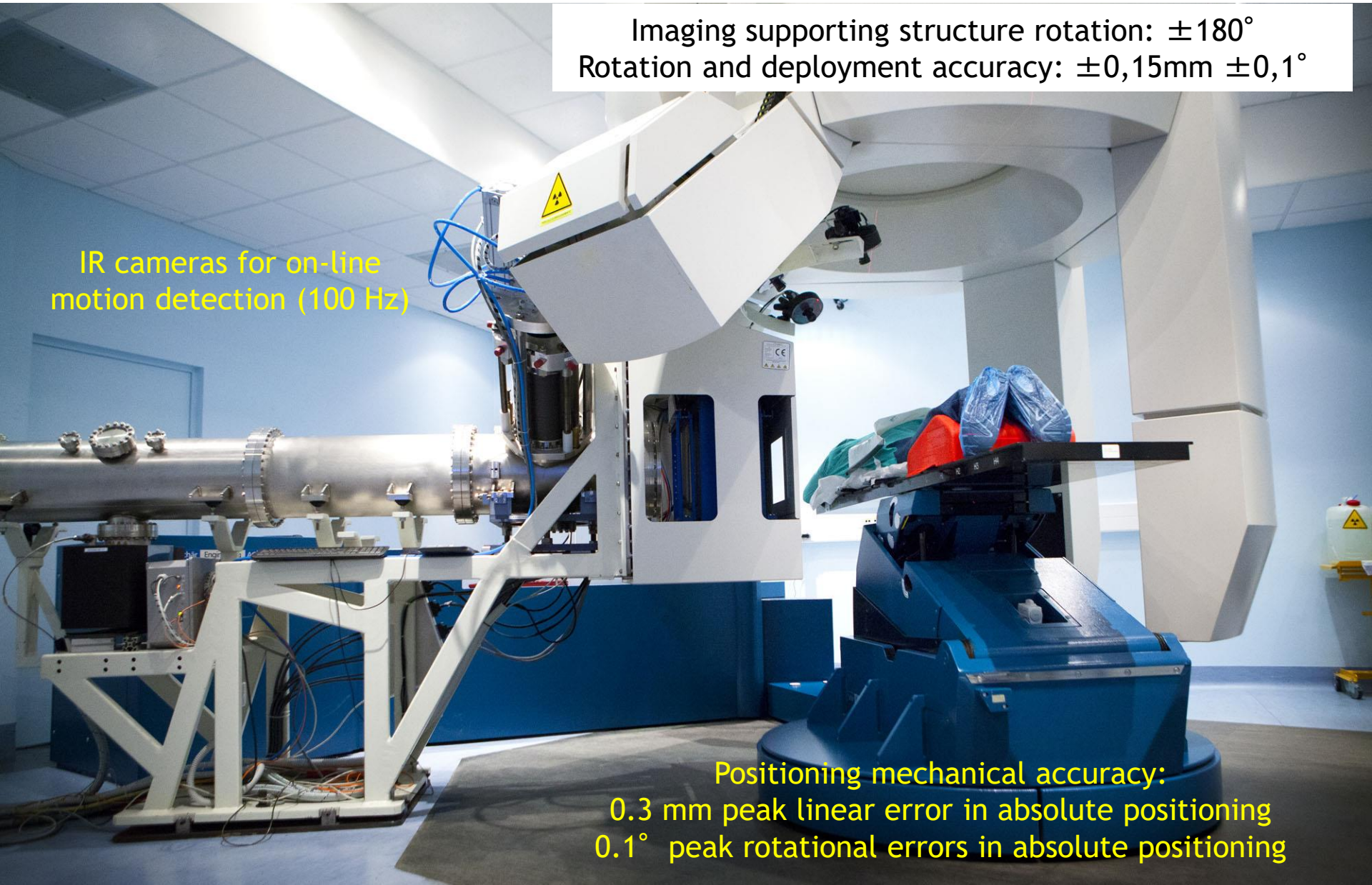
Research room built
in collaboration with INFN



Field size (mm × mm)	200 × 200
Beam size (FWHM) (mm)	4-10
Beam position precision (mm)	0.1


Trasfer-lines
tow. patients
Sources
to generate
Linac
to pre-accelerate
1 RF cavity
to accelerate
16 Dipoles
to bend
20 Correctors
to steer
24 Quadrupoles
to focus

Positioning and verification systems



Imaging supporting structure rotation: ±180°
Rotation and deployment accuracy: ±0,15mm ±0,1°

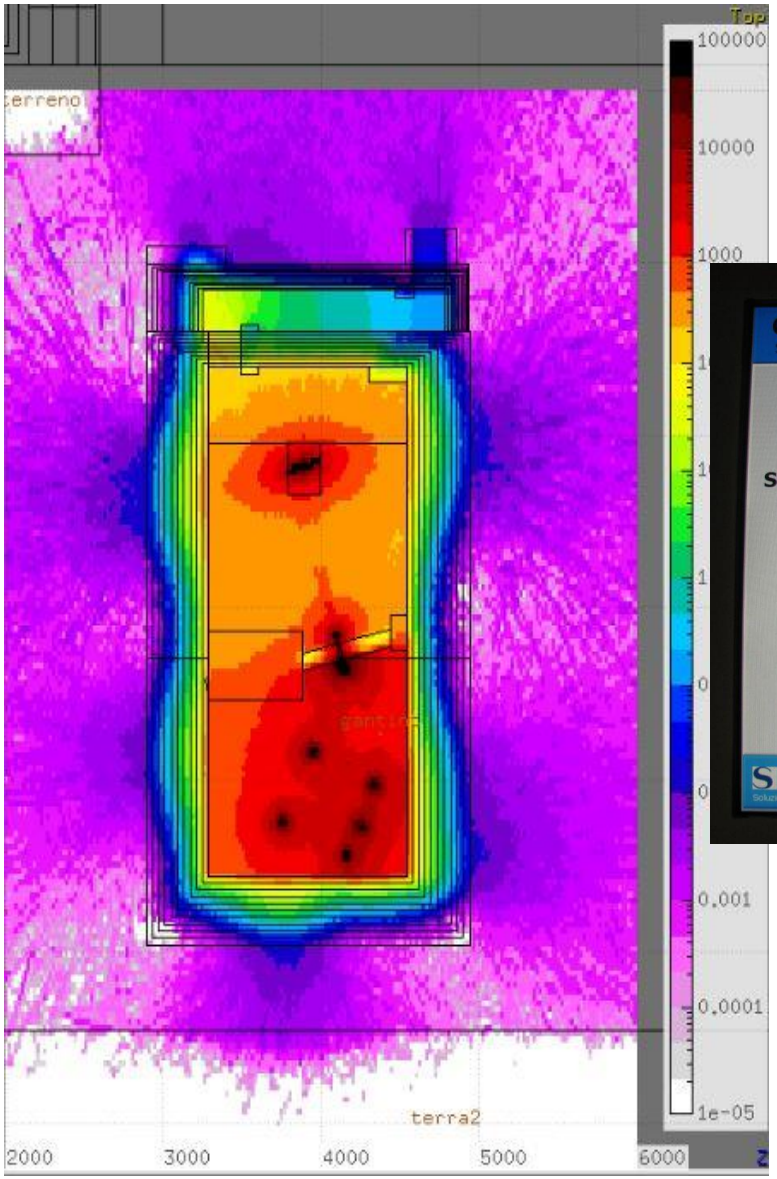
IR cameras for on-line motion detection (100 Hz)

