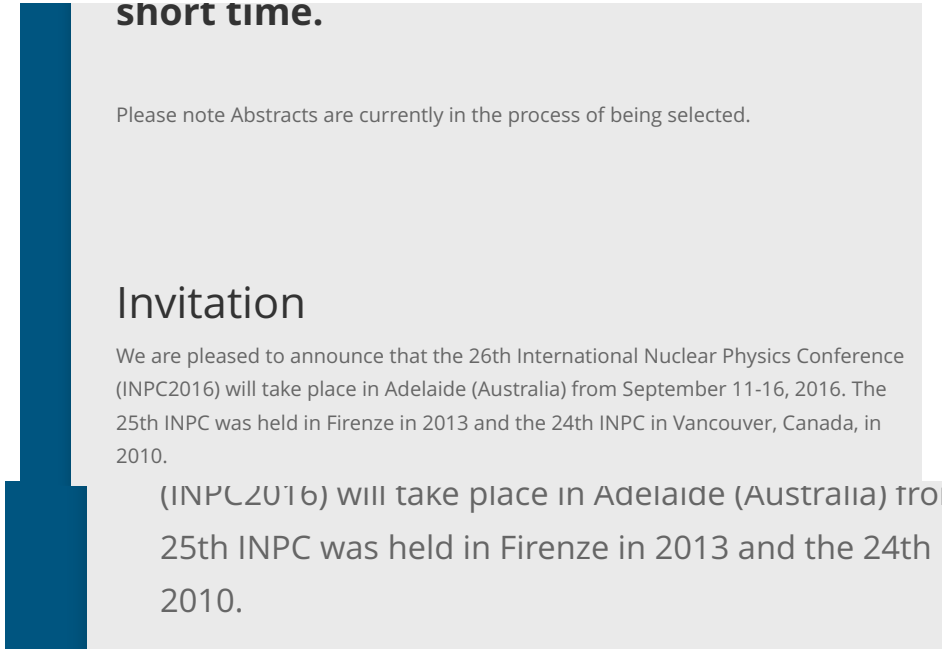
CERN-MEDICIS :
Non-conventional radioisotopes for medical applications

A.P. Bernardes[1], R. Catherall[1], K. Kershaw[1], S. Marzari[1], T. Stora[1], J. Prior[2], L. Buehler[3], O. Ratib[3], on behalf of the CERN-MEDICIS Collaboration

[1] CERN, Geneva, Switzerland
[2] CHUV, Lausanne, Switzerland
[3] HUG, Geneva, Switerland


short time.

Please note Abstracts are currently in the process of being selected.

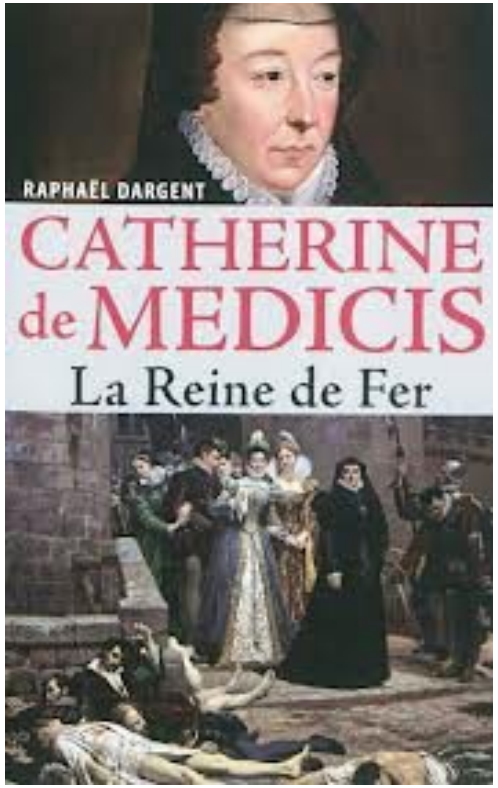
Invitation

We are pleased to announce that the 26th International Nuclear Physics Conference (INPC2016) will take place in Adelaide (Australia) from September 11-16, 2016. The 25th INPC was held in Firenze in 2013 and the 24th INPC in Vancouver, Canada, in 2010.

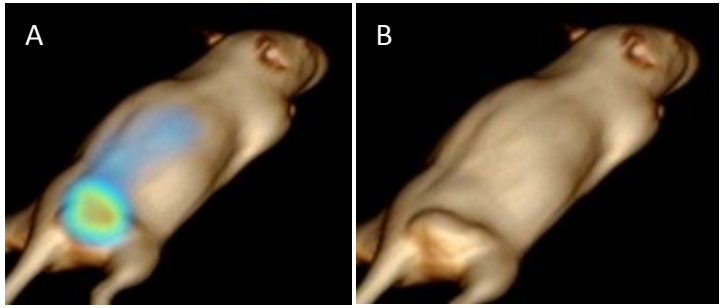
(INPC2016) will take place in Adelaide (Australia) fro
25th INPC was held in Firenze in 2013 and the 24th
2010.

What is MEDICIS

No !



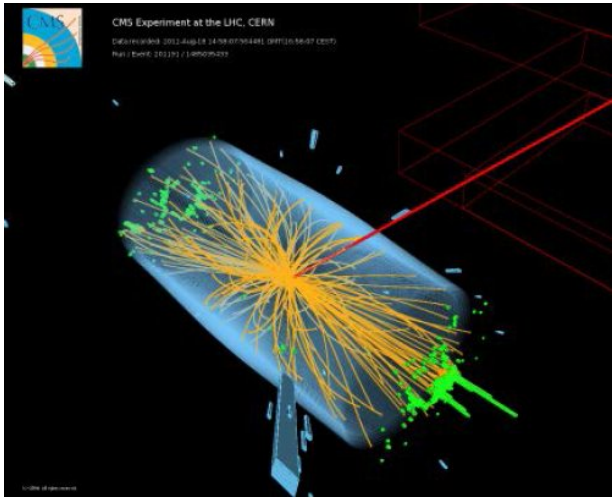
Yes :

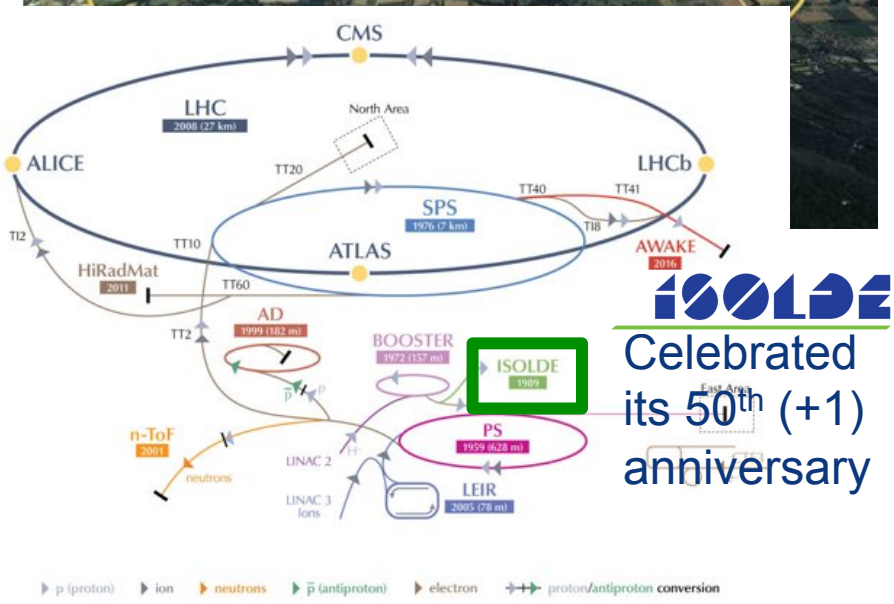


Imaging of prostate cancer gastrin releasing peptide receptor, GRPr, and targeted radiopeptide therapy combined with radiation therapy

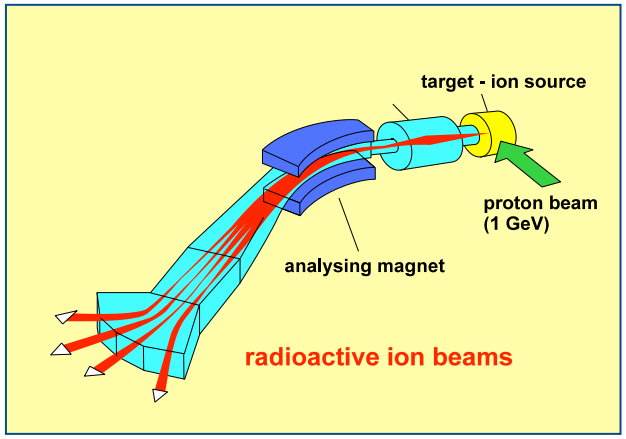
Franz Buchegger[1], David Viertl[1,2*], Eleni Gourni[3], John O. Prior[1], Thierry Stora[4], Leo Bühler[5], Beatrice Waser[9], Marek Kosinski[6]; Raymond Miralbell[7], Cristina Müller[8], Jean Claude Reubi[9], Helmut R. Maecke[3] and Rosalba Mansi[3]

What CERN is best known for …





ISOLDE Celebrated its 50th (+1) anniversary



LHC Large Hadron Collider SPS Super Proton Synchrotron PS Proton Synchrotron
Antiproton Decelerator CTF3 Clic Test Facility AWAKE Advanced WAKefield Experiment ISOLDE Isotope Separator OnLine DEvic
LEIR Low Energy Ion Ring LINAC LINear ACcelerator n-ToF Neutrons Time Of Flight HiRadMat High-Radiation to Materials

^{224}Radium octupole deformation by Coulex

Radioisotopes and nuclear medicine

99Technecium supply shortage

Classification of Isotopes for Medicine

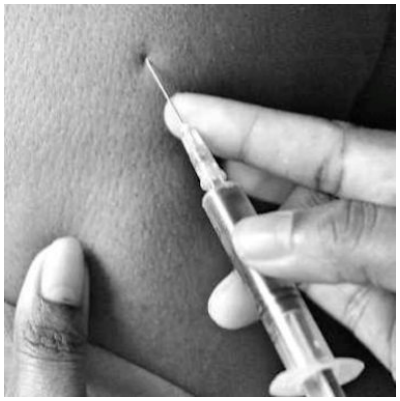
1. **Established isotopes** — **"industrial" suppliers**
   ^{99m}Tc, ^{18}F, ^{123,125,131}I, ^{111}In, ^{90}Y
   supply security
   optimization of production/scale effects > cost reduction

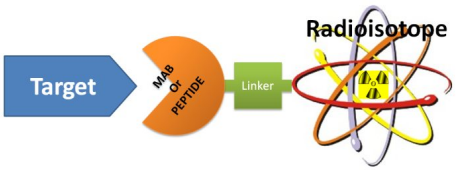
2. **Emerging isotopes** — **"small" innovative suppliers**
   ^{68}Ga, ^{82}Rb, ^{89}Zr, ^{177}Lu, ^{188}Re
   quality, GMP, certification

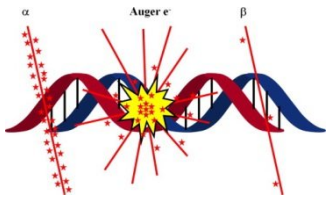
3. **R&D isotopes** — **research labs**
   ^{44,47}Sc, ^{64,67}Cu, ^{134}Ce, ^{140}Nd, ^{149,152,155,161}Tb, ^{166}Ho, ^{195m}Pt, ^{211}At, ^{212,213}Bi, ^{223}Ra, ^{225}Ac,...
   availability at affordable cost

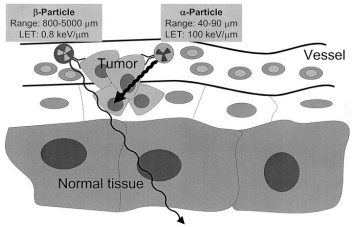
From U. Koester,
workshop on physics for Health in Europe
CERN, Feb. 2010

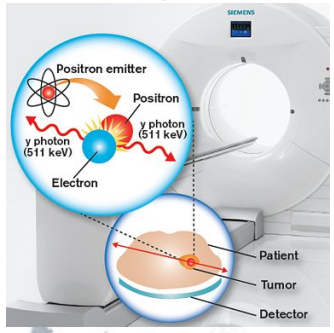
Concept of theranostics pairs

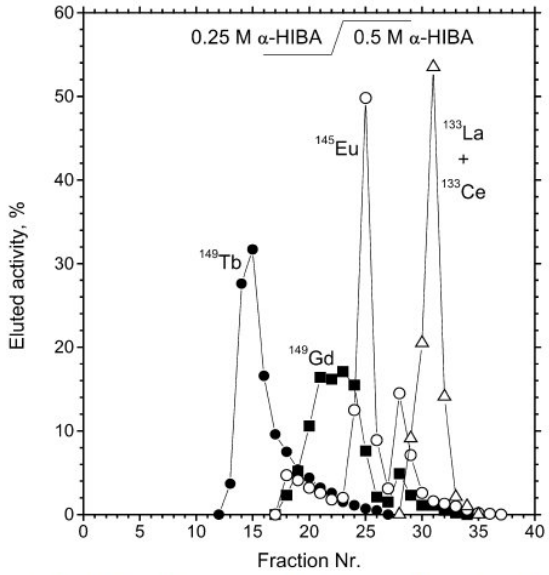


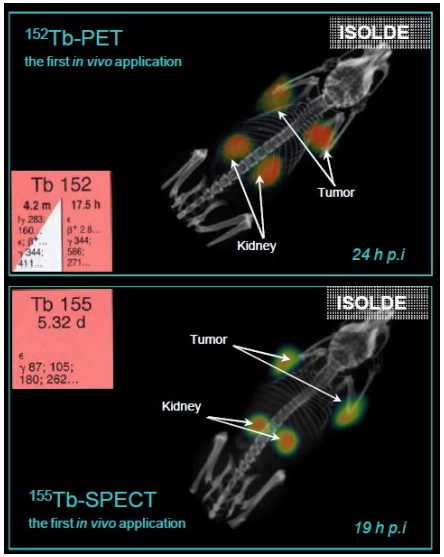












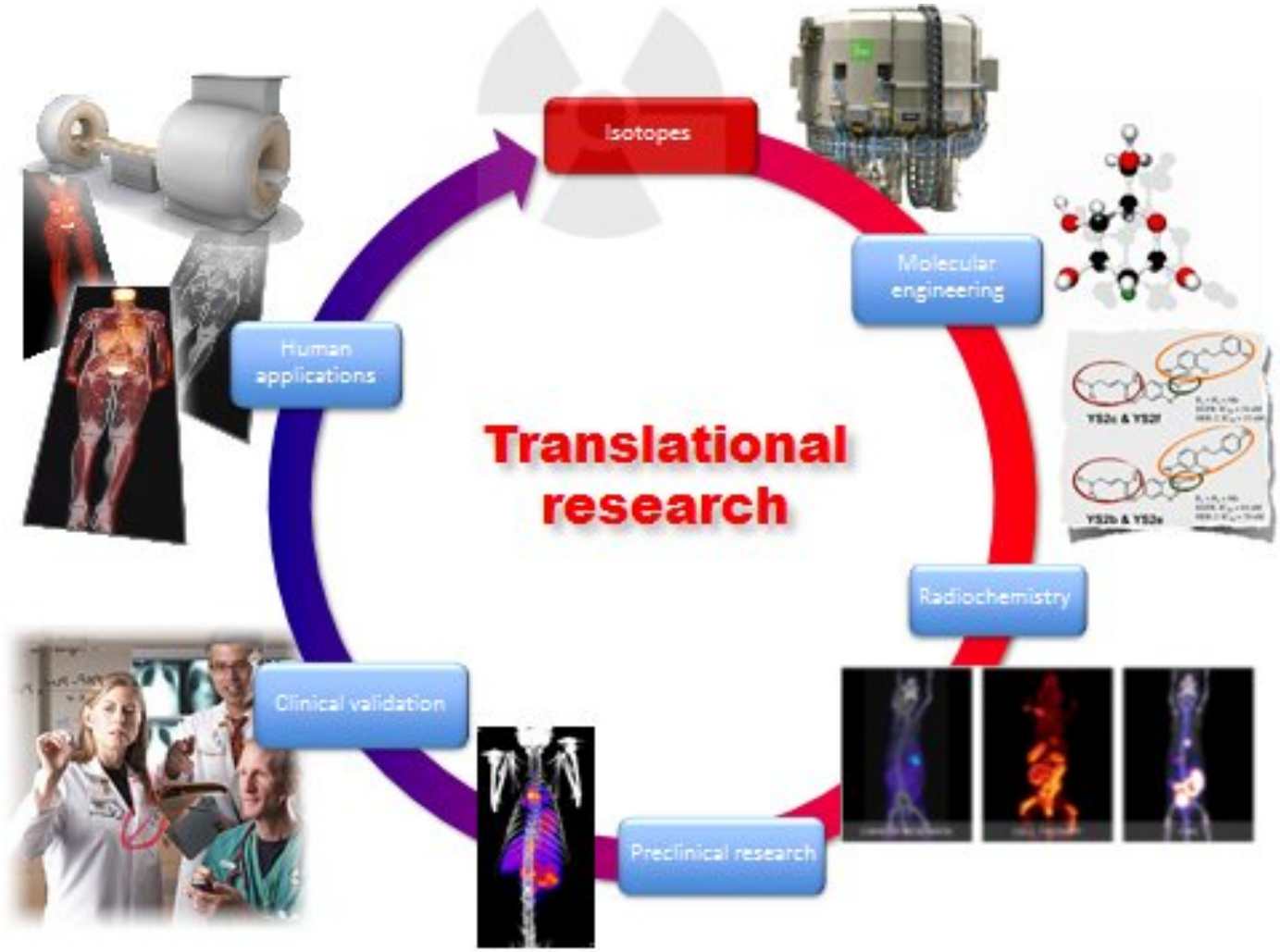
Targeted alpha therapy in vivo: direct evidence for single cancer cell kill using ^{149}Tb-rituximab

