Radio-isotopes/Nuclear Medicine Sessi

Executive Summary

1.- Needs for the community in the com

Radioisotopes are used in diagnostics, isotopes for diagnostics are 99mTc for were 131I and 90Y. Today new isotope therapy. We can expect that the use of applications extend much further than diseases, metabolism disorders, etc. Th range radiation to cure minimum residu are particularly suitable. Today alpha er Xofigo®, used for bone metastases of hc applications are "supply-limited".
While the 99mTc production crisis had bodies, the invisible "supply crisis" of su clinical development of extremely prom 99mTs is basically an industrial issue and future.
More generally, there is high need for lo be directly used in radiopharmacies at hospitals. Their supply should be reliable and organized across different production centers.
The concept of theranostic pairs of isotopes combines both a diagnostic and a therapeutic isotope from the same chemical element. This allows stratification (personalization) of the patients before treatment, monitoring of the response during treatment and possible recurrence.
Novel radioisotopes are required to fulfil these needs, such as 43/44Sc and 47Sc, 64Cu and 67Cu, 152/155Tb and 149/161Tb. Their selection will depend on the precise medical case, combining different physical half-lives, gamma emission properties, beta or alpha particle emission. This list of innovative isotopes is therefore by far not exhaustive.

Figure 1: First human imaging with 44Sc PET (Bad Berka).

2.- Which are the big challenges ?

First of all the access to a wide portfolio of ra innovative radioisotopes is urgently required. H radioisotopes must be coupled with the optimum markers, biodistribution and toxicity studies. Obv level in animal models and later on a clinical level.

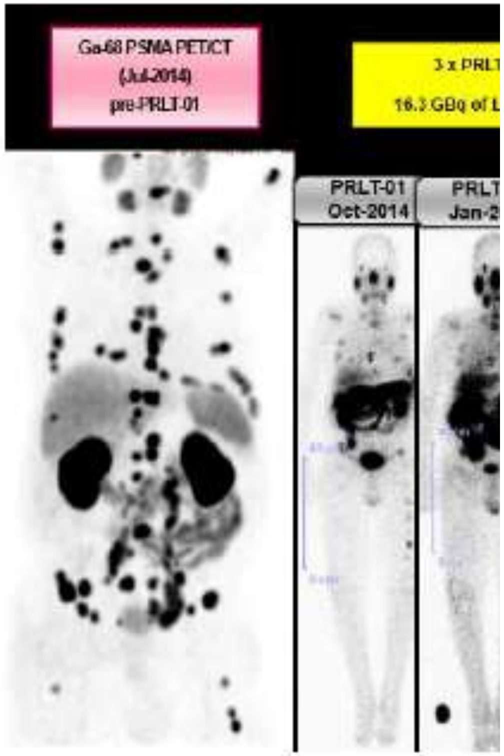


Figure 2: Success of Peptide Receptor Radio-Ligan resistant prostate cancer.

Short-lived isotopes cannot be distributed from a derived isotopes. Thus, there is a need for c Superconducting magnet technology or compact l machines would be placed in many hospitals, ther importance.

For other radioisotopes (43Sc, 117mSn, 211At, etc can provide intense beams of alpha particles (abo

Some positron emitters show moreover intense er nuisance as it enhances the dose to patients ar imaging equipment, so-called 3 photon-cameras or gamma-PET cameras, this property could be turned to an advantage. If a simple demonstrator of such a device could demonstrate feasibility of this method it would open new perspectives for a whole set of clinically interesting radioisotopes (52Mn, 86Y, 94Tc, 124I, etc.).

More generally, higher sensitivity of SPECT and PET cameras would allow to reduce the activity of the injected isotopes, and thus unnecessary dose exposition of the patients during the diagnostic phase. At the same time it reduces proportionally the challenge of isotope supply.

High specific activity and high radionuclidic purity are essential for most applications in nuclear medicine. In certain cases this is achieved by irradiation of targets consisting of highly enriched stable isotopes, then followed by radiochemical separation. However, this technique is not generally applicable. On the other hand spallation production with >100 MeV protons gives access to a wide range of radionuclides but has to be combined with mass separation to achieve radionuclidic purity.

For successful translation to clinical application the perspective of routine production of such innovative radionuclides must be shown.

3.- Who can do this and who are the natural partners?

Accelerators :
Linear accelerators: CERN, IAP Frankfurt, ADAMS, CEA Saclay, TERA...

Rare isotope enrichment :
Mainz, CERN,...

Production of innovative isotopes :
For all cases this challenge is interdisciplinary and has to be solved in a collaborative manner. The partners will naturally vary depending on the element in question.

Isotope mass separation : MEDICIS, KU Leuven..

Supplementary production: ILL (reactor), Bern (18 MeV cyclotron),...

Radiochemistry : PSI, Bern, Arronax/Subatech, CHUV, HUG, SINP (India),...

Centers performing clinical research: CHUV, HUG, Bad Berka...

4.- What do you want from CERN ?

CERN is constructing a dedicated facility for innovative isotope production: MEDICIS. It should provide access of isotopes for both preclinical and clinical pilot trials. We want a timely completion of CERN-MEDICIS and the rapid supply of radiolanthanides and alpha emitters from this facility. The increase of proton driver intensity would allow providing clinical batches suitable for clinical pilot trials of isotopes that are not yet available elsewhere. It should also contribute in the further development of the related production technologies.
CERN should also federate interdisciplinary collaboration and community actions in this field.

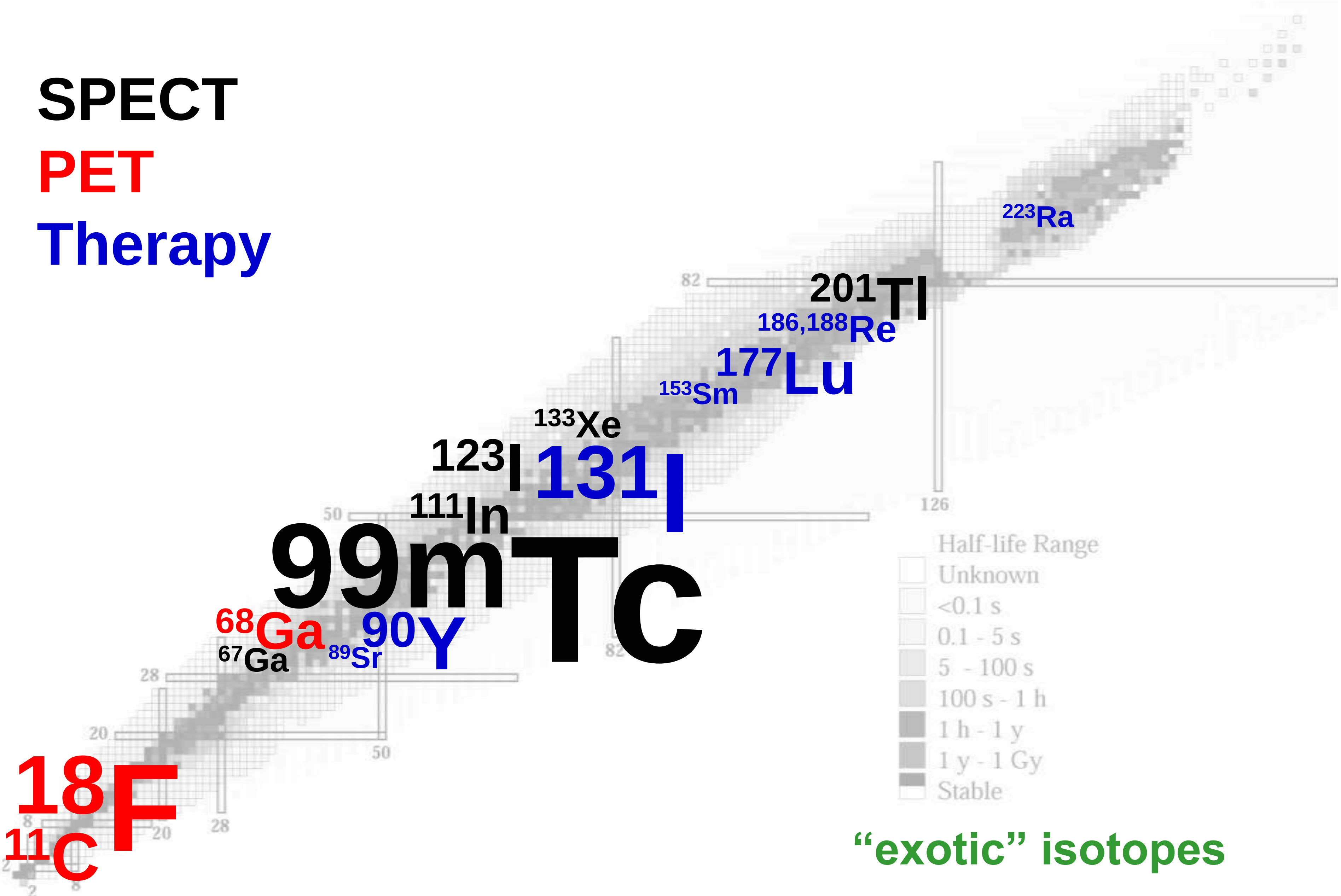
In the following, we propose a small number of focused, immediate actions requested to CERN.