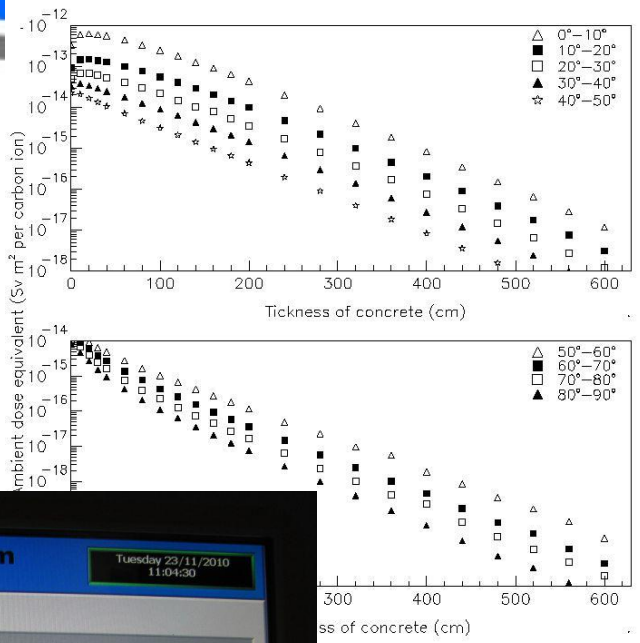
Positioning mechanical accuracy:
0.3 mm peak linear error in absolute positioning
0.1° peak rotational errors in absolute positioning

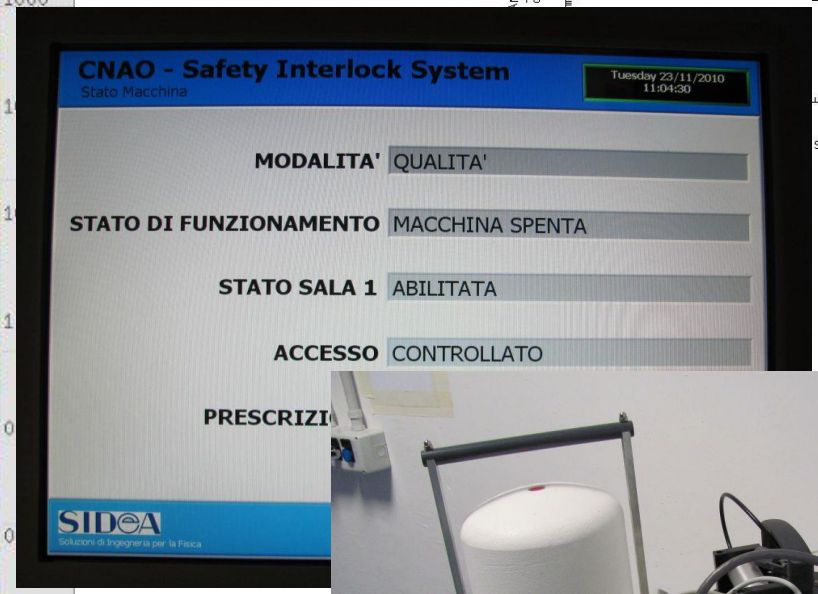
The numbers of CNAO during the construction phase

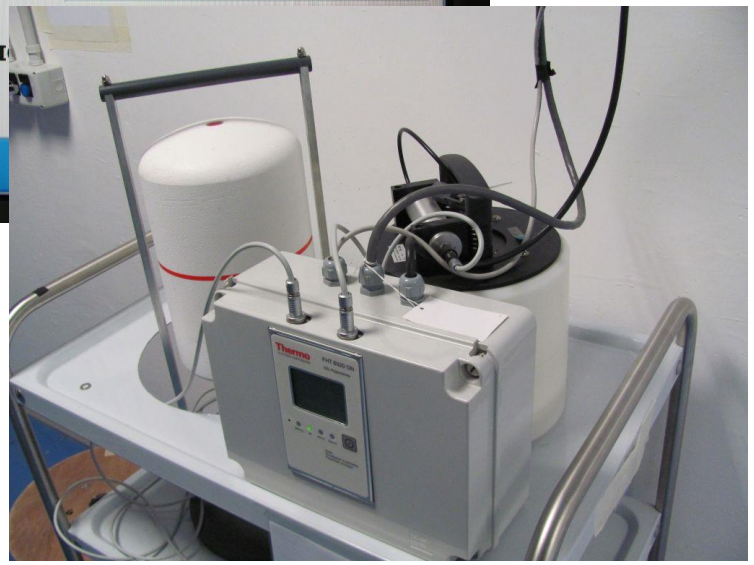
N. 14	European tenders completed
More than 1000	Orders and contracts
N.600 (500 Italian)	Firms worked for CNAO
About 80	Authorisation procedures completed

Radioprotection authorisation







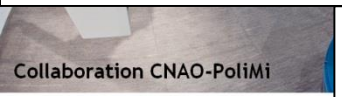


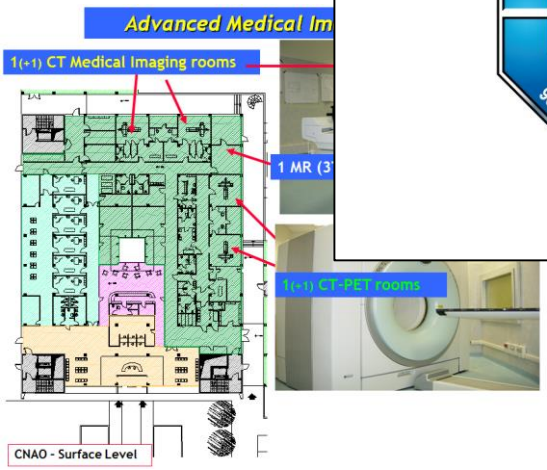
“LEGO Model”: integrated technical and medical solutions

The real challenge:

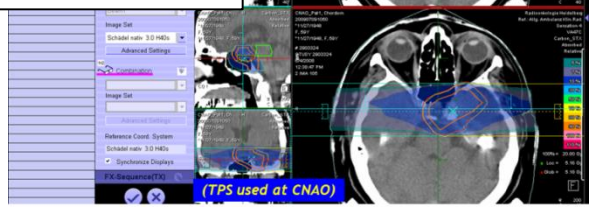
make ALL systems running together

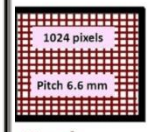
safely, efficiently, reliably and easily maintainable.





Organization Accredited
by Joint Commission International





Performance Sept. 2011 to Dec. 2022

Years from 2011 to 2021	Year 2022
➢ 3730 running days	➢ 325 dd
➢ 2737 treatment days	➢ 244 dd
➢ 276 dd ordinary maintenance	➢ 28 dd
➢ 40 dd system breakdown	➢ 3 dd
➢ System availability: 90.6%	➢ 89.0%
➢ System reliability(dd): 98.4%	➢ 98.8%
➢ System reliability (sessions)	➢ 96.1 % 413 (251+162) vs 10.699