15 years ago

G.-J. Beyer[1], M. Miederer[2], S. Vranješ-Đurić[3], J. J. Čomor[4], G. Künzi[5], O. Hartley[5], R. Senekowitsch-Schmidtke[6], D. Soloviev[1], F. Buchegger[1], and the ISOLDE Collaboration

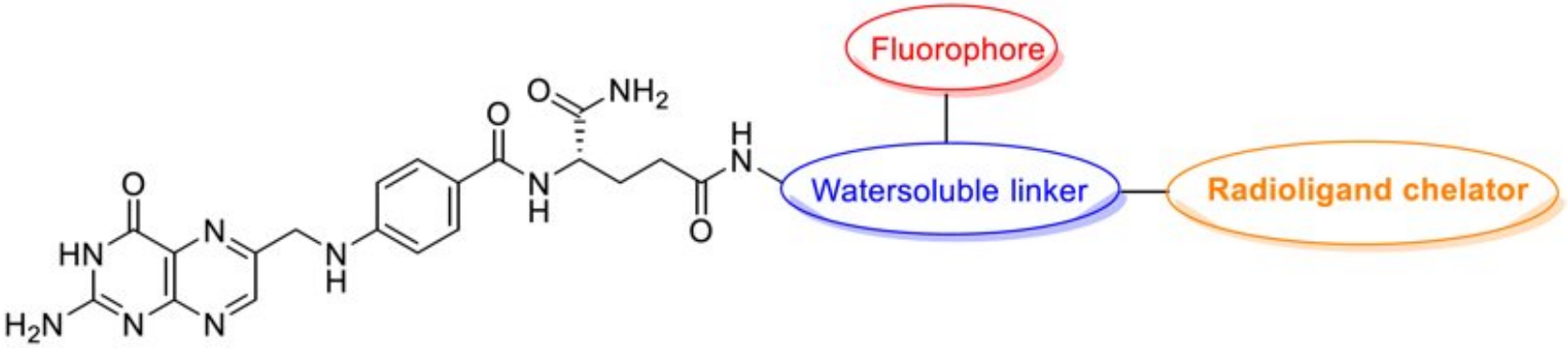
C. Muller et al. jnumed.112.107540v1

How to progress in the field ?



Courtesy Prof. MD Osman Ratib
in the context of CERN-MEDICIS

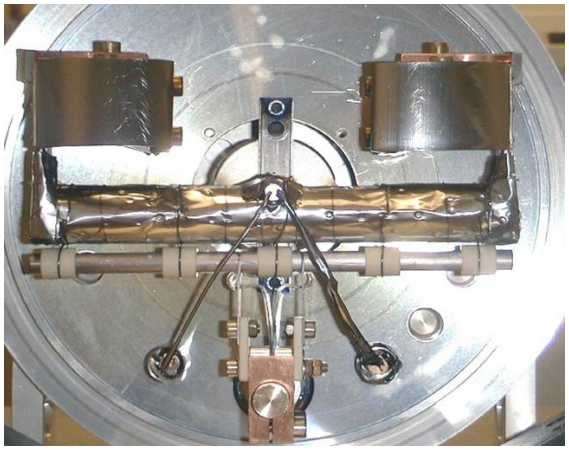
A first example
Added functionality :
Molecular engineering (inorganic chemistry)

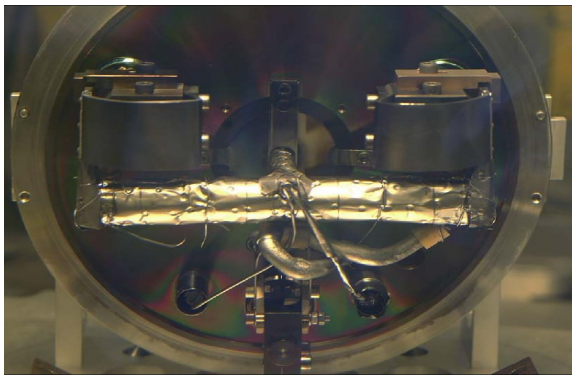


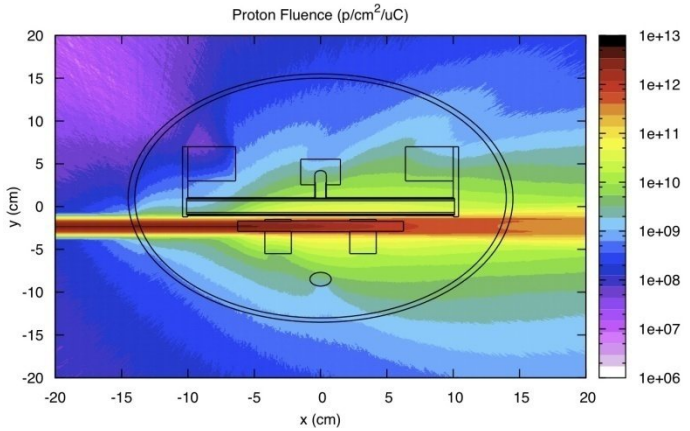
Folate bioconjugate with fluorescence and radioligand chelator
Tkhe Kyong Fam, Prof Dubikovskaya, EPFL

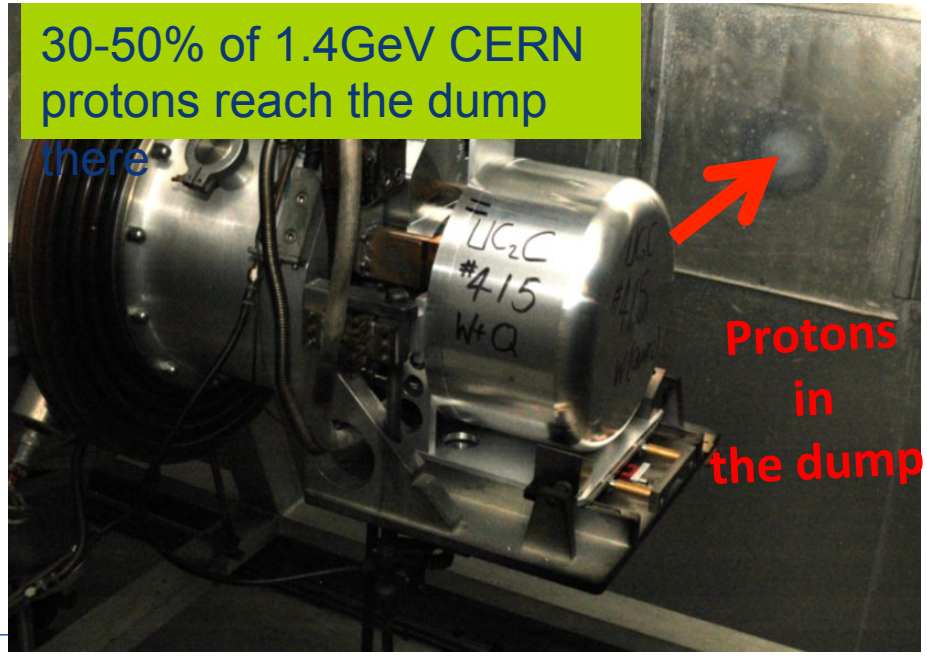
A second example : CERN-MEDICIS

When a CERN
proton beam
intercepts a target:
(and if you are not careful enough)





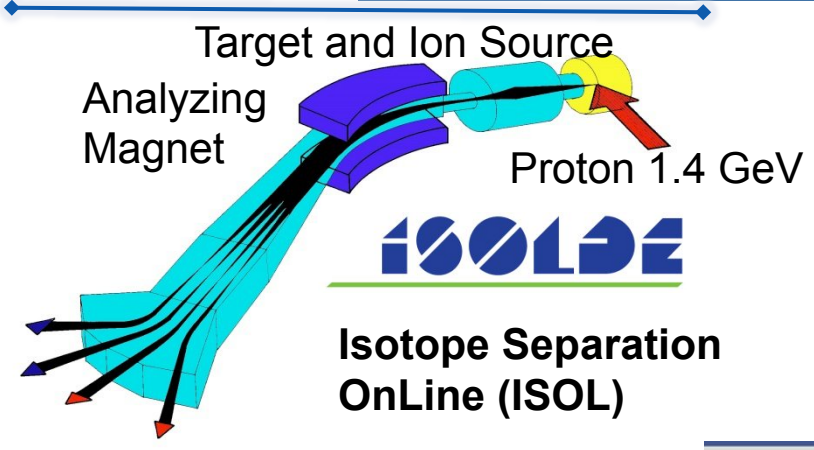




Radioisotope Beam Production at ISOLDE

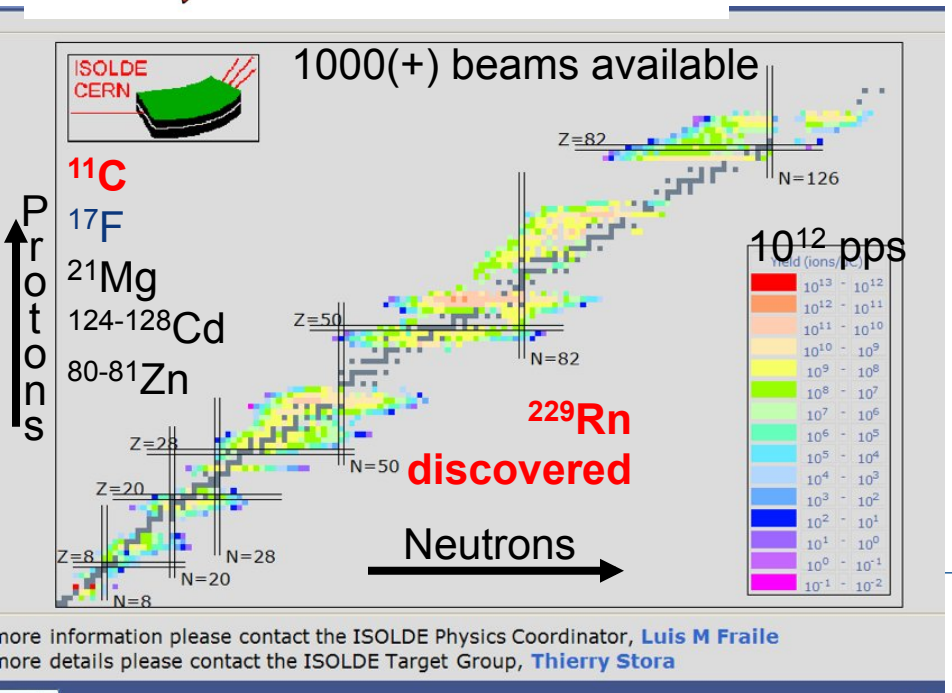
$$I_{[pps]} \sim \Phi_{[pps]}\ \sigma_{[barn]}\ N_{[g/cm2]}\ \varepsilon\ [\%]$$

10-100m



Isotope Separation OnLine (ISOL)

Intensity
Purity (quality)
Reliability



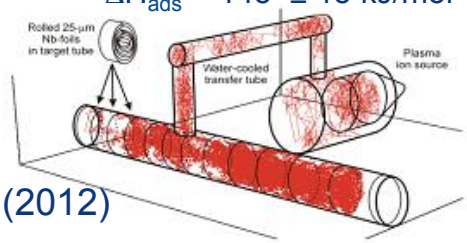
nore information please contact the ISOLDE Physics Coordinator, **Luis M Fraile**
nore details please contact the ISOLDE Target Group, **Thierry Stora**

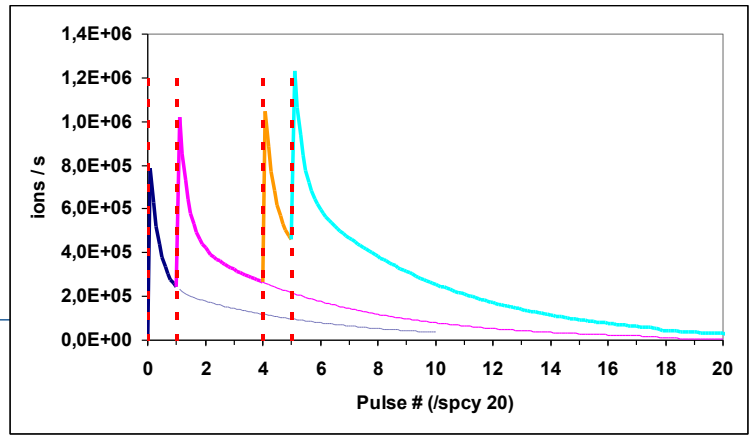
Diffusion
Physical Chemistry

$$p(t) \propto p_{eff}(t) \star p_{diff}(t$$

Eur. Phys. Lett. 98, 32001 (2012)

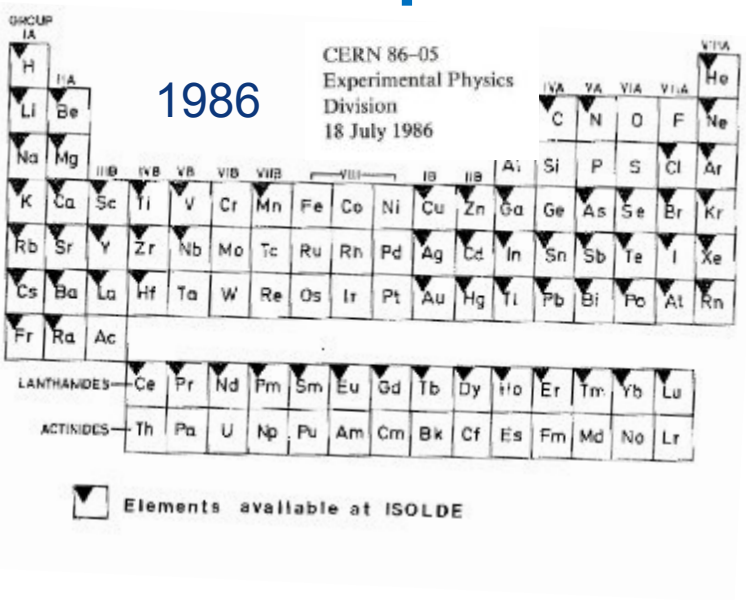
ΔH_{ads} = 145 ± 15 kJ/mol

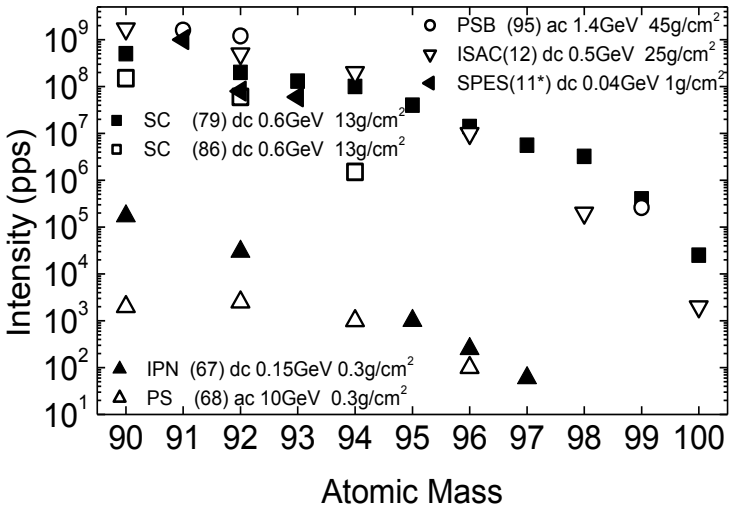




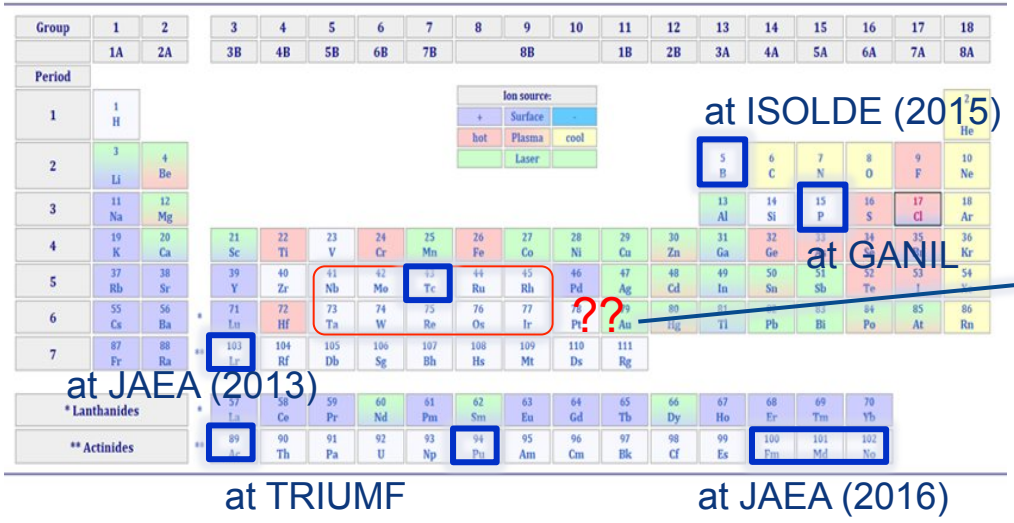
+1

New isotope beams by mass separatio (ISOL)





