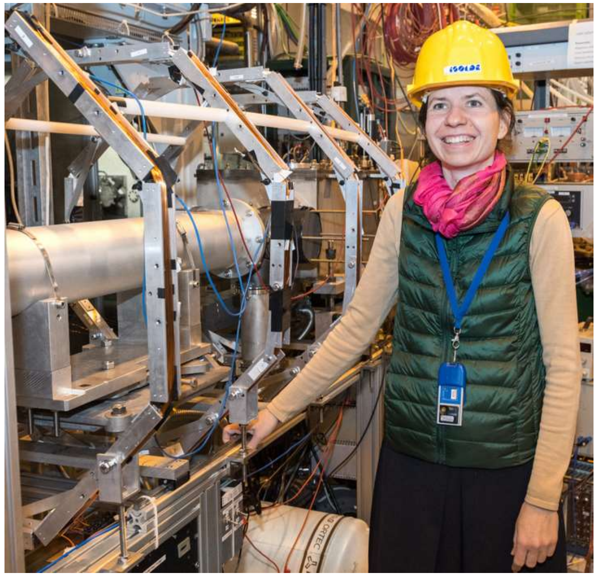
Medical applications of CERN technologies



Sparks! talk on
Future of detection and imaging

Prof. Magdalena Kowalska
CERN and University of Geneva

Knowledge Transfer Forum, Sept 2022:
https://indico.cern.ch/event/1089904/

Synergy between basic research at CERN and applications go together?

- (Beyond) state-of-the art basic research:
  - Encourages blue-sky thinking
  - Pushes the boundaries of knowledge
  - Requires (development of) novel techniques
  - Looks for solutions across fields – collaboration and interdisciplinarity
  - Is open to new, ‘crazy’ ideas
  - Allows to try things and fail, as a way of improving
  - Is made by humans who live in a society

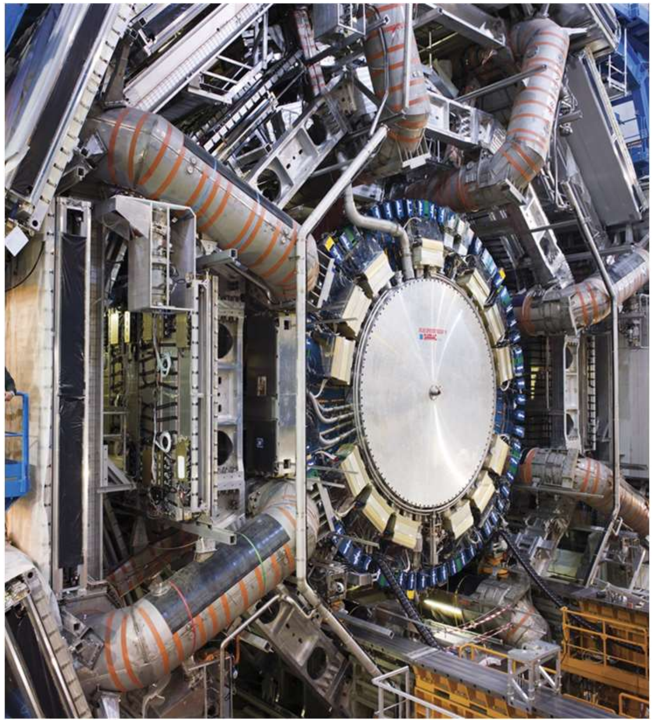
- Developing (paradigm-changing) applications:
  - Is made by people with open minds – basic-science researchers are ideal for that
  - Has many (above) points in common with
  - Needs support by their institution, business, and industry – they are of no help if there is no great idea and solid science
  - Excuse for not doing it: ‘it will take time from my basic research’: FALSE! You can’t plan discoveries, they might come from your applications (own experience)

Thoughts collected when preparing talk on ‘future of detection and imaging’ for Sparks! Serendipity Forum at CERN | Future Technology for Health: https://www.youtube.com/playlist?list=PLAk-9e5KQYEpGgaPbCn5spxOurTTgEm4h

Applications at CERN

- CERN = biggest basic science laboratory in world
- To understand what Universe is made of, requires:

Accelerators



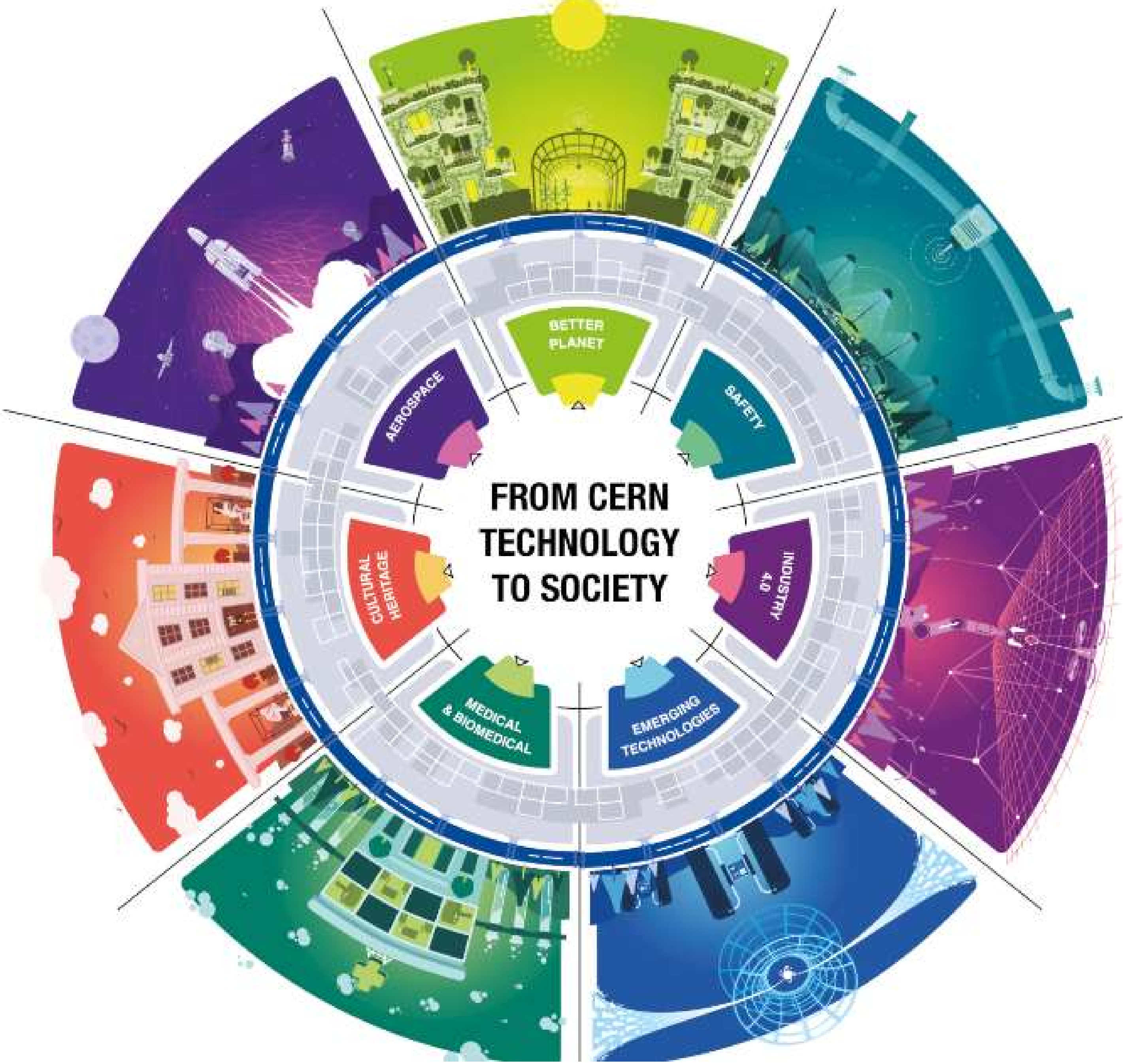
Detectors

Radiation

These tools can be translated into many useful technologies:

CERN technology transfer

- Fields:
  - Aerospace
  - **Healthcare**
  - Digital
  - Environment
  - Quantum



CERN Knowledge Transfer:
https://kt.cern/

From basic science to medical applications

- People doing basic-science research:
  - are also part of society and are interested in medical care
  - often realise that our aims are the same as medical doctors:

- Provide healthcare approaches that are:
  - SMALLER
  - CHEAPER
  - MORE PRECISE
  - MORE SENSITIVE

- We just might have a different view of how to achieve:
  - Bring the patient to the machine vs bring/scale the machine to the patient

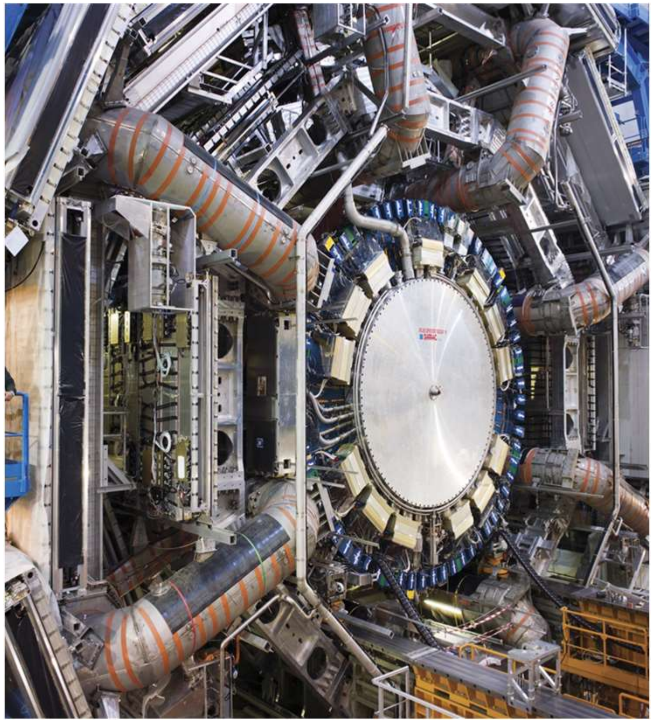
- Working in interdisciplinary teams is the key for success

Sparks! talk on Future of detection and imaging

Medical applications at CERN

- Using CERN tools to improve diagnosis and treatment of diseases:

Accelerators

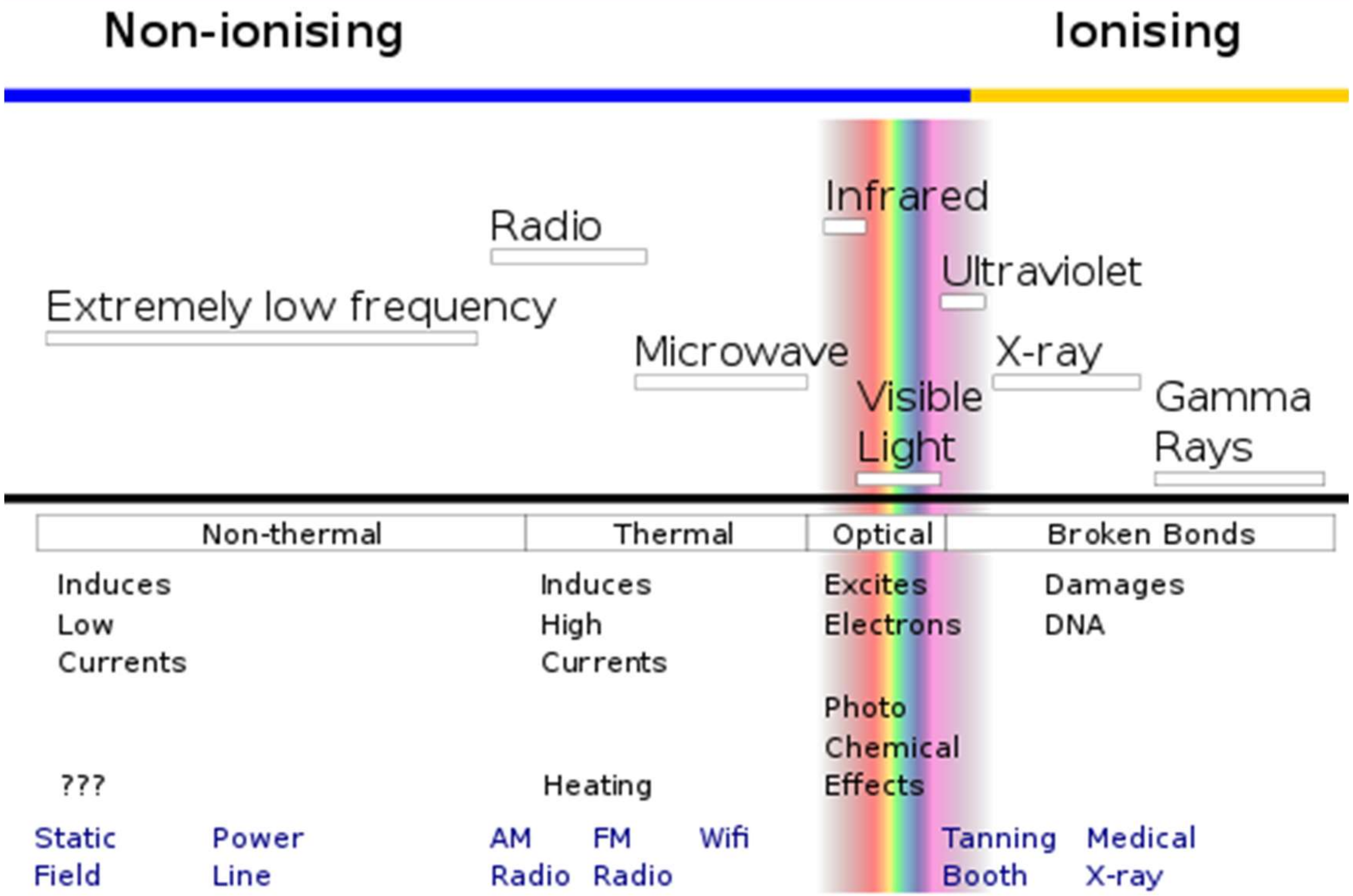


Detectors

Radiation

- Advantages:
  - Sensitive detection of radiation for diagnosis
  - Precise treatment with particles and radiation

Particles and ionising radiation



Non-ionising

Ionising

Extremely low frequency

Radio

Microwave

Infrared

Visible Light

Ultraviolet

X-ray

Gamma Rays

Non-thermal	Thermal	Optical	Broken Bonds
Induces Low Currents	Induces High Currents	Excites Electrons	Damages DNA
		Photo Chemical Effects	
???	Heating		

Static Field

Power Line

AM Radio

FM Radio

Wifi

Tanning Booth

Medical X-ray

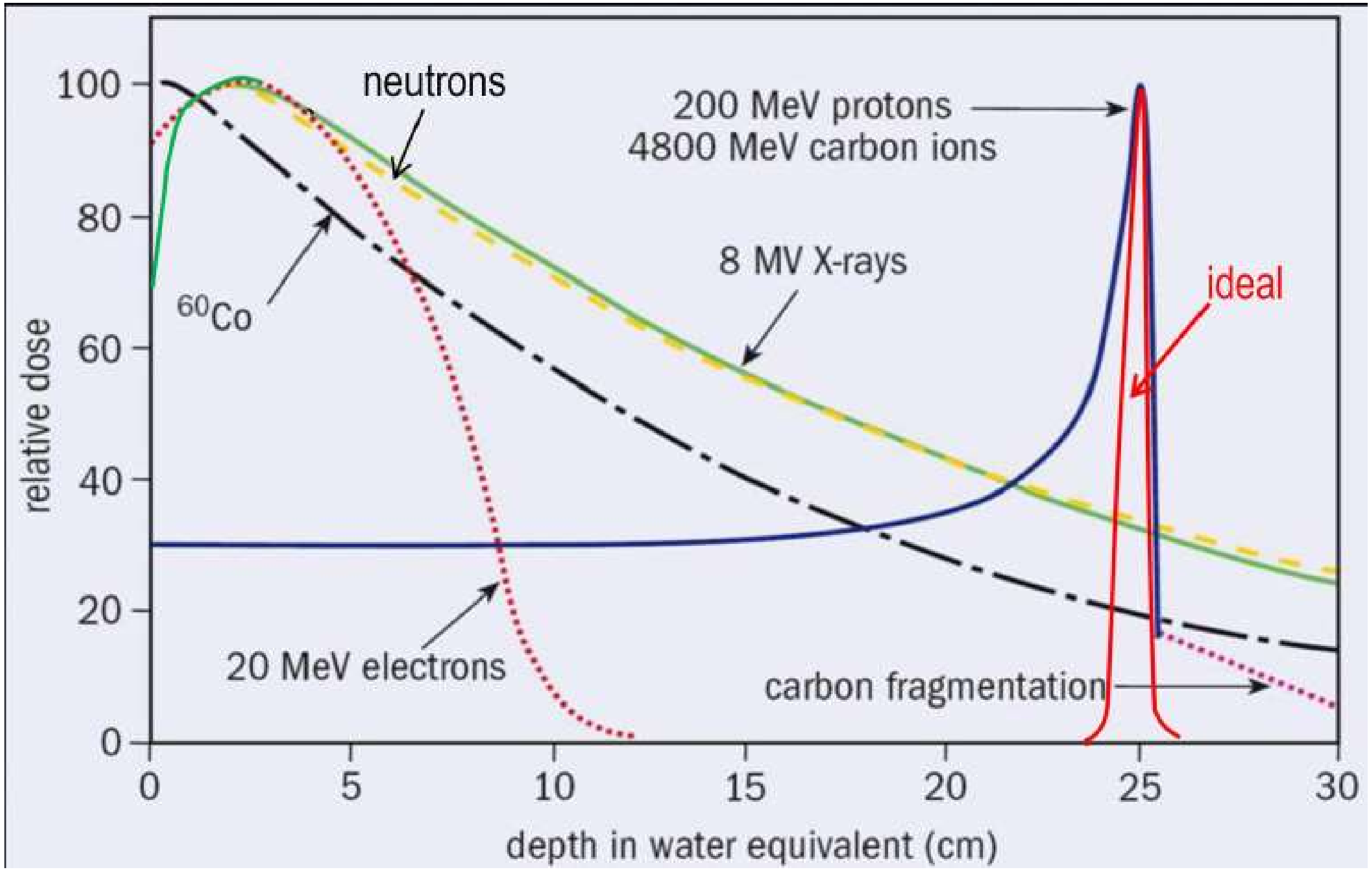
Particles:

- Beta (e- and e+)
- Protons
- ‘heavy ions’ (12C, 16O, in the future – also unstable 11C?)

