Radioactive Ion Beams for Medical Applications II :

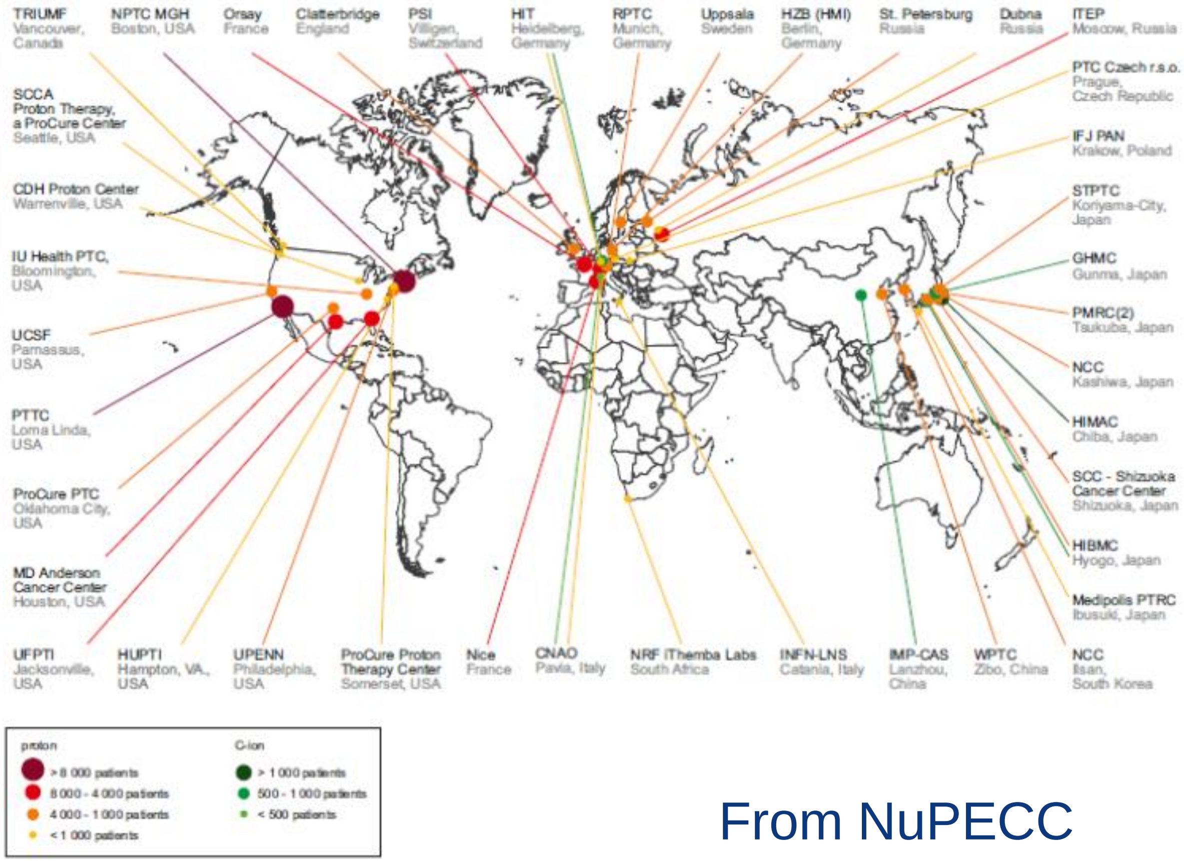
CERN-MEDICIS, non-conventional radioisotopes for medical applications

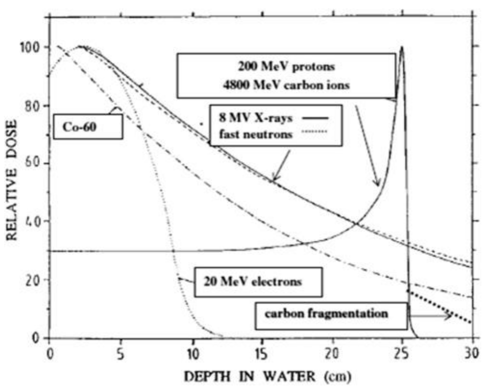
Thierry.stora@cern.ch

University of Oslo,

Spring workshop on nuclear and particle physics

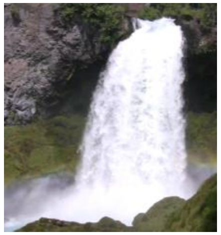
World map of hadrontherapy centers

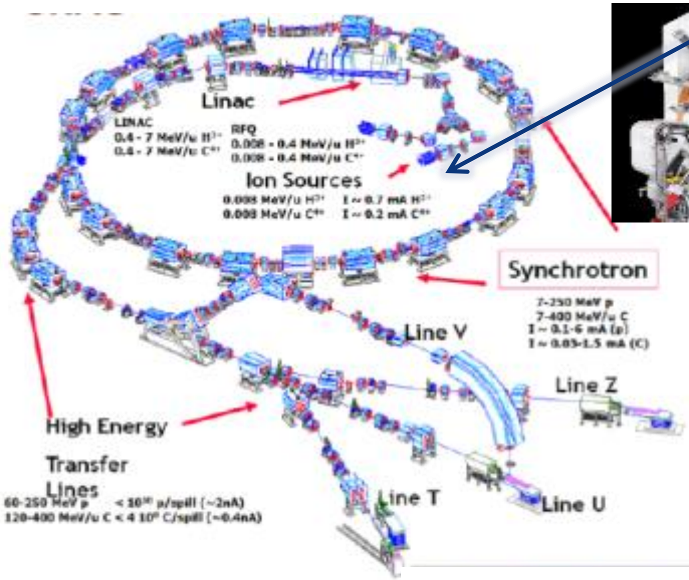


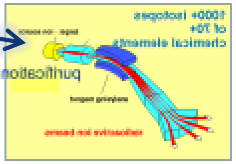


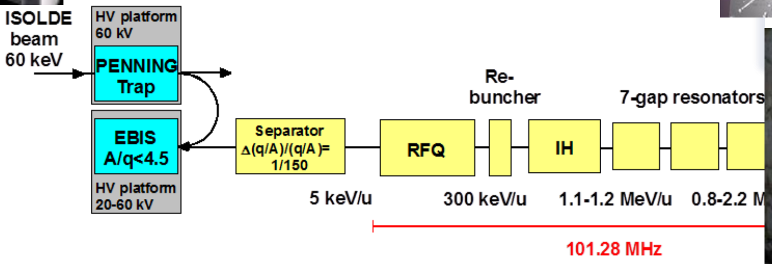
From NuPECC 2013

Possible acceleration schemes : efficiencies matter









"A la Isolde"