2012 And more recently

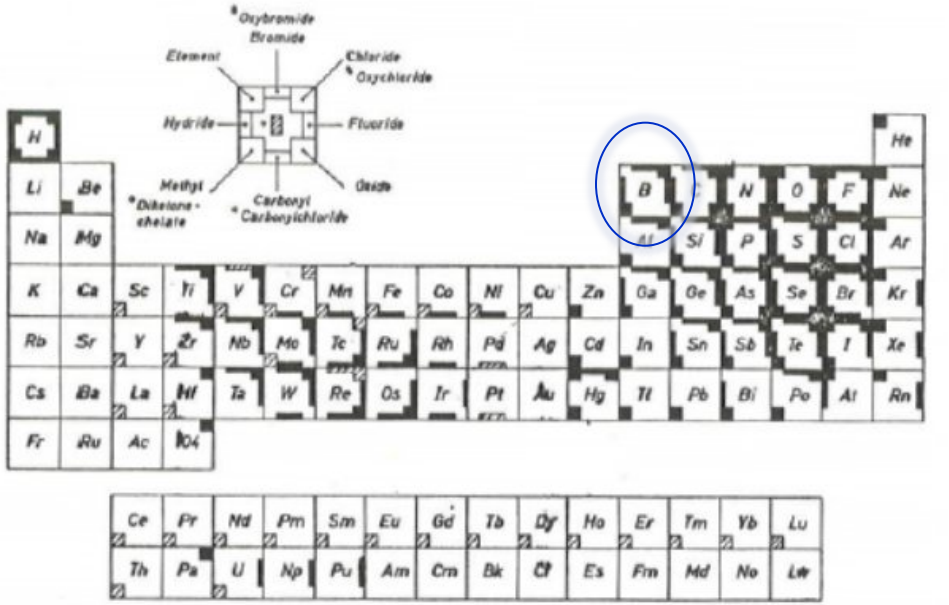


We don't evaporate/release refractory elements in atomic Form : Developments ongoing

T. Sato, et al. http://dx.doi.org/10.1063/1.4789772 (2013).

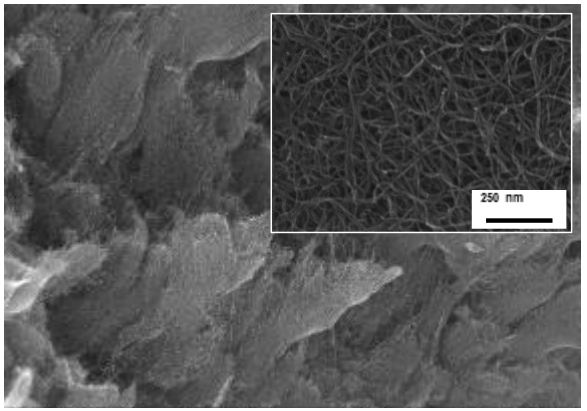
1st Boron ISOL beams: $^{8}BF_2^{+}$ from carbon nanotubes

$^{8}BF_2^{+}$ (T1/2 880ms) produced
from multiwall carbon nanotube target (fast diffusion)
and CF_4 reactive gaz injection (volatile BF_3 molecule)
« CHEMICAL EVAPORATION »



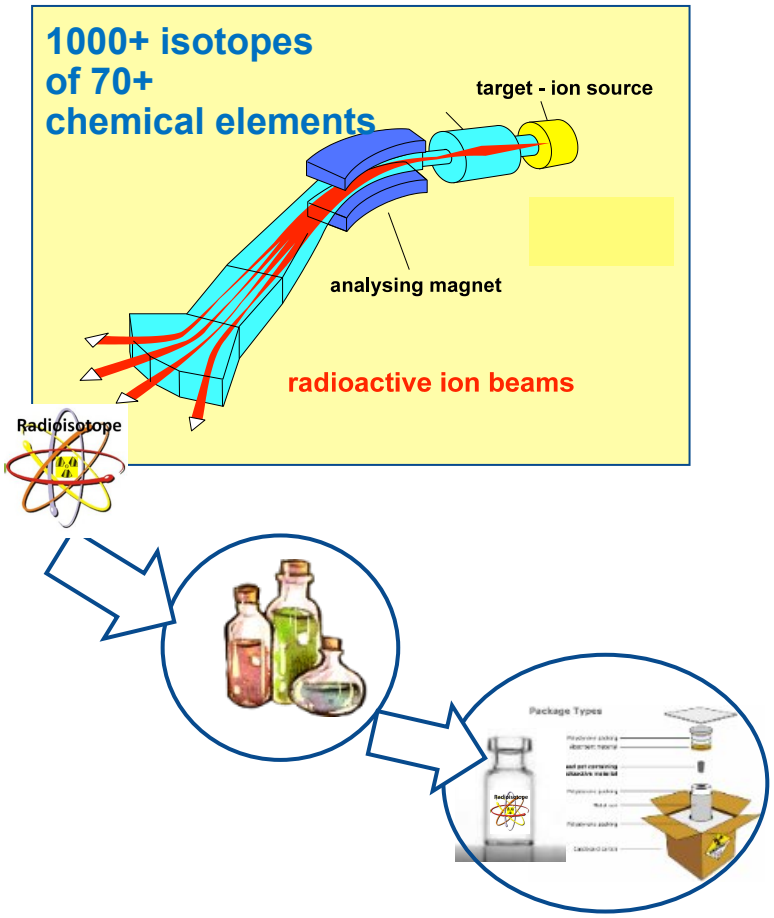
C. Seiffert, Production of radioactive molecular beams for CERN-ISOLDE.
PhD thesis TU Darmstadt, CERN (2015)

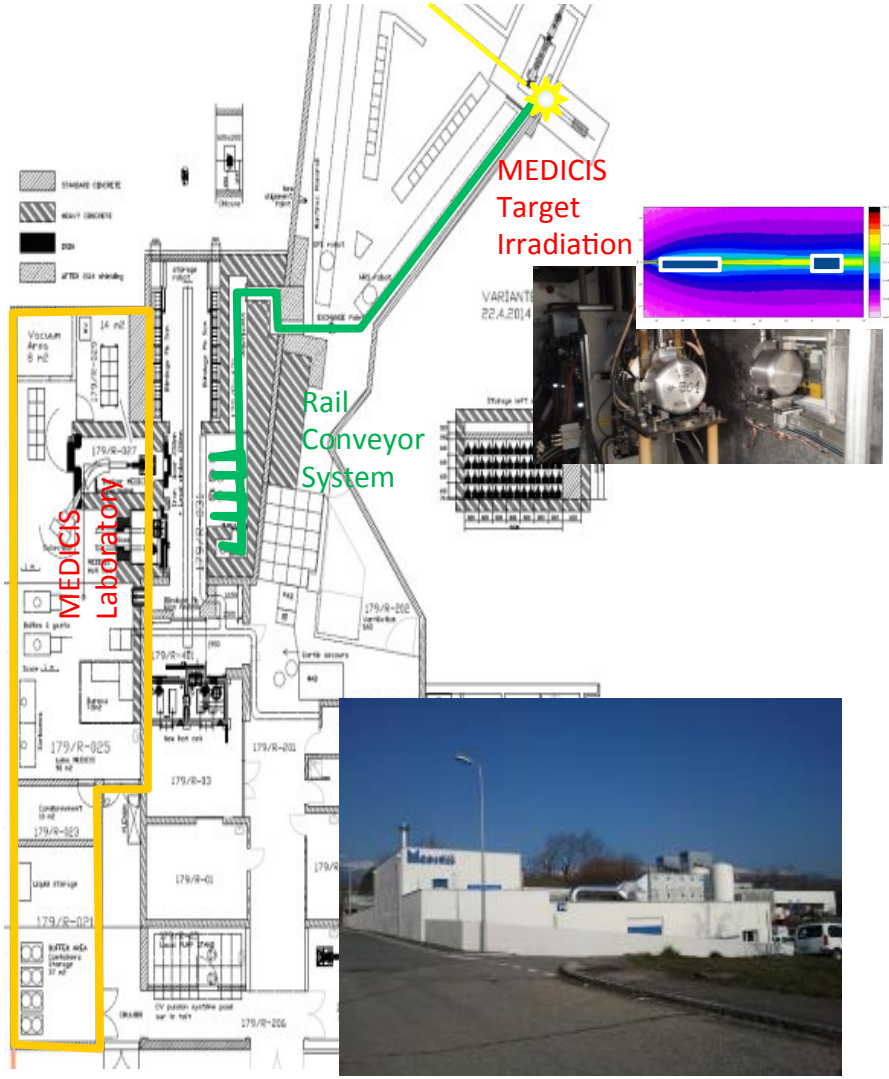
Multiwall Carbon Nanotubes



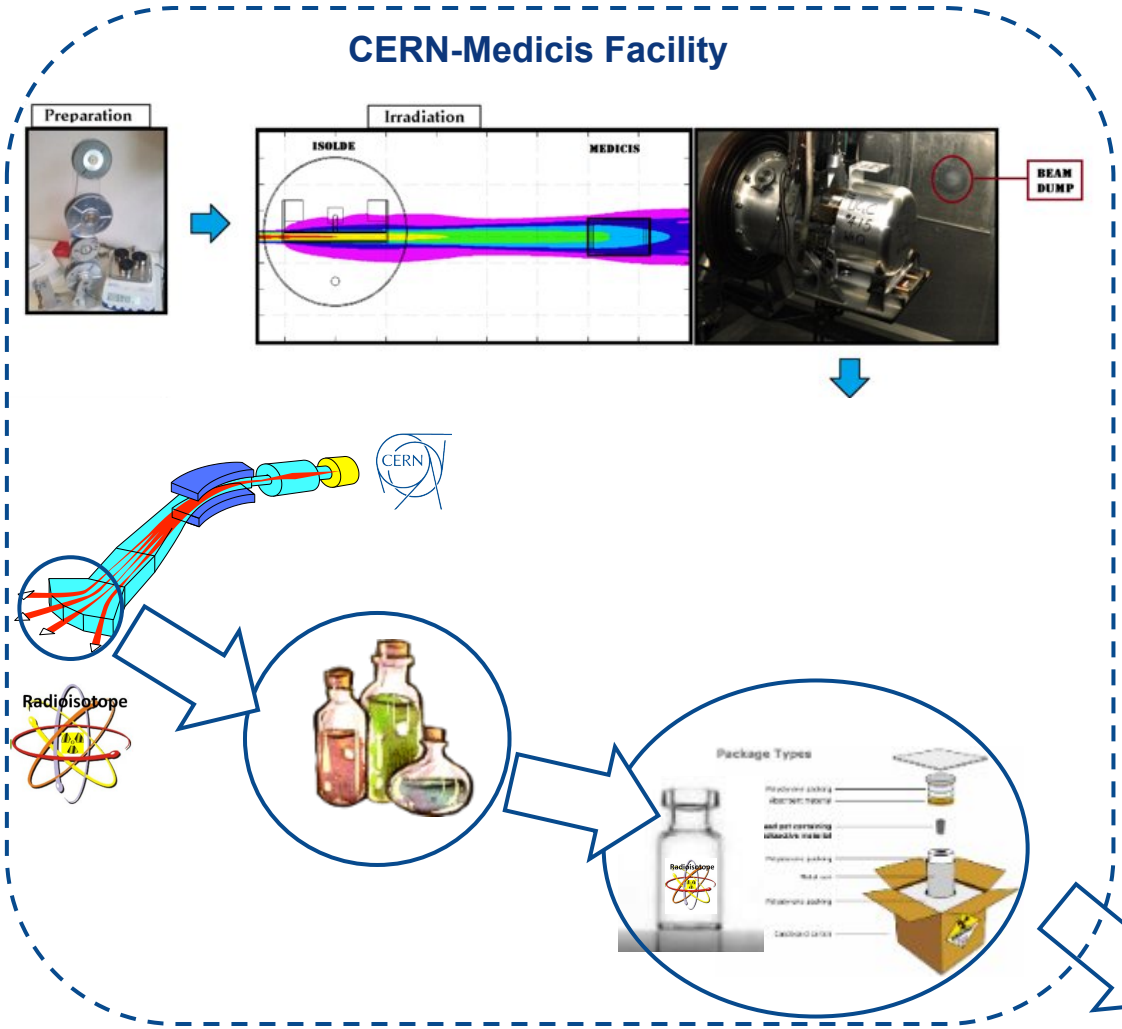
A dedicated mass separation facility for medical applications

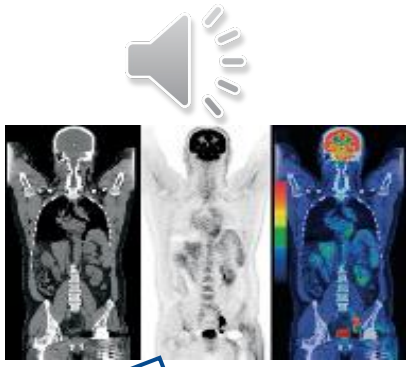
Start operation 2017





The complete cycle of MEDICIS





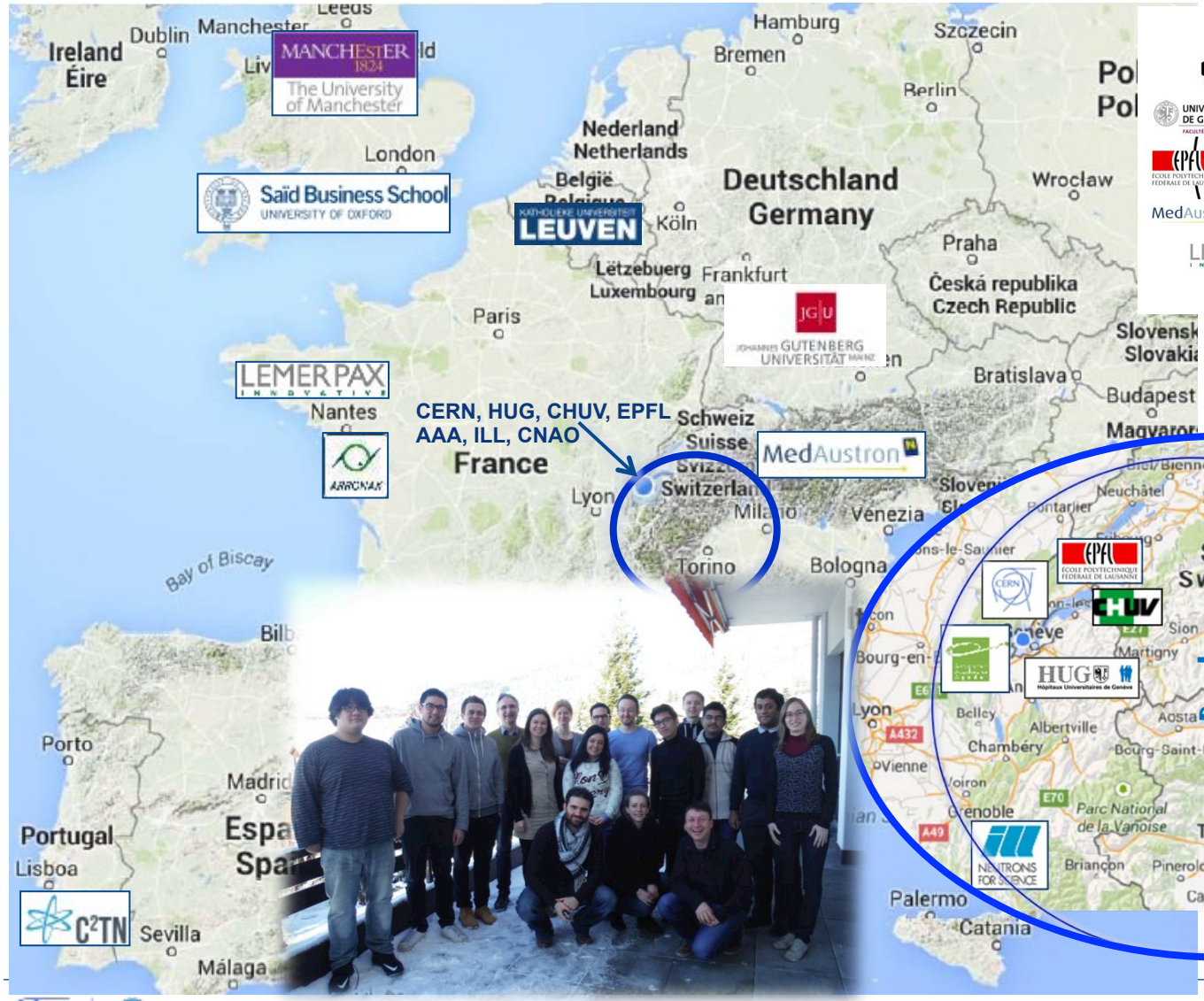
MEDICIS-PROMED

« MEDICIS-Produced radioisotope beams for medicine »

Apr 2015 – March 2019

The intersectorial distributed network

15 PhD students



Overview of the Research Network

MEDICIS-PROMED: Innovative treatments based on radioactive ion beam production, transport and preclinical studies

MEDICIS_PROMED training network

Coordination Dr. T. Stora, CERN — Medical coordination : PhD, MD J. Prior, CHUV

"Timely Innovations"

WP3 : theranostic pharmaceuticals/surgery for new ovarian cancer personalized treatment

Terbium isotope theranostic pairs
Biological targets for ovarian cancers

- **AAA (FR) lead- radiopharmaceuticals - ESR6**
- IST (PT)/dna targetting - ESR8
- CERN MEDICIS (EU)/molecular break-up - ESR1
- *HUG (CH)/surgery - ESRCH3*
- *CHUV(CH)/preclinical tests - ESRCH2*

"Timely Innovations"

WP 1 : mass separation of new medical isotopes

Graphene
CERN-MEDICIS
Ti:Sa Ion sources
α-isot. Transp.