Accelerators

(Cancer) treatment with external beams

- Energy deposited by radiation and particles in matter:

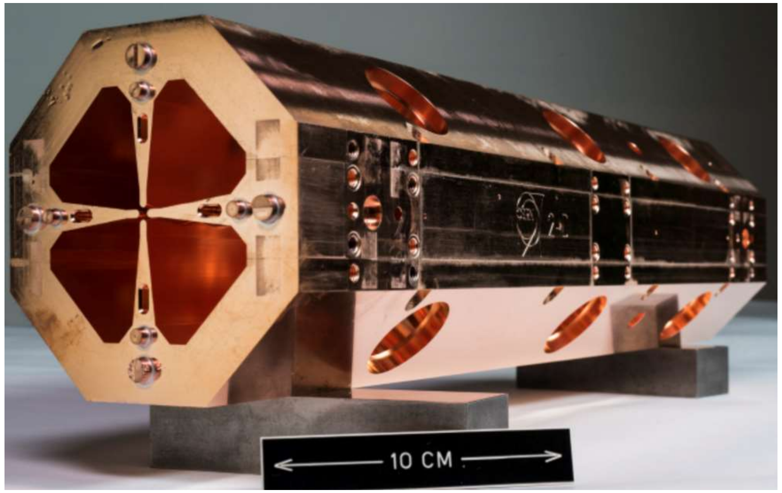


- Approach:
  - Irradiate from several sides to maximise dose in volume to be healed (e.g. tumour)
  - Protons and ‘heavy ions’ most selective: most dose at the end of particle’s path

Proton accelerators

(CERN) particle accelerators:

- Production of isotopes for PET and SPECT (hospital cyclotrons) for nuclear-medicine diagnosis
- Already used for hadron therapy:
  - Cancer and cardiac-problem treatment with energetic beam of protons, deuterons, and even carbon ions
  - Energy deposited cm inside body, at the end of particle's path

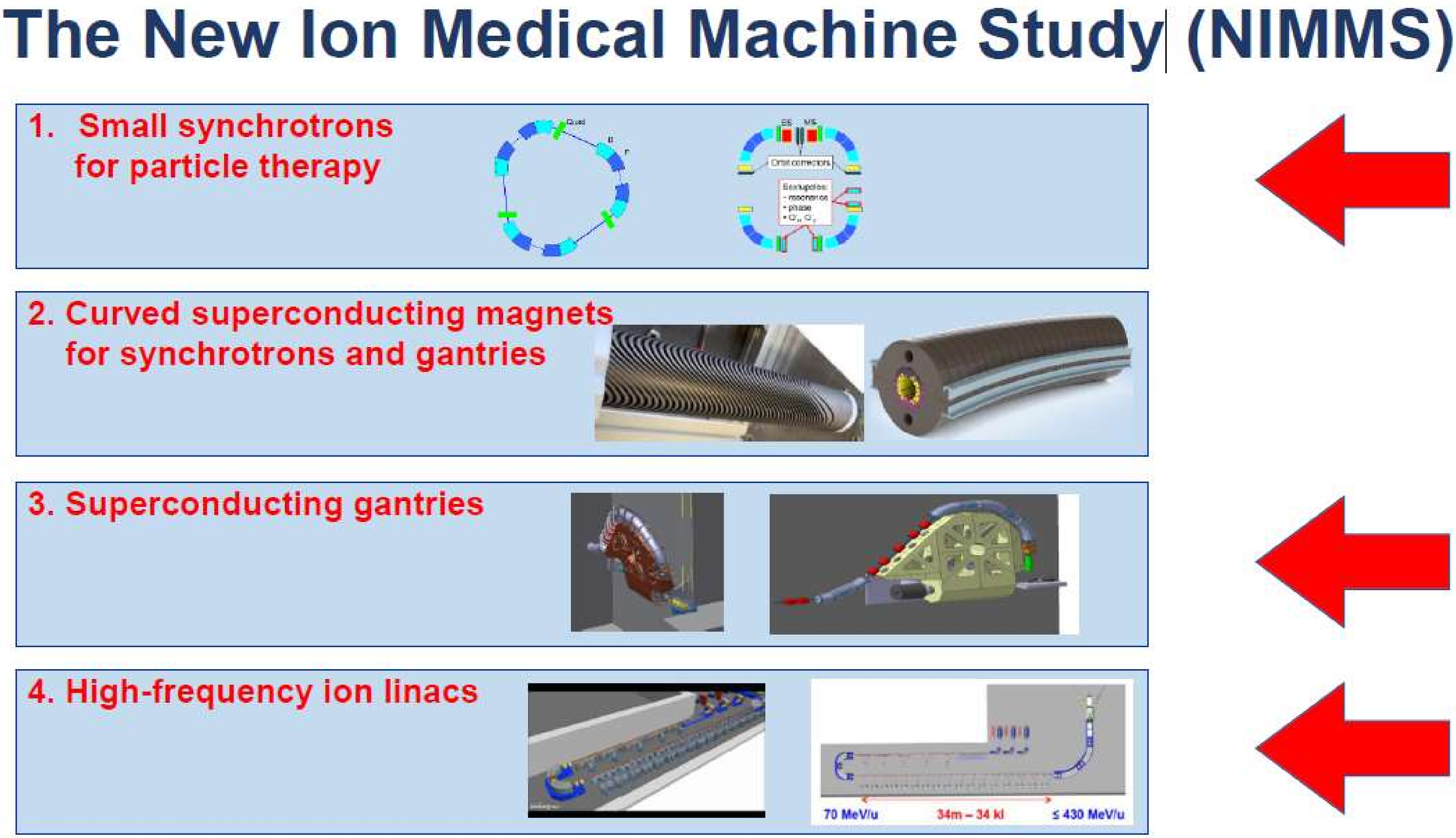


CNAO The National Center for Oncological Hadrontherapy Pavia, IT

Half of accelerators in the world are used for medical purposes

Tera foundation (U. Amaldi), CERN spin-off: ADAM

NIMMS project: compact ion accelerators



The New Ion Medical Machine Study (NIMMS)

1. Small synchrotrons for particle therapy
2. Curved superconducting magnets for synchrotrons and gantries
3. Superconducting gantries
4. High-frequency ion linacs

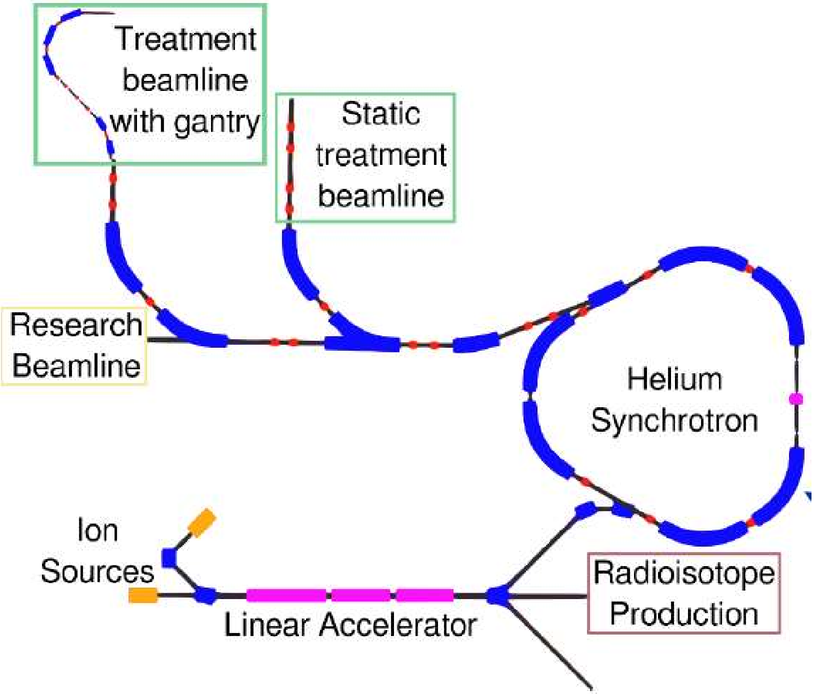
He synchrotron

He radiotherapy: under advanced study at carbon therapy centres.

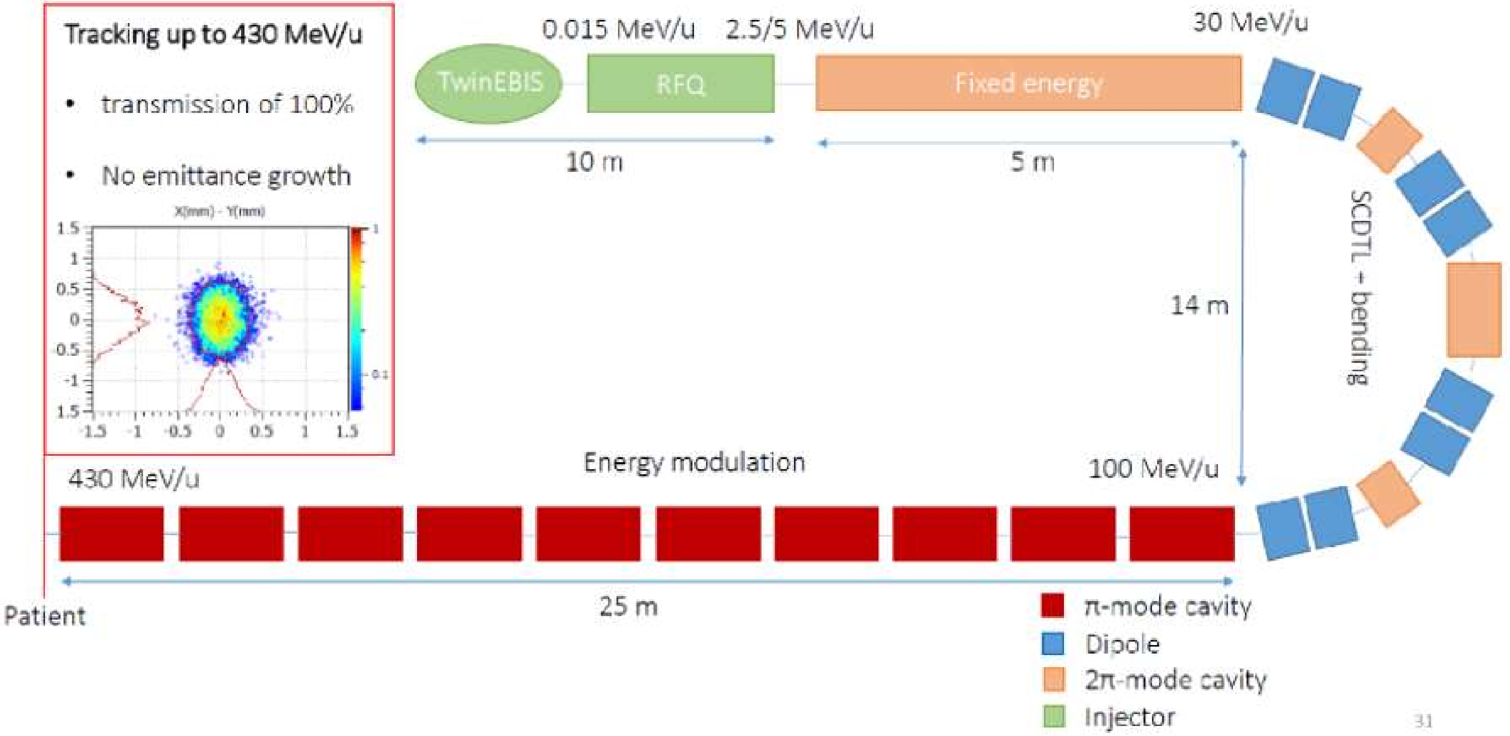
- First patient treated in September 2021 at the Heidelberg Ion Therapy (D).
- Clinical trials starting

An accelerator designed for helium treatment can easily produce protons for standard treatment, and be used for research with helium and heavier ions.

Advantages
- reduced lateral scattering w.r.t. protons,
- lower fragmentations than carbon,
- lower neutron dose than protons or carbon, reducing risks in paediatric patients,
- could treat some radioresistant tumours at lower cost than carbon.



NIMMS bent linac



Carbon acceleration

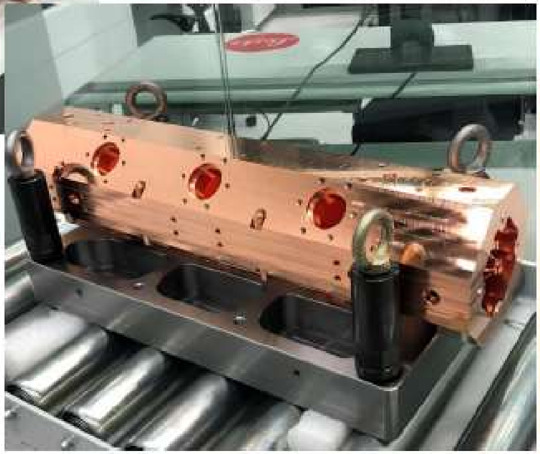
Fast and accurate dose delivery to the tumour

Innovative «folded» version to save space

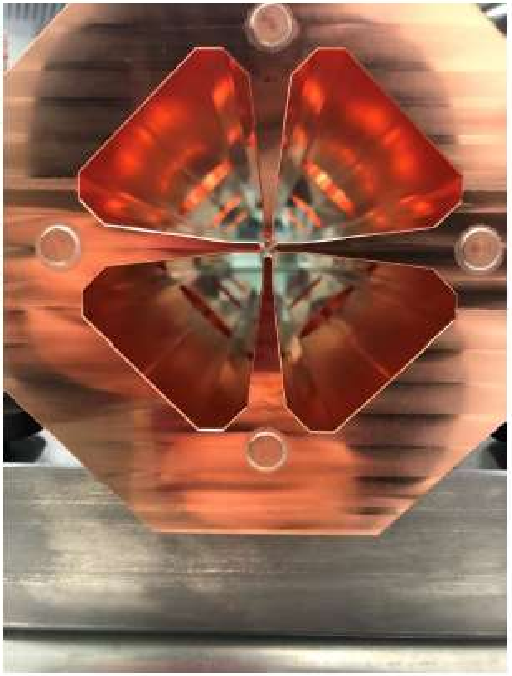
Particle tracking completed
Prototype EBIS source under commissioning
RFQ designed

A. Lombardi, V. Bencini, D. Gibellieri, F. Wenander, BE/ABP
A. Grudiev, H. Pommerenke, S. Ramberger, M. Khalvati, BE/RF J. Navarro, C. Oliver, D. Perez, CIEMAT

Rfq pre-injector



First (of 4 sections) completed



Agreement with CIEMAT and CDTI for construction of pre-injector in collaboration with Spanish industry

2.0 m long - 750 MHz
Will deliver Carbon (or Helium) at 5 MeV (total energy)

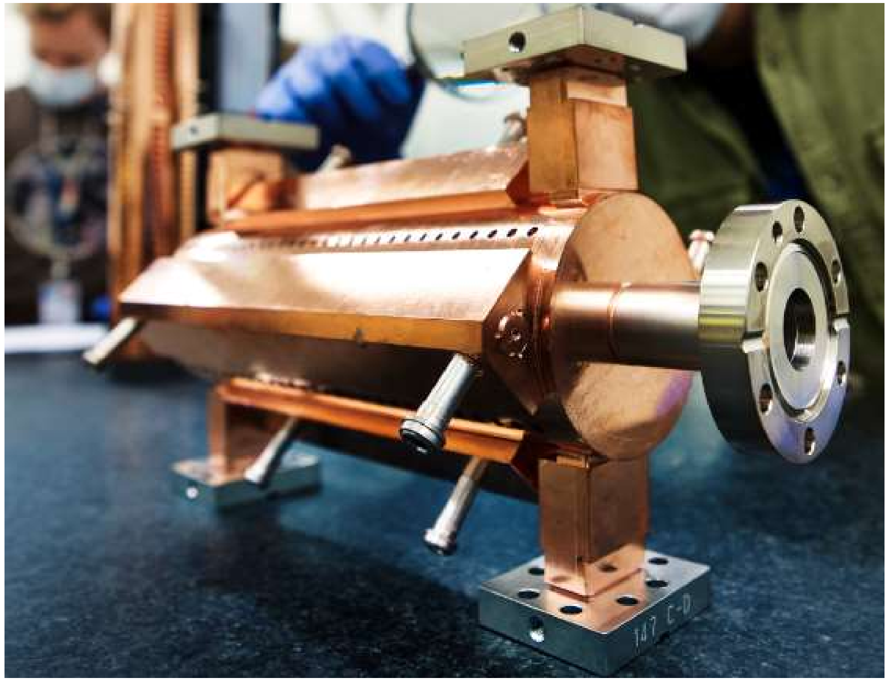
Designed at CERN built by Spanish Industry