- Capitalization on ISOLDE and rapid construction of CERN-MEDICIS to improve the offer of medical innovative radioisotopes.
  Shifts allocated by INTC, the scientific committee of Isolde for biomedical research in 2014 and Feb 2016
- and rapid construction of CERN-MEDICIS to improve the offer of medical innovative radioisotopes :
  management review on March, tentative completion end of this year for start up 1st protons in 2017.
- Approach ESS to promote technology transfers for large scale production of the interesting isotopes identified at CERN. :
  done, pending on ESS side
- Contacts and collaborative projects are already ongoing with the ISOL@MYRRHA facility.:
  isotopes a MEDICIS is high in ISOL@Myrrha, frequent collaboration on various topics ongoing
- \- Create and join Marie-Curie ITN programs for the next H2020 call on 9^{th} April 2014. : **MEDICIS-PROMED**
- \- Approach the European Commission for the creation of an ERANET on medical imaging and radiometabolic therapy.
  MEDICIS is in the INFRA call; structuring into a network of isotope productions,
  through MEDICIS PROMED, MEDICIS, French MI2B GDR

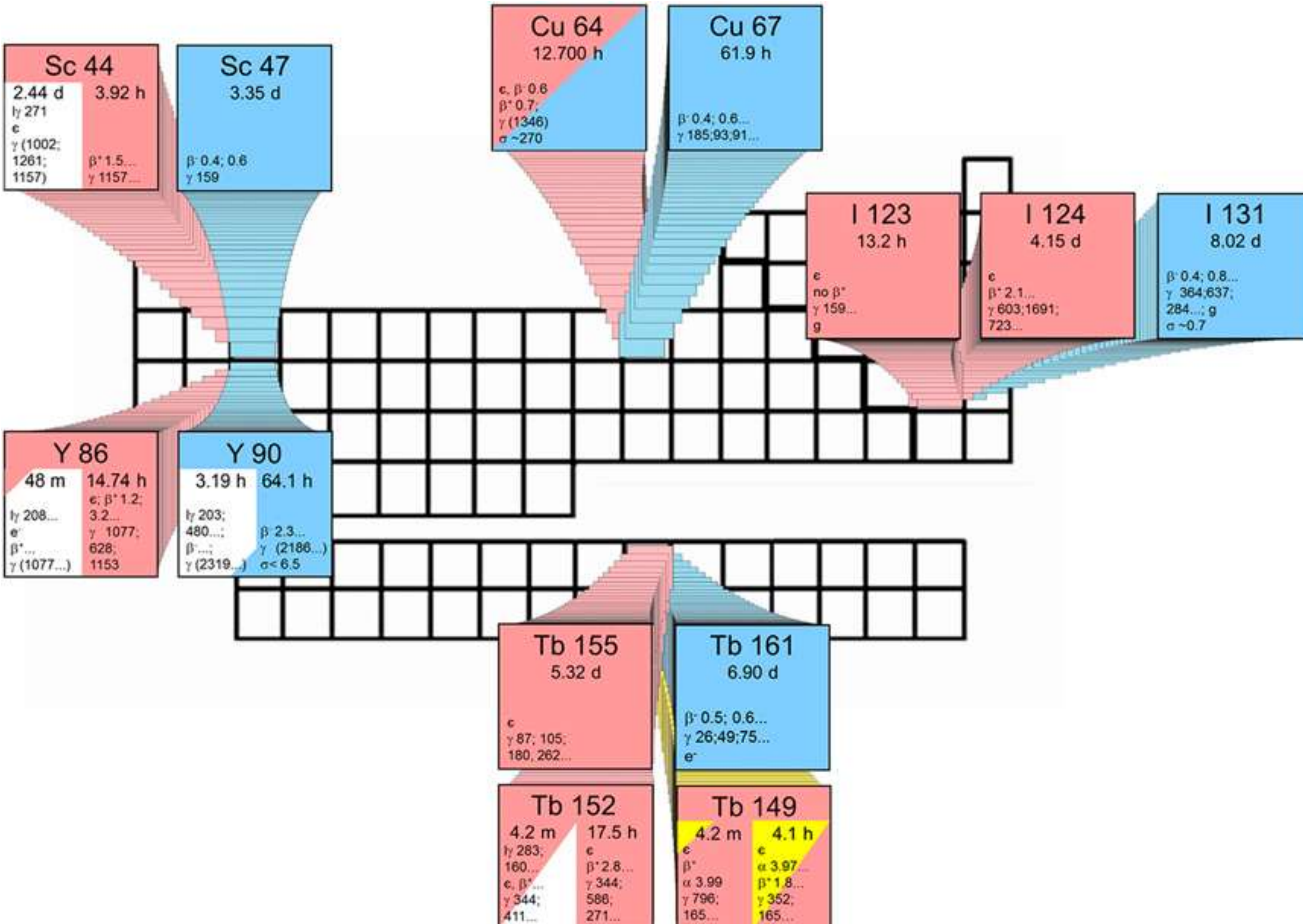
Some other more specific items are listed in the following part and might become increasingly relevant in a near future:

- \- Ramping up the supply of the ^{149}Tb alpha emitter at ISOLDE/MEDICIS :
  large improvements of delivery from Isolde through laser/target/shipping improvemetns witnessed in 2014.
- \- Develop the spallation production of ^{225}Ac/^{213}Bi alpha emitter/generator at ISOLDE/MEDICIS
  approved Letter of Intent at INTC 2015, JRC are full member of the future MEDICIS collaboration board
- \- Establish links and provide long-term production perspectives in a network of high power facilities such as ESS, MYRRHA, J-PARC, TRIUMF, LANL, SNS, etc : **initiated**
- \- Develop a cheap 7.5MeV/u, A/Q=2, high current Linac :
  compact RFQ of Maurizio Vretenar prototyped, soon to be tested normally
- \- Share molten Bi target technology for ^{211}At production, with e.g. ARRONAX :
  LIEBE high power target ongoing, ARRONAX/GANIL collaboration possible
- \- Develop ^{211}Rn/^{211}At spallation production route : **project of ESR student in MEDICIS PROMED**
- \- Organize or join a network for ^{211}At production : **french GDR MI2B, last meeting at CERN dec 2015, EU project?**
- \- Increase the supply of R&D isotopes such as ^{152}Tb, ^{155}Tb, ^{67}Cu, ^{117m}Sn, etc from ISOLDE/MEDICIS : **done for 152/155Tb**
- \- Develop the offline mass separation of reactor produced radioisotopes at MEDICIS, for e.g., non-carrier added ^{169}Er isotopes :
  ILL - MEDICIS collaboration to be signed
- \- Earmark a share of shifts at ISOLDE for medical isotope production : **???**
- \- Foresee collimators or dumps comprising Sc/Ti/V alloys for the production of 44Ti/Sc generators **???**
- \- Attract and train radiochemists, radiopharmacists and nuclear medical doctors : **MEDICIS-PROMED, PSI to join MEDICIS**
- \- Strengthen complementary technologies, such as 3-photons cameras **???**
- conceptual design of a high current e^- ERL for future γ beams, **???**
- post-accelerated PET isotope beam such as ^{11}C for image guided hadron therapy, **4x MEDICIS PROMED ESR**
- develop the tools for detailed microdosimetry of Auger electron emitters **Fluka started for nuclear medicine cases**