Directly in the ECRIS

Ion. eff. Trap & EBIS Linac Synchrotron

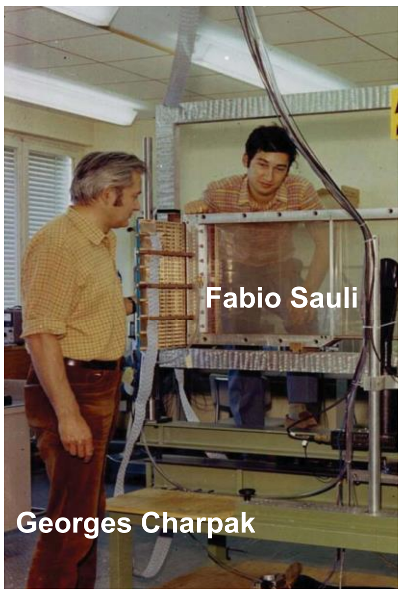
$$0 \xrightarrow{5\%} 1^+ \xrightarrow{45\% \;\&\; 30\%} 4^+/6^+ \xrightarrow{90\%} \text{Injection} \xrightarrow{60\%} \text{Ejection}$$

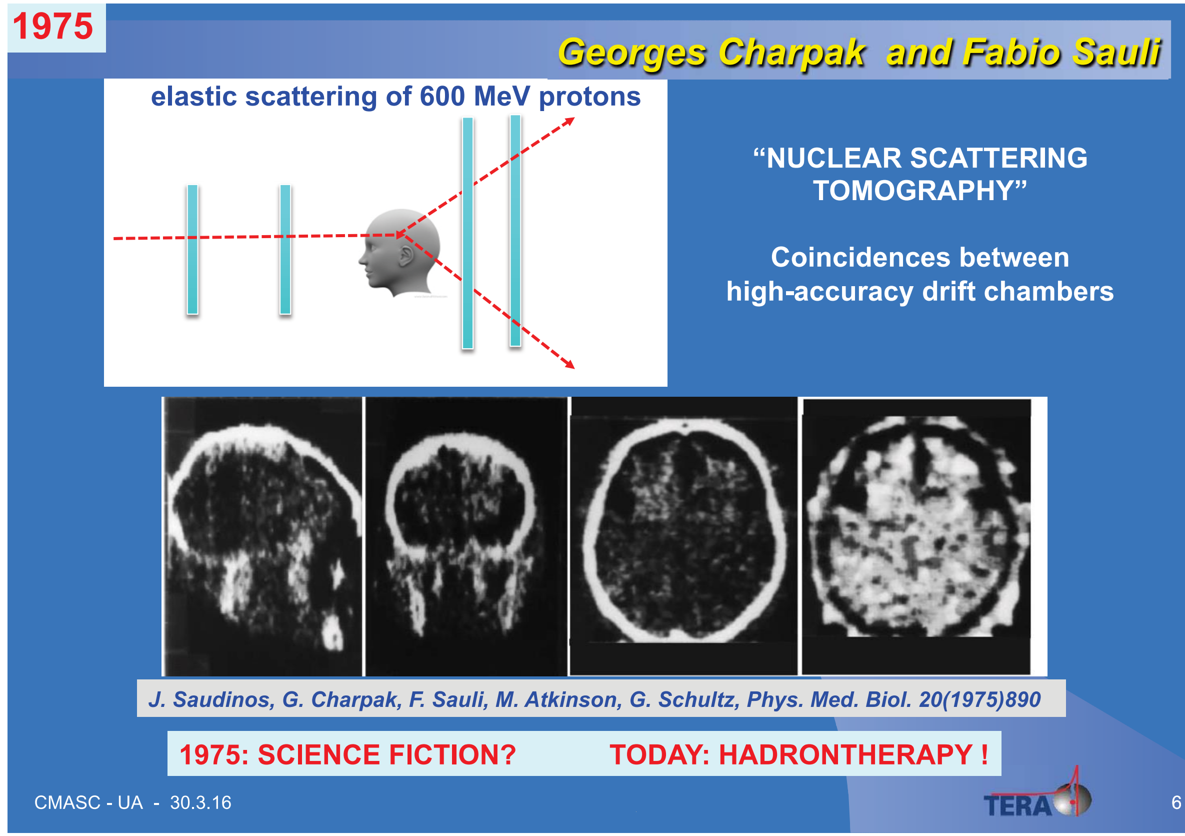
Main parameters for ^{11}C production.

Method	Cyclotron		Target	Reaction	In target production [pps]	Trap charging time (ms)	Injector [p/injection cycle]	Injector repetition rate [Hz]
	E [MeV]	I[μA]						
PET production (production batch)	22	150	N_2 (⩽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)

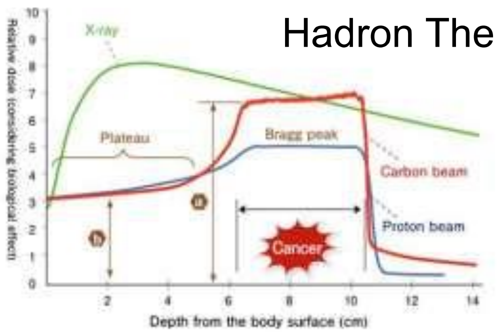
Pioneering input from well known physicists