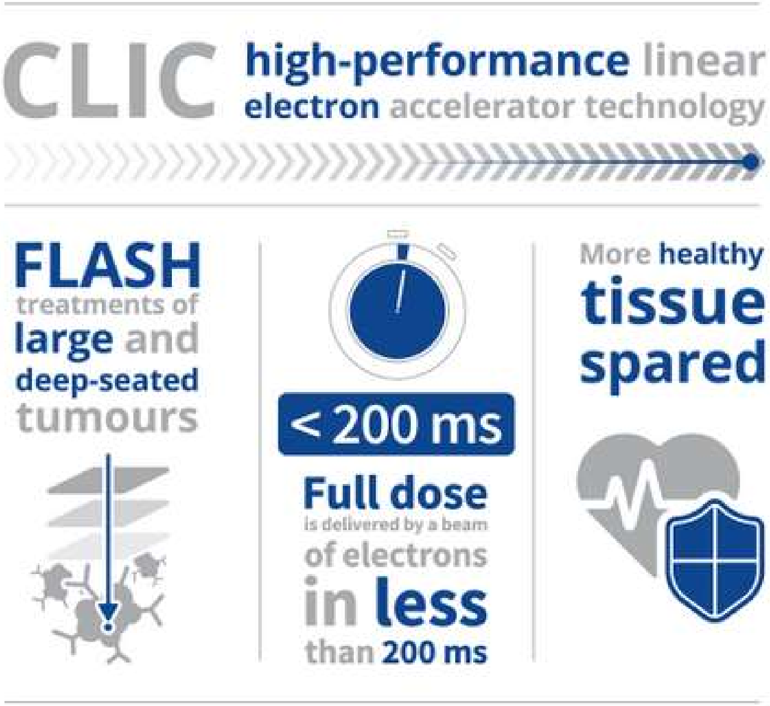
Status: 2/4 sections completed – delivery June 2023

Electron accelerators

Compact electron accelerator:

- Following CLIC (compact linear collider) R&D at CERN
- FLASH: short-pulse electron radiotherapy
- Facility to be built at Lausanne Hospital





Video: https://videos.cern.ch/record/2295068

https://kt.cern/flash-radiotherapy

FLASH therapy with electrons

- https://videos.cern.ch/record/2295068

Vozenin et al
Clin Cancer Res
2018

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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*

1a : Day 0

1b : 3 weeks

1c : 5 months

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.

From B. Frisch, CERN KT team,

CLIC project and FLASH therapy

Very intense electron beams

- CLIC –to provide brightness needed for delicate physics experiments
- FLASH –to provide dose fast for biological FLASH effect

Very precisely controlled electron beams

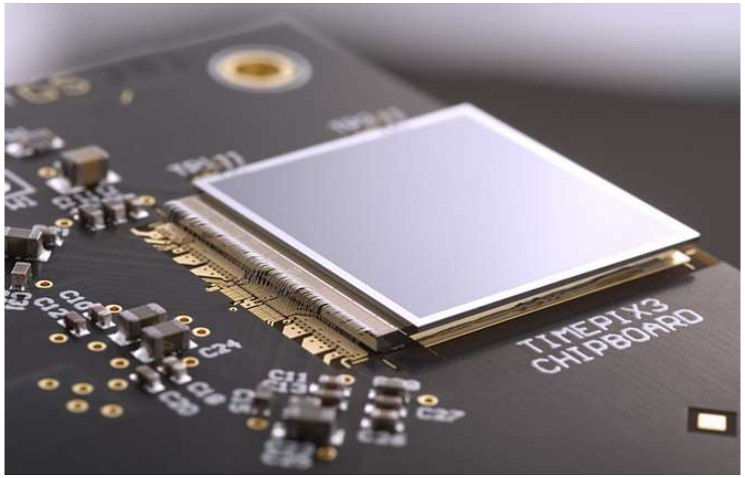
- CLIC –to reduce the power consumption of the facility
- FLASH –to provide reliable treatment in a clinical setting

High accelerating gradient (beam energy gain per meter)

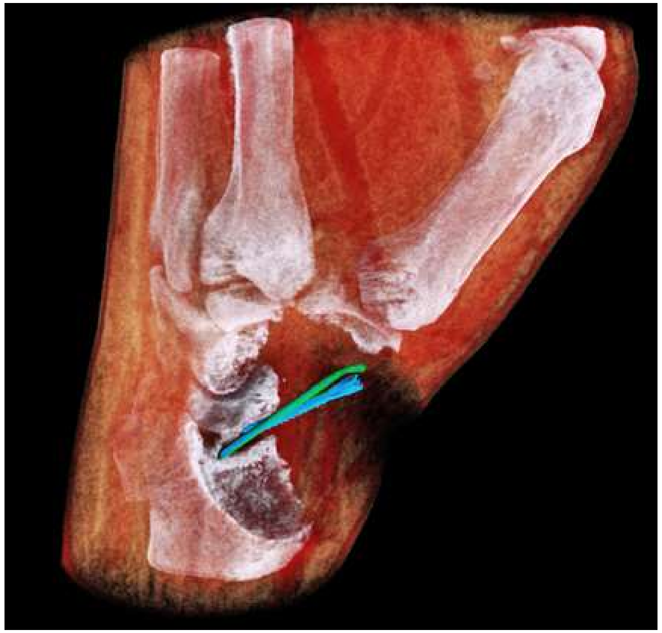
- CLIC –fit facility in Lac Leman region and limit cost
- FLASH –fit facility on typical hospital campuses and limit cost of treatment

Detectors

Diagnosis with photon counting x-ray detectors



- MEDIPIX, TIMEPIX collaboration at CERN
- High-resolution hybrid pixel detectors for particle tracking at LHC
- Applications in many fields
- x-ray photon-counting in CT medical diagnosis:
  - Lower does
  - Higher spacial resolution
  - X-ray energy resolution
- 1st portable CT scanner in Europe in Lausanne

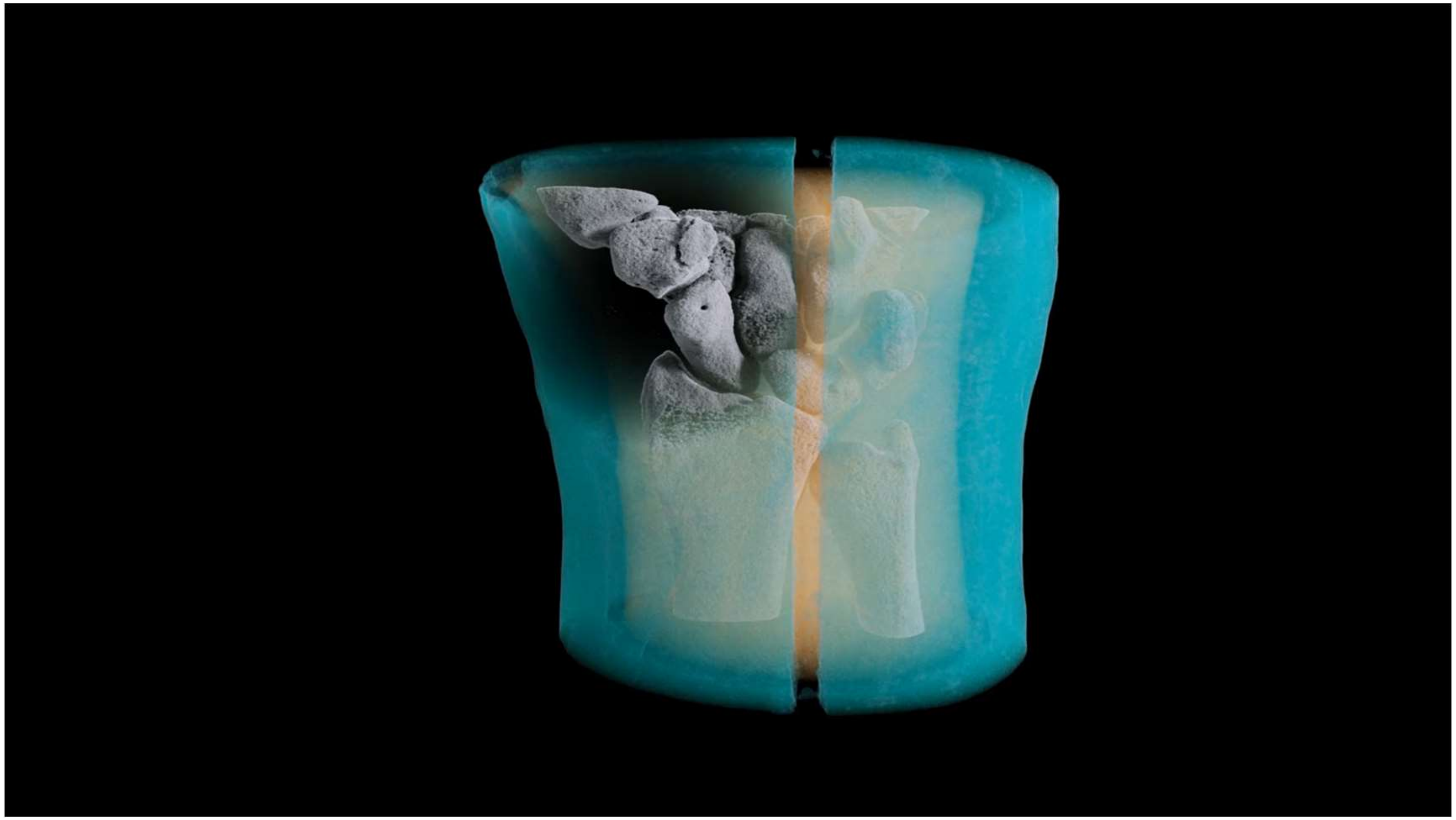


metallic screw (blue), K-wire (green)

Technology transfer e.g. to MARS, New Zealand, and Czechia

Computed tomography with photon counting

- Wrist image with colour x-ray:

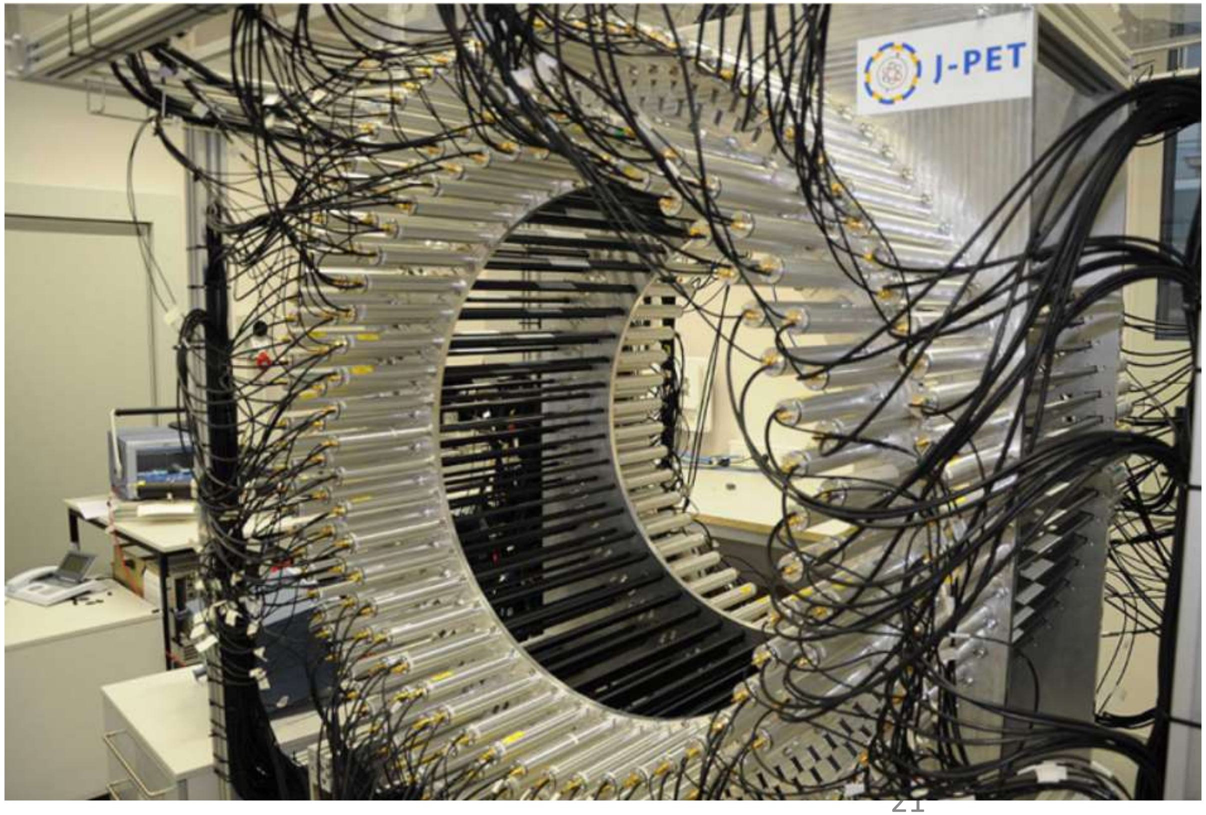


Source: MARS bioimaging

511-keV PET detectors from basic science

- Detectors with ns and ps time resolution - better localisation:
  - As in ATLAS tracer: monolytic Si detector – TT-PET project, Uni Geneva
  - Fast scintillating crystals from CMS: CrystalClear at CERN
  - As in nuclear fast timing: U Complutense Madrid

- Cheaper materials:
  - Organic scintillators: J-PET in Krakow



Radioactive nuclei

Medical diagnosis with unstable nuclei

- Diagnosis with radioactive nuclei:
  - Radioactive nucleus usually connected chemically to a biological ‘ligand’
  - ‘ligand’ finds areas to be diagnosed: sugars go to cells that need energy, e.g cancer
  - Emitted radiation shows the localisation of the interesting region
  - Efficient particle detectors detect very low unharmful nM or pM concentrations

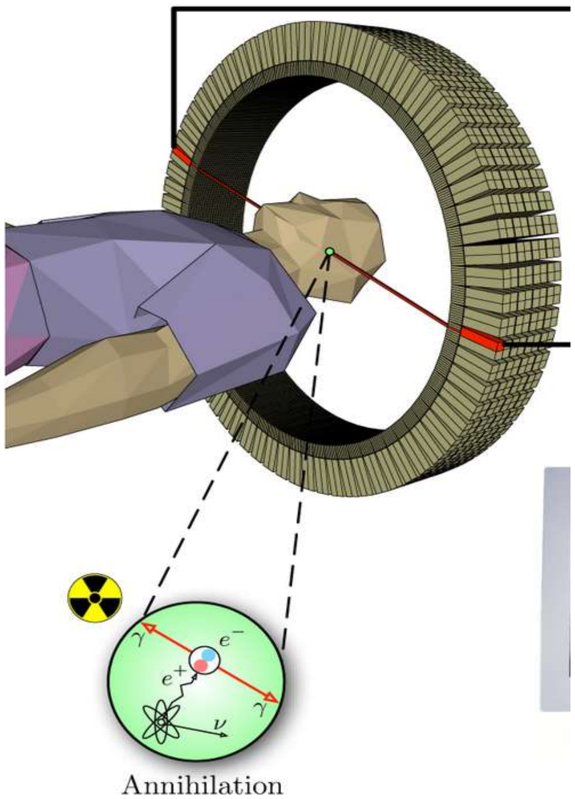
- Suitable isotopes:
  - Isotope of element that can bind to biological ligands
  - Lifetime long enough for delivery and short enough for a body: hours to days
  - Right type of radiation and its energy

- Detection: radiation not particles, because it gets stopped less in the body
  - Gamma rays from decay or annihilation of emitted beta+ particle

- Approaches (nuclear medicine):
  - PET
  - SPECT

PET: Positron emission tomography

- Signal from beta+ (positron) emitting nuclei
  - Emitted positron stops after travel of some mm in tissue
  - Positron = antimatter, so it annihilates with an electron from a neighbouring molecule (E=mc2)
  - 2 gamma rays of 511keV are emitted at 180 degrees
- Detection:
  - Based on time and position of hits in detectors, place of annihilation is identified

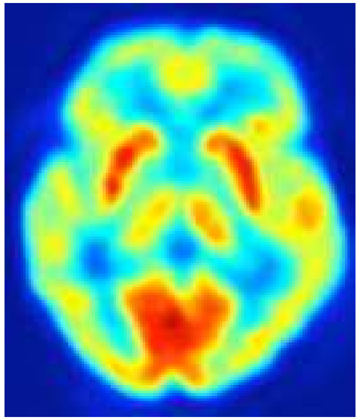


PET and CERN

- PET developed in Geneva Hospital in 1977
    - 1st isotopes were produced at CERN