- **JOGU (DE) lead - laser purification - ESR5**
- UNI MANCHESTER (UK)/adv material- ESR4
- CERN MEDICIS (EU)/ production safety - ESR2
- Lemer-Pax (FR) /transport - ESR10
- IST (PT)/nanofibers - ESR7

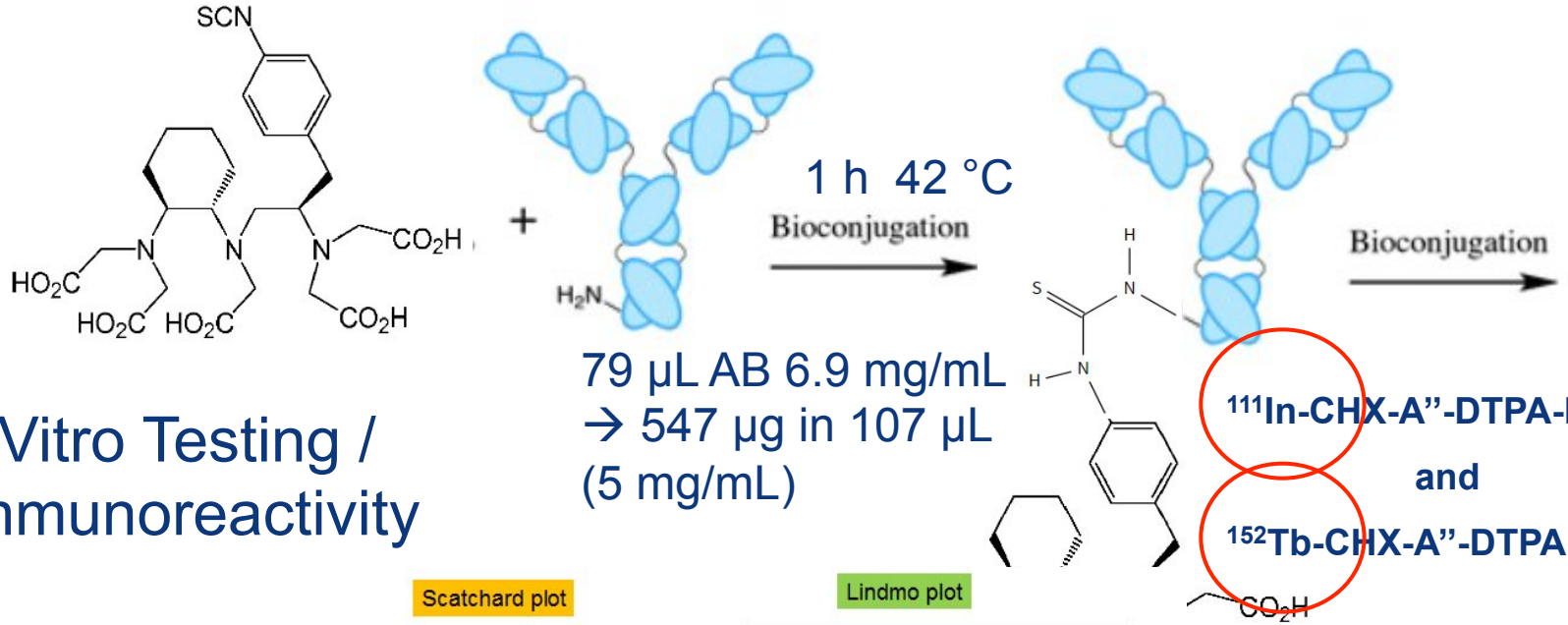
WP 2 : Pet aided 11C hadrontherapy

- **CNAO (IT) lead - 11C hadrontherapy - ESR9**
- KUL (BE) - mass sep 11C - ESR11
- CERN MEDICIS (EU) - 11C acceler. - ESR3
- *HUG (CH) - imaging tests -ESRCH1*
- *EPFL (CH) - biochemical synthesis - ESRCH4*
- *Medaustron (AT) - hadrontherapy*

"Timely Innovations"

Medaustron animal models

Labelling of 78Fc anti-TEM1 with radiometals



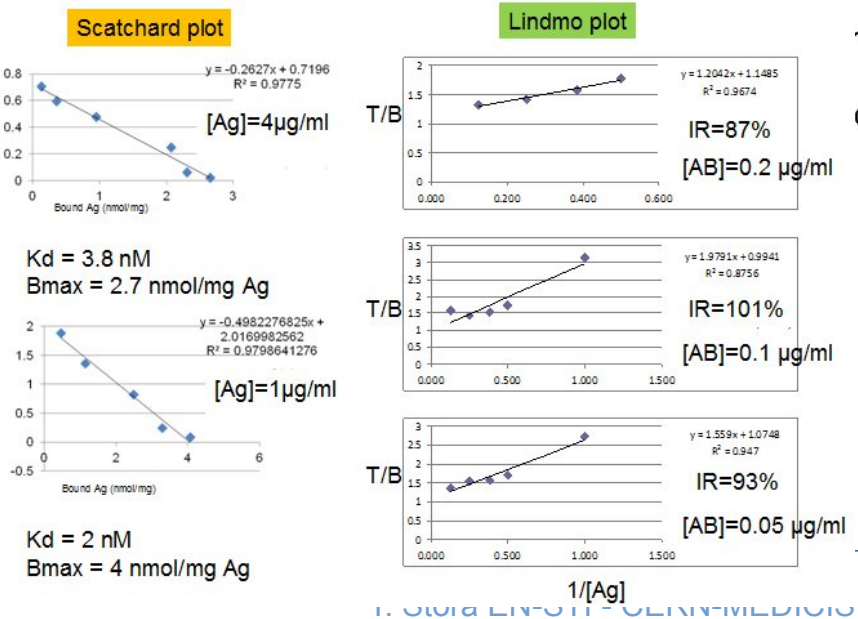
79 µL AB 6.9 mg/mL
→ 547 µg in 107 µL
(5 mg/mL)

^{111}In-CHX-A"-DTPA-FcTEM1

and

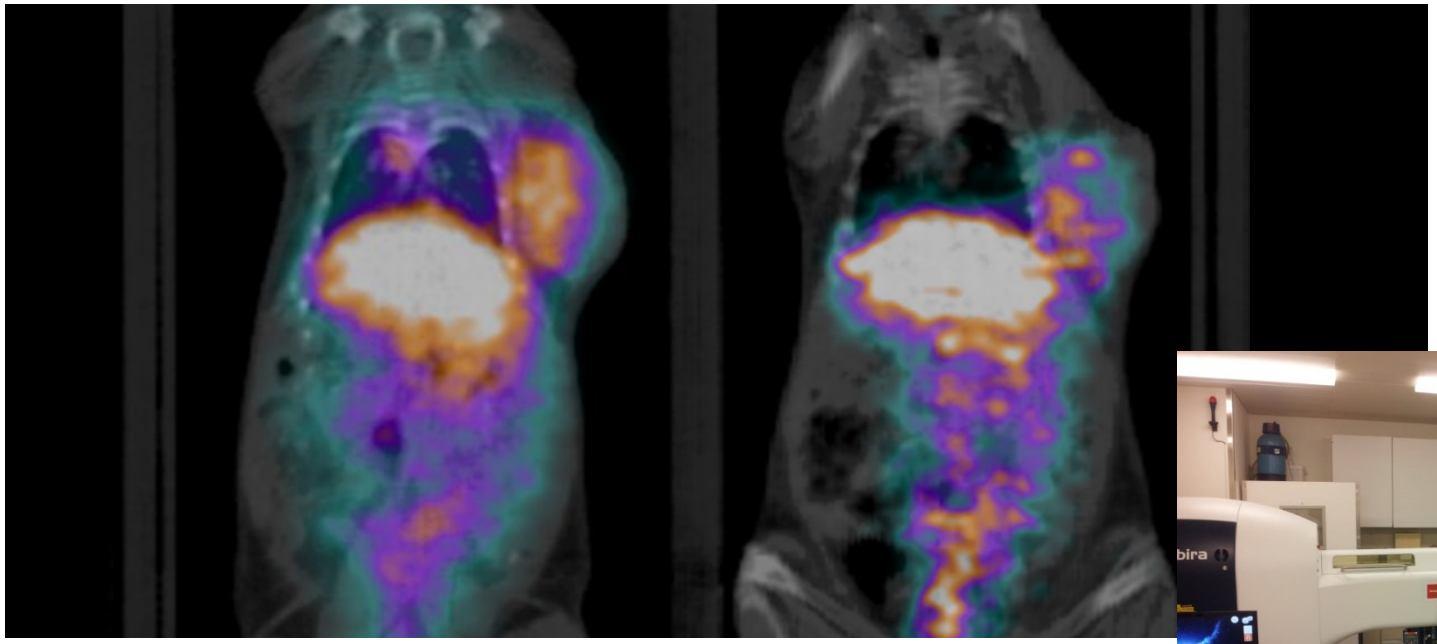
^{152}Tb-CHX-A"-DTPA-FcTEM1

In Vitro Testing / Immunoreactivity



First PET imaging of ^{152}Tb-CHX-A”-DTPA-ScFv78Fc

Ewing Sarcoma cell line A673

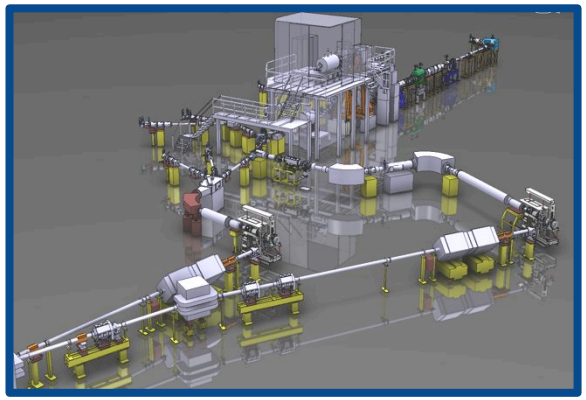


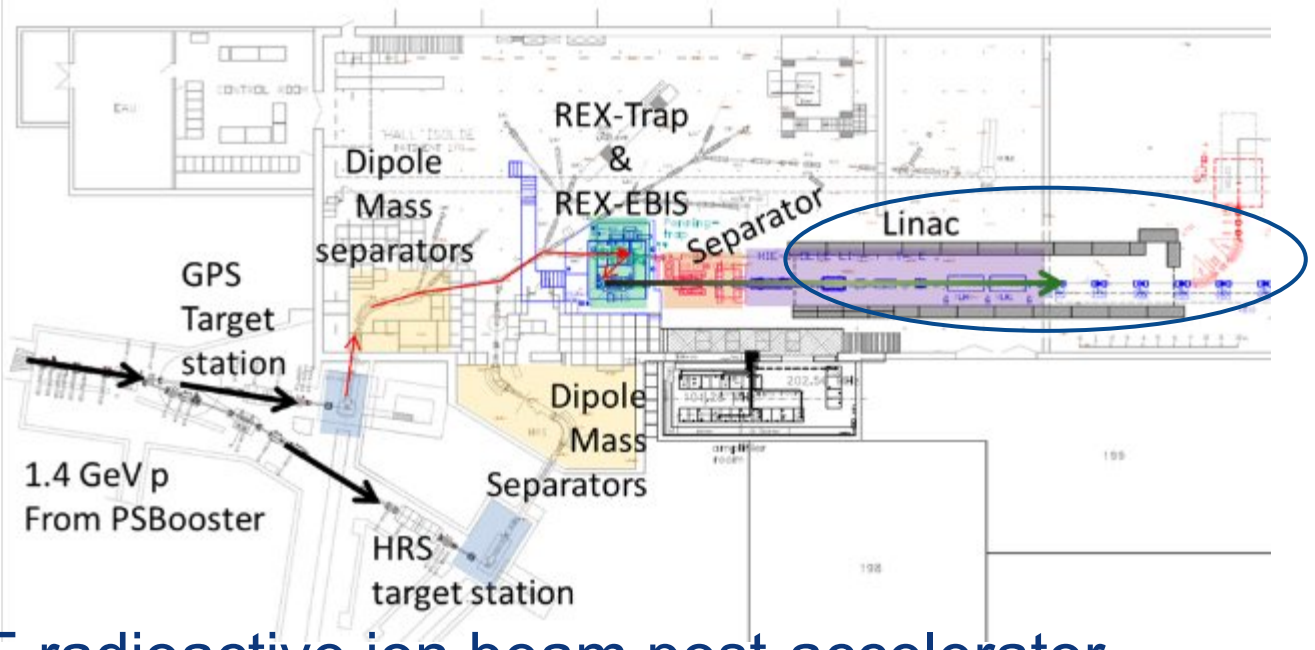
24 hours p.i.

60 hours p.i.

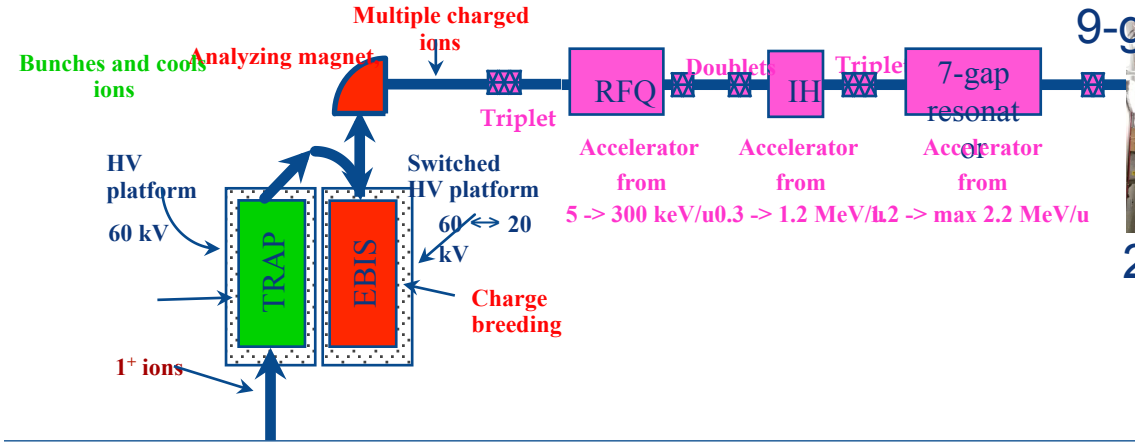
Isotope mass separation and post acceleration

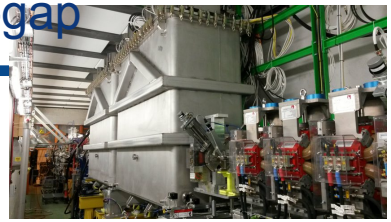
>1e7pps 110Sn 4.5MeV/n delivered in sept 2016 !