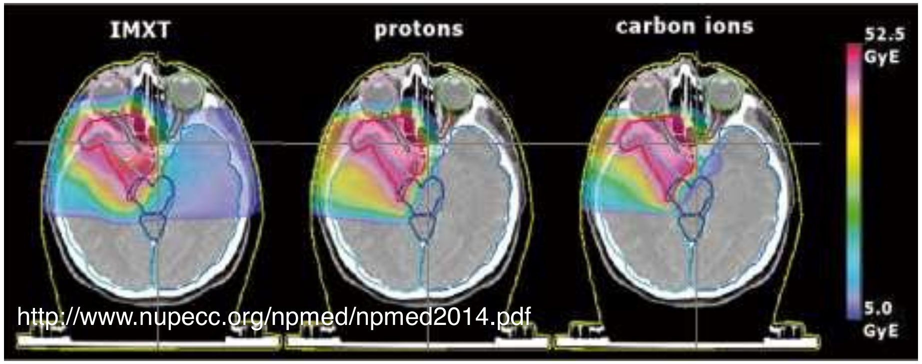


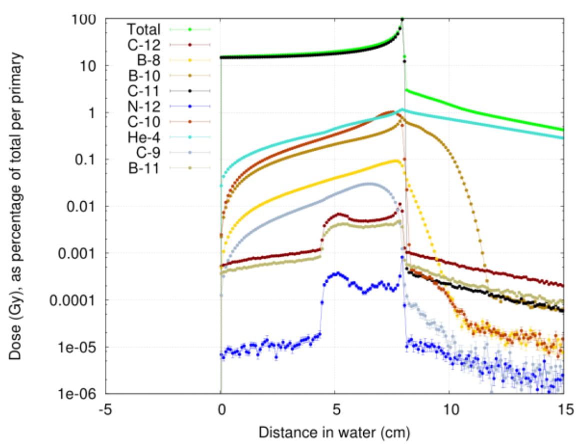


^{11}C Beams for combined PET/Hadron therapy

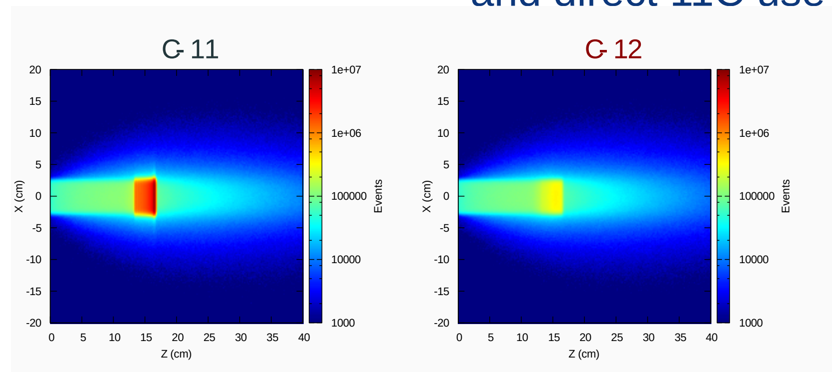
Hadron Therapy

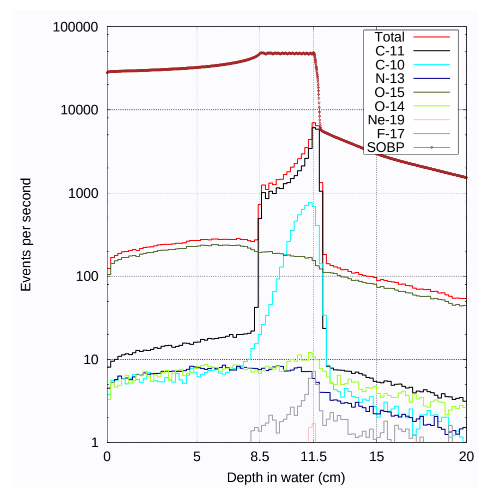




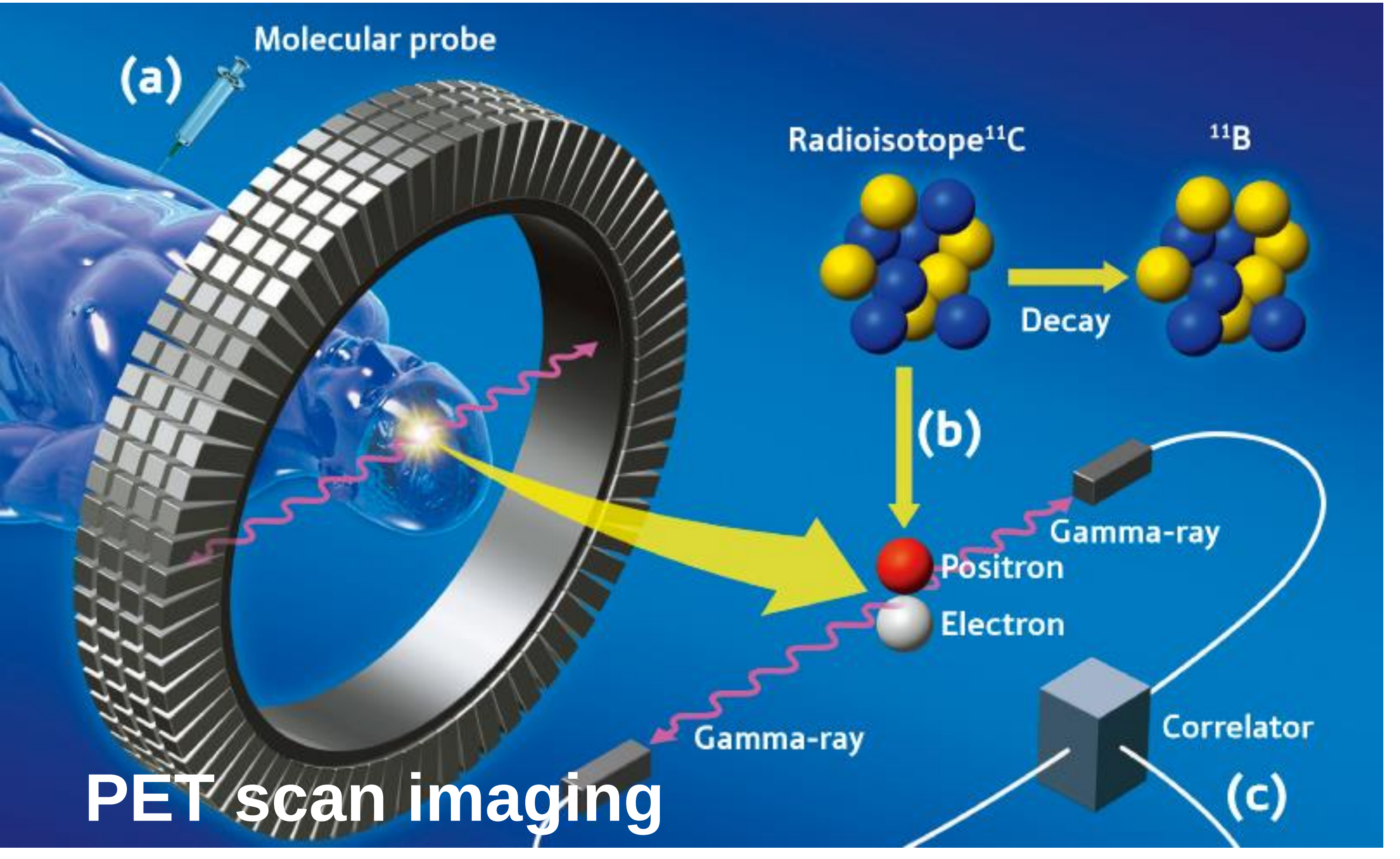


Comparison of
in-beam PET with fragment 12C (11C, 15O)
and direct 11C use

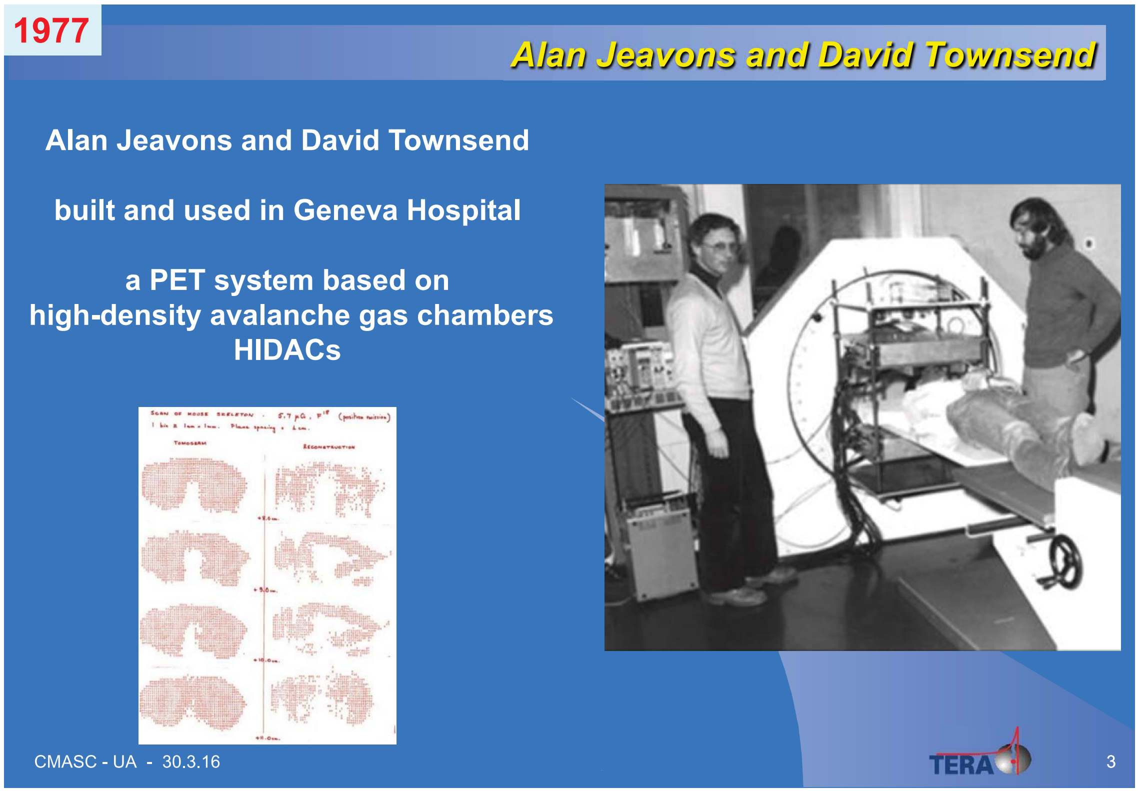




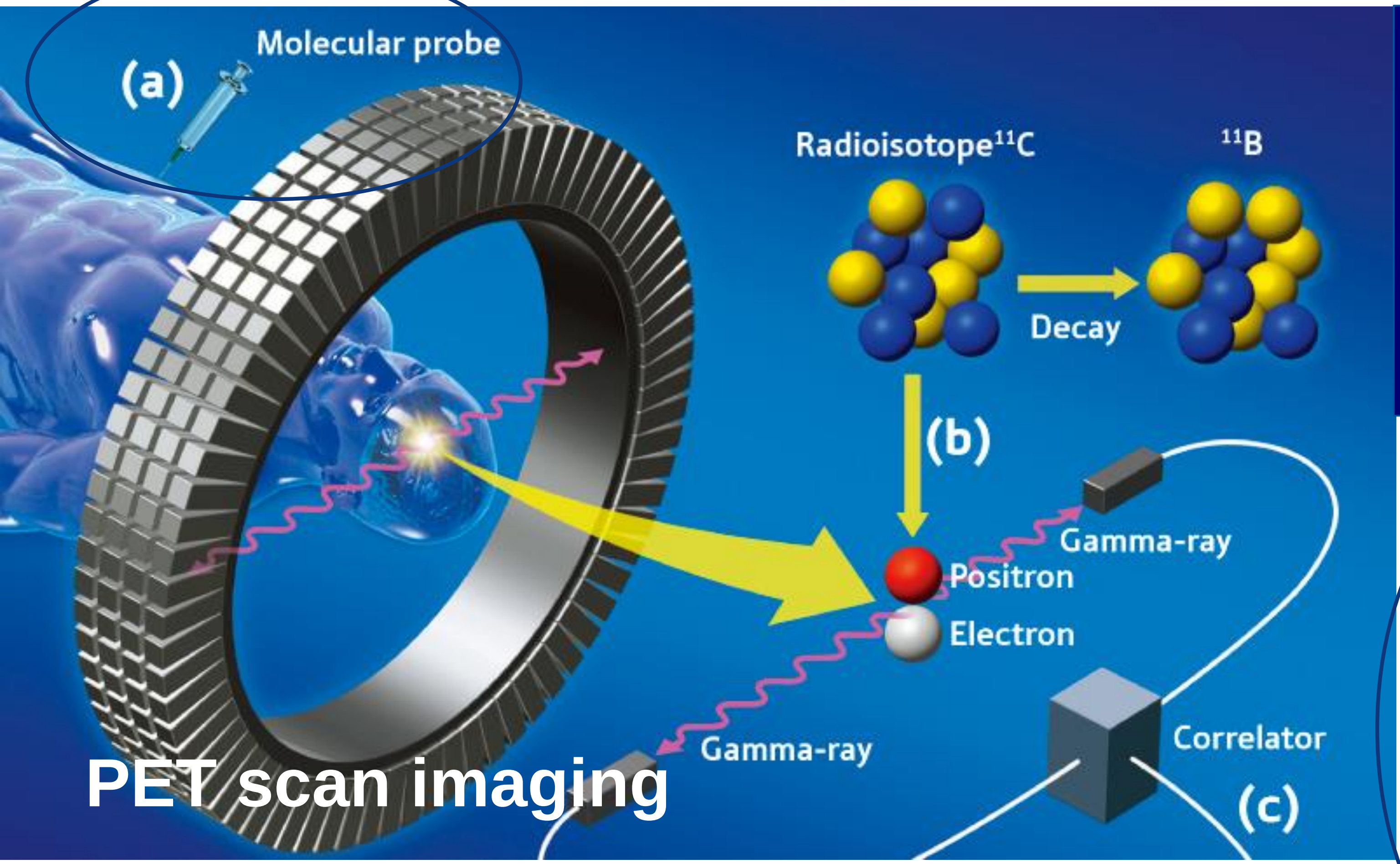
^{11}C Principle of PET scan imaging

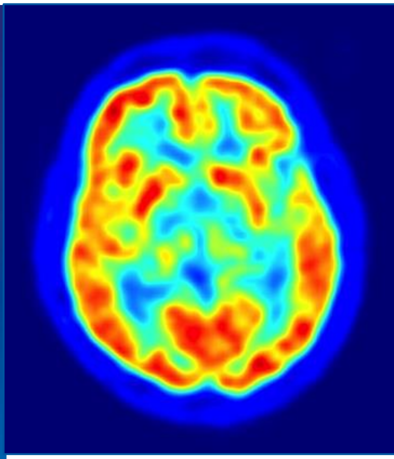


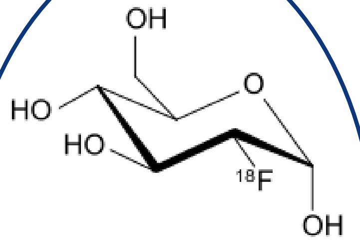
PET-CT scan imaging



PET scan in nuclear medicine : using molecular probes







Fluorodésoxyglucose (^{18}F)

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NATURE | NEWS FEATURE

Radioisotopes: The medical testing crisis

With a serious shortage of medical isotopes looming, innovative companies are exploring ways to make them without nuclear reactors.