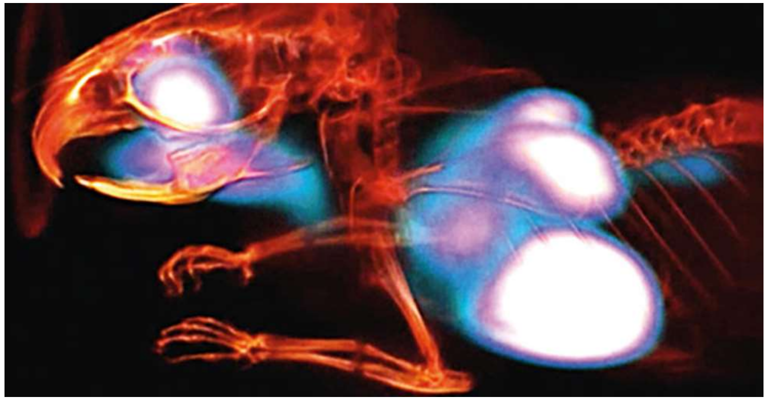
- Detector developments at CERN and around
    - CMS-related activity: CrystalClear
    - Fast response for localizing better
    - Cheaper, more efficient

- Novel PET Isotopes:
    - ISOLDE and MEDICIS (ISOLDE sister)



- Strengths:
    - Extremely sensitive

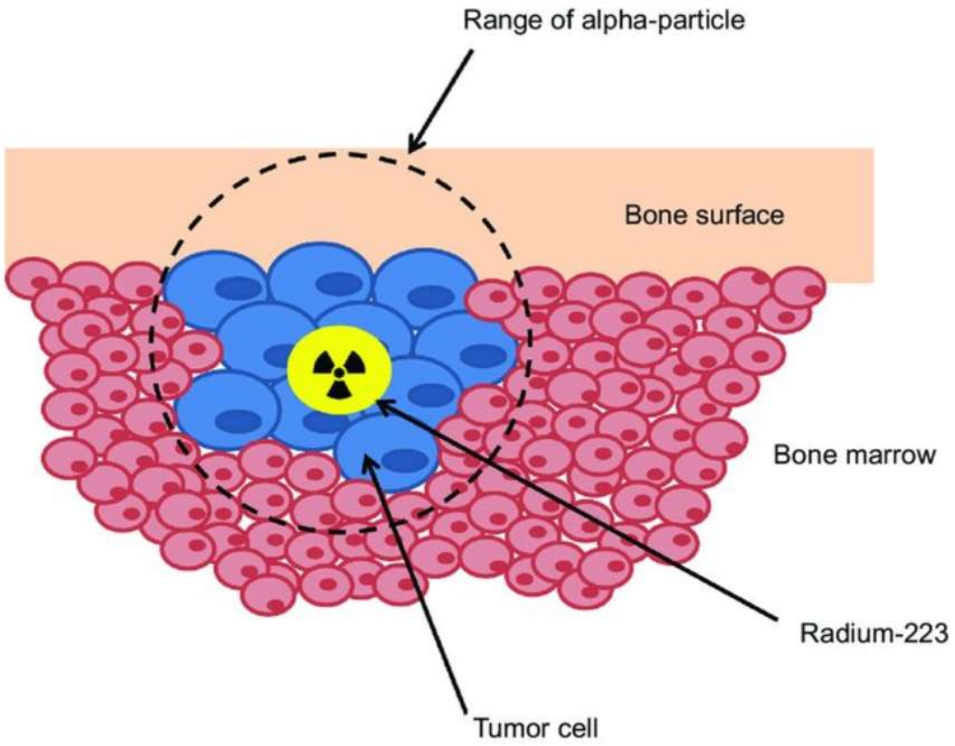
- Relative weaknesses:
    - Time resolution of detectors crucial -> can pinpoint annihilation location better
    - Coincidence between 2 gammas: relatively complex machine and event reconstruction
    - e+ can travel several mm before annihilating: limit in resolution

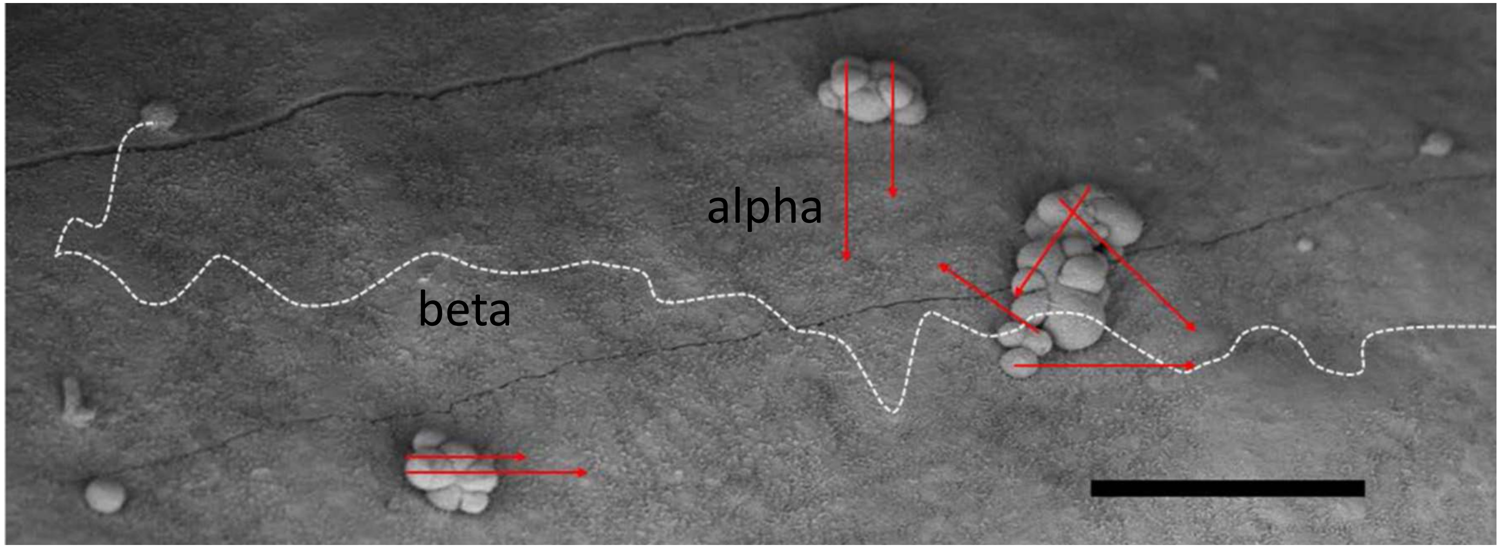


https://home.cern/news/news/knowledge-sharing/forty-years-first-pet-image-cern

Cancer treatment with radionuclei

- Treatment via cell (mostly DNA) damage:
  - High dose beta radiation
  - Alpha radiation: heavier, so shorter range but higher lethality
- Isotope delivery to cancer – as in diagnosis: connection to ligand
- Isotope:
  - Suitable half-life
  - Alpha emission

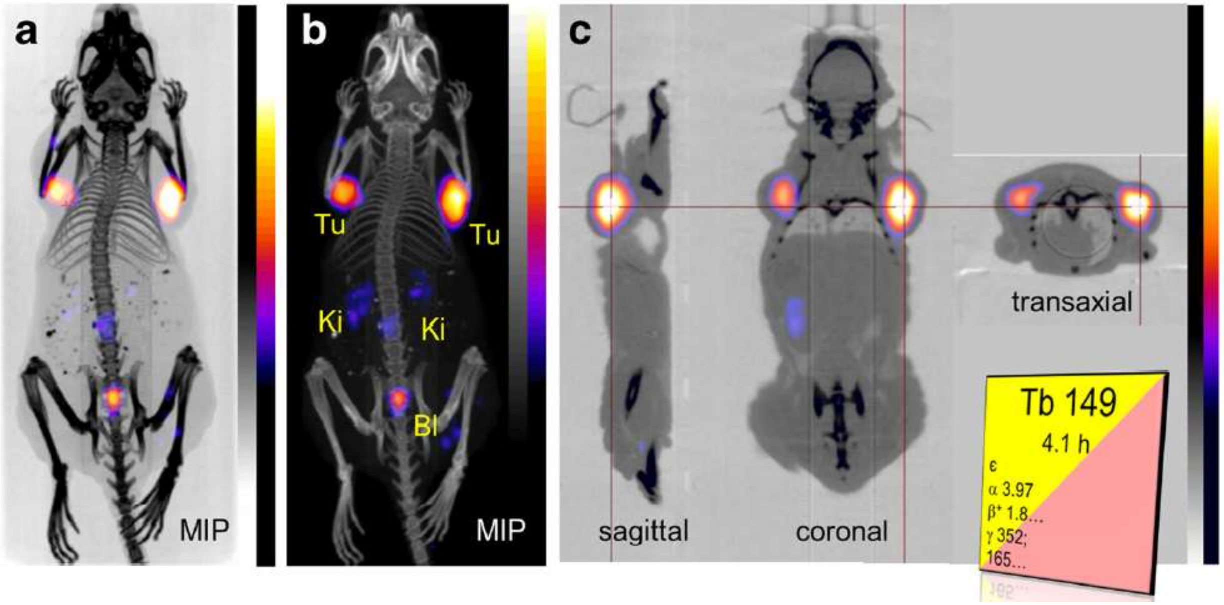


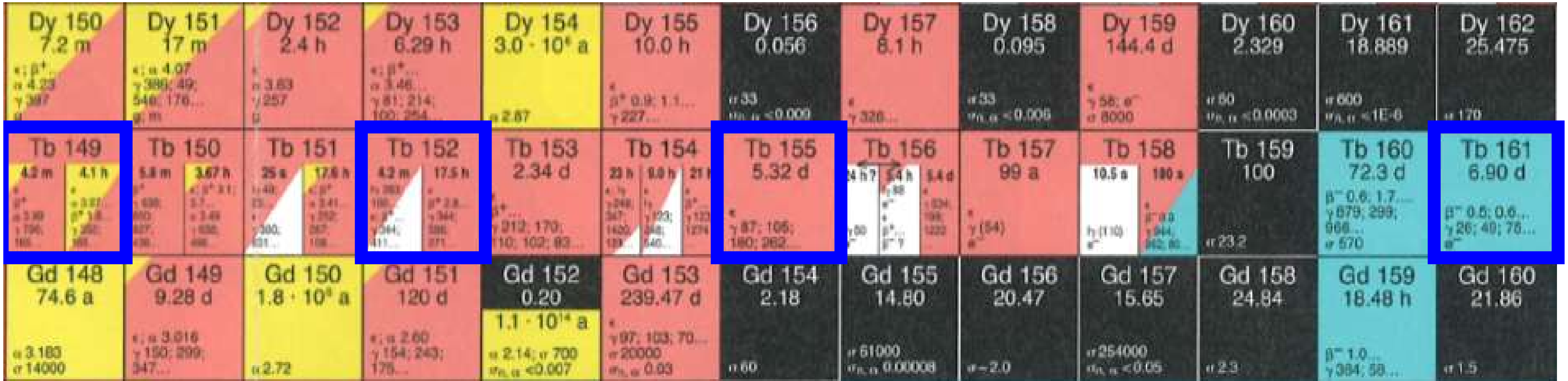


Theranostics with unstable nuclei

After U. Koster, C Müller et al. 2012 J. Nucl. Med. 53, 1951

- Theranostics = therapy and diagnostics together
  - One isotope does diagnosis (e.g. PET)
  - Another isotope of the same element: treatment
- At ISOLDE and Medicis

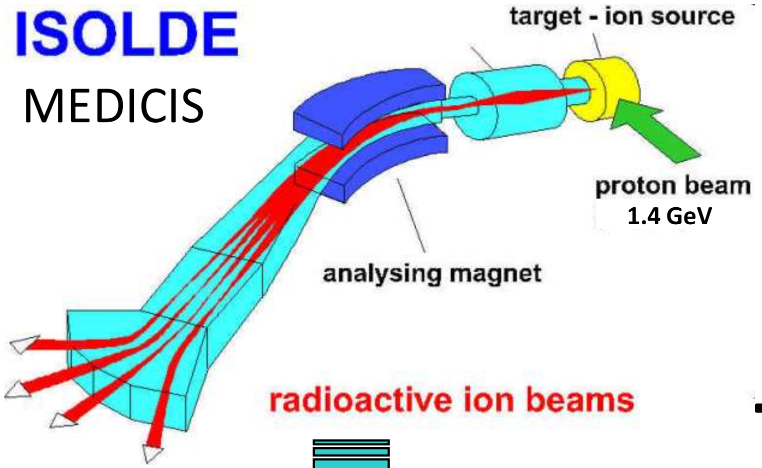




Dy 150 7.2 m	Dy 151 17 m	Dy 152 2.4 h	Dy 153 6.29 h	Dy 154 3.0 · 10⁶ a	Dy 155 10.0 h	Dy 156 0.056	Dy 157 8.1 h	Dy 158 0.095	Dy 159 144.4 d	Dy 160 2.329	Dy 161 18.889	Dy 162 25.475
Tb 149 4.2 m 4.1 h	Tb 150 5.8 m 3.67 h	Tb 151 25 s 17.6 h	Tb 152 4.2 m 17.5 h	Tb 153 2.34 d	Tb 154 23 h 9.0 h 21 h	Tb 155 5.32 d	Tb 156	Tb 157 99 a	Tb 158 10.5 s 180 a	Tb 159 100	Tb 160 72.3 d	Tb 161 6.90 d
Gd 148 74.6 a	Gd 149 9.28 d	Gd 150 1.8 · 10⁶ a	Gd 151 120 d	Gd 152 0.20 1.1 · 10¹⁴ a	Gd 153 239.47 d	Gd 154 2.18	Gd 155 14.80	Gd 156 20.47	Gd 157 15.65	Gd 158 24.84	Gd 159 18.48 h	Gd 160 21.86