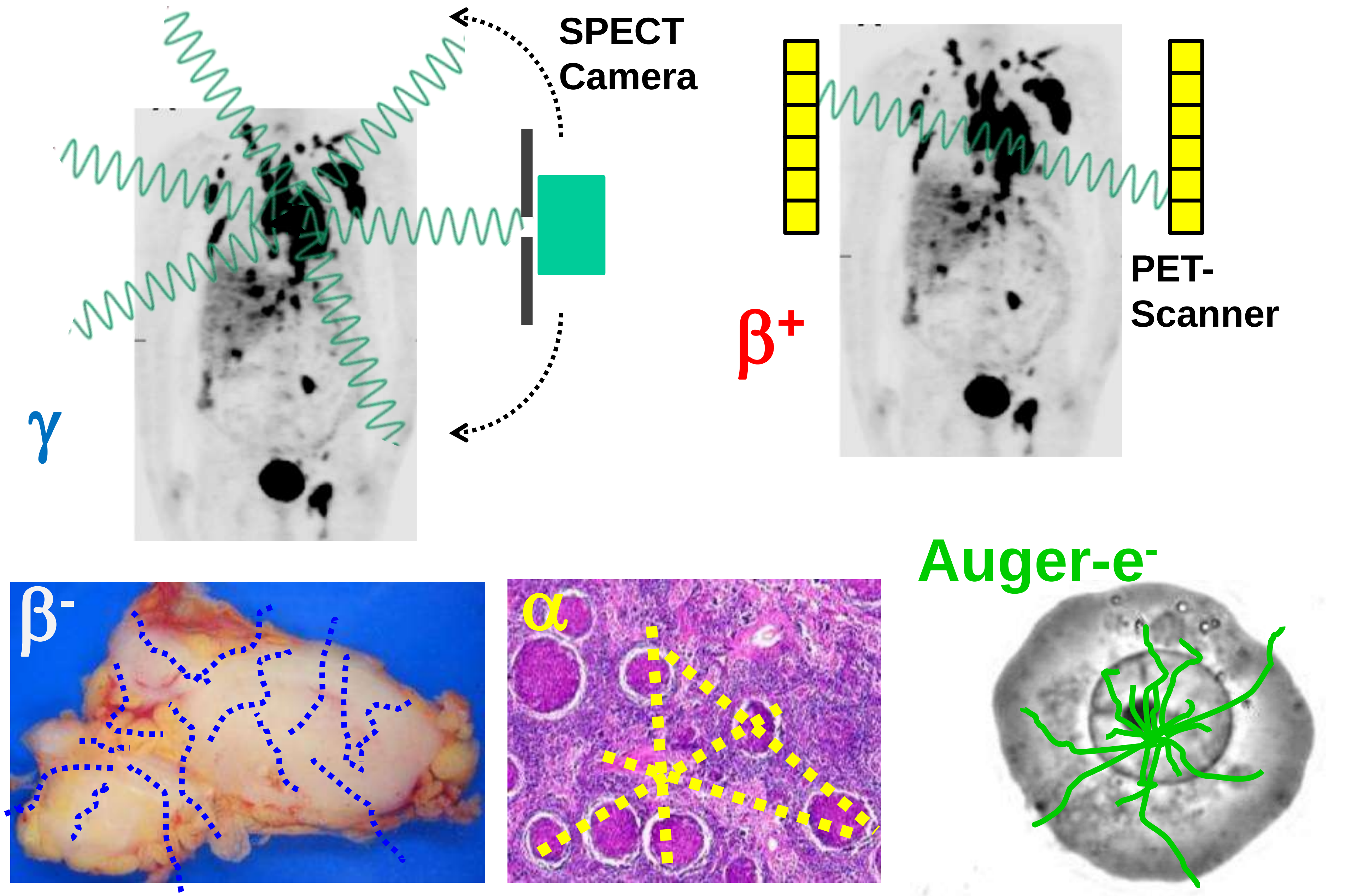
The chart of nuclides – nuclear medicine perspective