Richard Van Noorden

11 December 2013

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Classification of isotopes for Medicine:

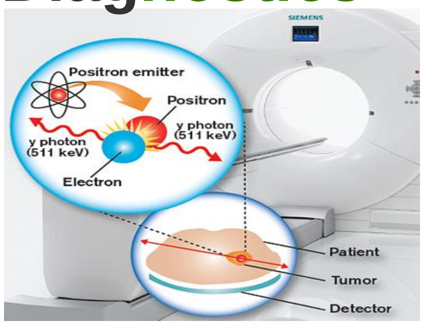
1. Established isotopes > Industrial suppliers
^{99m}Tc, ^{18}F, ^{123,125,131}I, ^{111}In, ^{90}Y

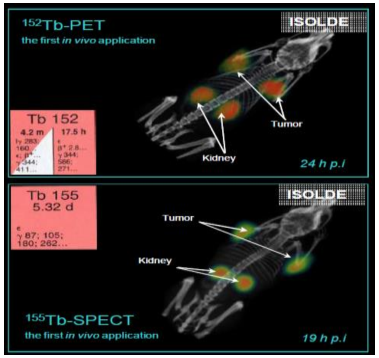
2. Emerging isotopes > Small innovative suppliers
^{68}Ga, ^{82}Rb, ^{89}Zr, ^{177}Lu, ^{188}Re

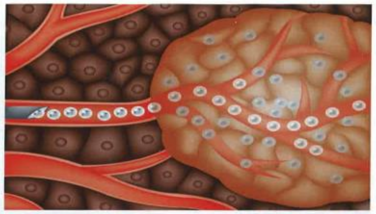
3. R&D isotopes > Research labs
^{44,47}Sc, ^{64,67}Cu, ^{134}Ce, ^{140}Nd, $^{149, 152, 155, 161}$Tb, ^{166}Ho, ^{195m}Pt, ^{211}At, $^{212, 213}$Bi, ^{223}Ra, ^{225}Ac,…

New concept of THERAnostics pairs

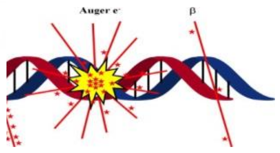
Diagnostics

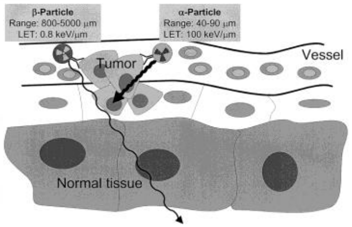






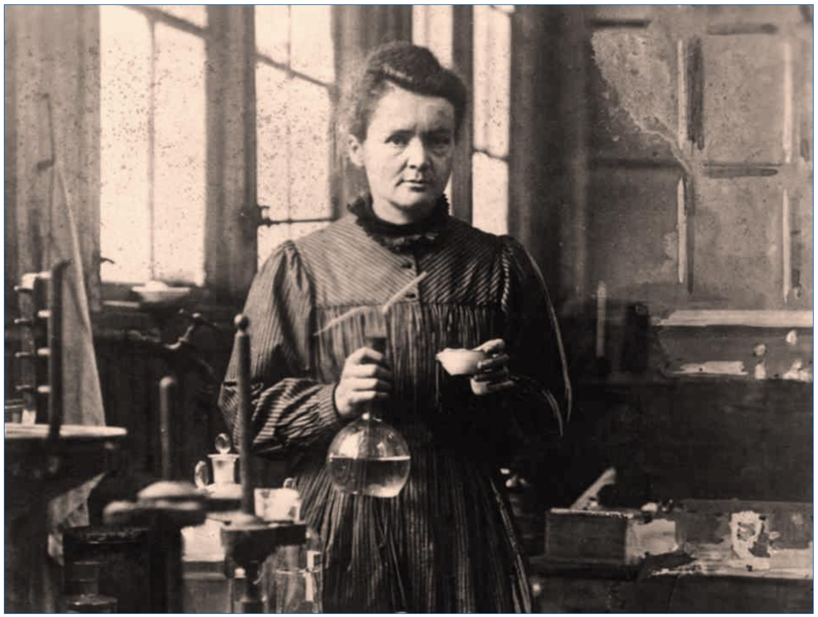
THERAPY





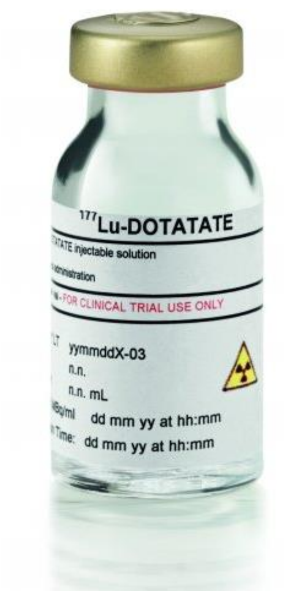
New radiopharmaceuticals for therapy

Xofigo® has been approved by the FDA (Food Drug Administration) and in Europe for castration resistant prostate cancer with metastasis



1921

2015



2017

Courtesy prof O. Ratib

Advantages: it will target the dispersed tumours

While flying in 2015
to a workshop in Manchester

100 Advertorial

Mikrokugeln gegen Leberkrebs
Tiny beads used to treat liver cancer

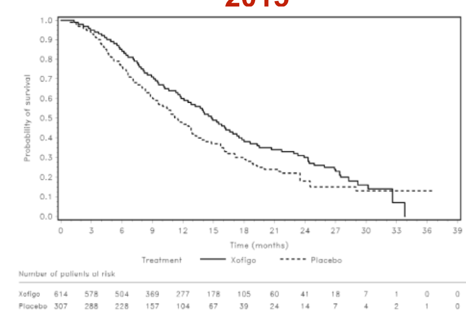
Die Hirslanden Klinik St. Anna in Luzern führt eine neuartige Behandlung für Lebertumore durch, bei der hohe Strahlungsdosen mittels kleinster Kügelchen direkt in die Tumore injiziert werden.

Hirslanden Klinik St. Anna in Lucerne, Switzerland, provides a new high-dose radiotherapy treatment for liver tumours which works by injecting tiny beads straight into the tumours.

Courtesy Prof. Ratib, ITMI Geneva

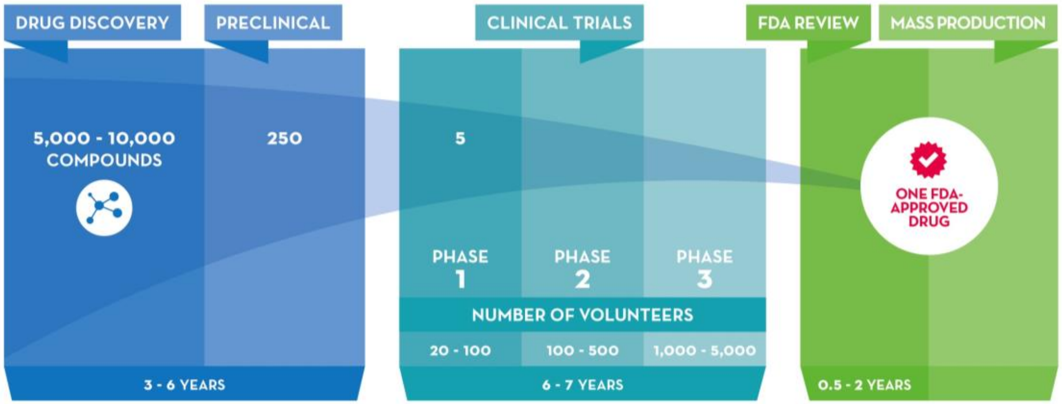
Figure 1 – Courbes de survie globale de Kaplan-Meier (analyse actualisée)