New medical isotopes from CERN

i. Collection at ISOLDE

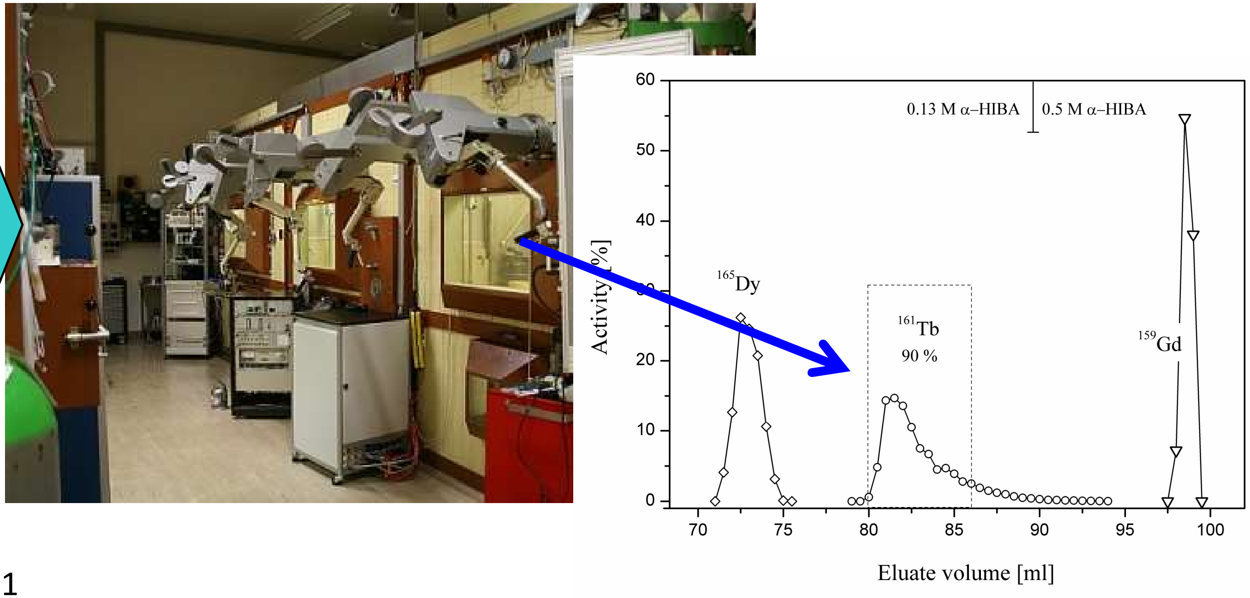


iv. Injection into mouse

v. PET/SPECT imaging and tumor treatment

ii. Shipping to PSI

iii. Radiochemical purification and labeling

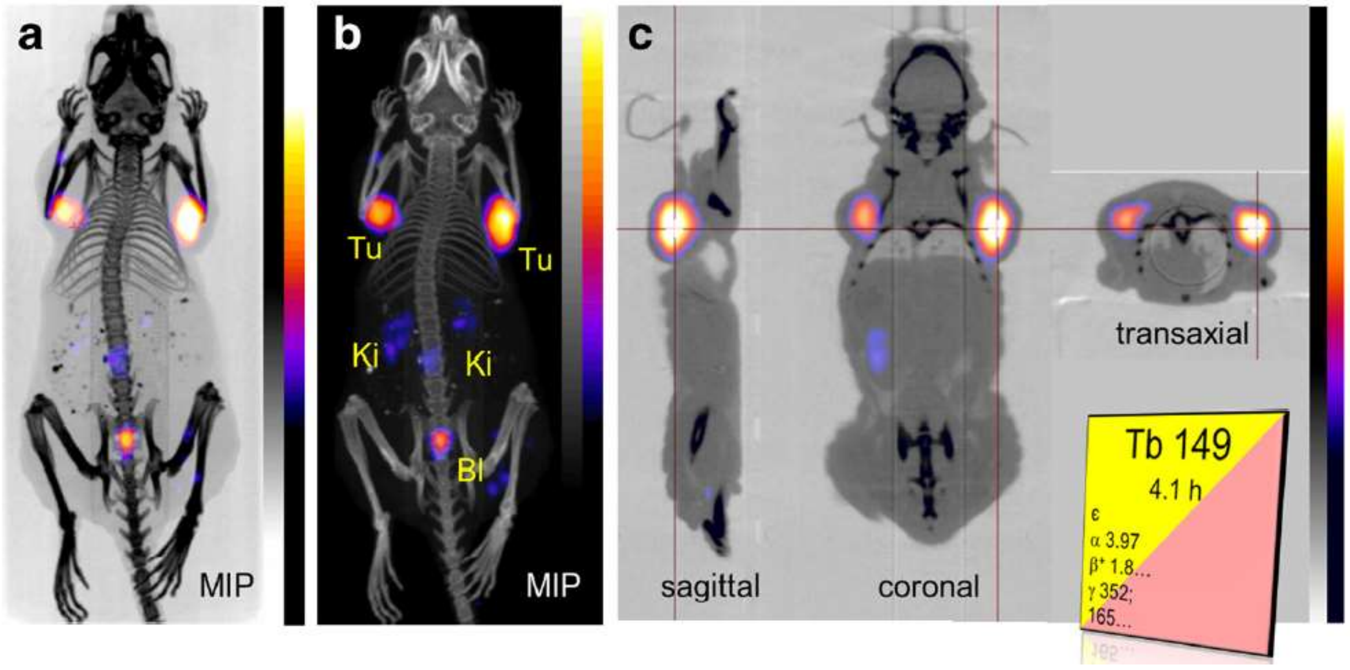


After U. Koster

C Müller et al. 2012 J. Nucl. Med. 53 1951

Cancer treatment with radionuclei

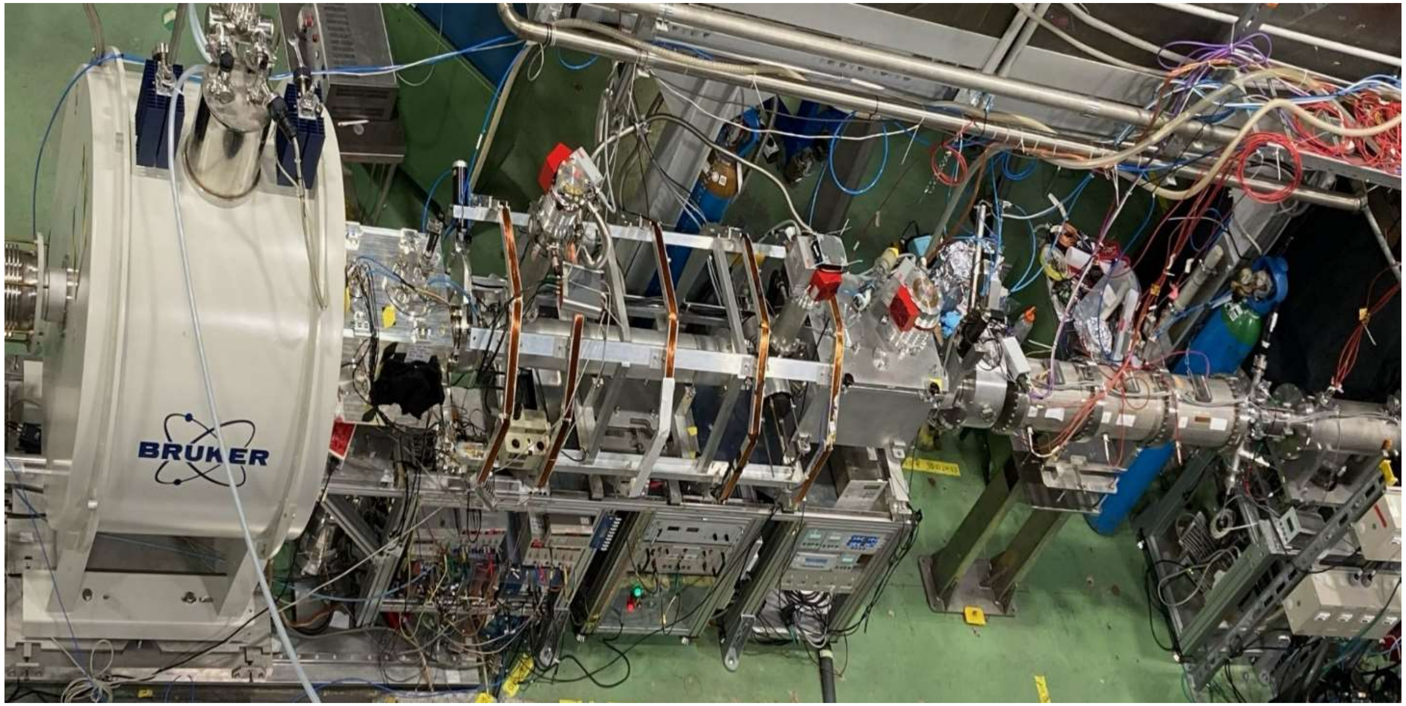
- Theranostics = therapy and diagnostics together
- Several isotopes of same element bound to biological ligand
  - Gamma-emitters: SPECT diagnosis, Beta-emitters: PET diagnosis
  - Alpha-emitter: cancer cell killing (small range, high does)
- Production at CERN (ISOLDE and MEDICIS labs) or in partner labs (e.g. reactors)
- Radiochemistry at partner institutes
- Used for pre-clinical studies

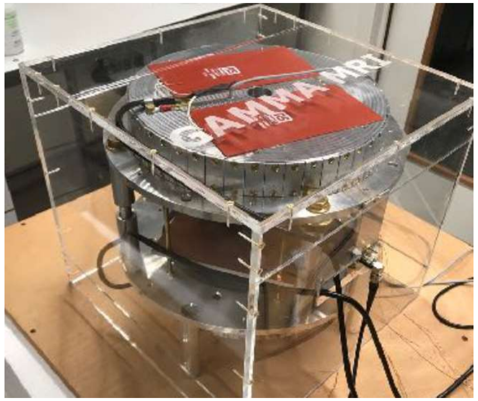


Müller et al. EJNMMI Radiopharmacy and Chemistry (2016) 1:5

Ultrasensitive magnetic resonance imaging

- My own projects
- Radiation-detected Nuclear Magnetic Resonance (NMR) and Imaging (MRI)
  - Use of unstable nuclei
  - Signal detection via direction of radiation, not signal pickup in a coil
  - Up to 10^{10} more sensitive than conventional NMR
- Interdisciplinary team
  - Worldwide collaborations
  - Applications in different fields





Beamline at ISOLDE

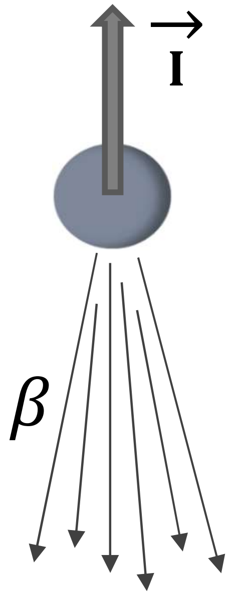
Why are polarized radio-nuclei special?

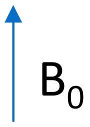
- **Their beta and gamma decay is anisotropic in space**

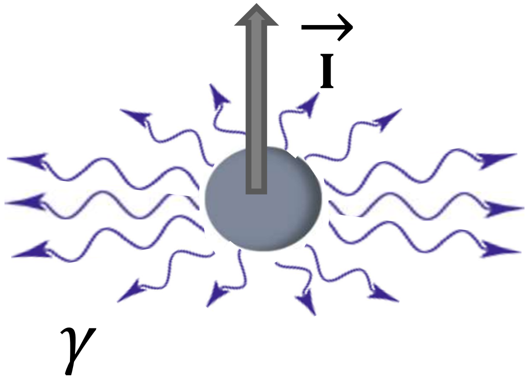
Beta decay, I>0

Gamma decay, I>1/2

Parity non-conservation of weak interaction, Mme Wu experiment





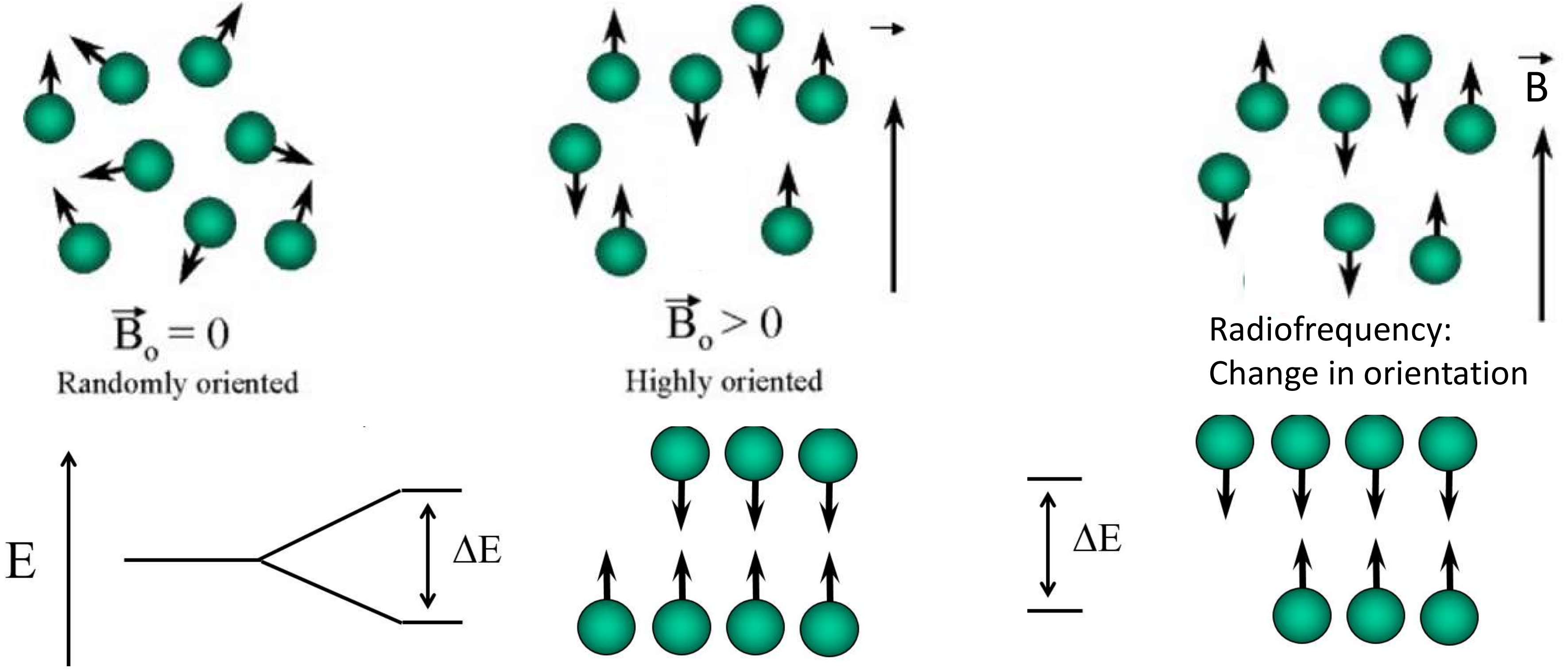


depend on degree and order of spin polarization and transition details (initial spin, change of spin)

- Observed decay asymmetry can be used to perform sensitive Nuclear Magnetic Resonance

Principles of Nuclear Magnetic Resonance

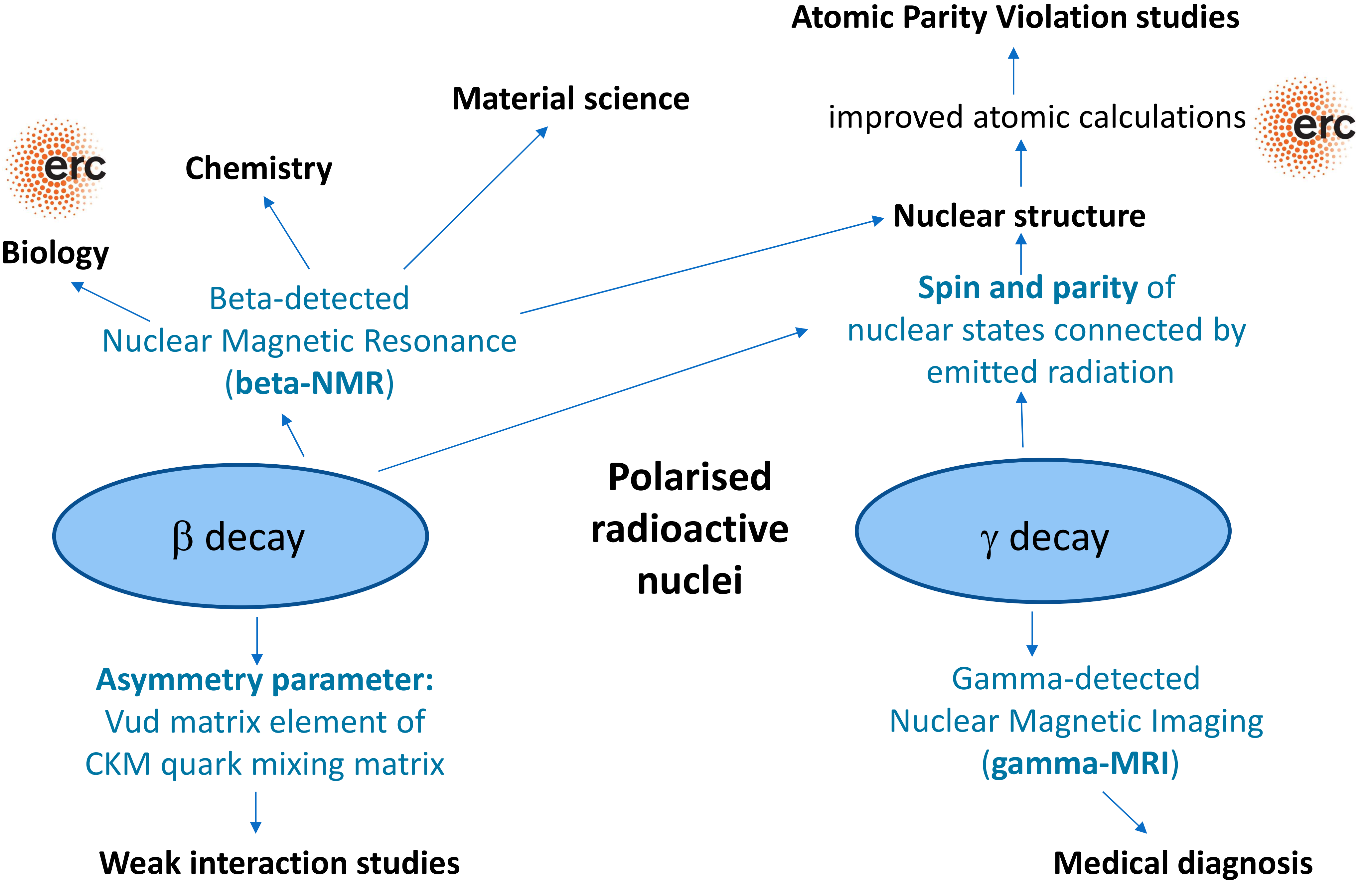
- Participants:
  - Probe nuclei with spin different from 0
  - Sample/ environment
- Magnetic field
  - Strong static field (B0)
  - Weaker perpendicular field (B1) oscillating at radio-frequency (MHz)



Radiofrequency:
Change in orientation

Larmor frequency in magnetic field is shifted by environment (electrons in molecules)

What are polarised radio-nuclei good for?