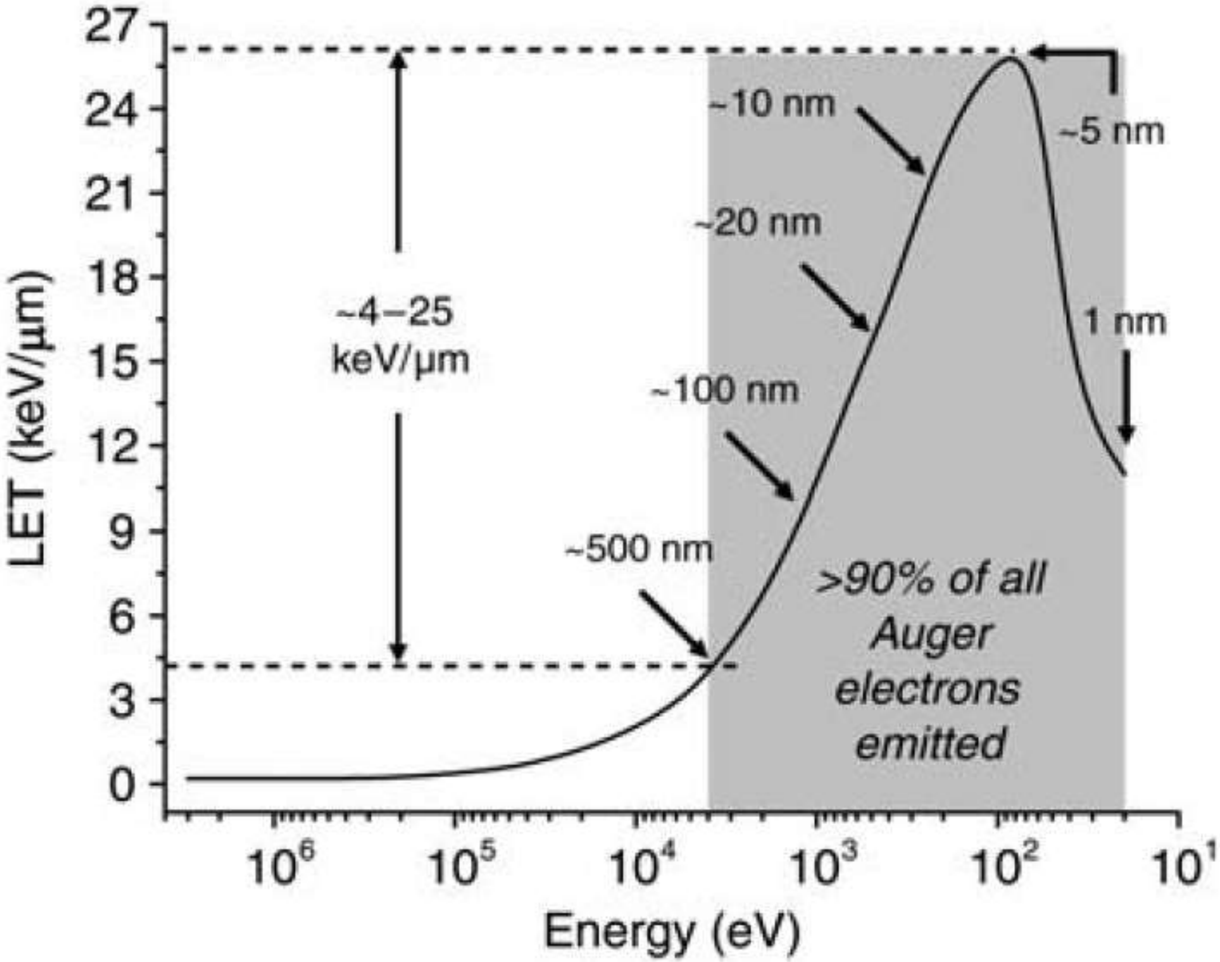
Matched pairs for theranostics

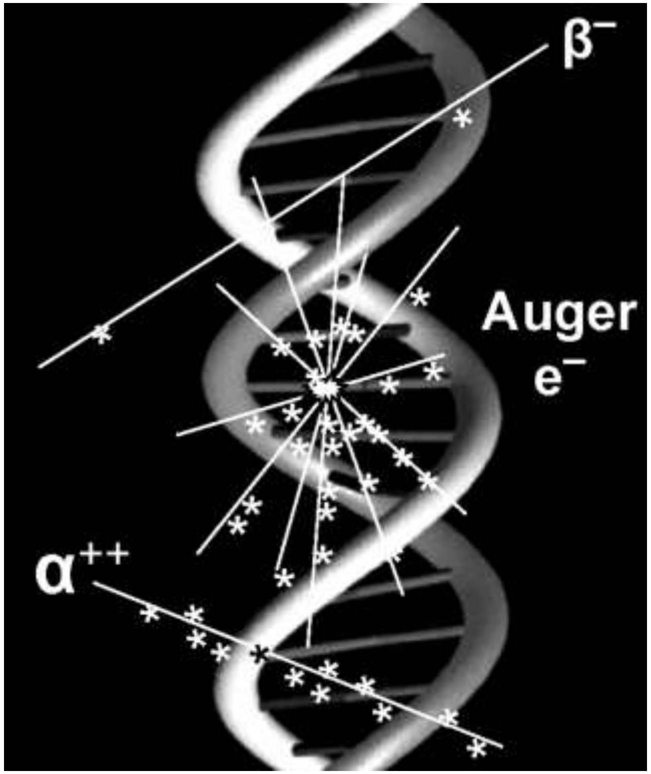


The Nuclear Medicine Alphabet



Radiobiological effectiveness of Auger electrons





A.I. Kassis, Rad. Prot. Dosimetry 2011;143:241.

Radionuclides for RIT and PRRT

Radio-nuclide	Half-life	E mean (keV)	Eγ (B.R.) (keV)	Range
Y-90	64 h	934 β	-	12 mm
I-131	8 days	182 β	364 (82%)	3 mm
Lu-177	7 days	134 β	208 (10%) 113 (6%)	2 mm
Tb-161	7 days	154 β 5, 17, 40 e^-	75 (10%)	2 mm 1-30 μm
Tb-149	4.1 h	3967 α	165,..	25 μm
Ge-71	11 days	8 e^-	-	1.7 μm
Er-165	10.3 h	5.3 e^-	-	0.6 μm

cross-fire

Estab-lished isotopes

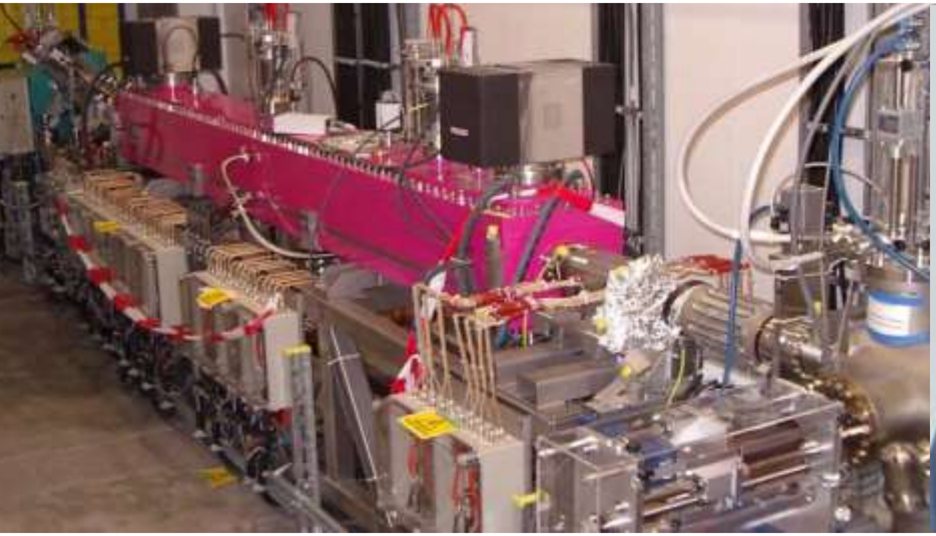
Emerging isotopes

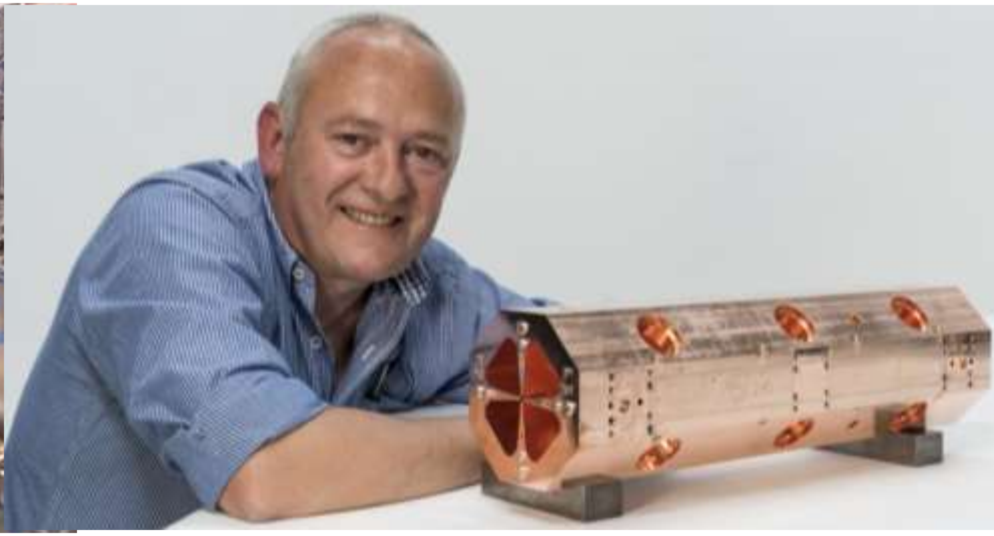
R&D isotopes: supply-limited!

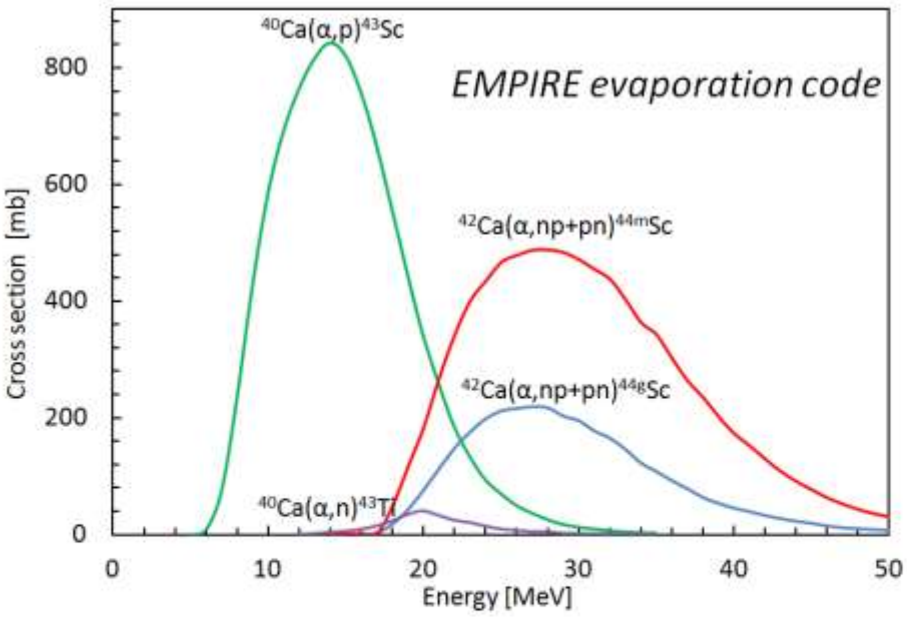
localized

Modern, better targeted bioconjugates require shorter-range radiation ⇒ need for adequate (R&D) radioisotope supply.