2015



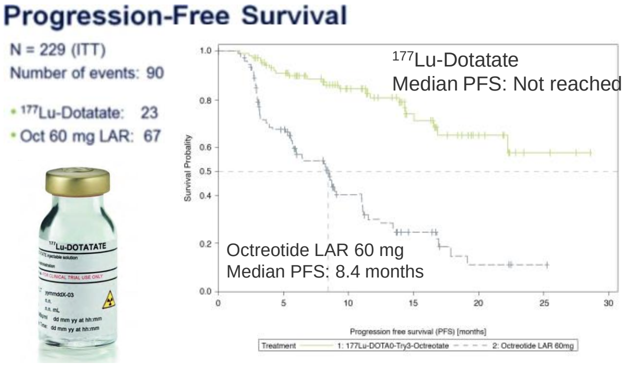
ALSYMPCA Phase III clinical trial
http://omr.bayer.ca/omr/online/xofigo-pm-fr.pdf

Drug development cycle



NETTER 1 Phase III Clinical trial for Luthatera®

Carcinoid Tumor of the Small Bowel
Neuroendocrine Tumour



Jonathan Strosberg et al. J Nucl Med 2016;57:629

What do we need to know for « useful isotopes ? »

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

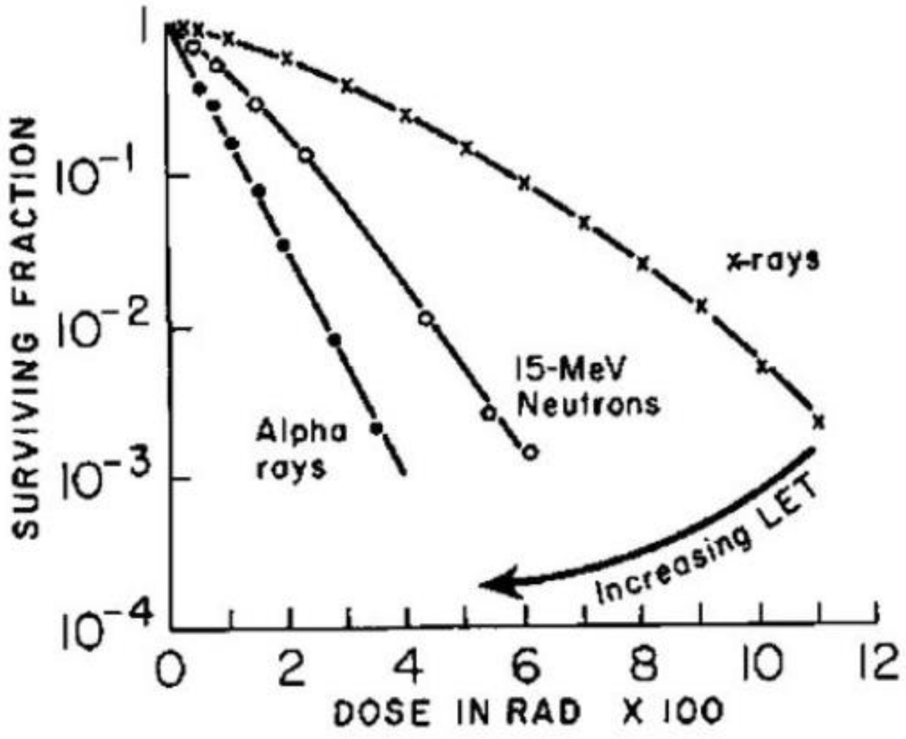
Estab-lished isotopes

Emerging isotopes

R&D isotopes: supply-limited!