Atomic Parity Violation studies

improved atomic calculations

Material science

Chemistry

Biology

Nuclear structure

Beta-detected
Nuclear Magnetic Resonance
(**beta-NMR**)

Spin and parity of
nuclear states connected by
emitted radiation

β decay

**Polarised
radioactive
nuclei**

γ decay

Asymmetry parameter:
Vud matrix element of
CKM quark mixing matrix

Weak interaction studies

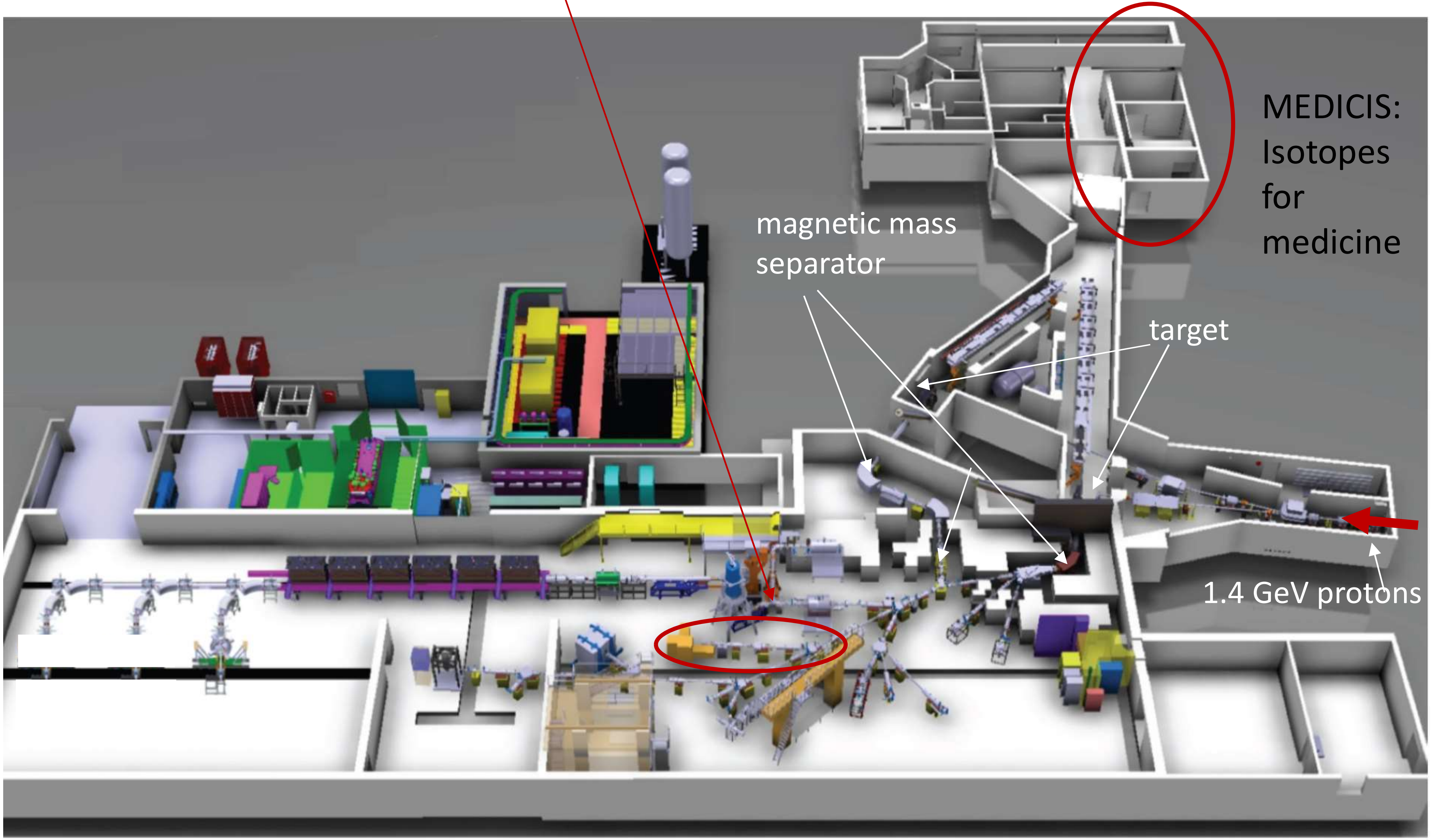
Gamma-detected
Nuclear Magnetic Imaging
(**gamma-MRI**)

Medical diagnosis

Where to find many unstable nuclei?

ISOLDE facility at CERN: devoted to production and studies of unstable nuclei (>1300)

Laser-polarization and β-NMR at VITO beamline

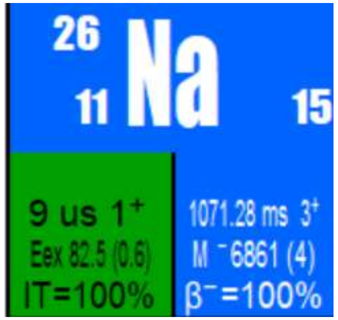


Radiation-detected NMR in liquids

betaDropNMR

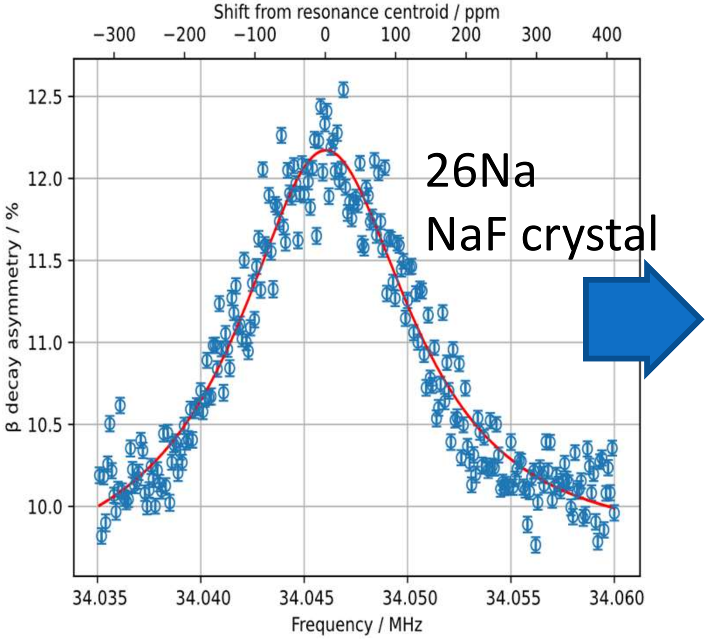
Beta-radiation detected NMR in liquids

- NMR: part per million shift in Larmor frequency due to direct environment of probe nucleus
- Up to billion times higher sensitivity than conventional NMR (down to 1e6 nuclei)
- much narrower resonances than in solids: 10^2-10^3 higher precision (part-per-million)



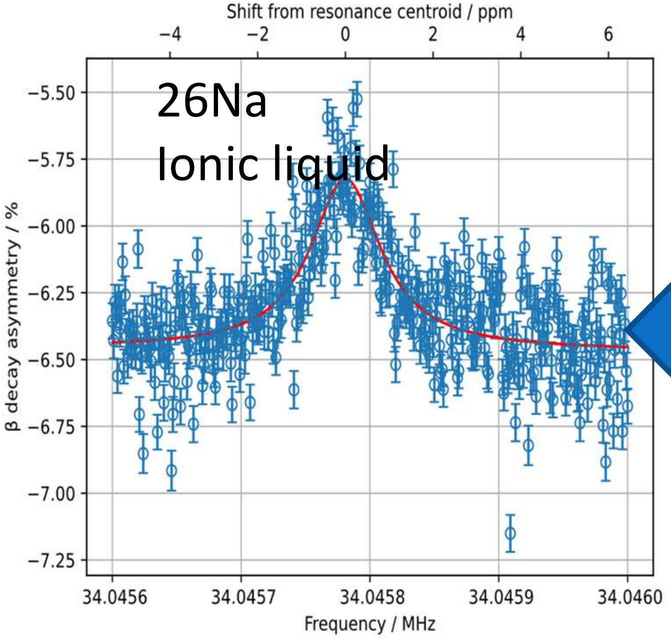
Can address chemical elements and samples inaccessible in conventional NMR

E.g metal-ion interaction with biomolecules



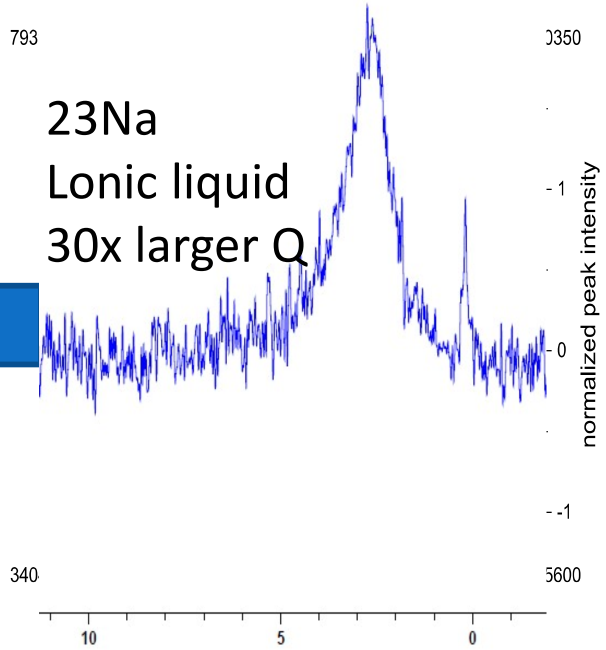
^{26}Na β-NMR in a NaF crystal

1e7-1e8 Na nuclei in sample



^{26}Na β-NMR in an ionic liquid

1e7-1e8 Na nuclei in sample



Conventional NMR scan of ^{23}Na (black)

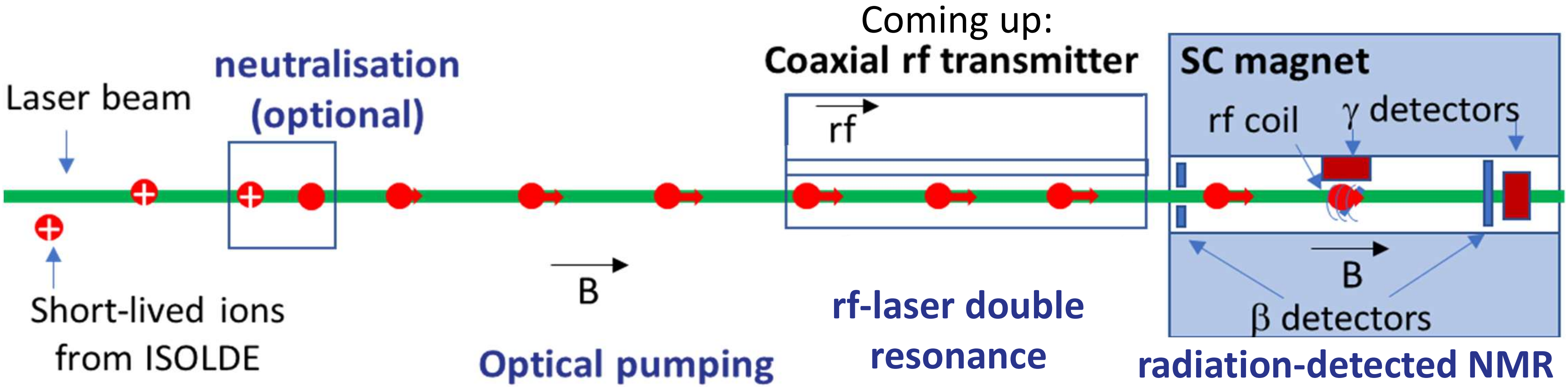
1e19 Na nuclei in sample

Harding, …, Kowalska, Phys. Rev. X., 10, 041061 (2020)

Laser polarisation & b-NMR setup at ISOLDE

β-asymmetry and β-NMR measurements at 4.7 T

Design: S. Warren, N. Azaryan, J. Croese



Coming up:

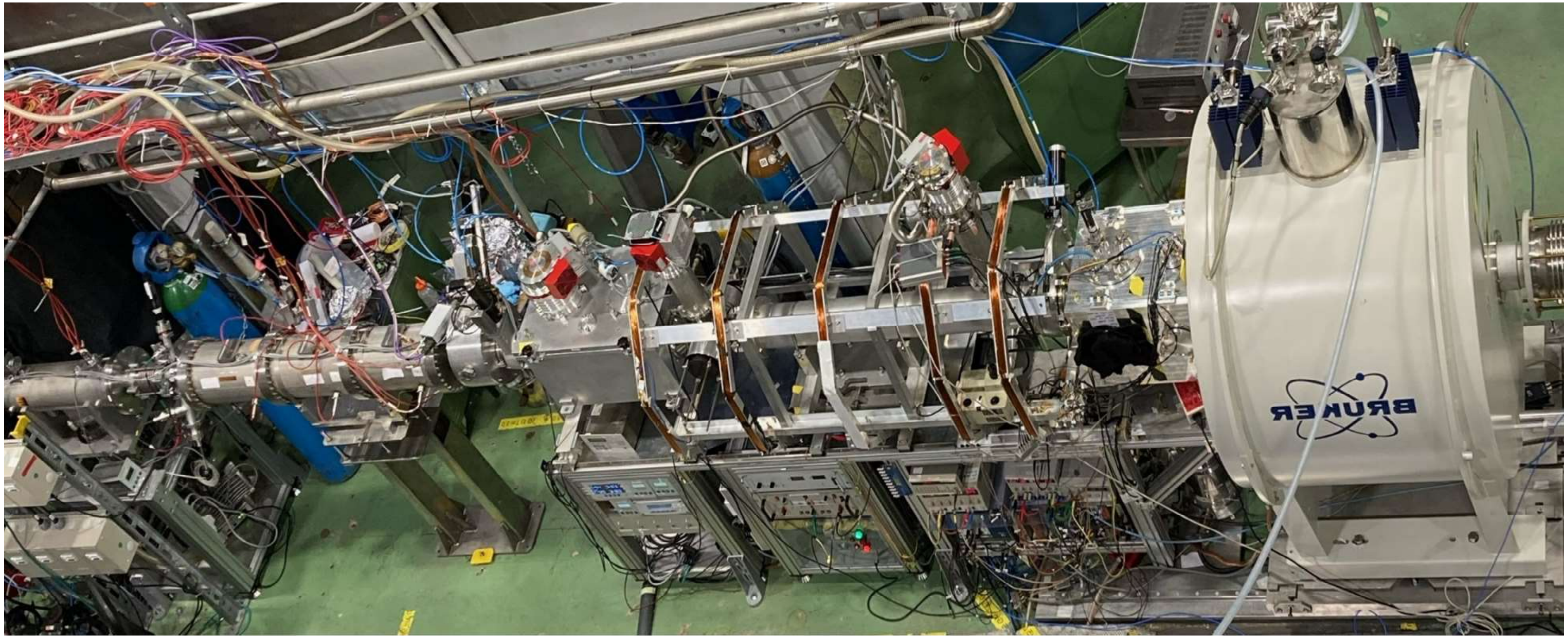
Coaxial rf transmitter

neutralisation (optional)