7.2-11 MeV/u light ion LINAC A/q=2

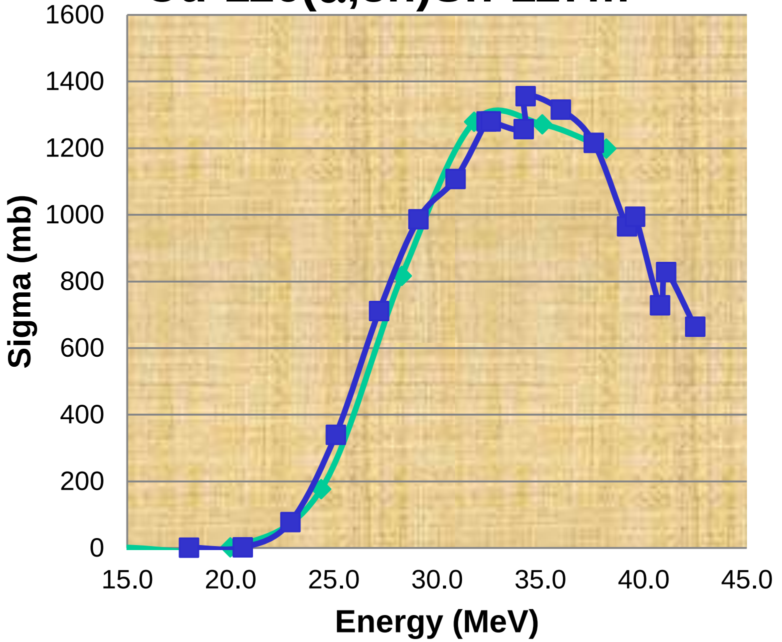






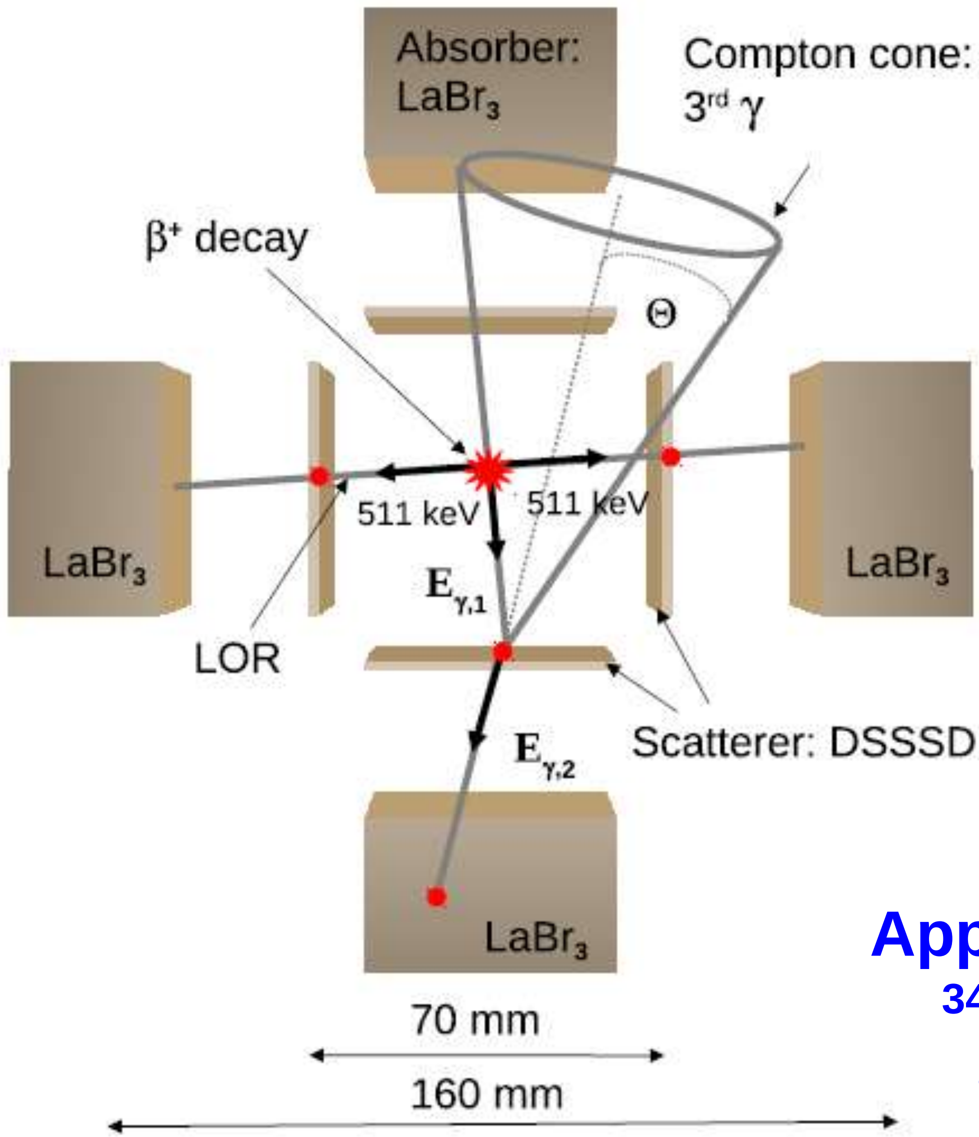
J. Jastrzębski. ICTR-PHE2016

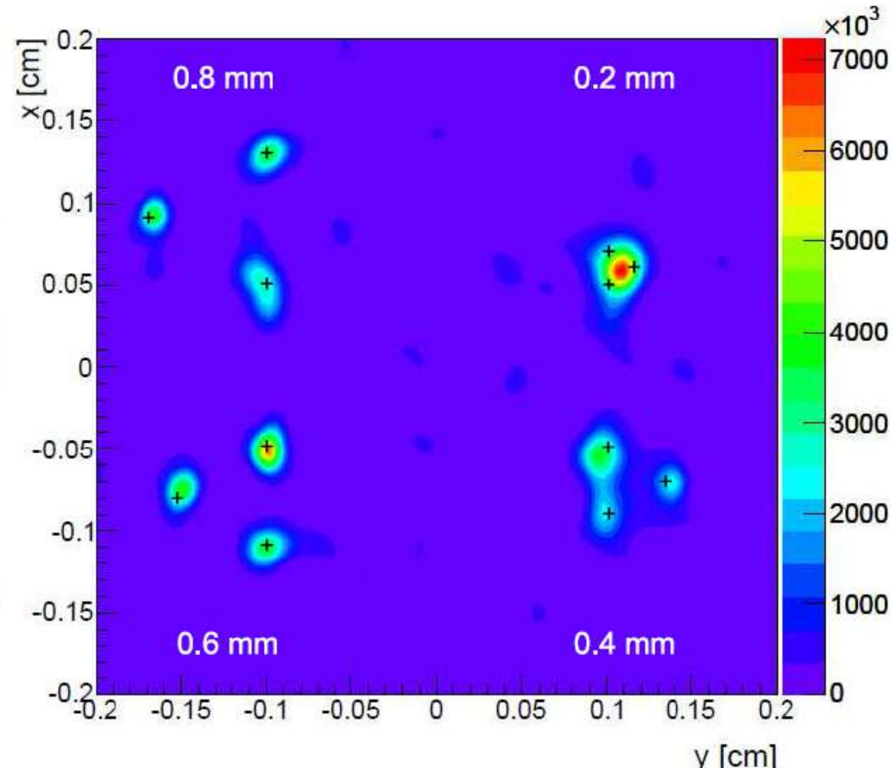
Cd-116(α,3n)Sn-117m



N. Stevenson. ICTR-PHE2016

3-photon-camera: PET-SPECT



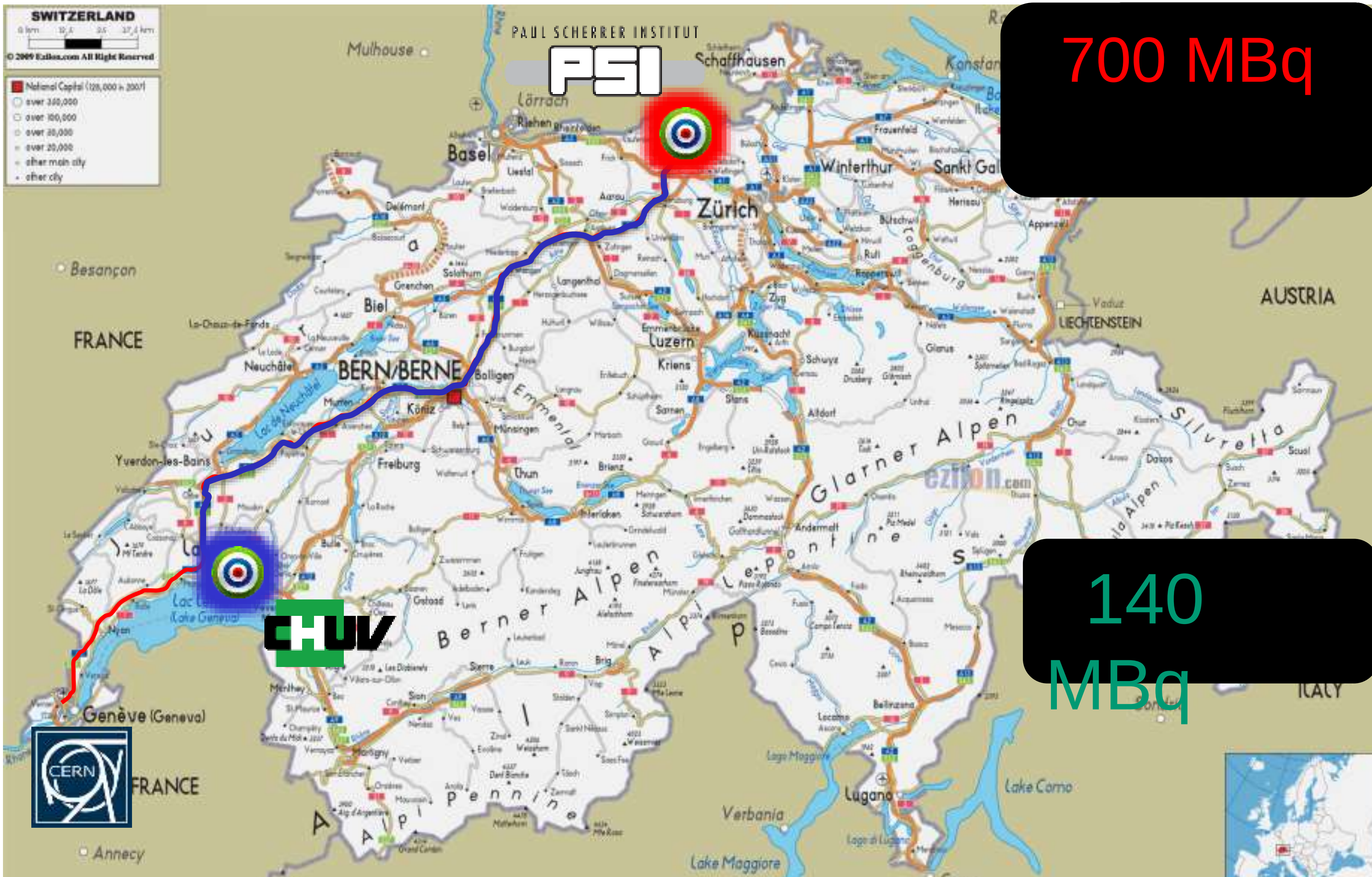


Applications:

^{34m}Cl, ^{44}Sc, ^{44m}Sc, ^{52}Mn, ^{52m}Mn, ^{86}Y, ^{94g}Tc, ^{94m}Tc, ^{124}I, ^{10}C, ^{14}O

C. Lang et al. JINST 2014;9:P01080.

The Travel Challenge : ^{152}Tb

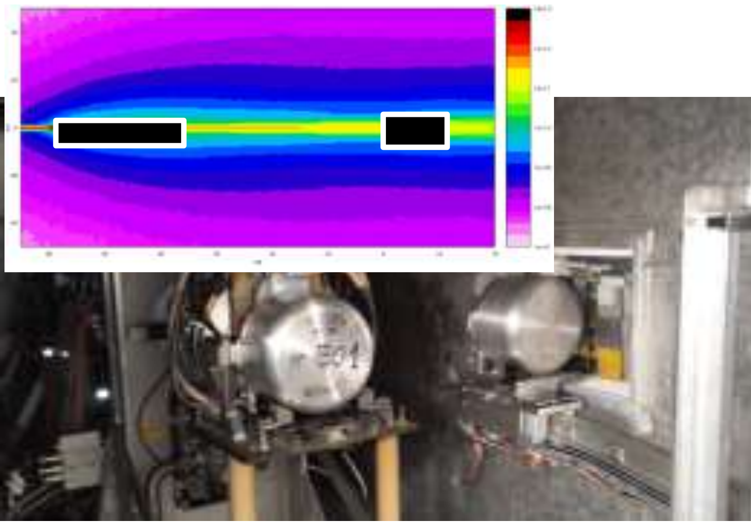


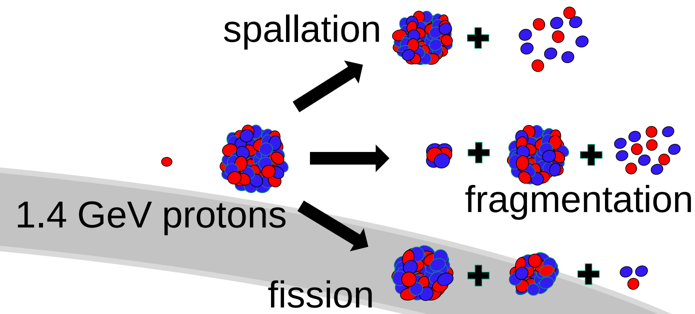
700 MBq

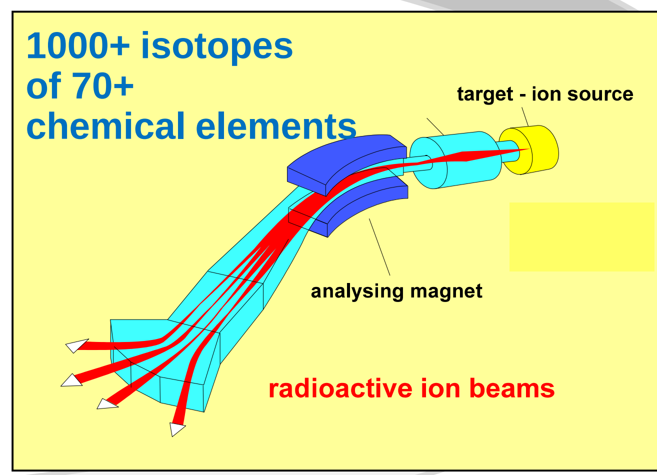
140 MBq

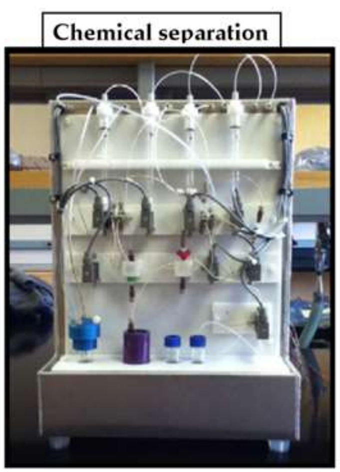
N. van der Meulen et al., PSI, ICTR-PHE2016.