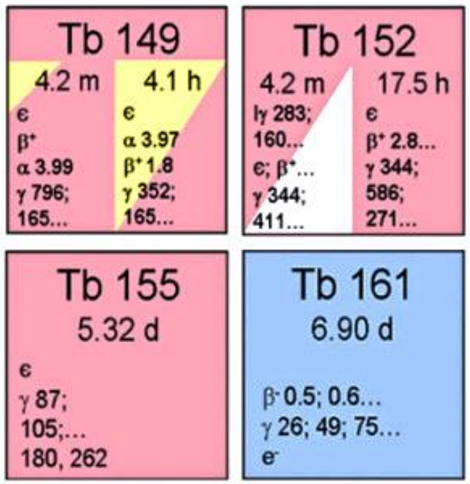
localized

We also need to know the Relative Biological Effectiveness

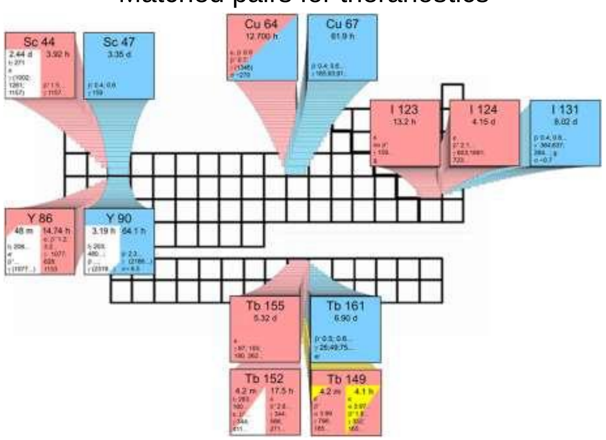


Nuclear Physics : ISOLDE and MEDICIS

14 years ago – now :
Innovative radioisotopes



Matched pairs for theranostics

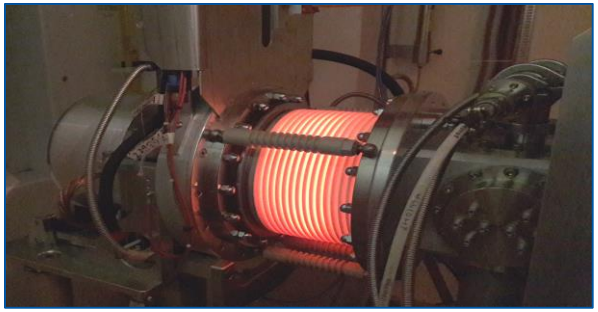


CERN-MEDICIS : A new facility

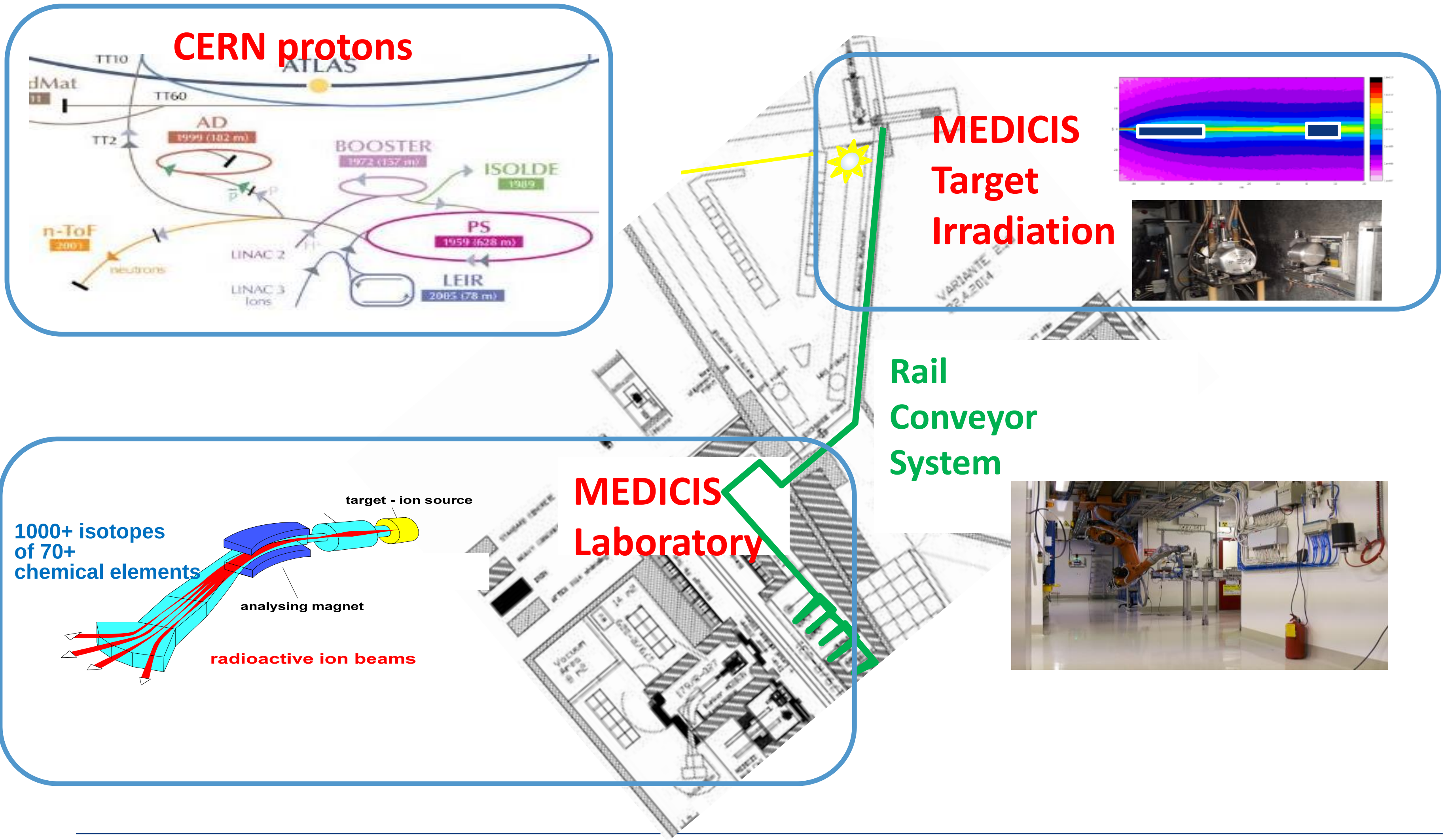
September 2013

October 2014

Today:



Full cycle of isotope production



Non exhaustive isotope availability estimates

Medical pplication	Isotope half-life	Parent isotope beam	Target - Ion source	ISOLDE† In-target Production rate (pps)	ISOLDE† In-target ActivityEOB (Bq)	RIB Ɛext** (%)	CERN-MEDICIS† In-target ActivityEOB (Bq)	CERN-MEDICIS† Extracted Activity EOB (Bq)	CERN-MEDICIS 2GeV 6μA Possible gain Ɛext (%)	CERN-MEDICIS 2GeV 6μA In-target Activity EOB (Bq)	CERN-MEDICIS 2GeV 6μA Extracted Activity EOB (Bq)	Comments
3- therapy/ ːT/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
ιuger 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
ι 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

^{40}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

CERN-MEDICIS partners : 1st Board in February

- Dr. Forni (Clin. Carouge, Geneve)
- Prof. Morel, Prof. Buehler, Prof. Ratib, Prof Walter (HCUGE, Geneve)
- Prof. R. Jolivet (CERN/UNIGE, Geneve)
- Prof. D. Hanahan (ISREC), Prof A. Pautz (EPFL, Lausanne)
- Prof. J. Prior (CHUV, Lausanne)
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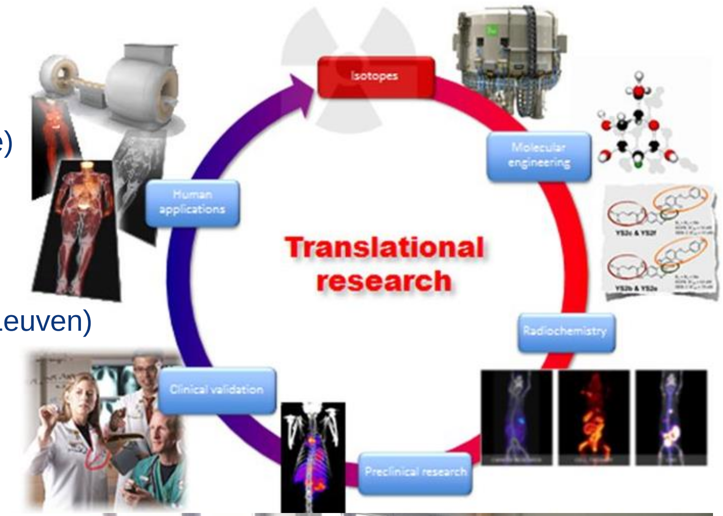
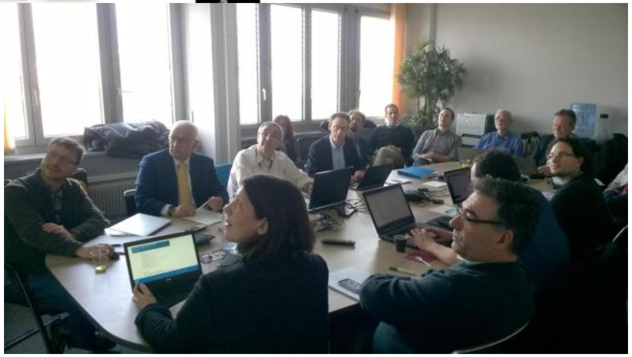
- Dr. Owen, EANM