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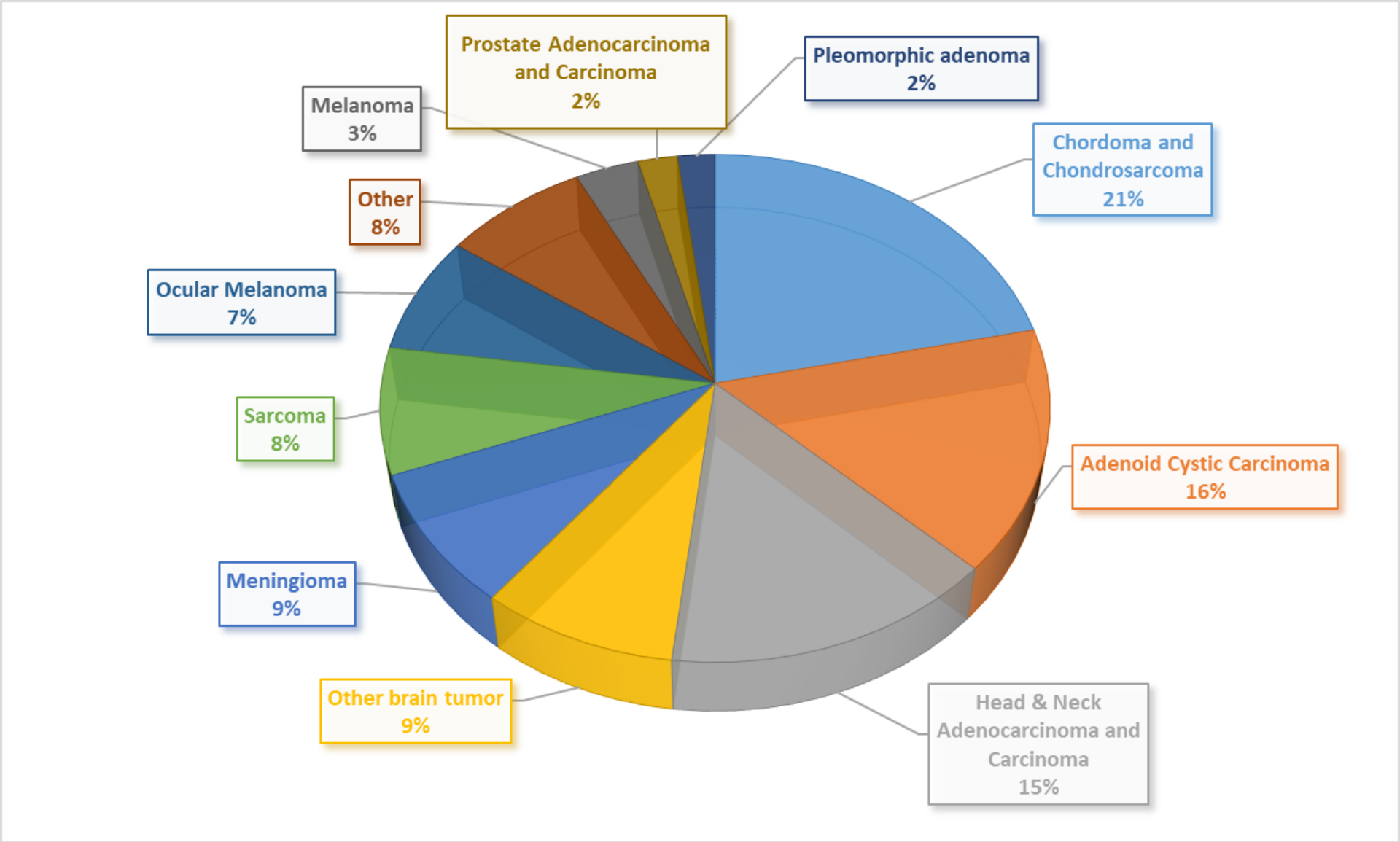
CNAO: >4500 patients

54% carbon ions- 46% protons

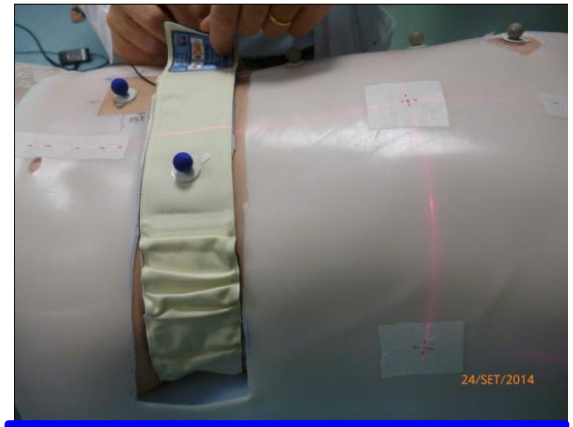


Pre-treatment procedures available on site

CT

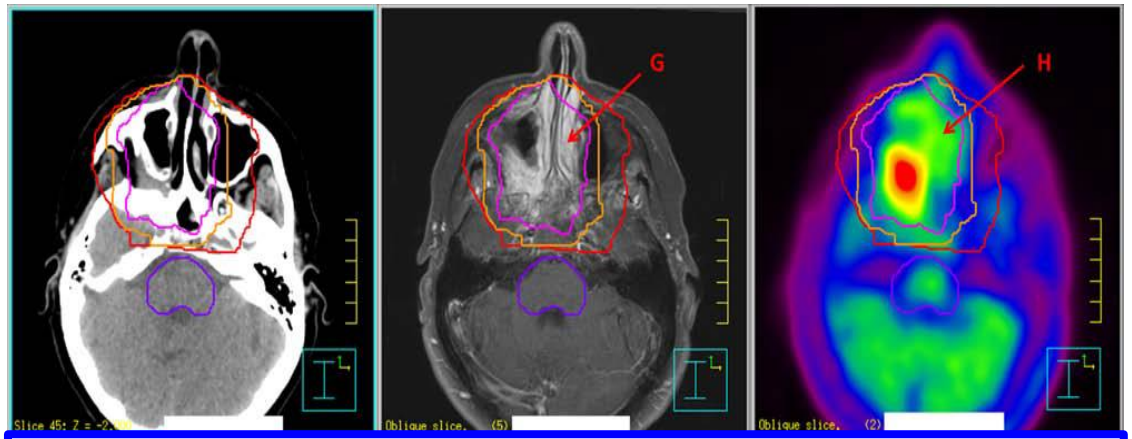
NMR

CT/Pet



ANZAI and OTS

Moving organs:
4-D treatment
Gating and rescanning



Images Fusion - TPS

Pathologies approved by Italian National Health System

1. **Chordoma & chondrosarcoma base/spine**
2. **Meningiomas**
3. **Brain tumors (trunk)**
4. **ACC Salivary Glands**
5. **Orbit tumors including eye melanoma**
6. **Sinonasal carcinoma**
7. **Soft Tissue & bone Sarcoma (every sites)**
8. **Recurrent tumors (retreatment)**
9. **Patients with immulogical desorders**
10. **Pediatric solid tumors**
11. **Tumors for which hadrontherapy guarantees a better dose distribution wrt the best alternative providing a 10% better result in terms of NTCP or TCP (under discussion)**

In Italy (60 million inhabitants) estimated cases 1-10:

Protons: about 5.000 patients/year

Carbons: about 1.000 patients/year

Patient recruitment: the need of a network!

direzionemedica@cnao.it
serviziomedico@cnao.it

Tel 0382 078963

http://folder.cnao.it

Prima Visita

22%
Medical Service

In 2019 MS received 12.000 contacts
About 3% selected for first visit
Of them 40% is routed to treatment
1.3% contacts are real patients !

46% Top 10 Institutes

32% Other Institutes

Yearly Trend

International networks of clinical research
Multidisciplinar approach

STARTER
STarting an Adult Rare Tumour European Registry

G7 Head & neck

Exploiting and enlarging collaboration

EURACAN

UK registry

Clinical data
Biological samples
Imaging

Head and Neck Cancer International Group

JANE PROJECT - Joint Action on Networks of Expertise

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First patient treatment: September 2011