Optical pumping

rf-laser double resonance

radiation-detected NMR

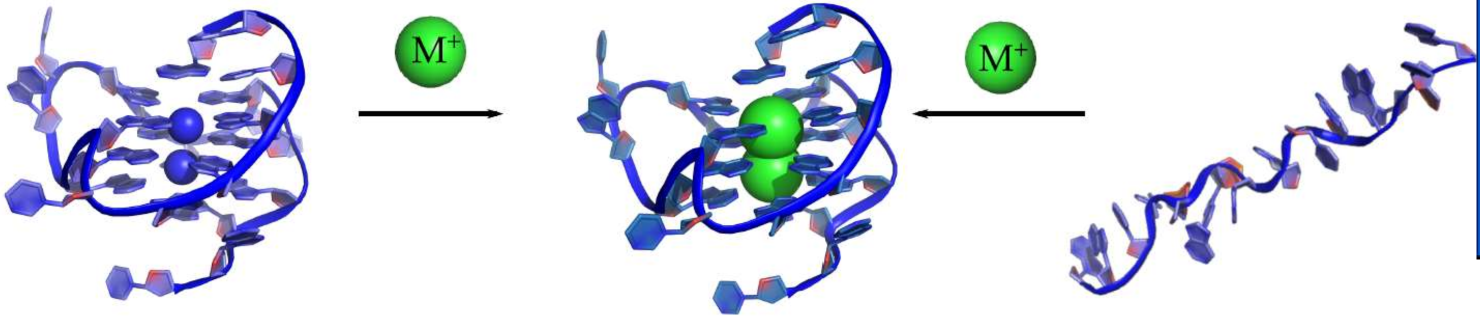


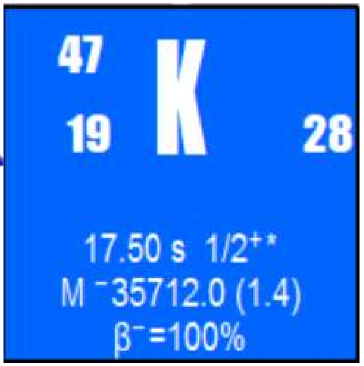
M. Jankowski et al, in preparation

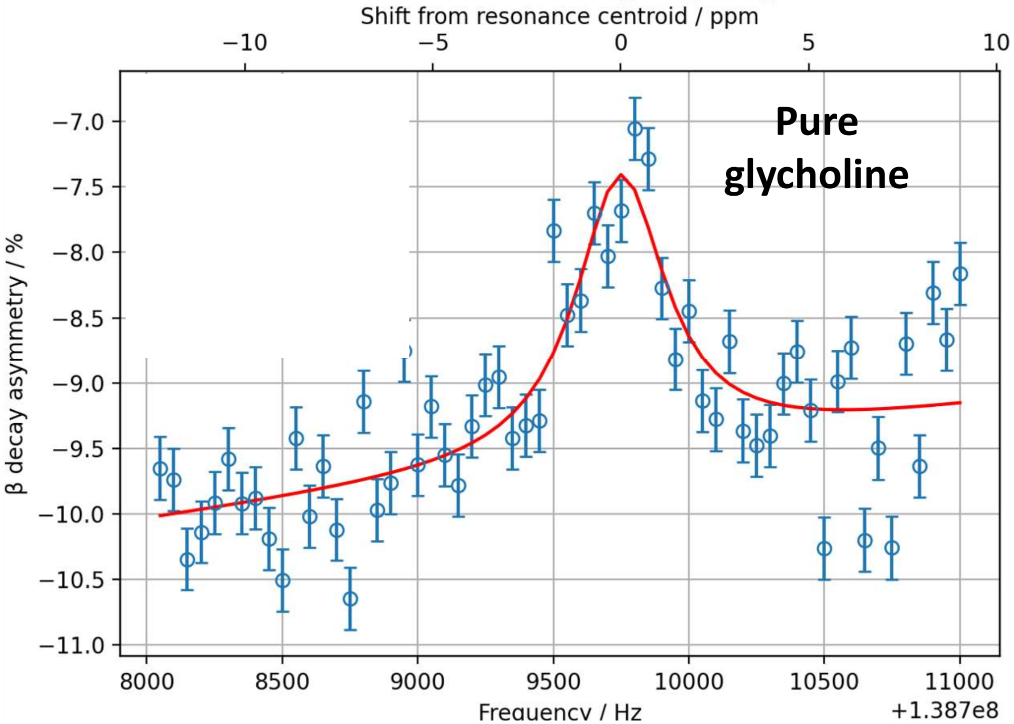
Potassium binding to DNA G-quadruplexes

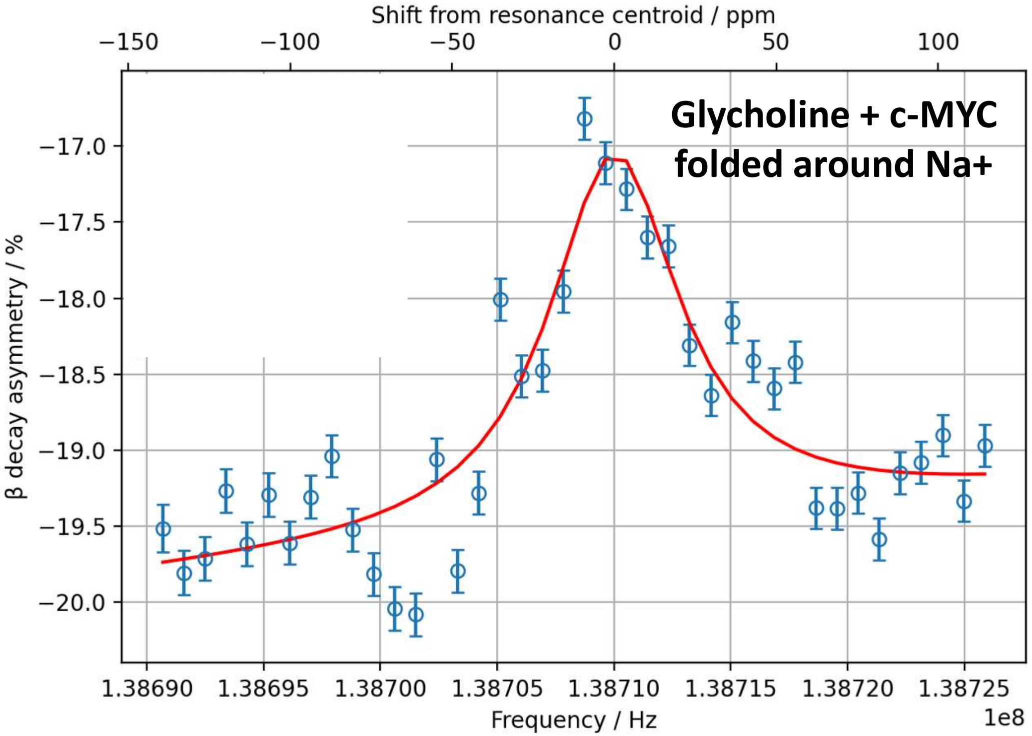
B. Karg

- G-quadruplexes:
  - present e.g in telomers, crucial: binding to alkali metals
- β-NMR experiments in 2022: ^{47}K implanted into glycholine DES + DNA





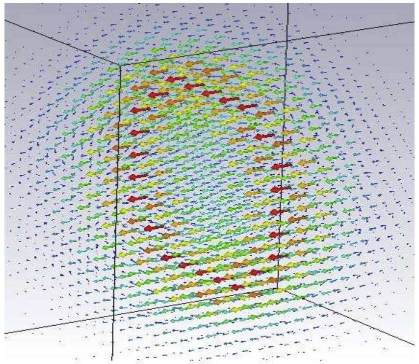




In presence of DNA: K resonance shifted and broadened: implanted K replaces Na inside G-quadruplex?

Distribution of magnetisation in radio-nuclei

Measure Hyperfine Anomaly in unstable nuclei, not neglect it



Magnetic Hyperfine Anomaly = Bohr-Weisskopf effect

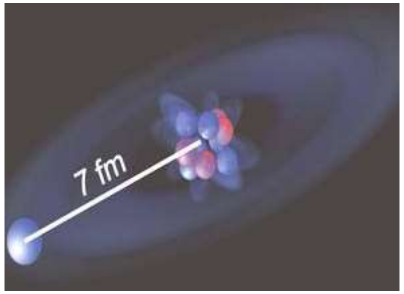
- Effect of **finite nuclear magnetisation** on hyperfine structure
- Probes **distribution of nuclear magnetisation** and, via it, unpaired **neutrons**
- Very small effect, **down to 10^{-6}** (up to 10^{-2} in rare cases)

What do we require to determine it experimentally?

- **magnetic dipole moment** down to **10^{-5}-10^{-6} accuracy**
- **magnetic hyperfine structure constant** down to **10^{-4}-10^{-5} accuracy**

erc PreSOBEN

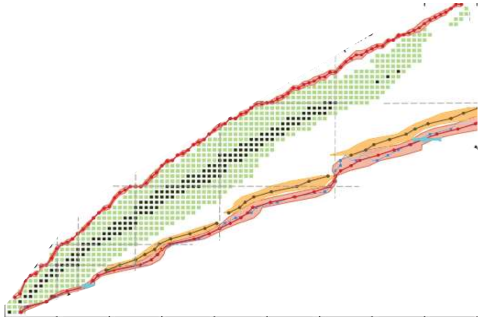
Neutron halos: radius of halo orbit



^{11}Be

Nuclear force at large distances

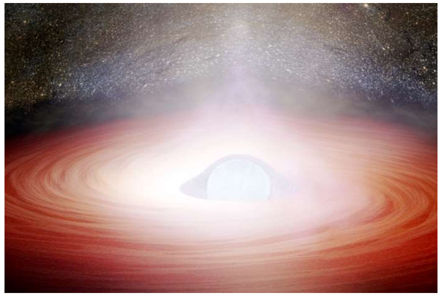
Magnetic observables in nuclear theory (with J. Dobaczewski)



^{49}K, ^{49}Ca

Limits of existence of nuclei Nucleosynthesis path

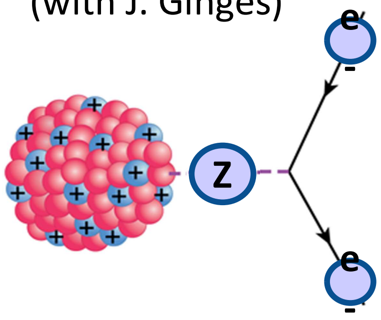
Neutron skins: emergence and size



^{51,53}Ca

Equation of State of neutron-rich matter

Precision atomic calculations in the region of nucleus (with J. Ginges)



^{225}Rn, ^{226}Fr, ^{231}Ra

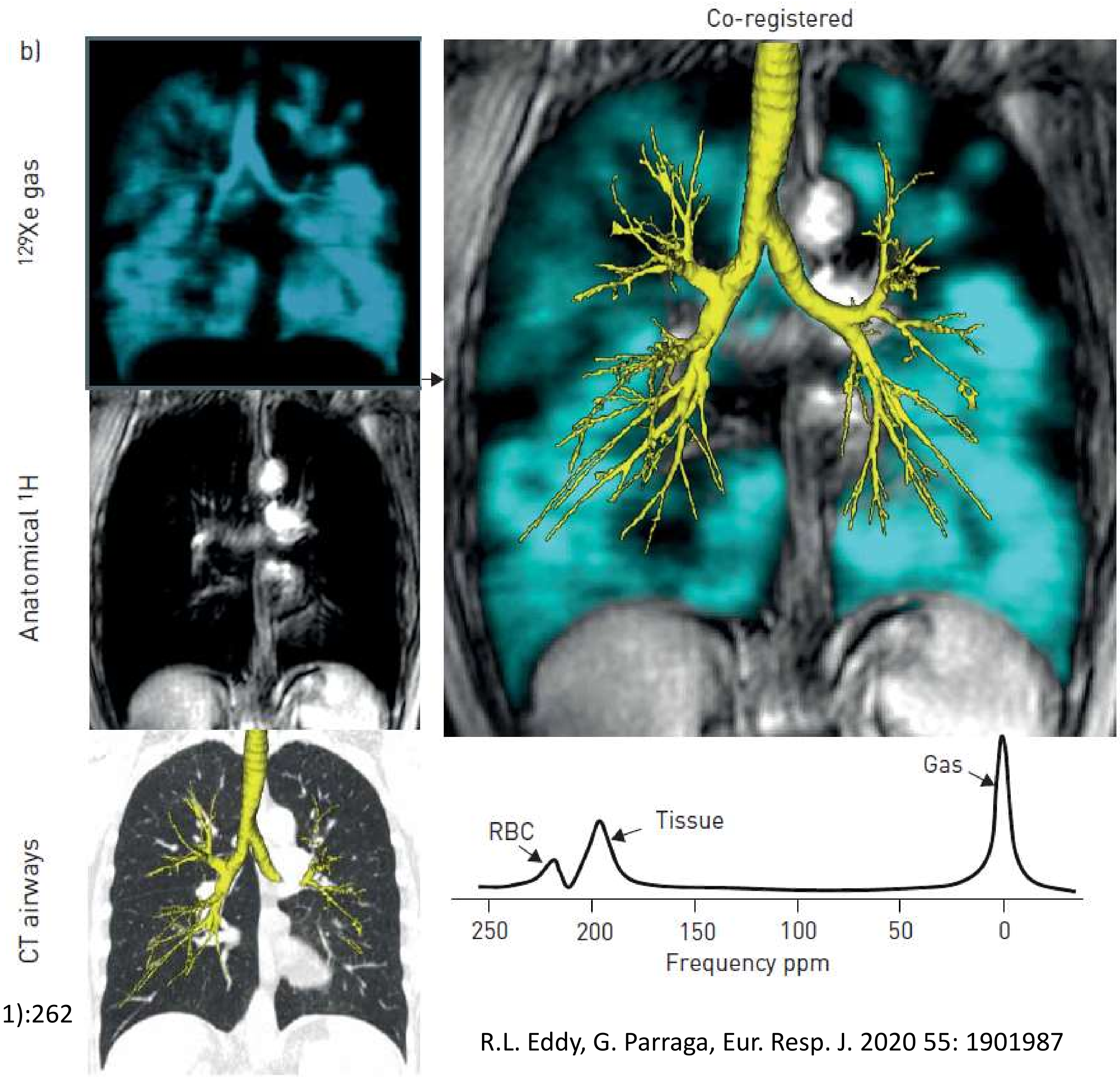
Atomic parity violation

Stable ^{129}Xe Magnetic Resonance Imaging

- Provides information on:
  - pulmonary ventilation
  - tissue microstructure
  - gas exchange

- Features:
  - Sensitive
  - Fast (< 10 s)
  - Precise (3 mm)
  - No proton background
  - Chemical information

- Applications:
  - Respiratory diseases
  - Emerging: functional images of highly perfused organs: kidneys, brain



R.L. Eddy, G. Parraga, Eur. Resp. J. 2020 55: 1901987

J. Chacon-Caldera, Magn Reson Med. 2020;83(1):262

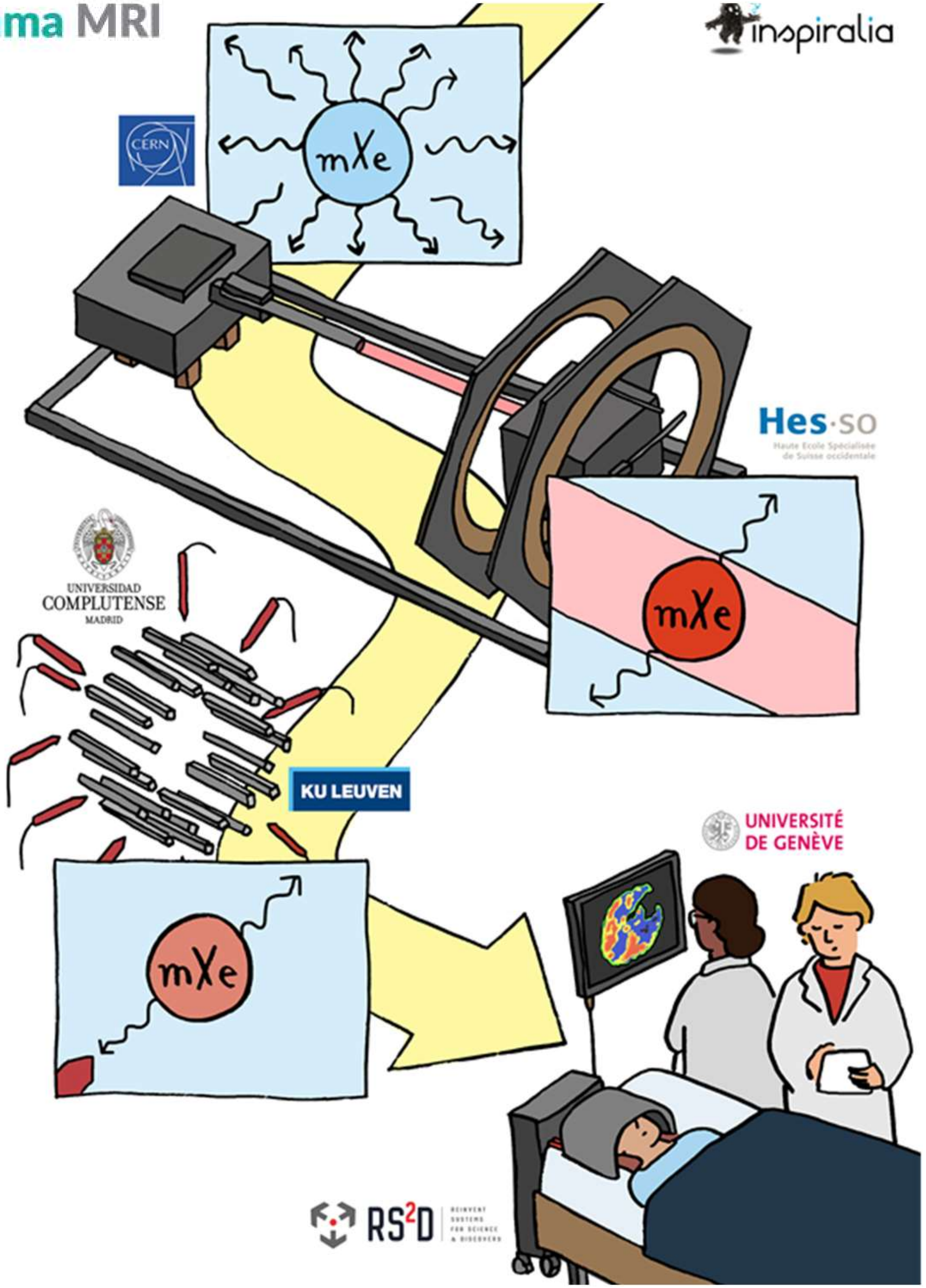
Y. Shepelytskyi, Magn Reson Med. 2022;88:83

γ-MRI with long-lived Xe isomers

EU FET-OPEN

- Simultaneous exploitation of gamma (γ) detection sensitivity + spatial resolution and flexibility of MRI
  - Use of polarised unstable tracers
  - Increase MRI sensitivity and nuclear medicine resolution
  - positioning given by MRI sequences
  - tracer amount given by degree of asymmetry of γ-emission