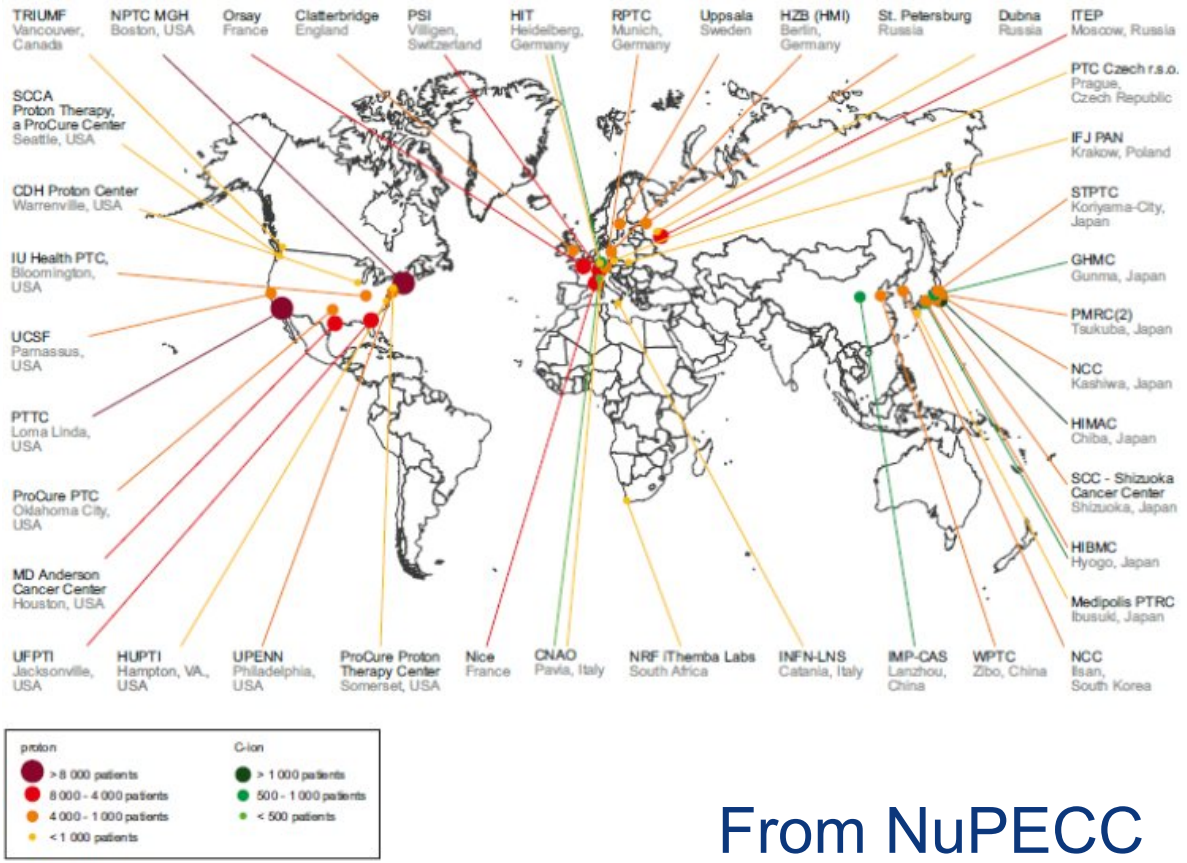
REX-ISOLDE radioactive ion beam post-accelerator





2nd cryomodule @ HIE-ISOLDE

World map of hadrontherapy centers

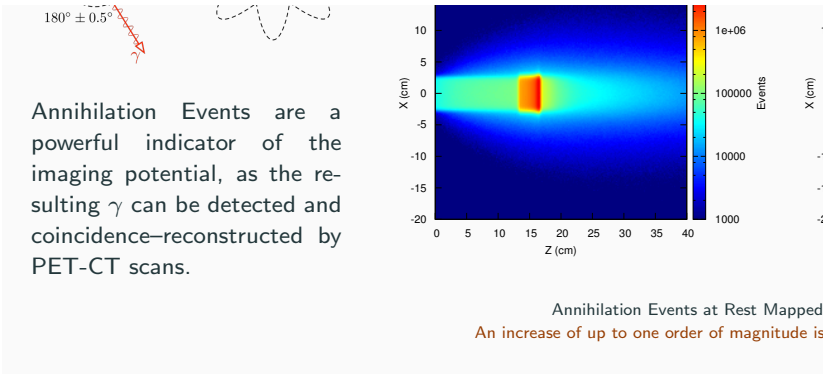


From NuPECC 2013

^{11}C Beams for combined PET/Hadron therapy

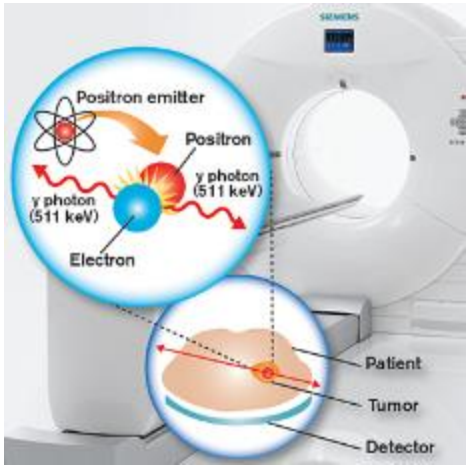
Comparison of in-beam PET with fragment 12C (11C, 15O) and direct 11C use

Monte Carlo is extrem
And therefore. . . is not compe



Annihilation Events are a powerful indicator of the imaging potential, as the resulting γ can be detected and coincidence–reconstructed by PET-CT scans.

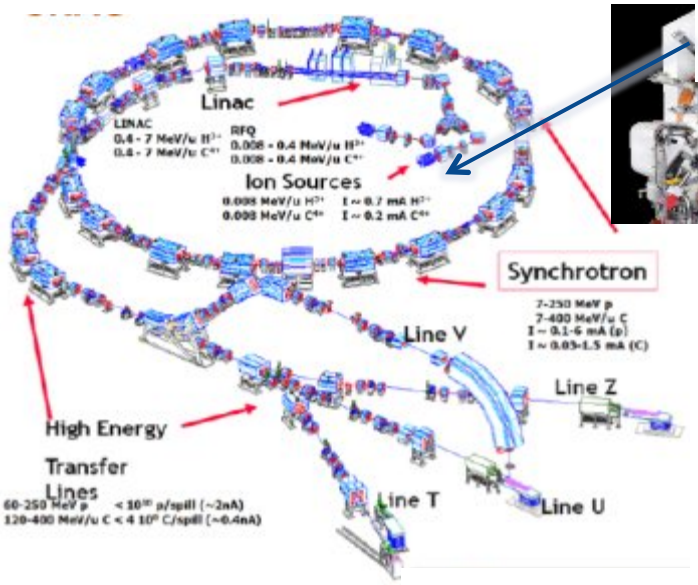
Annihilation Events at Rest Mapped
An increase of up to one order of magnitude is

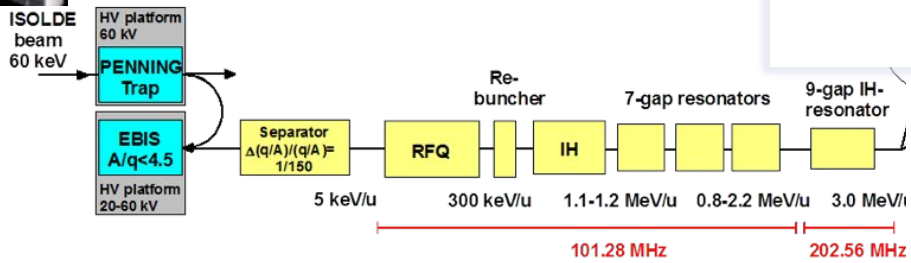


R. Augusto et al.

These studies have been performed at HIMAC, NIRS

Possible acceleration schemes : efficiencies matter





"A la Isolde"

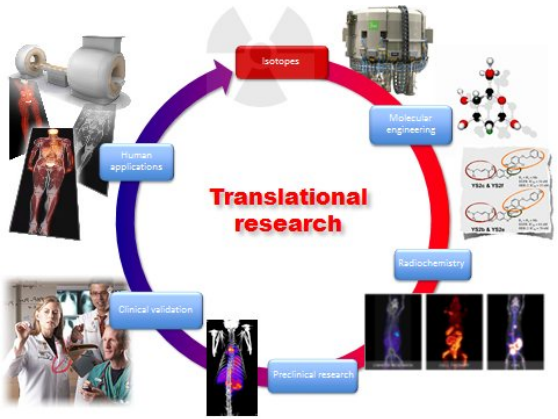
Directly in the ECRIS

PET production (production batch)	22	150	N_2 ($\leqslant$1 atm)	$^{14}N(p,\alpha)^{11}C$	3×10^{10}	741	1.5×10^{8}	1.3
REX-ISOLDE (ISOL)	70	1200	NaF:LiF eutectic	$^{19}F(p,2\alpha n)^{11}C$	4×10^{11}	56	1.5×10^{8}	18

- T.M. Mendonca et al., CERN-ACC-2014-0
  S. Hojo, et al. NIMB 240, 75 (2005).
- R. Augusto et al NIMB, 376, 374 (2016)

CERN-MEDICIS partners

- Dr. Forni (Clin. Carouge, Geneve)
- Prof. Morel, Prof. Buehler, Prof. Ratib (HCUGE, Geneve)
- Prof. D. Hanahan (ISREC, EPFL, Lausanne)
- Prof. J. Prior (CHUV, Lausanne)
- Prof M. Huyse, prof. P. van Duppen, prof. T. Cocolios (KUL, Univ. Leuven)
- Prof. S. Lahiri (SINP, Kolkata)
- Prof. A. Goncalves, Prof. A. Raucho (CT2N, Lisbon)
- Prof. F. Haddad (ARRONAX)
- F. Bruchertseifer, A. Morgenstern (JRC-ITU, Karlsruhe)
- S. Judge, P. Regan, (National Physical Laboratory, Surrey)
- N. Vd Meulen, C. Mueller (Paul Scherrer Institut, Villingen)



"Noah, tell me again who's your project sponsor?"

www.cern.ch/medicis-promed

Training in Manchester with prof. Kostya Novozelov

This research project has been supported by a Marie Skłodowska-Curie Innovative Training Network Fellowship of the European Commission's Horizon 2020 Programme under contract number 642889 MEDICIS-PROMED.

Thank you !!

(INPC2016) will take place in Adelaide (Australia) fro
25th INPC was held in Firenze in 2013 and the 24th
2010.

multiforme (a form of very aggressive brain cancer) or pancreatic adenocarcinoma. The latter is a leading cause of cancer death in the developed world and surgical resection is the only potential treatment, although many patients are not candidates for surgery. Although external-beam gamma radiation and chemotherapy are used to treat patients with non-operable pancreatic tumours, and survival rates can be improved by combined radio- and chemo-therapy, there is still a clear need for novel treatment modalities for pancreatic cancer.

A new project at CERN called MEDICIS aims to develop non-

RESERVE

Some yield estimates

Medical application	Isotope half-life	Parent isotope beam	Target - Ion source	ISOLDE† In-target Production rate (pps)	ISOLDE† In-target Activity EOB (Bq)	RIB εext** (%)	CERN-MEDICIS† In-target Activity EOB (Bq)	CERN-MEDICIS† Extracted Activity EOB (Bq)	CERN-MEDICIS 2GeV 6μA Possible gain εext (%)	CERN-MEDICIS 2GeV 6μA In-target Activity EOB / Extracted Activity EOB (Bq)		Comments
3- therapy/ CT/dosimetry	^{213}Bi 45.6m	^{225}Ac	UCx-Re	1.5E9*	7.2E8	^{221}Fr 10	2.8E8	2.8E7	50	8.4E8	4.2E8	Only mass separation
,β therapy	^{212}Bi 60.6m	^{224}Ac	UCx-Re	1.5E9*	1.4E9	^{220}Fr 10	1.7E9	1.7E8	50	5.1E9	2.5E9	Only mass separation
β therapy	*^{177}Lu 6.7d*	*^{177}Lu RILIS/VD*	*Ta-Re/ Re-VD5*	*3.3E9*	*7.4E8*	*^{177}Lu 1*	*6.4E8*	*6.4E6*	*20*	*8.3E8*	*1.7E8*	*Chemical purification*
ger therapy	^{166}Yb 56.7h	^{166}Yb	Ta-Re	1.4E10	5.4E10	^{166}Yb 5	4.1E10	2.1E9	20	5.4E10	1.1E10	Chemical purification
β therapy	*^{166}Ho 25.8h*	*^{166}Ho*	*Ta-Re*	*1.4E7*	*1.2E7*	*^{166}Ho 5*	*9.6E6*	*4.8E5*	20	*2.9E7*	*6.0E6*	Chemical purification
uger therapy	*^{161}Tb 6.9d*	*^{161}Tb*	*UCx-Re*	*2.1E7*	*2.7E7*	*^{161}Tb 5*	*1.9E7*	*9.5E5*	*20*	*2.7E7*	*5.4E6*	Chemical purification
3- therapy	*^{156}Tb 5.35d*	*^{156}Tb*	*Ta-Re*	*2.5E8*	*8.9E7*	*^{156}Tb 1*	*5.5E7*	*5.5E5*	*20*	*6.3E7*	*1.3E7*	Chemical purification
SPECT	^{155}Tb 5.33d	^{155}Dy/ Tb	Ta-Re	3.2E9/ 7.4E8	7.9E9	^{155}Dy 1	5.3E9	5.3E7	20	3.4E9	6.8E8	RILIS Dy
3 therapy	^{153}Sm 46.8h	^{153}Sm	UCx-Re	1.5E8	2.2E9	^{153}Sm 5	2.8E9	1.4E8	20	5.2E9	1.0E9	Chemical purification
PET/CT	^{152}Tb 17.5h	^{152}Dy/ Tb	Ta-Re	1.3E10/ 3.3E9	5.6E10	^{152}Dy 1	3.7E10	3.7E8	20	1.1E11	2.2E10	RILIS Dy
t therapy	^{149}Tb 4.1h	^{149}Tb	Ta-Re	1.1E10	6.0E10	^{149}Tb 1	3.8E10	3.8E8	20	1.2E11	2.4E10	Chemical purification

^{140}Pr-PET/ ger therapy	^{140}Nd 3.4d	^{140}Nd	Ta-Re	1.8E9	2.0E10	^{140}Nd 5	1.2E10	6.0E8	20	2.0E10	4.0E9	Chemical purification
- therapy	^{89}Sr 50.5d	^{89}Sr	UCX-Re	1.2E10	2.3E9	^{89}Sr 5	2.0E9	1.0E8	20	2.7E9	5.4E8	Only mass searation
PET	^{82}Sr 25.5d	^{82}Sr	UCX-Re	3.6E10	4.6E9	^{82}Sr 5	1.7E9	8.5E7	20	2.0E9	4.0E8	Only mass separation
- therapy	^{77}As 38.8h	^{77}As	UCX-VD5	5.7E9	1.1E10	^{77}As 5	5.8E9	2.9E8	20	9.4E9	1.4E9	Chemical purification
PET	^{74}As 17.8d	^{74}As	Y_2O_3 -VD5	6.5E9	1.2E9	^{74}As 5	3.8E8	1.9E7	20	4.5E8	9.0E7	Chemical purif
PET	^{72}As 26.0d	^{72}As	Y_2O_3 -VD5	1.6E10	2.8E10	^{72}As 5	9.1E9	4.6E8	20	1.5E10	3.0E9	Chemical purification
PET	^{71}As 65.3h	^{71}As	Y_2O_3 -VD5	1.8E10	1.8E10	^{71}As 5	5.9E9	3.0E8	20	8.0E9	1.6E9	Chemical purification
3 therapy	^{67}Cu 61.9h	^{67}Cu	UCX-Re	2.7E9	3.4E9	^{67}Cu 7	1.5E9	1.1E8	20	2.7E9	5.4E8	Chemical purification
PET	^{64}Cu 12.7h	^{64}Cu	Y_2O_3 -VD5	1.1E10	2.3E10	^{64}Cu 5	7.1E9	3.6E8	20	2.1E10	3.6E9	Chemical purification
, dosimetry	^{61}Cu 3.3h	^{61}Cu	Y_2O_3 -VD5	7.7E9	1.7E10	^{61}Cu 5	5.1E9	2.6E8	20	2.1E10	4.0E9	Only mass separation
3 therapy	^{47}Sc 3.4d	^{47}Sc	Ti	6.4E10	5.0E10	^{47}Sc 5	4.2E10	2.1E9	20	5.9E10	1.2E10	Evaporation
PET	^{44}Sc 4.0h	^{44}Sc	Ti	4.4E10	6.6E10	^{44}Sc 6.4	5.7E10	2.9E9	20	1.6E11	3.2E10	Evaporation
PET	^{11}C 20.3m	^{11}CO	NaF-LiF-VD5◊	-	-	- 15	-	1.4E9	-	-	4.2E9	Only mass separation

Training : Events and models

Kick-off week – CERN (EU) 8-12 feb 2016, before ICTR-PHE 2016

General training 1 – Manchester (UK)

Workshop on functional multimodal SPECT/PET imaging – Lausanne/Geneva (CH)

Specialized training 2 – Leuven (BE)

Summer school 1 at CNAO – Pavia (IT).