Phase 3: clinical trials → Years: 2010 - 2013

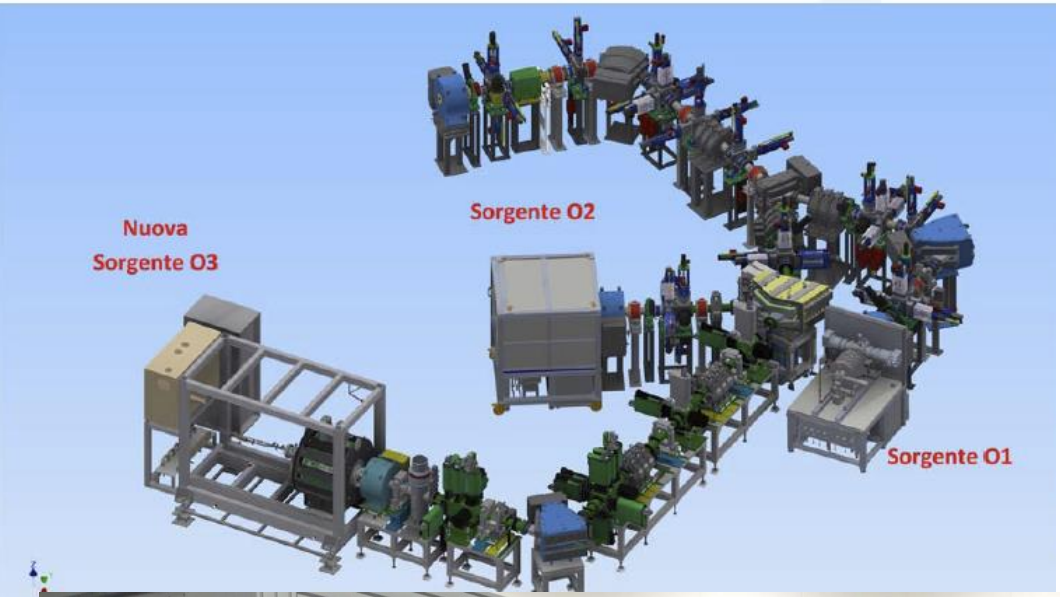
CE marking and approval in NHS

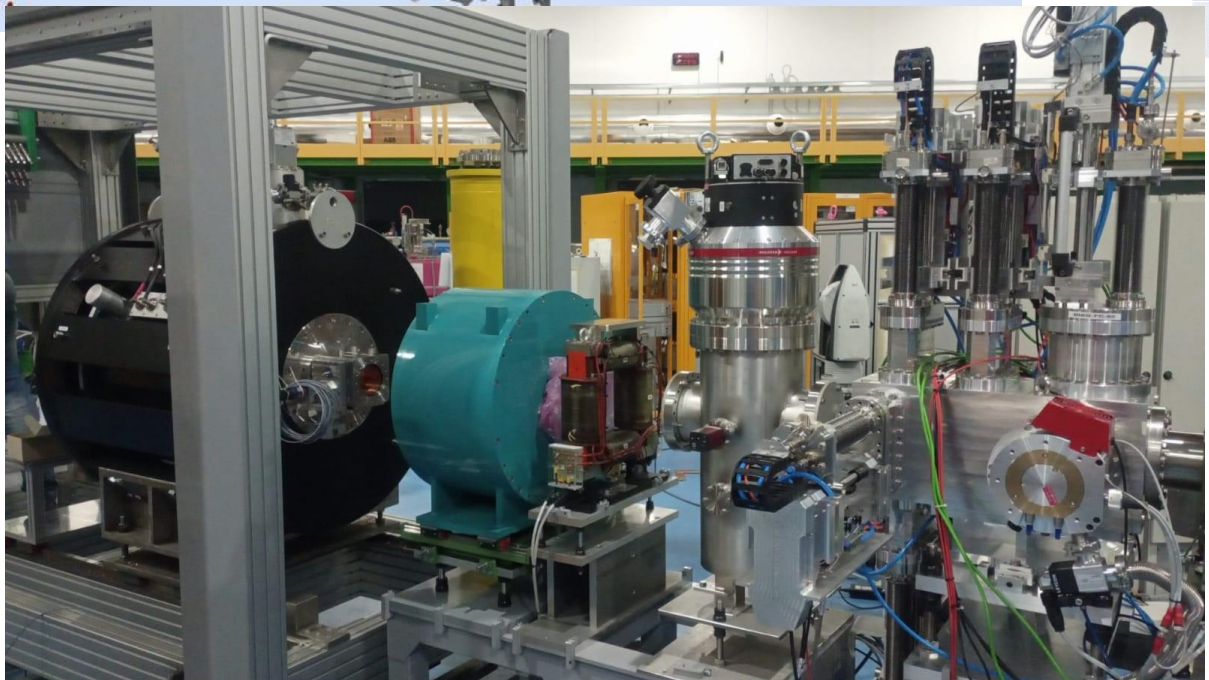
Phase 4: running → Years: 2014 - …

Phase 5: expansion → Years: 2019 - …

INSpIRIT: new ion source

Collaboration CNAO-INFN-HiFuture





Expected currents

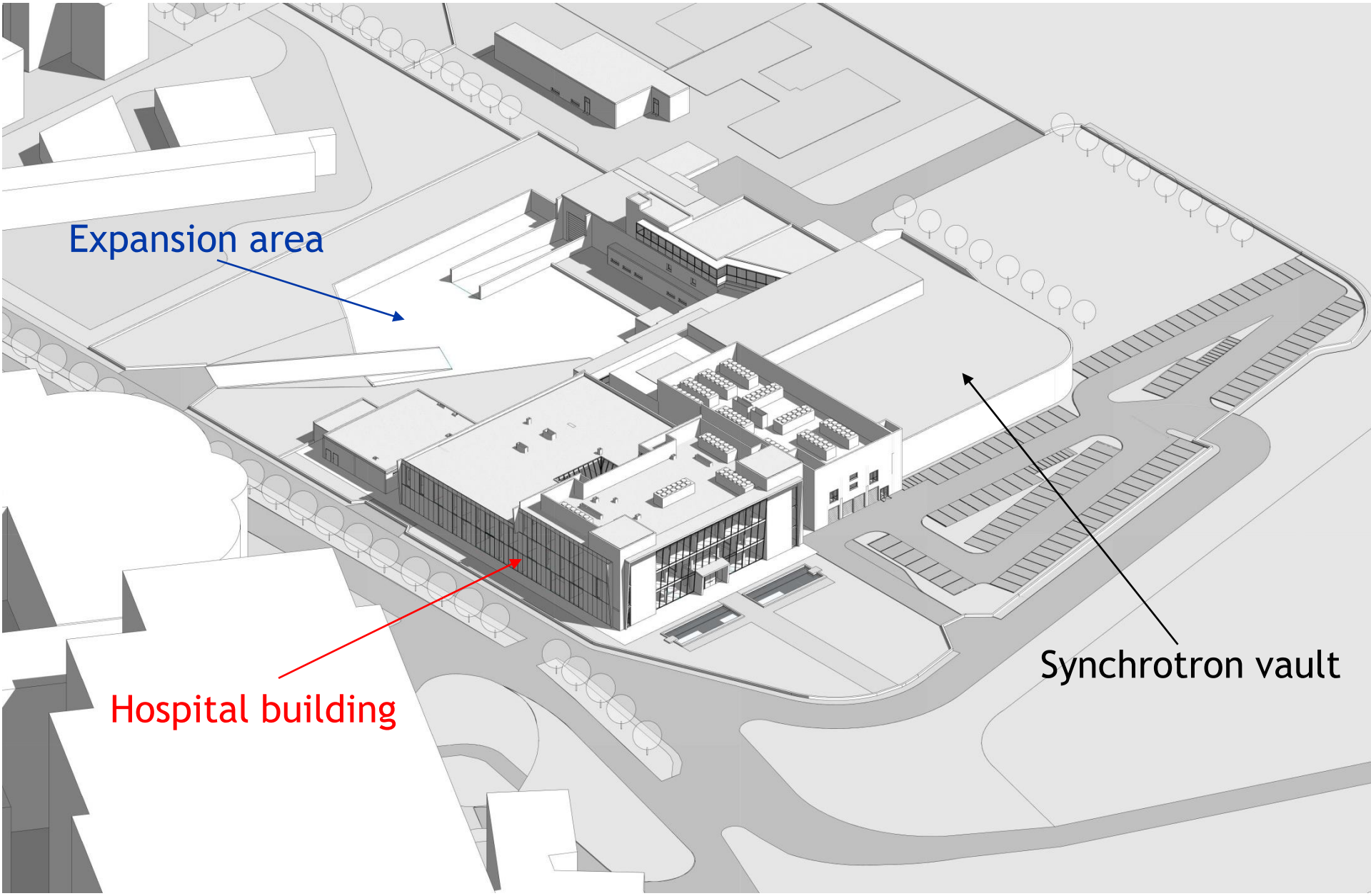
Ion beam production (eμA)