Isotope production in the dump and mass separation in the lab





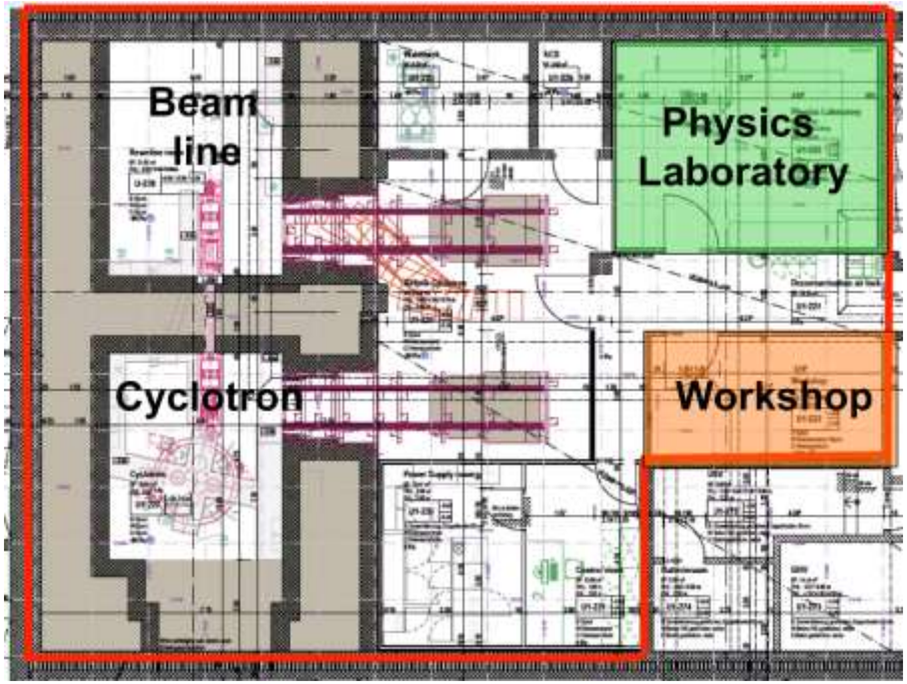




Pure isotope batch

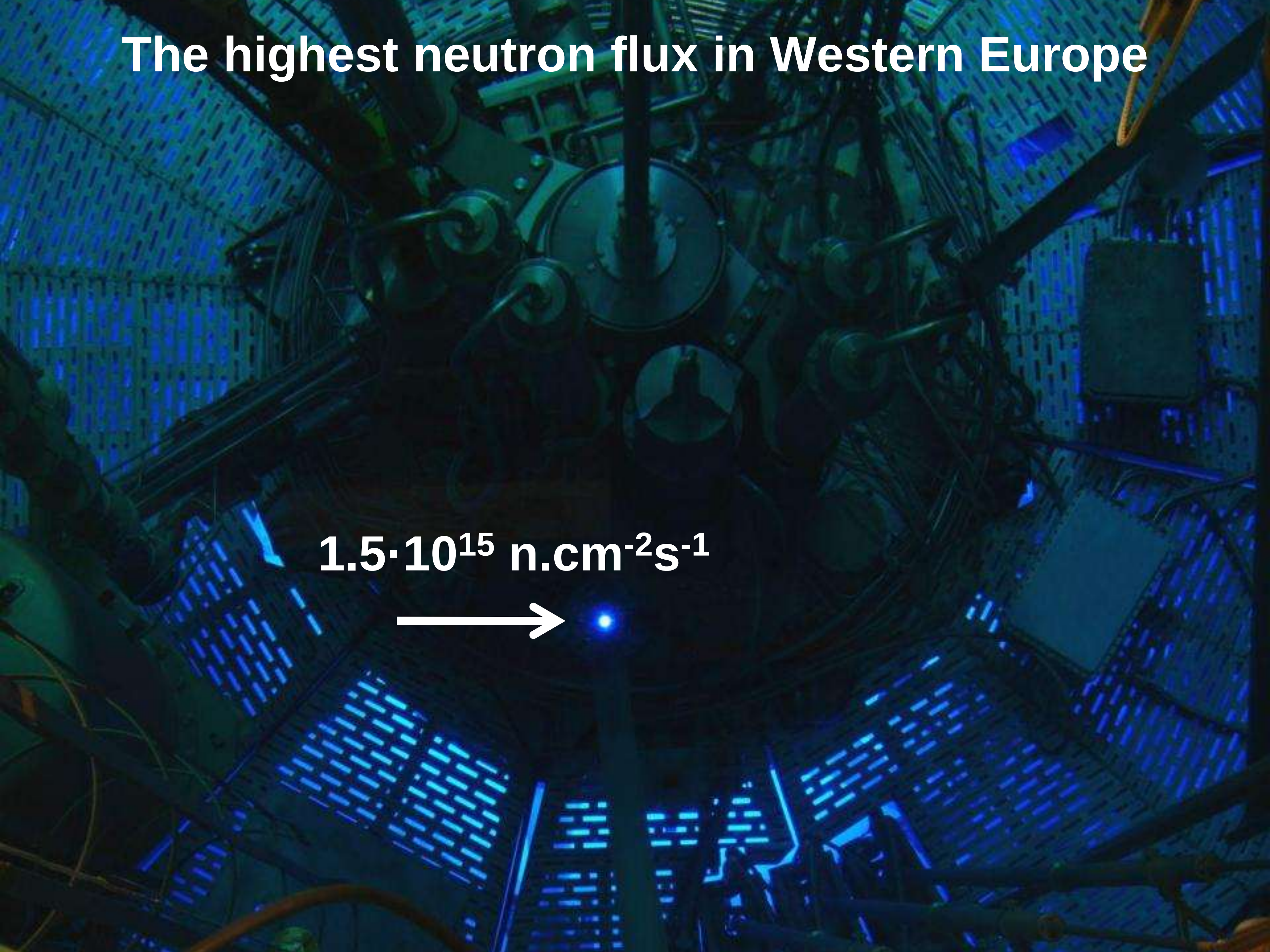
Non-carrier added isotope production (from CERN or external sources, eg reactors)