Work on prototype MRI device ongoing



γ-detected MRI and Xe imaging

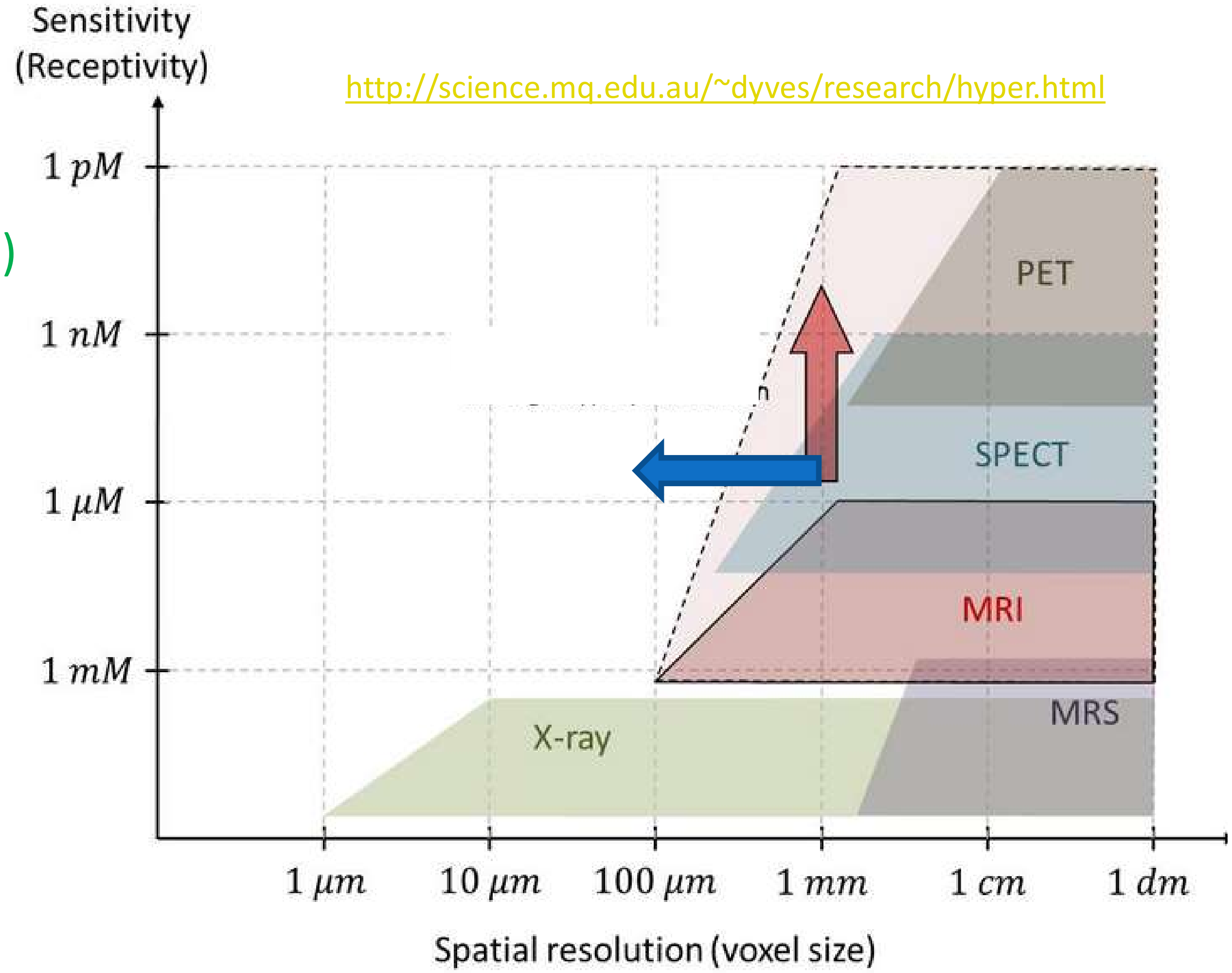
Aim: combine advantages of nuclear medicine and MRI in one modality

- Record MRI signals from PET/SPECT-type nuclei
- Hyperpolarize spins and observe asymmetry of gamma decay
- Result - high efficiency (γ detection) and high resolution (MRI)

- Gamma-MRI Equipment:
  - I>1/2 gamma-emitting nuclei
  - Spin-polarizer
  - MRI magnet
  - **Gamma detectors inside B field**

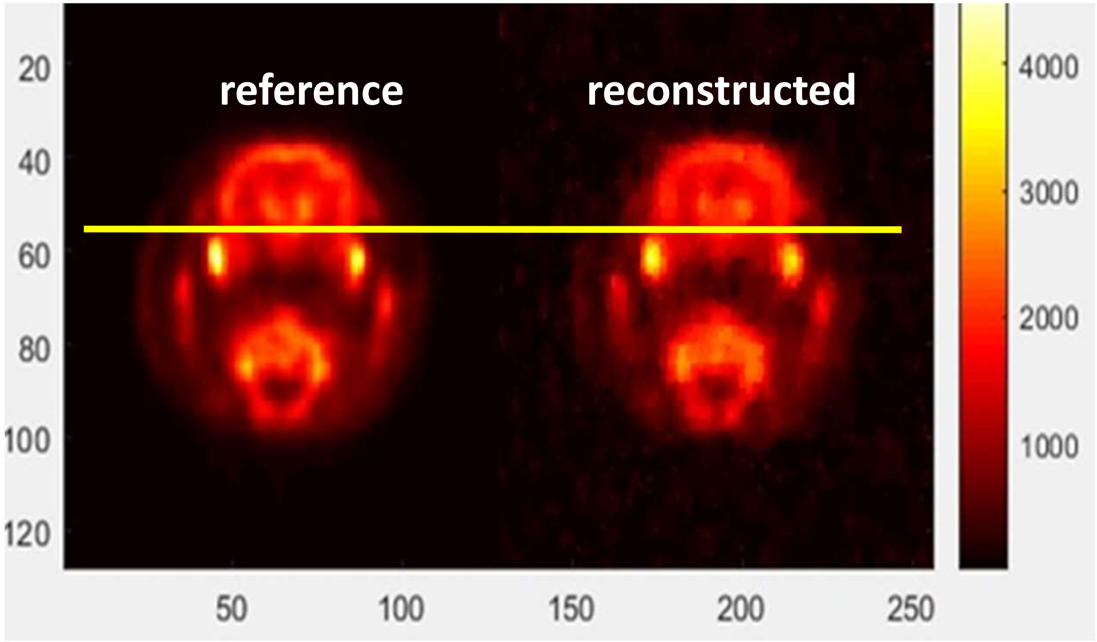
- **Shown to work in 2D by:**

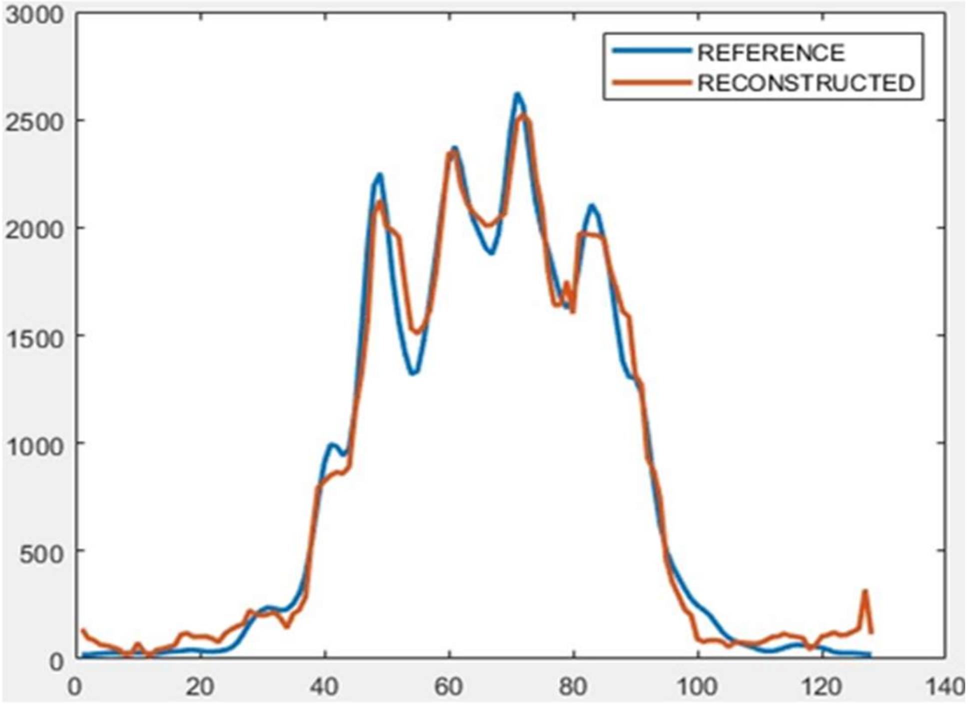
Y. Zheng, G.W. Miller, W.A. Tobias, G.D. Cates, Nature 537, 652 (2016)



Figures of merit

Technique	Activity	Sensitivity	Resolution
MRI	0	mM to µM	< 1 mm
HP ^{129}Xe MRI	0	100s of nM	< 1 mm
PET	~400 MBq	pM	1-3 mm
SPECT	500~1000 MBq	pM	1 mm
γMRI	1-10 MBq (1 mm resolution)	pM	< 1 mm (for tens of MBq)





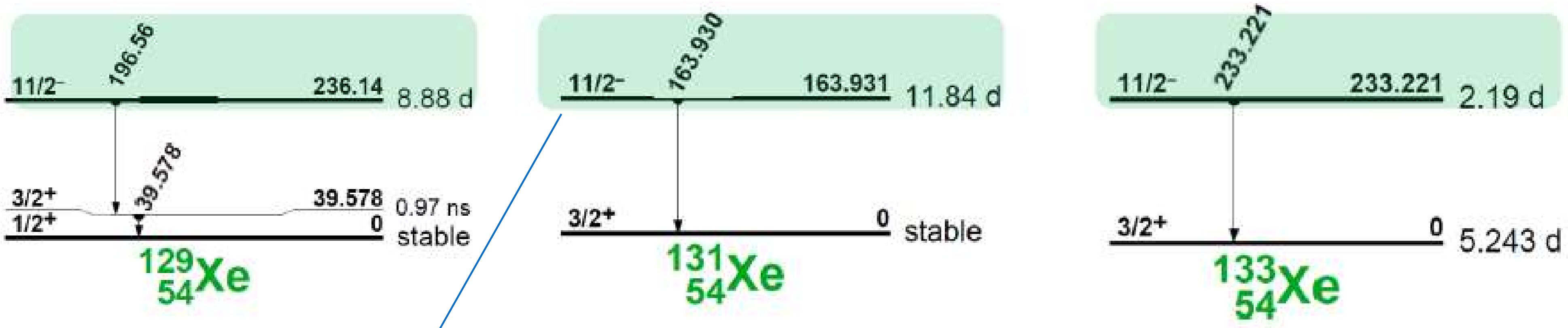
Expected signal in prototype:

- rat brain infused with 10 MBq of mXe, 12 s recording time
- reconstructed with compressed sensing strategies in 0.5 mm pixels

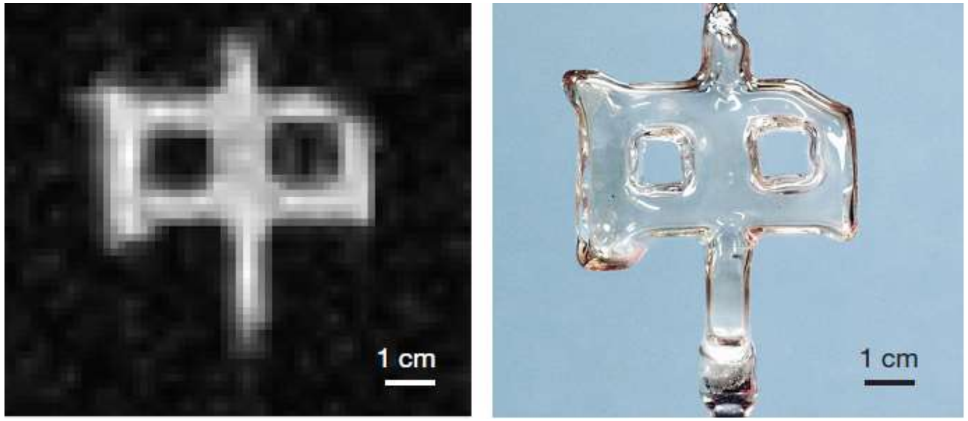
γ-MRI and lung & brain imaging

Imaging using long-lived ^{129m,131m,133m}Xe long-lived nuclear states (isomers):

- Xe: biologically neutral, yet binding to biomolecules and passing blood-brain barrier
- Stable ^{129}Xe used for MRI lung (and brain) imaging
- Unstable ^{133}Xe used for SPECT brain imaging



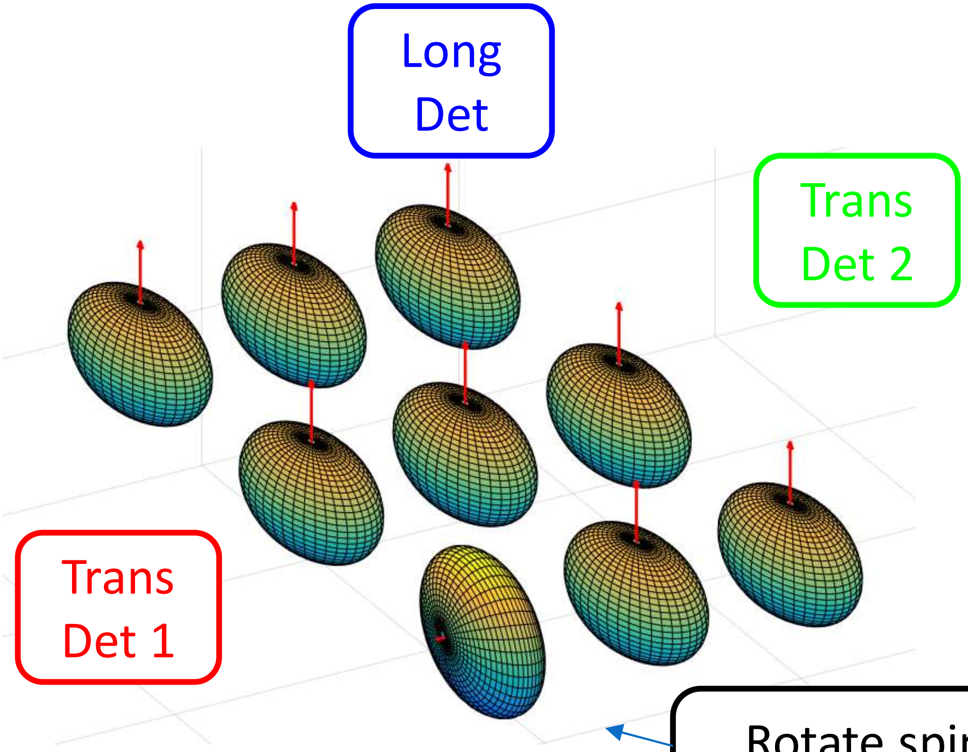
Gain: higher MRI sensitivity or higher nuclear-medicine resolution

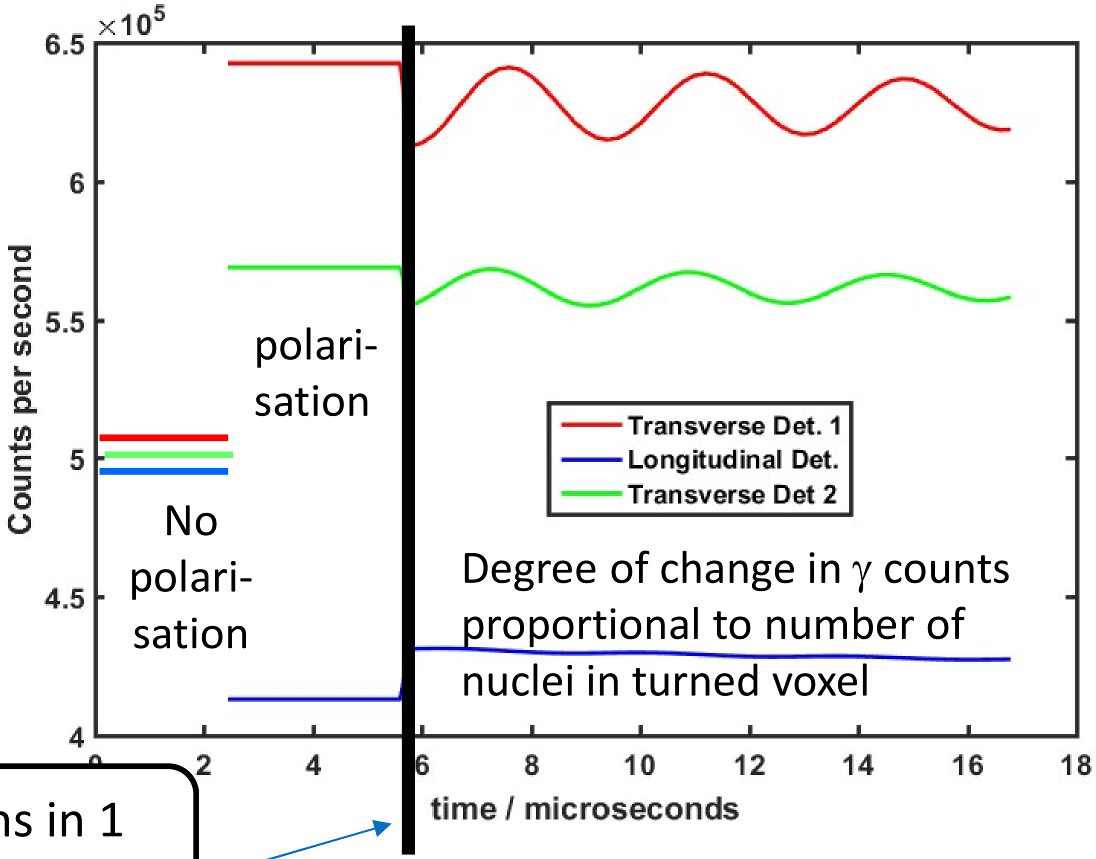


Y. Zheng, G.W. Miller, W.A. Tobias, G.D. Cates, Nature 537, 652 (2016)

Gamma MRI – spatial resolution

- Pixel size
  - defined by slope of B-field gradients and spectral width of rf pulse
  - more nuclei -> smaller pixels possible up to B gradient and rf limit
- 1 pixel in resonance: change in gamma counts visible in each detector





Degree of change in γ counts proportional to number of nuclei in turned voxel

Rotate spins in 1 pixel by 90°

Simulations: R. Engel

mXe production

- Irradiation of stable Xe with thermal neutrons at reactor core
- Implantation into foils at radioactive ion beam facility
- Decay of commercial ^{131}I samples

NEUTRONS FOR SCIENCE

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Summary

CERN basic science triggers medical applications from our:

- Accelerators
- Detectors
- Radionuclei

- Interest: medical diagnosis and treatment

- Aim – medical devices that are:
  - SMALLER
  - CHEAPER
  - MORE PRECISE
  - MORE SENSITIVE

- Many examples at different stages of maturity