Summer school 2 at C2TN-IST – Lisbon (PT)

K. Novoselov, Graphene Institute – Physics Nobel Prize 2010 – Scientific Innovation and Advanced Materials

U. Koester, ILL- chairman of the NuPECC working group for *Nuclear Physics for Medicine-Radioisotope production*– Production of medical radioisotopes

P. Van Duppen, KUL – Adv ERC – Radioactive Ion Beams and Lasers

S. Buono, AAA – Radiopharmaceuticals marketing and Entrepreneurship

G. Coukos, CHUV – Adv. ERC – Immunotherapy and cancer treatment

P. Lecoq, CERN – Adv ERC – Detectors and Medical imaging

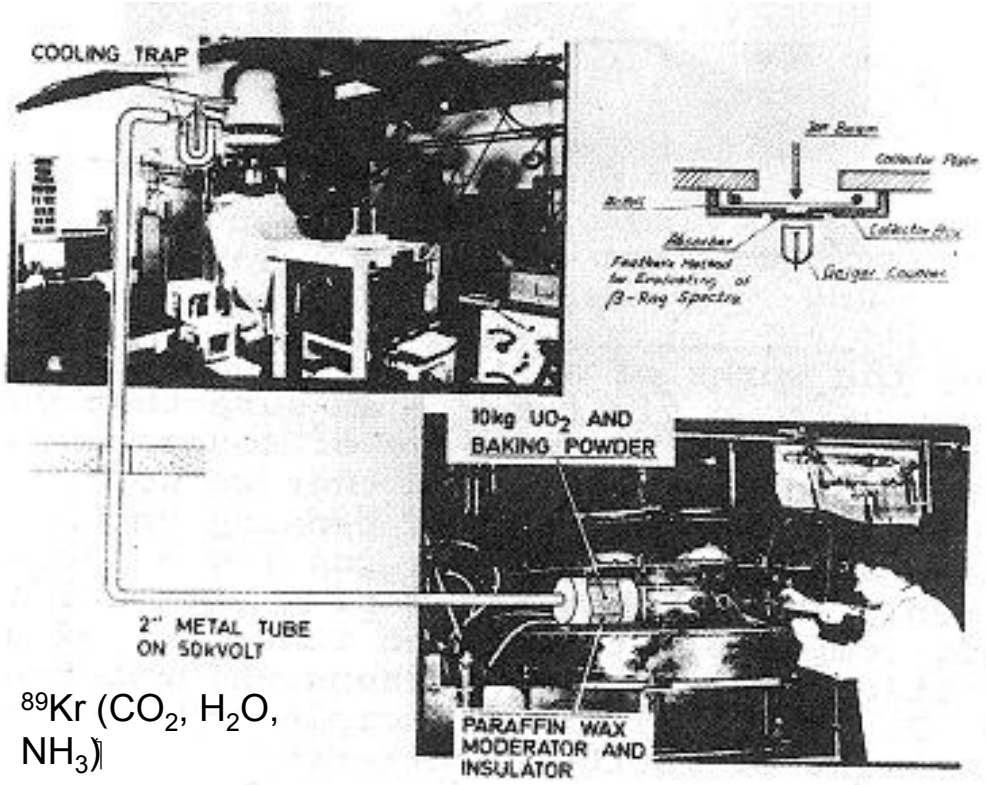
K. Noda-san – NIRS – PET-aided hadron therapy with carbon ions

Program cohesion : Oxford University Said Business School (ECTS, PhD)

THE BIRTH OF ON-LINE ISOTOPE SEPARATION

ISOLDE "0"

O.Kofoed-Hansen
K.O. Nielsen
Dan. Mat.Fys.Medd. 26, no. 7 (1951)



^{89}Kr (CO_2, H_2O, NH_3)

10 MeV deuterons
d-to-n converter (Be)
n moderator (wax)
UO_2 (10 kg)
Baking powder

From CERN 76-13, 3rd conf. nuclei far from stability

Translational approach

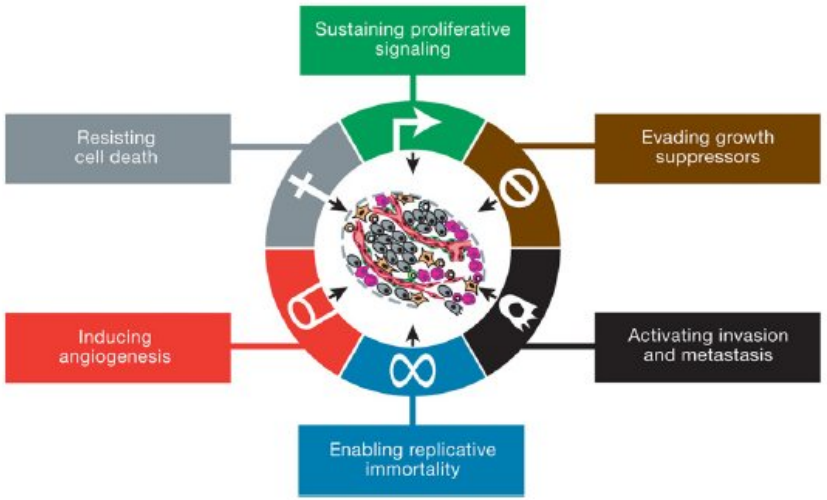
Prof D. Hanahan, Swiss Inst. For Exper. Cancer Research
Lauréat du prix 2014 « Contribution pour l'impact global tout au
Long d'une carrière » assoc. Americaine Rech. Cancer

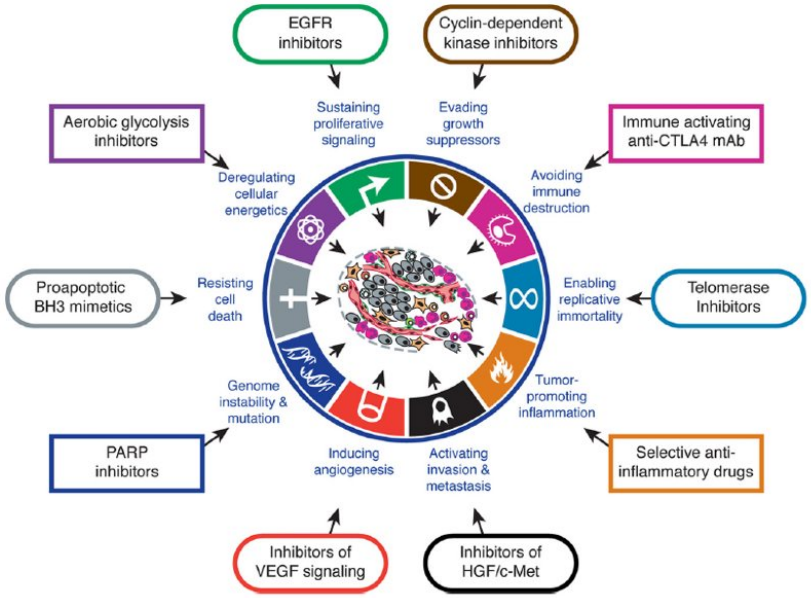
Cell

Leading Edge
Review

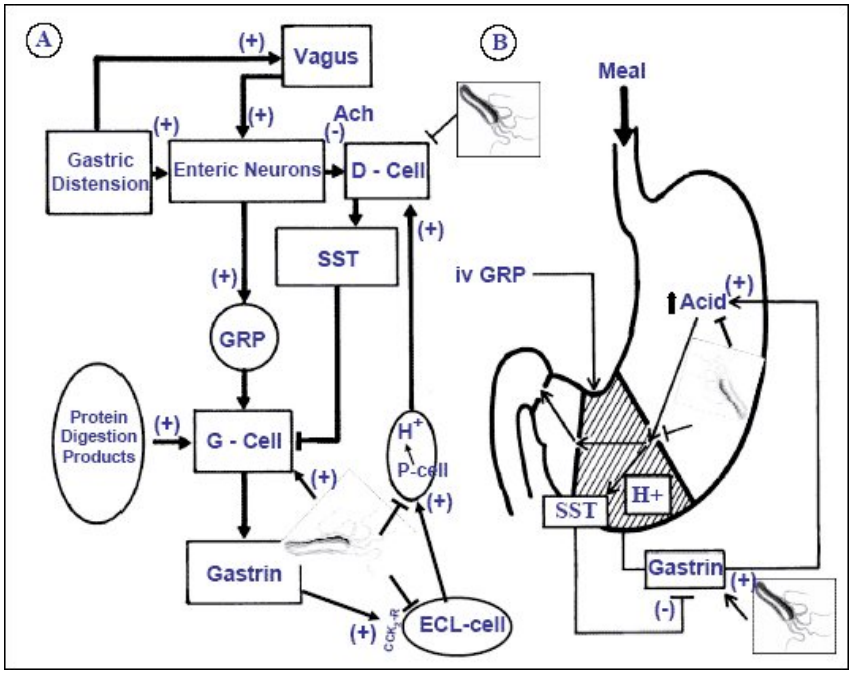
Hallmarks of Cancer: The Next Generation

Douglas Hanahan[1,2,*] and Robert A. Weinberg[3,*]
[1]The Swiss Institute for Experimental Cancer Research (ISREC), School of Life Sciences, EPFL, Lausanne CH-1015, Switzerland
[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
[3]Whitehead Institute for Biomedical Research, Ludwig/MIT Center for Molecular Oncology, and MIT Department of Biology, Cambridge, MA 02142, USA
*Correspondence: dh@epfl.ch (D.H.), weinberg@wi.mit.edu (R.A.W.)

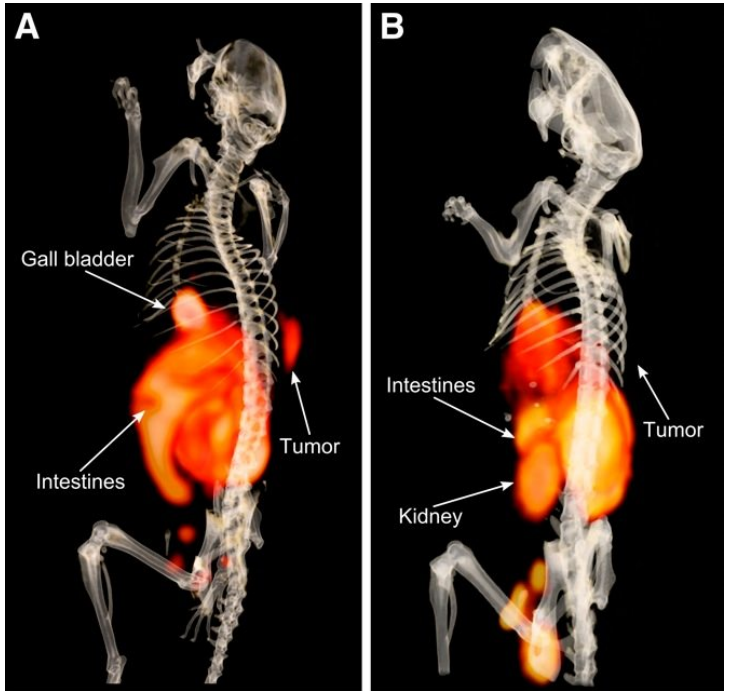




GRPr : Gastrin Releasing Protein receptor



In the Stomach tissues (Gastric acid)



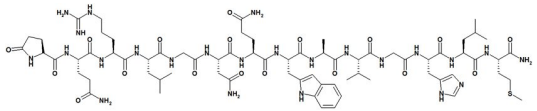
And also overexpressed in some cancer tissue

I. Dijkgraaf et al., JNM 53, 947 (2012)

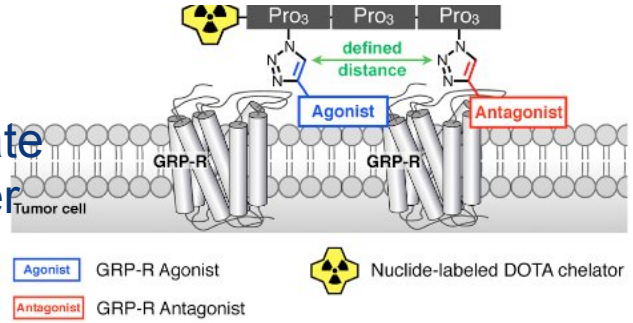
Trials in 2012

ICTR-PHE 2014

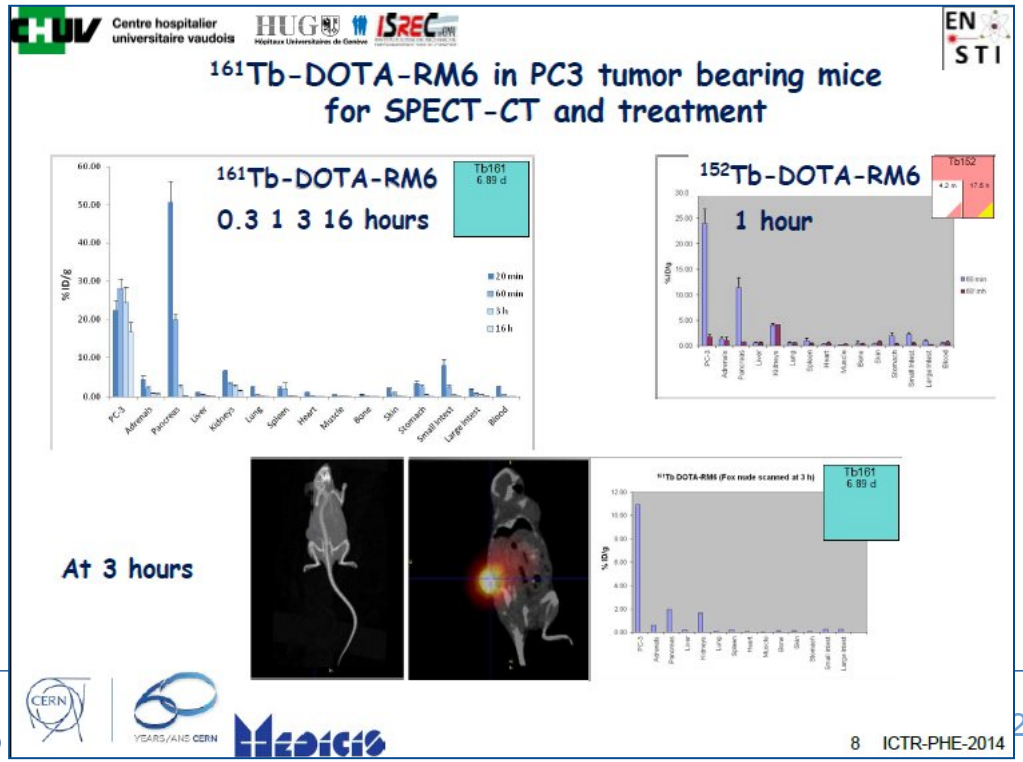
Bombesin analog from *Bombina bombina*



Prostate Cancer cells



152Tb Collected at ISOLDE



Neurokinin subtype I receptor (NK1R) is overexpressed in glioma cells and tumor v

11mer Substance P (SP) is member of the tachykin peptide neurotransmitters famil

SP:Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met

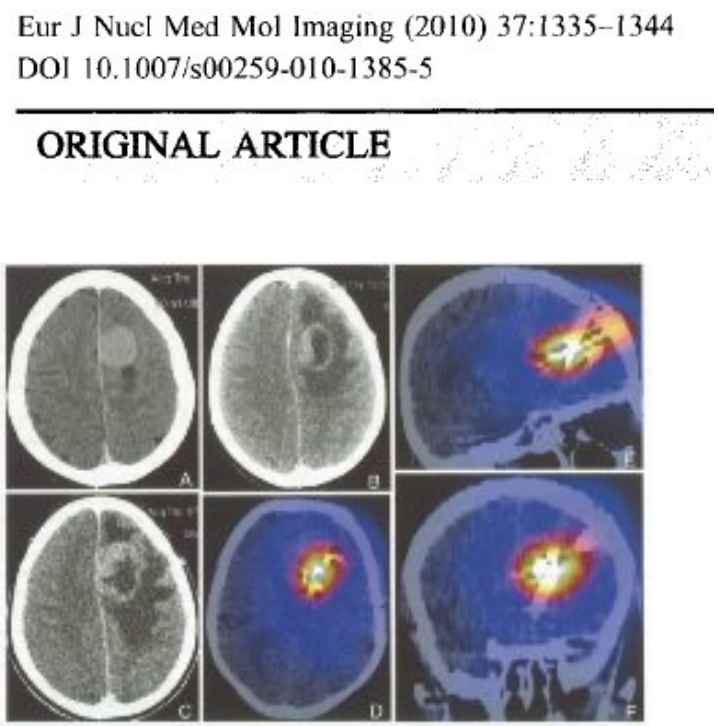
213Bi-DOTAGA-Arg1-SP
213Bi-DOTA-[Thi8,Met(O2)11]-SP

Neoadjuvant and adjuvant intracavity treatment before resection.