Ion	Supernanogan (14 GHz)	AISHa (18 GHz + TFH)
H^+	2000	4000
H_2^+	1200	2000
H_3^+	1000	1500
$^3He^+$	800	2000
$^{12}C^{4+}$	250	800
$^6Li^{2+}$ - $^7Li^{2+}$	//	800
$^{10}B^{3+}$ - $^{11}B^{3+}$	//	600
$^{18}O^{6+}$	400	1000
$^{21}Ne^{7+}$	120	500
$^{36}Ar^{12+}$	20	150

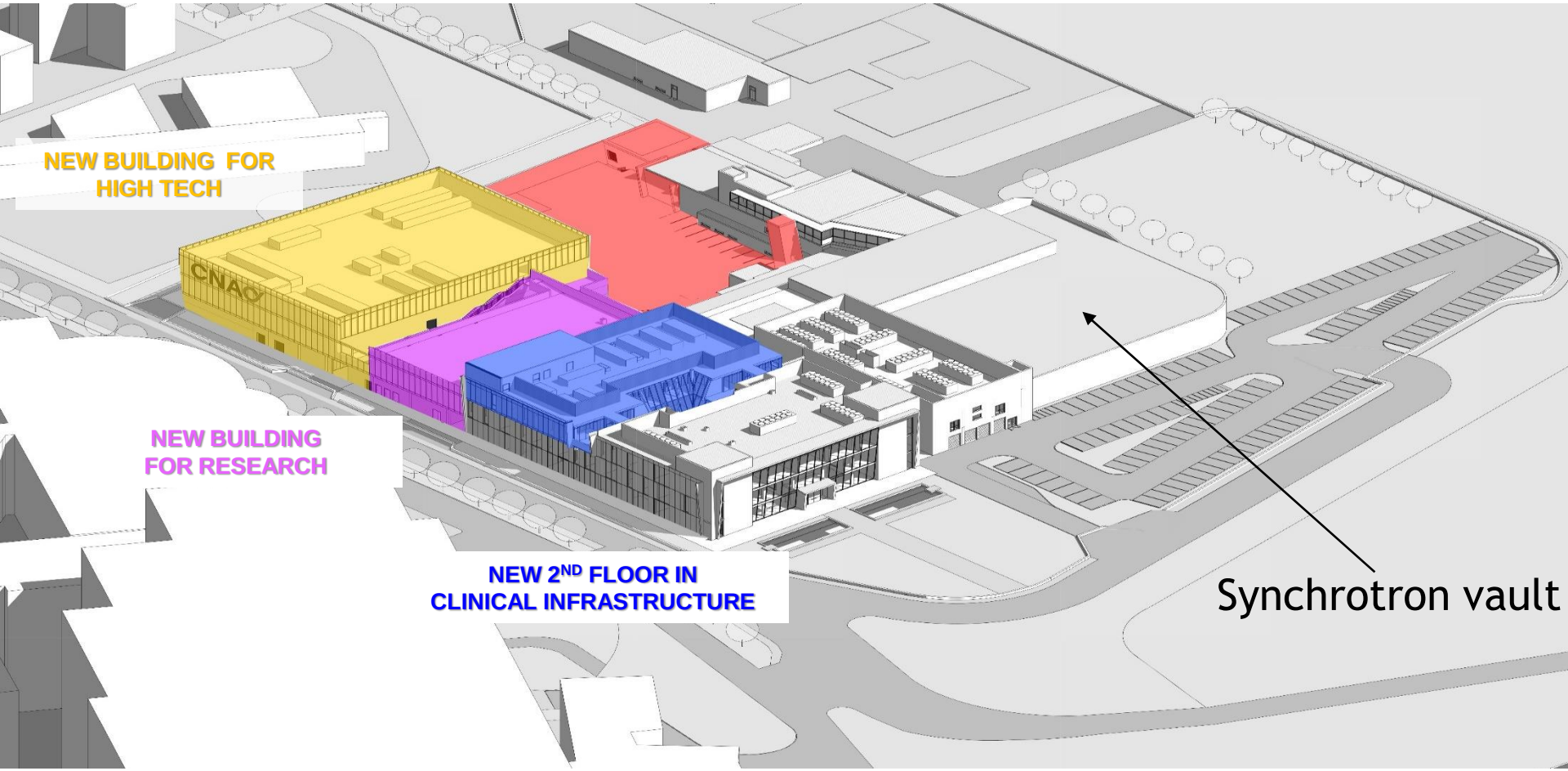
Status: waiting for radioprotection authorisation