The Bern cyclotron laboratory

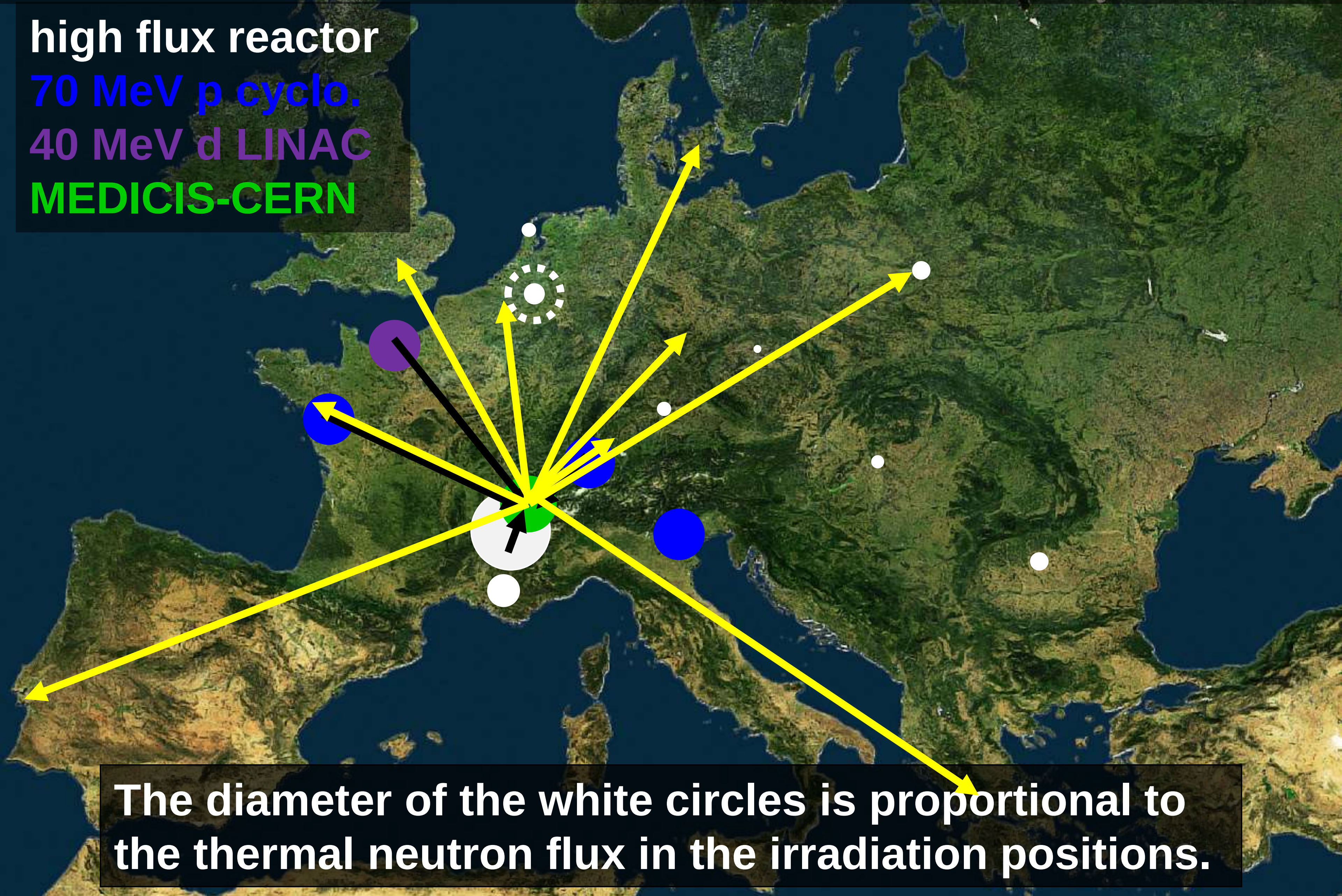


- Location: Bern University Hospital (Inselspital)
- Medical PET cyclotron + GMP radiopharmacy
- Daily production of ^{18}F for FDG
- **Research: External beam line in a separate bunker**

The highest neutron flux in Western Europe



Production of innovative radioisotopes in 2020



The diameter of the white circles is proportional to the thermal neutron flux in the irradiation positions.


Kahramanmaraş
Şanlıurfa
Gaziantep
Adana
Mersin
Alanya
Κύπρος
Cyprus
سوريا
Syria
لبنان
Lebanon
دمشق
Damascus

Some Chemical Properties of Element 43

C. PERRIER AND E. SEGRÈ,
Royal University, Palermo, Italy

(Received June 30, 1937)

1. INTRODUCTION

PROFESSOR E. O. LAWRENCE gave us a piece of molybdenum plate which had been bombarded for some months by a strong deuteron beam in the Berkeley cyclotron. The molybdenum has been also irradiated with secondary neutrons which are always generated by the cyclotron. The molybdenum plate shows a strong activity, chiefly due to very slow electrons. The radioactivity is due to more than one substance of a half-value period of some months and to the radioactive phosphorus isotope P^{32}.[1] The substance was sent from Berkeley on December 17, 1936 and we started our chemical investigation on January 30, 1937; all short period substances have decayed in these 6 weeks and we could

[1] We will give more details on the radioactive side of this investigation in a later paper to appear in the *Physical Review*.

Nuclear Isomerism in Element 43

We wish to report briefly an interesting case of isomerism which has appeared during an investigation of the short-lived radioactive isotopes of element 43. The irradiation of molybdenum with deuterons or slow neutrons produces a radioactive molybdenum isotope with a half-life of 65 hours which emits electrons with an upper energy limit of approximately 1 Mev. (This molybdenum activity has also been reported recently by Sagane, Kojima, Miyamoto and Ikawa.)[1] This molybdenum decays into a second activity which has a half-life of 6 hours and which emits only a line spectrum of electrons. Since the molybdenum emits electrons, the daughter activity must be ascribed to element 43;

E. SEGRÈ
G. T. SEABORG

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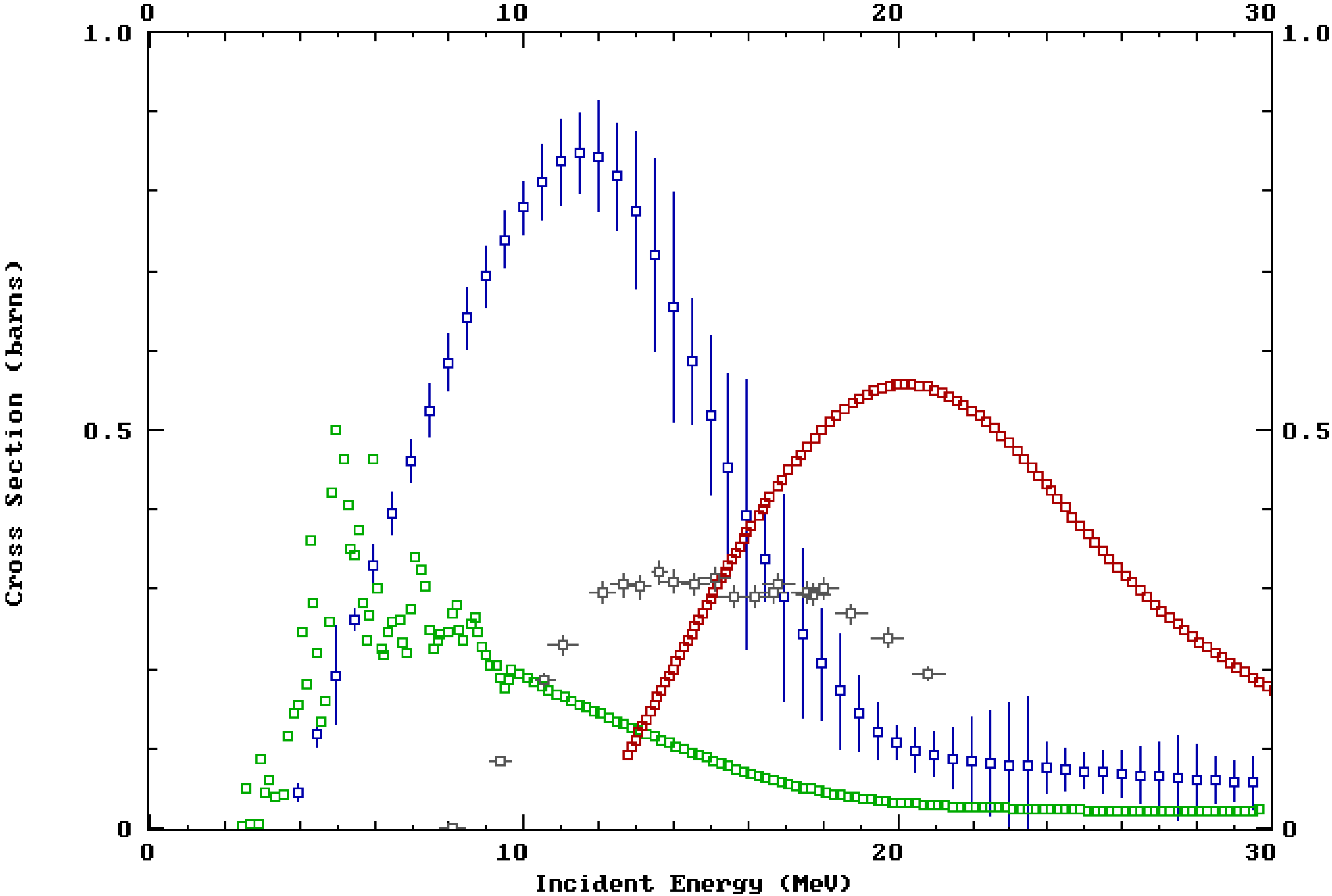
Department of Physics (E.S.),
Department of Chemistry (G.T.S.),
University of California,
Berkeley, California,
October 14, 1938.

The “ease” of production



The “ease” of production