Comparaison with external radiotherapy

Therapeutic nuclear medicine (medical radiology series, R. P. Baum Ed, Springer, 2

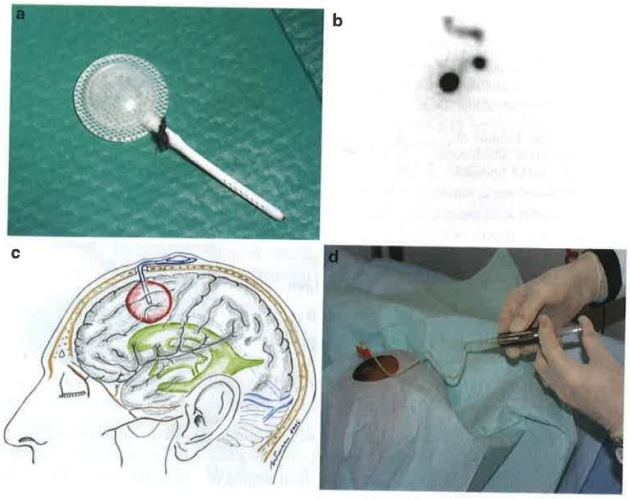
Collaboration with JRC-ITU



Cf prof. Merlo :

Intracavity injection+resection of Glioblastoma

Intracavity injection +resection of Glioblastoma



Targeted alpha-radionuclide therapy of functionally critically located gliomas with ^{213}Bi-DOTA-[Thi^{8},Met(O$_2$)^{11}]-substance P: a pilot trial

D. Cordier · F. Forrer · F. Bruchertseifer · A. Morgenstern · C. Apostolidis · S. Good · J. Müller-Brand · H. Mäcke · J. C. Reubi ·

Eur J Nucl Med Mol Imaging (2010) 37:1335–1344
DOI 10.1007/s00259-010-1385-5

ORIGINAL ARTICLE

Pat. No.	Age at Dx (years)	Diagnosis/location of tumour	Cycles/activity (GBq)	Tumour volume (cm^3)	Barthel Index pre-/post-therapeutic	PFS (months)	OS (months)
1	60	GBM frontal L callosal	1/1.07	41.6	75/ 90	2	16
2	40	GBM frontal L (SMA precentral)	1/1.92	76.0	80/ 90	11	19
3	55	Astro WHO grade III fronto-opercular L	4/7.36	74.3	100/100	24+	24+
4	33	Astro WHO grade II frontal R (SMA)	1/1.96	12.0	100/100	23+	23+
5	39	Astro WHO grade II occipital R	1/2.00	17.1	100/100	17+	17+

PFS progression-free survival, *OS* overall survival, + ongoing, *SMA* supplemental motor area, *L* left, *R* right, *Astro* astrocytoma, *GBM* glioblastoma multiforme, *Dx* diagnosis

Neurokinin subtype I receptor (NK1R) is overexpressed in glioma cells and tumor vessels

11mer Substance P (SP) is member of the tachykin peptide neurotransmitters family

SP:Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met

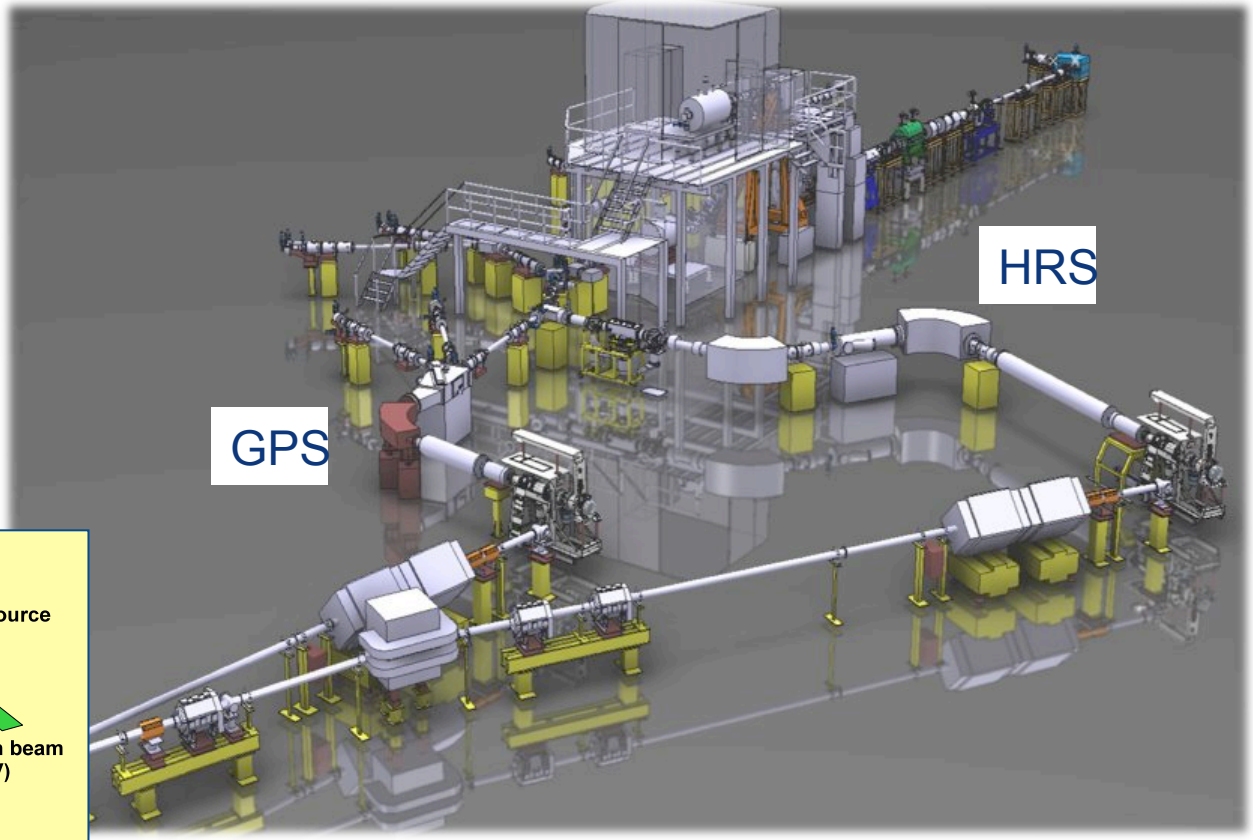
213Bi-DOTAGA-Arg1-SP
213Bi-DOTA-[Thi8,Met(O2)11]-SP

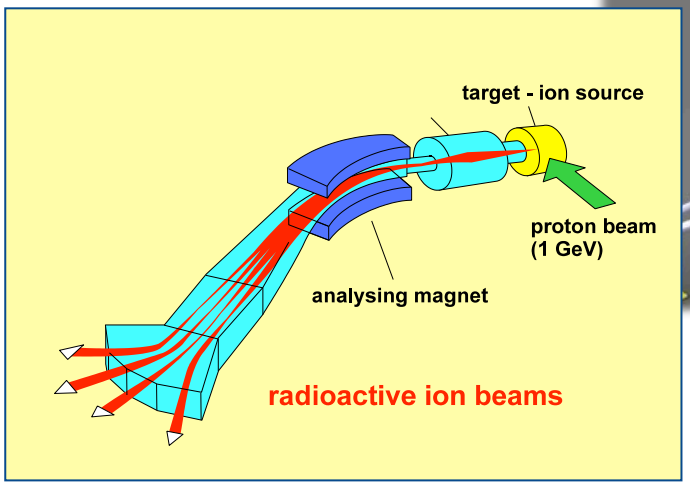
Neoadjuvant and adjuvant intracavity treatment before resection.

Comparaison with external radiotherapy

Therapeutic nuclear medicine (medical radiology series, R. P. Baum Ed, Springer, 2014)

Mass spectrometers





Click Chemistry

Click Chemistry: Diverse Chemical Function from a Few Good Reactions

Hartmuth C. Kolb, M. G. Finn, and K. Barry Sharpless*

Dedicated to Professor Daniel S. Kemp

Examination of nature's favorite molecules reveals a striking preference for making carbon–heteroatom bonds over carbon–carbon bonds—surely no surprise given that carbon dioxide is nature's starting material and that most reactions are performed in water. Nucleic acids, proteins, and polysaccharides are condensation polymers of small subunits stitched together by carbon–heteroatom bonds. Even the 35 or so building blocks from which these crucial molecules are made each contain, at most, six contiguous C–C bonds, except for the three aromatic amino acids. Taking our cue from nature's approach, we address here the development of a set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C–X–C), an approach we call "click chemistry". Click chemistry is at once defined, enabled, and constrained by a handful of nearly perfect "spring-loaded" reactions. The stringent criteria for a process to earn click chemistry status are described along with examples of the molecular frameworks that are easily made using this spartan, but powerful, synthetic strategy.

Keywords: combinatorial chemistry · drug research · synthesis design · water chemistry

1. Introduction:
Beyond the Paradigm of Carbonyl Chemistry

Life on Earth requires the construction of carbon–carbon bonds in an aqueous environment. Carbonyl (aldol) chemistry is nature's primary engine of C–C bond formation. Not only do the requisite carbon electrophiles (carbonyls) and nucleophiles coexist in water, but water provides the perfect environment for proton shuttling among reactants, which is required for reversible carbonyl chemistry.

With CO_2 as the carbon source and a few good carbonyl chemistry based reaction themes, nature achieves astonishing structural and functional diversity. Carbonyl chemistry is used to make a modest collection of approximately 35 simple building blocks, which are then assembled into biopolymers. The enzymatic polymers serve, in concert with increments of energy provided by adenosine triphosphate, as selective catalysts which prevent nature's carbonyl chemistry based syntheses from collapsing into chaos. Since many biosynthetic pathways require a unique enzyme for each step, the enzyme-control strategy required a heavy investment of time and resources for catalyst development. With a few billion years and a planet at her disposal, nature has had both time and resources to spare, but we, as chemists on a human timescale, do not.

Nevertheless, carbonyl-based reac… profoundly appealing to students an… chemistry. It is our contention tha… ducted, as it has been, in imitati… chemistry is ill-suited for the rapid di… with desired properties.

Many transformations that form… bonds are endowed with only a … driving force. In particular, equilibri… often energetically favorable by less… these processes to reach completio… additional "push" must be provided… Le Chatelier's principle (for exampl… water), by coupling the desired proc… reaction (for example, a strong "bas… by virtue of favorable entropic … intramolecular ring closure) without … as formation of strained rings). Thus… of one "equivalent" of ester, resonan…

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Dr. H. C. Kolb
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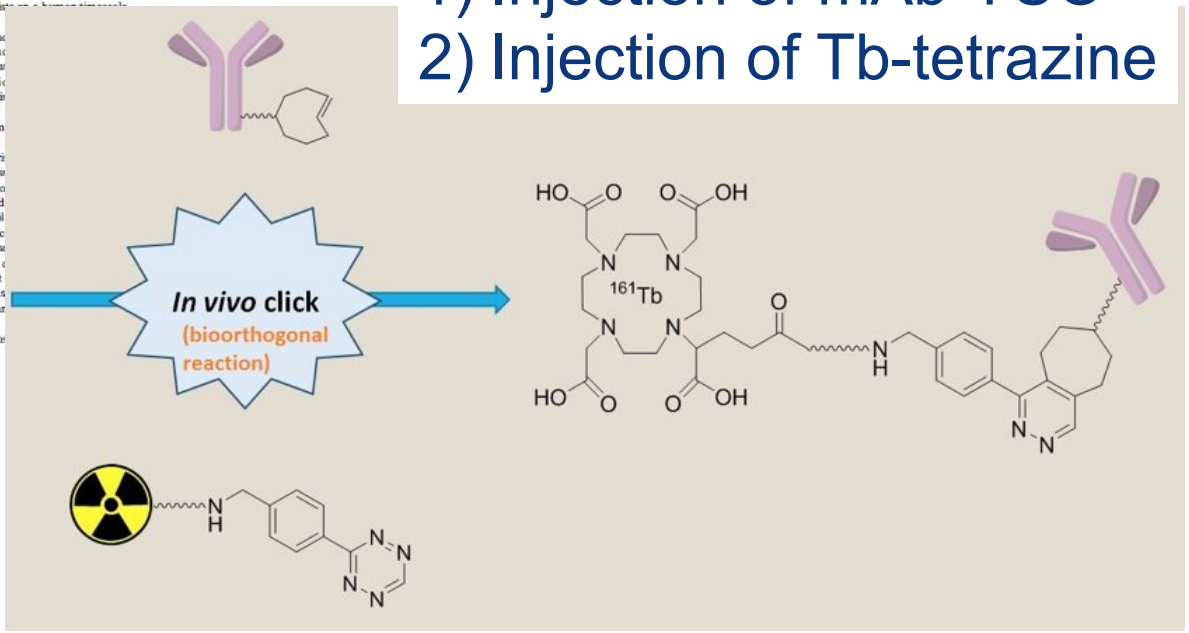
East Windsor, NJ 08520 (USA)

Angew. Chem. Int. Ed. **2001**, *40*, 2004–2021 1433-7851/01/4011-2005

Click = simple, fast, easily available, no/easy to remove solvent, simple isolation

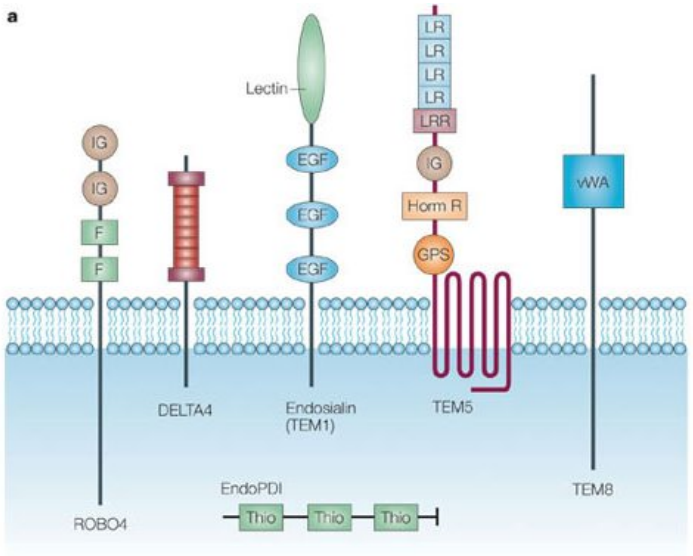
1) Injection of mAb-TCO
2) Injection of Tb-tetrazine



[ex. Tetrazine / *trans*-cyclooctene (TCO)

The Target : Tumor Endotelial Marker-1 (TEM1)

Overexpressed by:



Tumor Vessels

Tumor cells

Host microenvironment (fibroblasts, pericytes)

Morab 0004 (Clinical phase 2)

scFv78-Fc (78Fc)