Ready by end 2022

Present layout

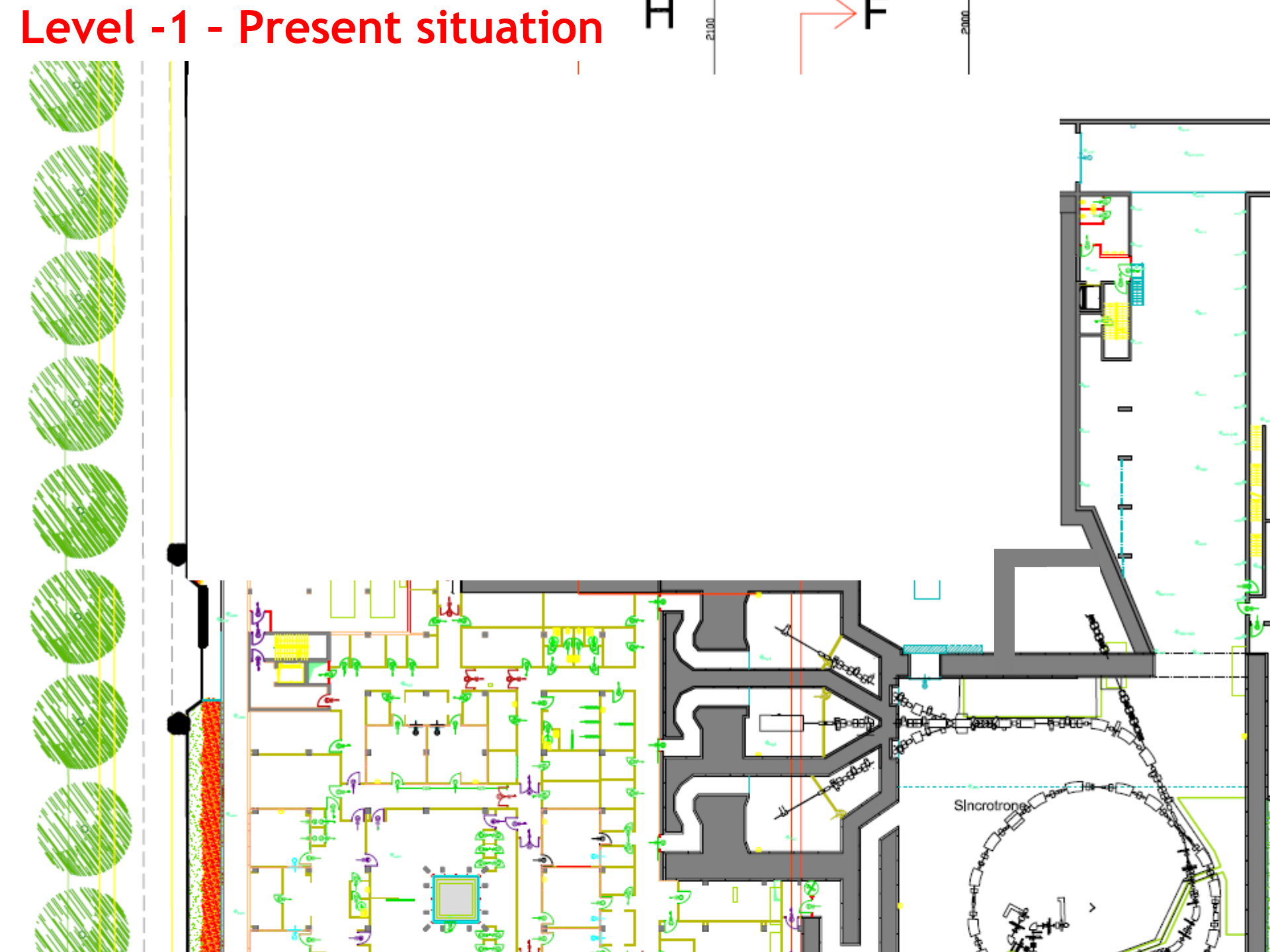


CNAO 2.0

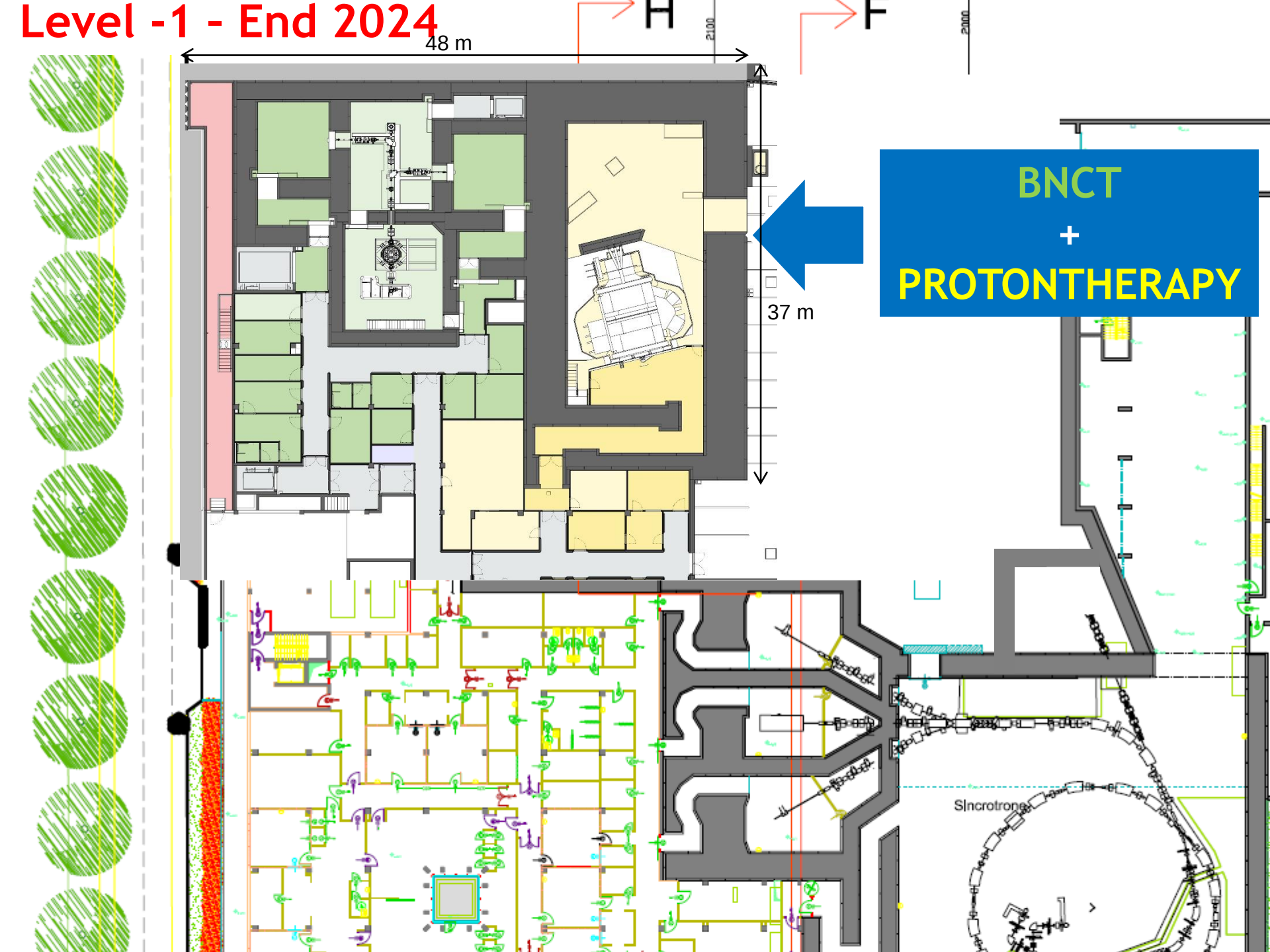


Layout by middle 2024

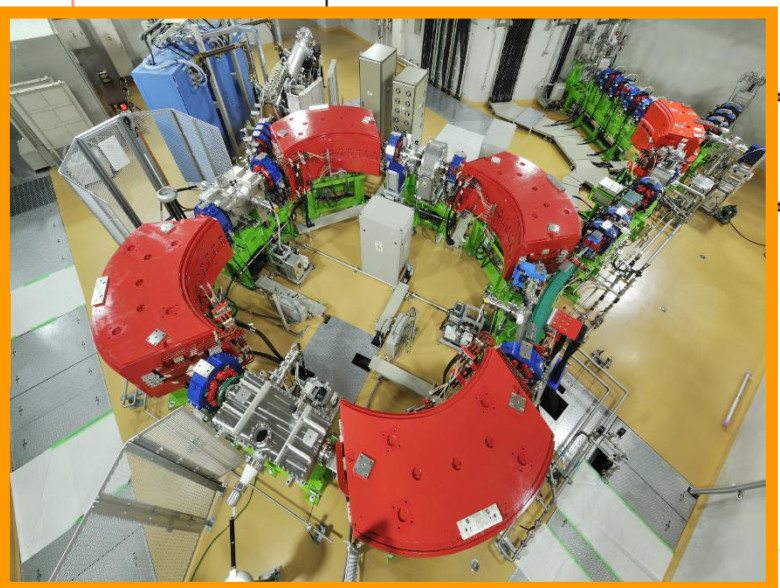
Level -1 - Present situation



Level -1 - End 2024



Level -1



tae LIFE SCIENCES

Installation of high-tech starts fall 2023


MUSSELLI
MUSSELLI
MUSSELLI
MUSSELLI

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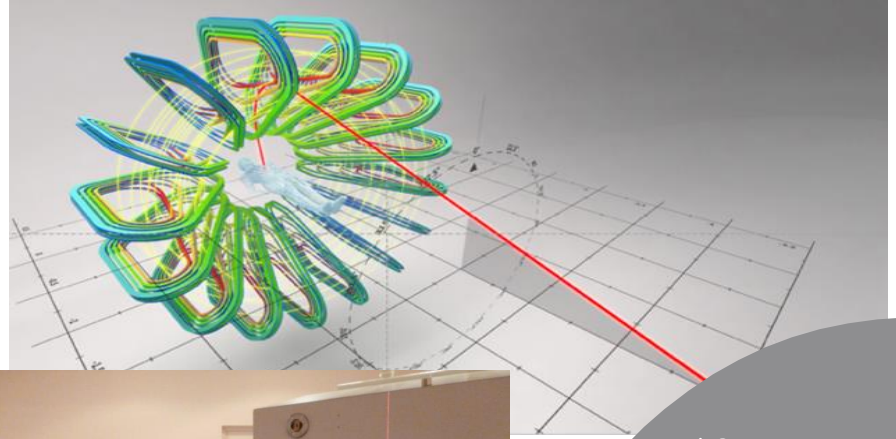
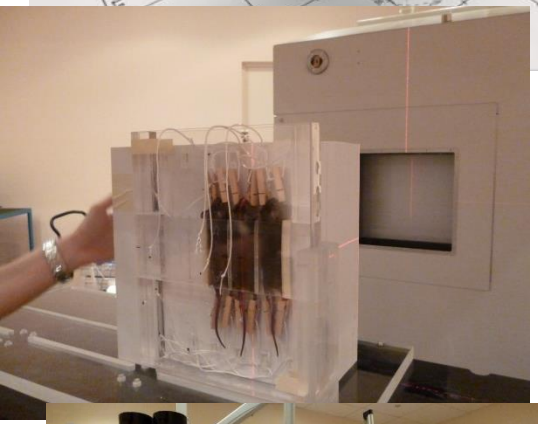
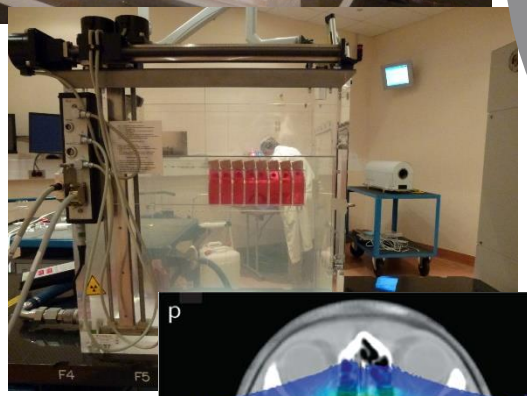






The *Hadron Academy*

(PhD Courses IUSS-CNAO)

Medicine and Biology

Physics and Engineering

Risk and complexity in high-tech medical innovation

Management and Innovation

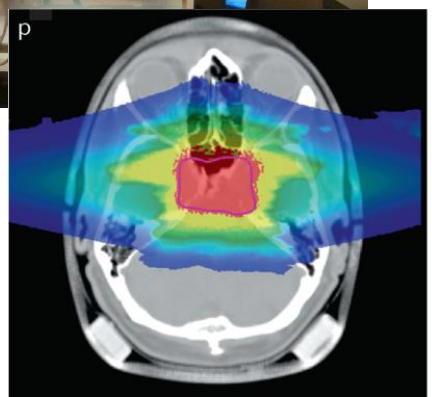
Research

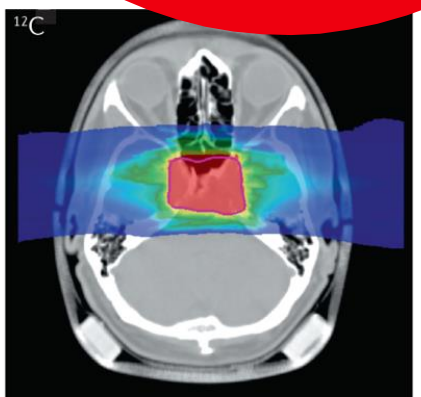
Post-graduate Education

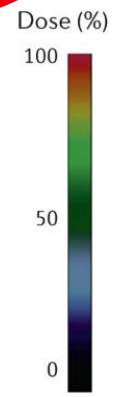
Clinical Activities

CNAO

Centro Nazionale di Adroterapia Oncologica







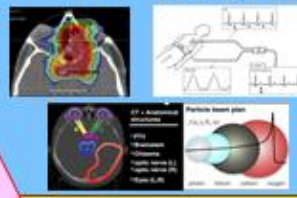
THE HADRON ACADEMY:
RISK AND COMPLEXITY IN HIGH TECH MEDICAL INNOVATION

IUSS
Scuola Universitaria Superiore Pavia

THE HADRON ACADEMY

AI

Medical physics



Radiobiology

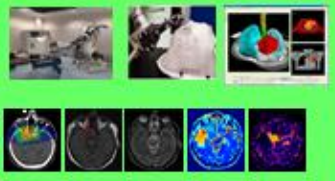
HADRONTHERAPY

ETHICS

RISK

COMPLEXITY

Bioengineering



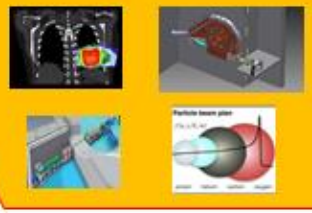
SYNCHROTRON

NORMS

Radioprotection

INNOVATION

Accelerator physics



New Projects
Protontherapy
Gantry
BNCT

Additional formation

- Informatics
- Languages
- Managment of research
- Technology transfer - IP

CNAO
Centro Nazionale di Adroterapia Oncologica

R&D: new carbon ion gantry

Collaboration CNAO-INFN-CERN-MedAustron

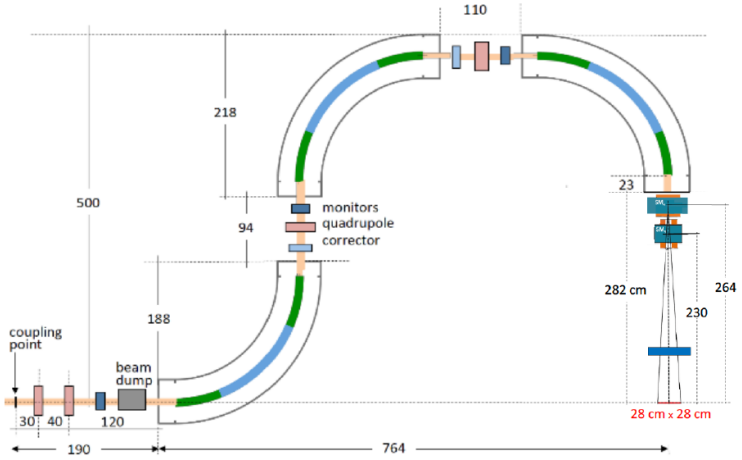
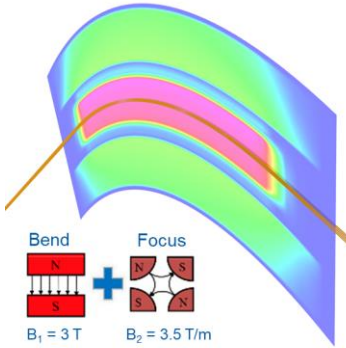
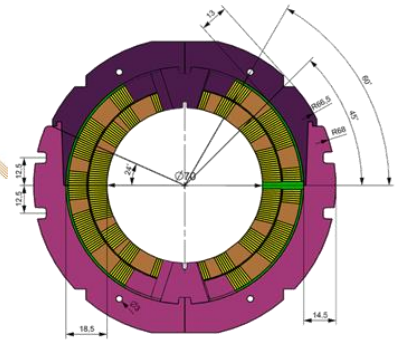


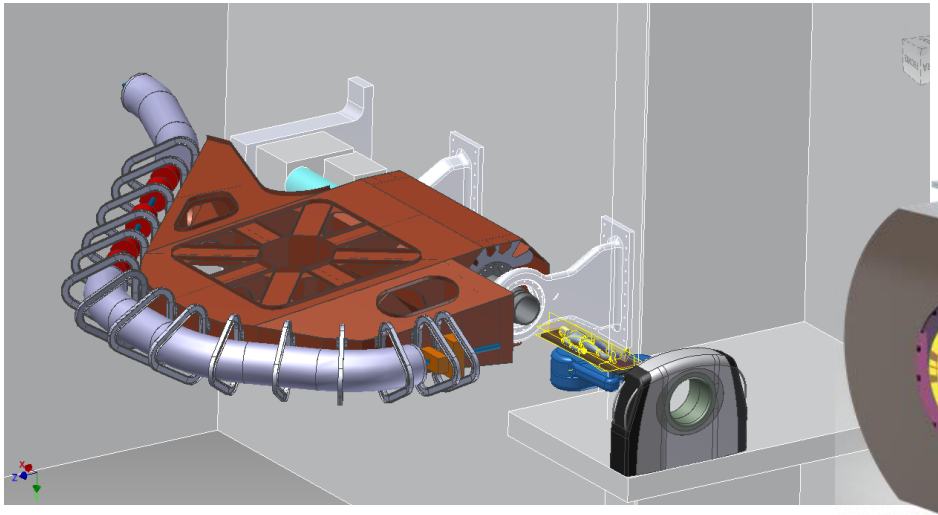
Figure 1. *Layout of the gantry and the scanning system based on 90° canted cosine theta magnets running at 4 T.*