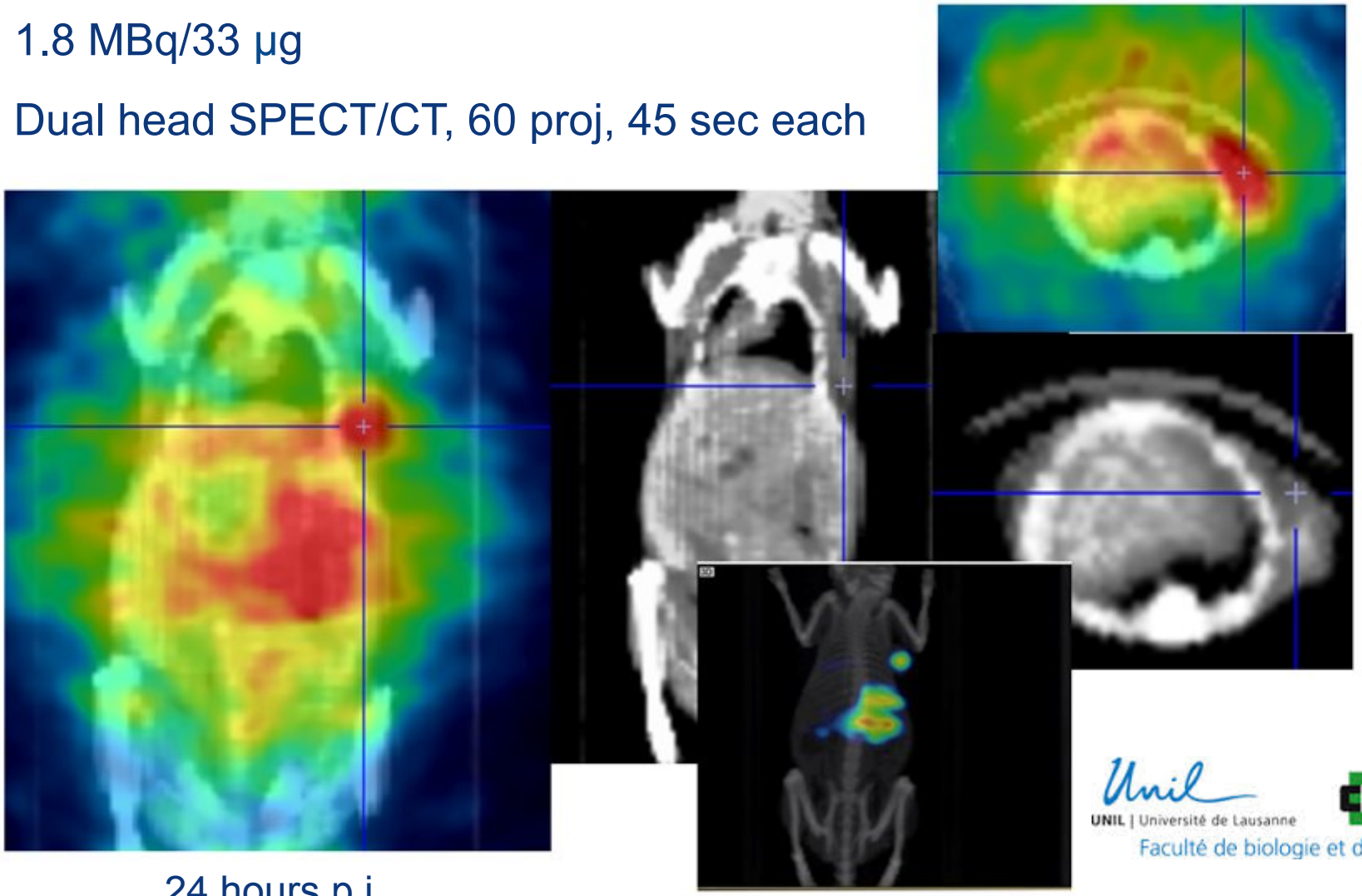
full IgG anti-TEM1

First SPECT imaging of ^{111}In-CHX-A”-DTPA-ScFv78Fc

Ewing Sarcoma cell line A673

1.8 MBq/33 µg

Dual head SPECT/CT, 60 proj, 45 sec each

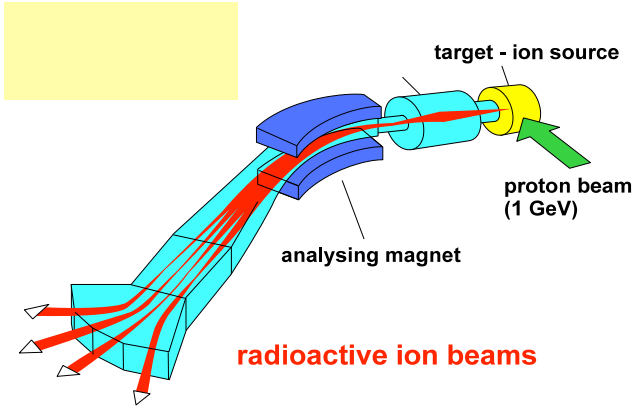


24 hours p.i.

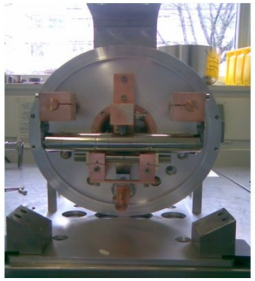
UNIL | Université de Lausanne
Faculté de biologie et de médecine

Cicone F et al. IRIST Conference, Lausanne 2016

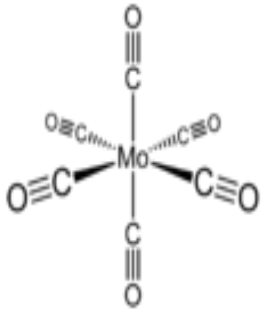
R&D towards Mo-99/Tc-99m mass separation at CERN-MEDICIS



- Method similar to that found in a neutron spallation facility (SNS, ESS, JSNS, ISIS, etc)



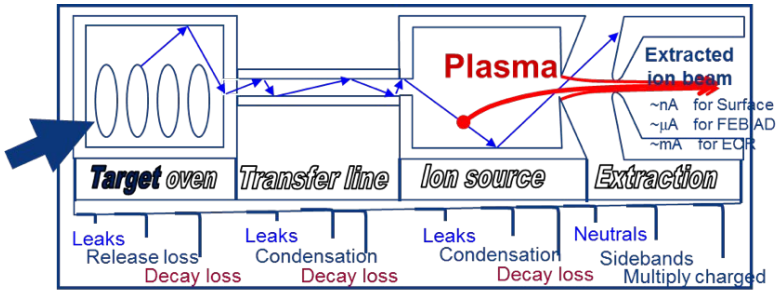
- ^{238}U is fissioned by fast neutrons to produce Mo
- Requires the use of μm thick ^{238}U metallic foil target for fission recoil
- However Mo is a refractory element, it cannot be released in atomic form.
- Our plan: react it with CO gas. Forms a complex which is volatile.



Formation of $Mo(CO)_6$ complex already achieved

J. Even, et al Radiochim Acta 2014

R&D towards Mo-99/Tc-99m mass separation at CERN-MEDICIS



Some challenges:
How to ionize $Mo(CO)_6$?

In order to form coordination complex, CO gas pressure should be high, however in order for the ion source to operate we require a low gas pressure. Potential solutions are the subject of current research.

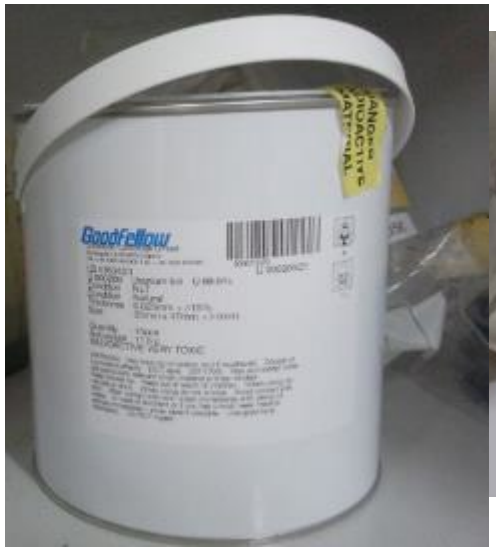
Ion source choices:

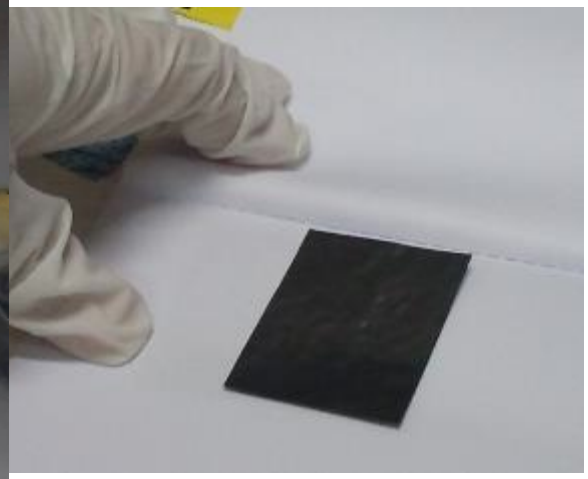
- Plasma ion source
  - Will complex survive this ion source?
- RF ion source

L. Penescu, et al. "Development of high efficiency Versatile Arc Discharge Ion Source at CERN ISOLDE." Review of Scientific Instruments 81.2 (2010): 02A906.
T. Stora, "Radioactive Ion Sources", CERN-2013-007, p331.

R&D towards Mo-99/Tc-99m mass separation at CERN-MEDICIS

- $Mo(CO)_6$ not very stable – can easily oxidize and dissociate at high temperature
- Requires the use of μm thick ^{238}U metallic foil target for fission recoil out (25 micron ^{nat}U foils) at low temperature
- Grow graphene:
  does not stop recoil isotopes, reduce oxidation and taylor $Mo(CO)_6$ adsorption





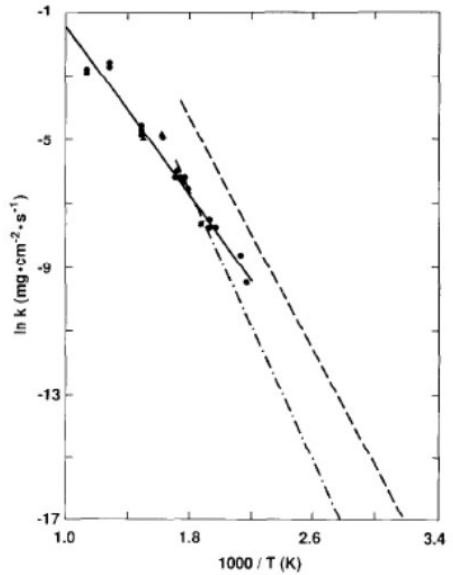


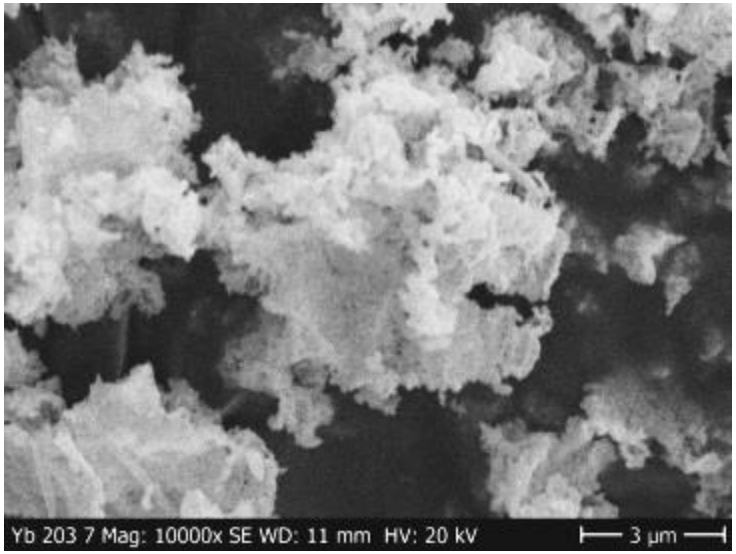
Fig. 4. Comparison of Ar–25% O_2 oxidation rates (circles) with dry-air oxidation rates from eqs. (6) (dashed line) and (7) (dot–dashed line) and from ref. [16] (triangles).

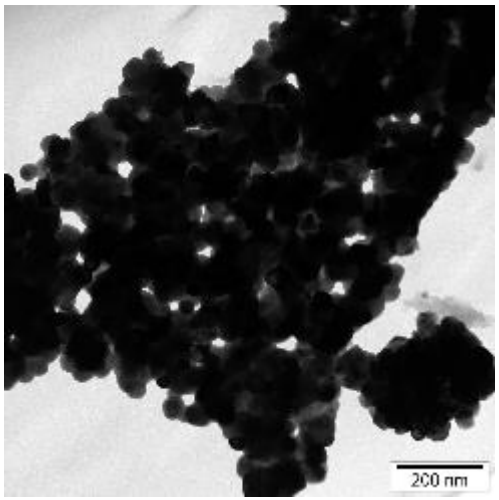
K.S. Novoselov and AH Castro Neto. "Two-dimensional crystals-based heterostructures: materials with tailored properties." Physica Scripta 2012.T146 (2012): 014006.
D. Prasai, et al. "Graphene: corrosion-inhibiting coating." ACS nano 6.2 (2012): 1102-1108.

P.J. Hayward et al., J. Nucl. Mat 187, (1992)

R&D towards Mo-99/Tc-99m mass separation at CERN-MEDICIS

- Alternative target materials : towards submicron uranium-based materials
- Work has started as with lanthanide precursors via electrospinning





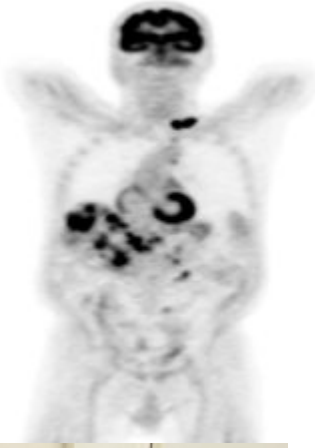
M. S. Henriques, et al. "Preparation of Yb2O3 submicron-and nano-materials via electrospinning." Ceramics International 41(9), 10795 (2015).

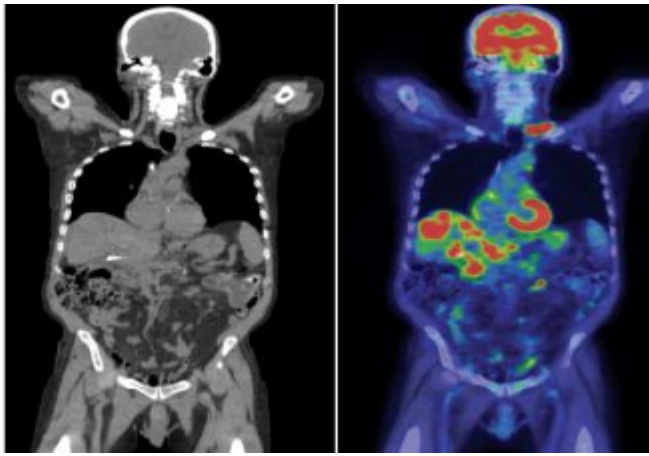
Tentative planning

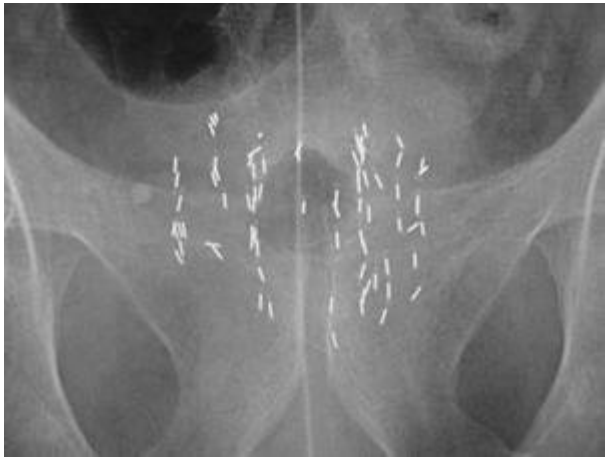
Phase	Action	Date
PHASE I	Commissioning: without beam (*)	2016
PHASE II	Commissioning with beam and light targets to gain operational experience	2017
PHASE II B	Isotope production with light targets	Mid 2017
PHASE III	Extending to heavy targets up to Tantalum	End 2017
PHASE IV	Collection of short lived alpha emitters (e.g. 149Tb)	2018
PHASE IV B	Operation with lasers	2018
PHASE V	Operation with uranium targets/possible proton beam upgrade	2019

* Preferable but may be hard to achieve

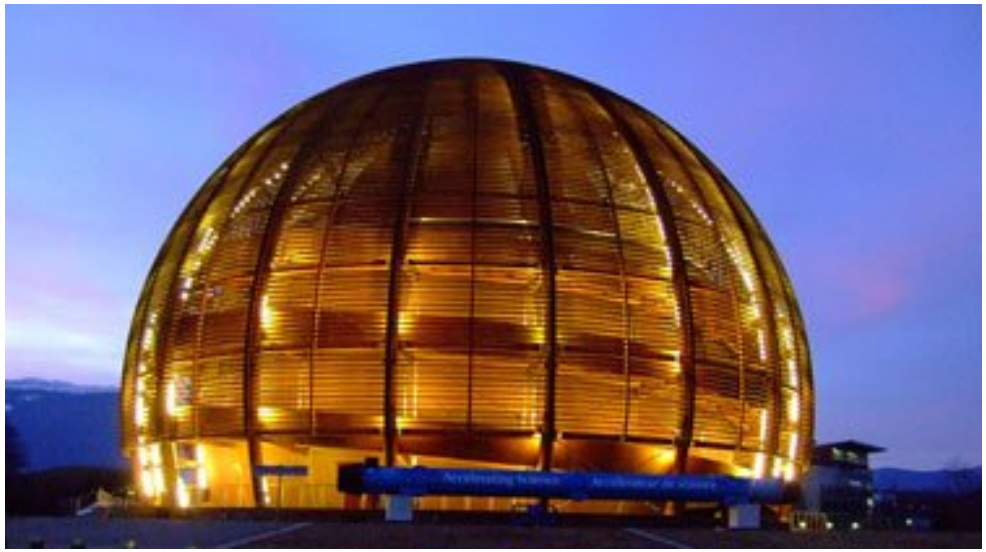
Plan for development of surgical methods (L. Buehler)







Outreach



1st Grace-MEDICIS collaboration/public lecture took place on 15th October 2014

The 2nd is in preparation : Prof W. Weber,

Memorial Sloan Kettering Cancer Center

Prof Doug Hanahan

Director ISREC Lausanne

AACR's Lifetime Achievement Award