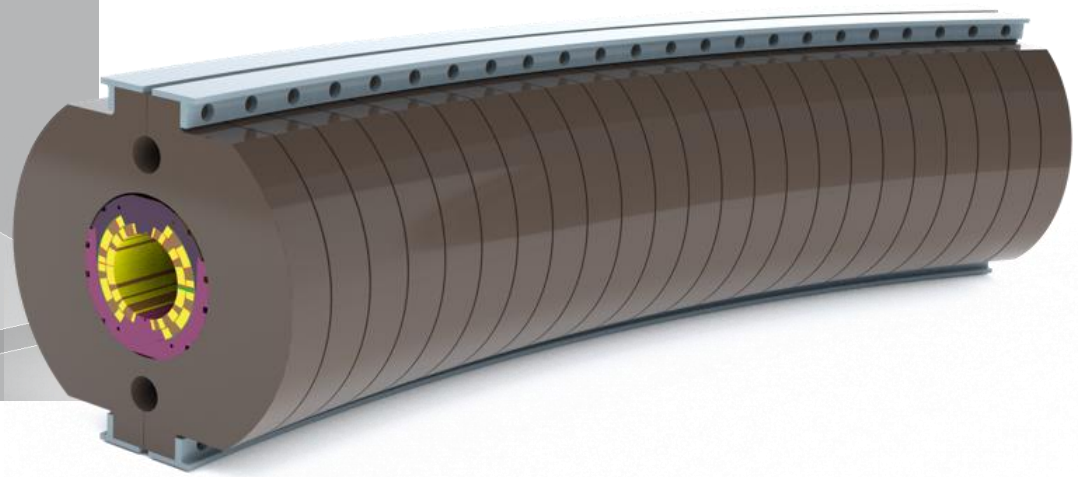
Superconducting Magnet Design



Final design: Dip+Quad
= combined funtion





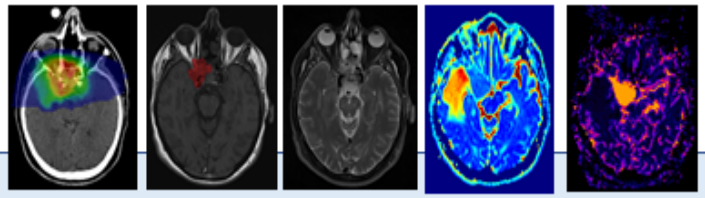


Radiomics, Dosiomic …

strategies for individual treatment optimization

and outcome prediction (Collaboraboration with PoliMi)

AIRC IG-2020 n. 24946
PI: Prof. Baroni G.



CT + dose maps
Anatomical MRI (T1-w, T2-w)
Quantitative MRI (DWI, PWI,…)

Technical framework

MULTI-PARAMETRIC IMAGING

PRE-PROCESSING
image segmentation, intensity normalization, …

FEATURE EXTRACTION
Radiomics, Dosiomics, candidate features, biomarkers, …

MACRO
modelling of properties at the MACRO level (e.g. DWI, PWI,…)

MICRO
modelling of properties at the MICRO level (e.g. cellularity)

MACHINE LEARNING-BASED MODELS

KNOWLEDGE-BASED RADIOBIOLOGICAL / STRUCTURAL MODELS
Tumour control probability (TCP), NTCP, microstructural model, …

VALIDATION

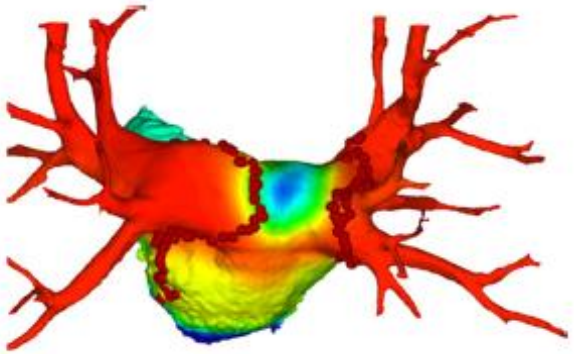
TECHNICAL

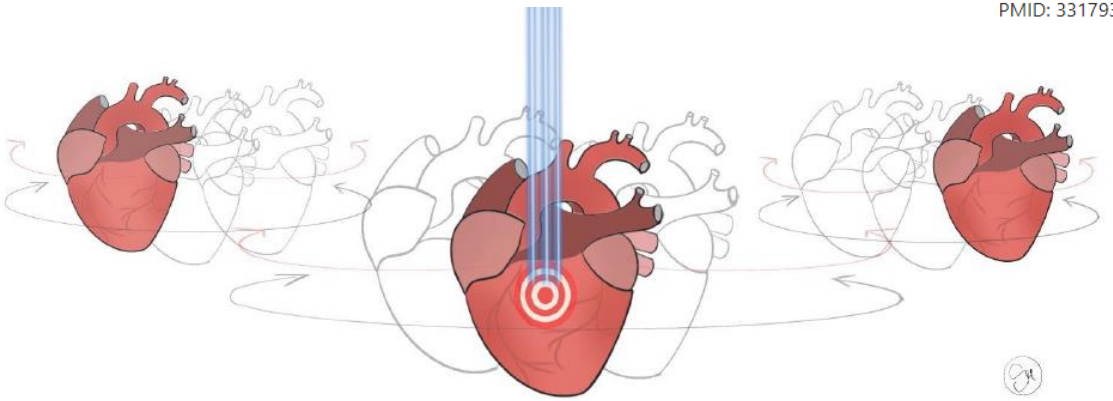
BIOLOGICAL – CLINICAL

Non oncological application: ventricular arrhythmia

(Collaboration with San Matteo Hospital, Pavia)

Published on:
European Journal of Heart Failure





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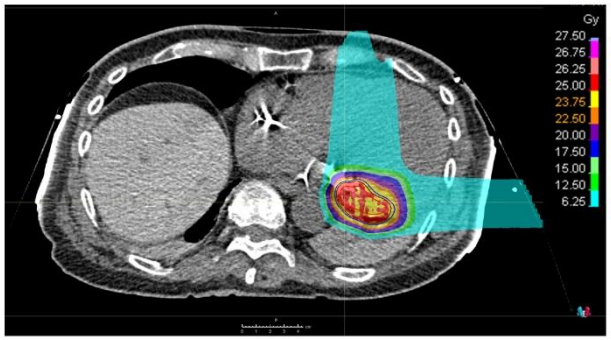
> Eur J Heart Fail. 2020 Nov 12. doi: 10.1002/ejhf.2056. Online ahead of print.

The First-in-Man Case of Non-invasive Proton Radiotherapy to Treat Refractory Ventricular Tachycardia in Advanced Heart Failure

Veronica Dusi [1 2], Viviana Vitolo [3], Laura Frigerio [1 4], Rossana Totaro [1 4], Adele Valentini [5], Amelia Barcellini [3], Alfredo Mirandola [3], Giovanni Battista Perego [6], Michela Coccia [2], Alessandra Greco [4], Stefano Ghio [4], Francesca Valvo [3], Gaetano Maria De Ferrari [7], Massimiliano Gnecchi [1 2], Luigi Oltrona Visconti [4], Roberto Rordorf [1 4]

Affiliations + expand

PMID: 33179329 DOI: 10.1002/ejhf.2056



From CNAO experience what I (we) have learned

Resilience - “it requires patience”

Prominence of scientific approach to problems

Precision and attention to details

Collaboration spirit

Take care of persons (personnel+patients)

Ethical attitude

CNAO
Centro Nazionale di Adroterapia Oncologica

THANK YOU!

HITRIplus
Heavy Ion Therapy Research Integration

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