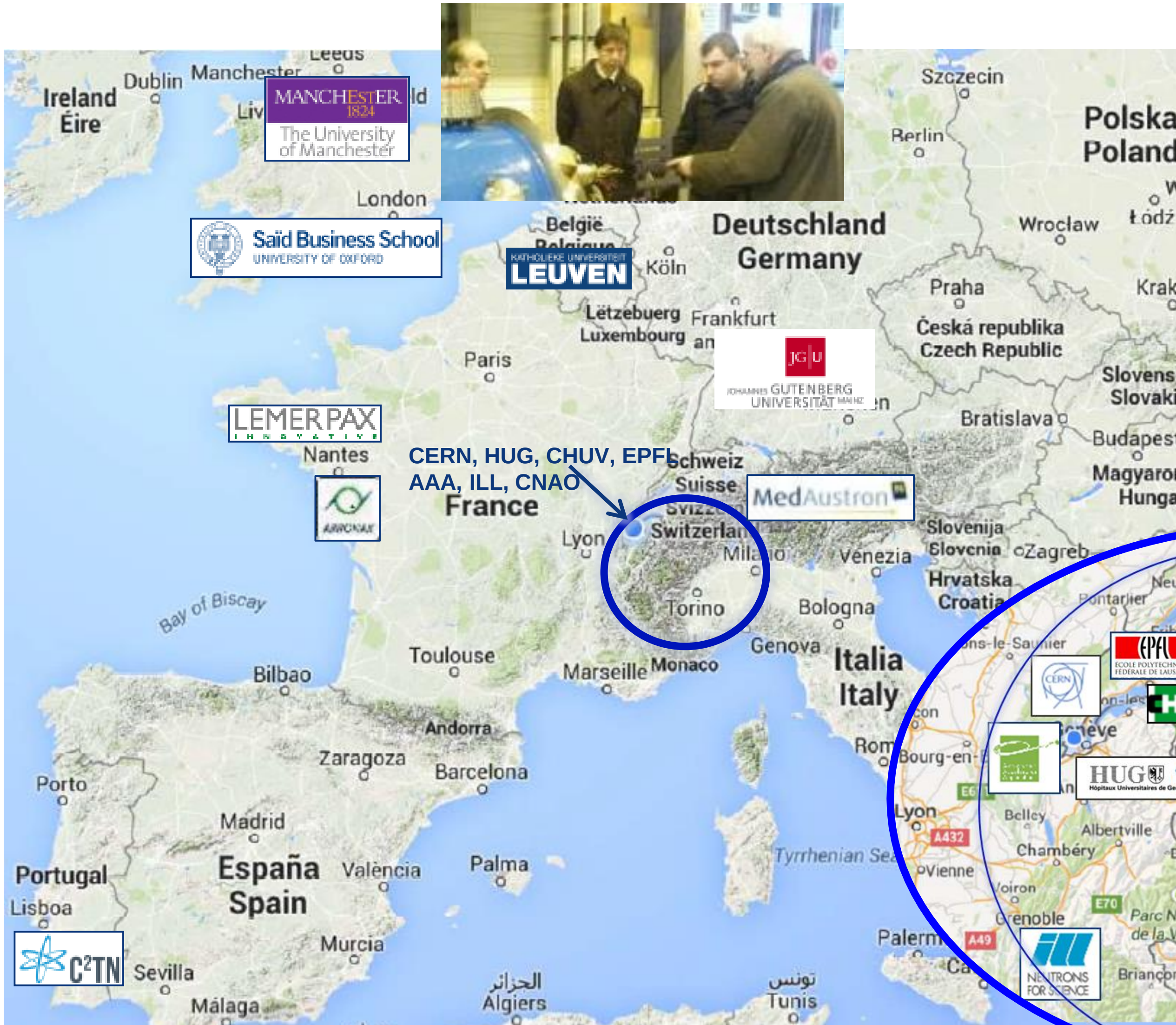


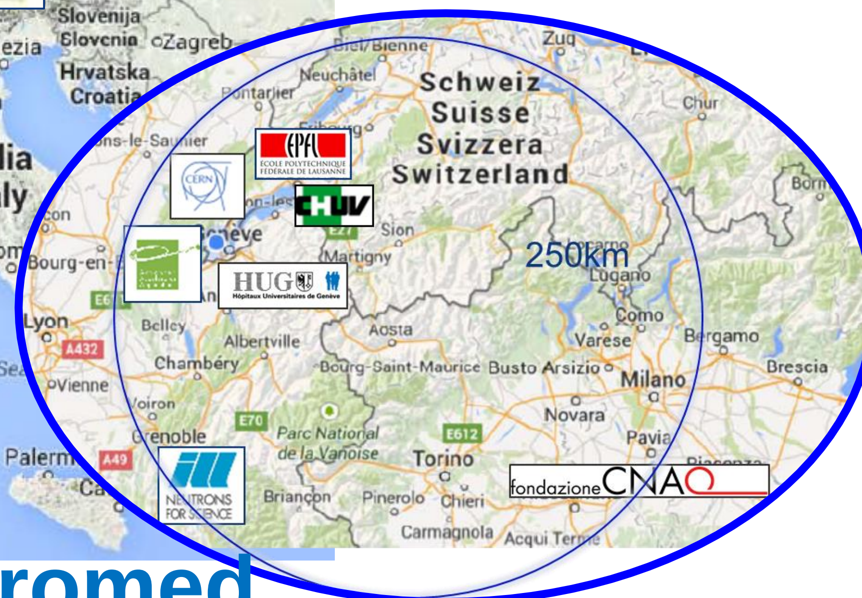


A marie-curie training network

MEDICIS Promed

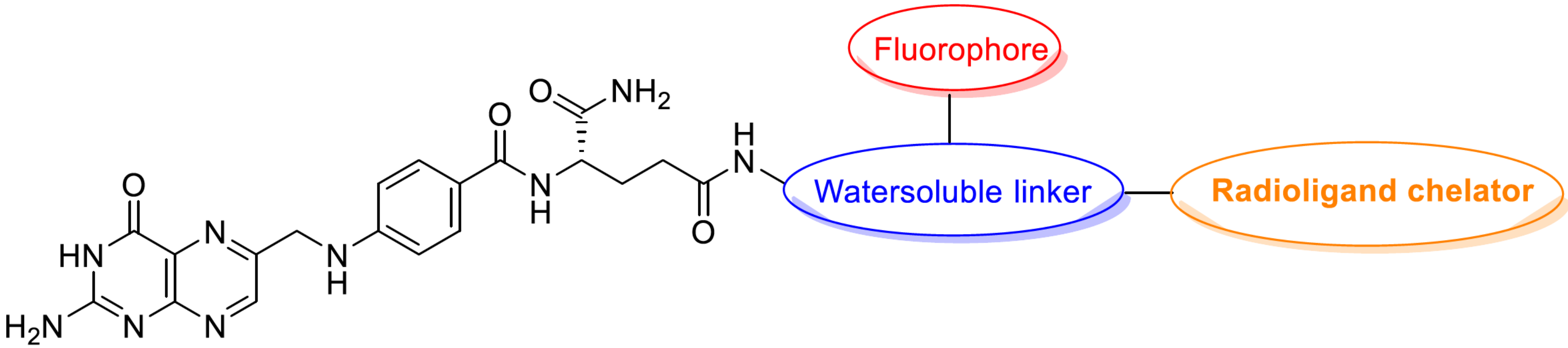
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 642889





www.cern.ch/medicis-promed

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



Folate bioconjugate with fluorescence and radioligand chelator
Prof Goun, EPFL

Link to experimental (neuro)-surgery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23 SEP 2015
CERN and the JRC to scale up production of alpha-emitters against cancer
A novel, accelerator-driven method could produce nuclides for targeted alpha therapy of cancer in practically unlimited amounts, overcoming current obstacles for its wider use due to a limited production of alpha-emitters. The JRC and the Conseil Européen pour la Recherche Nucléaire (CERN) have embarked to explore the potential of the jointly proposed method.
The method for production of
Current radiotherapy against cancer mostly uses beta-emitters as medical isotopes
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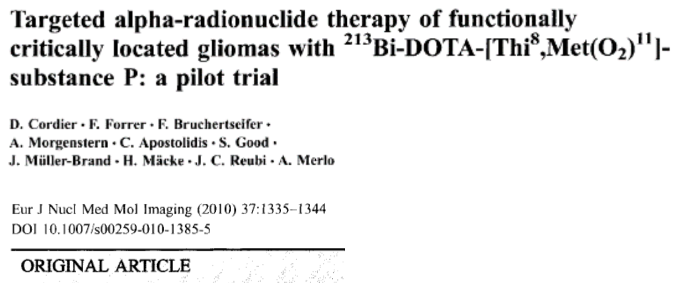
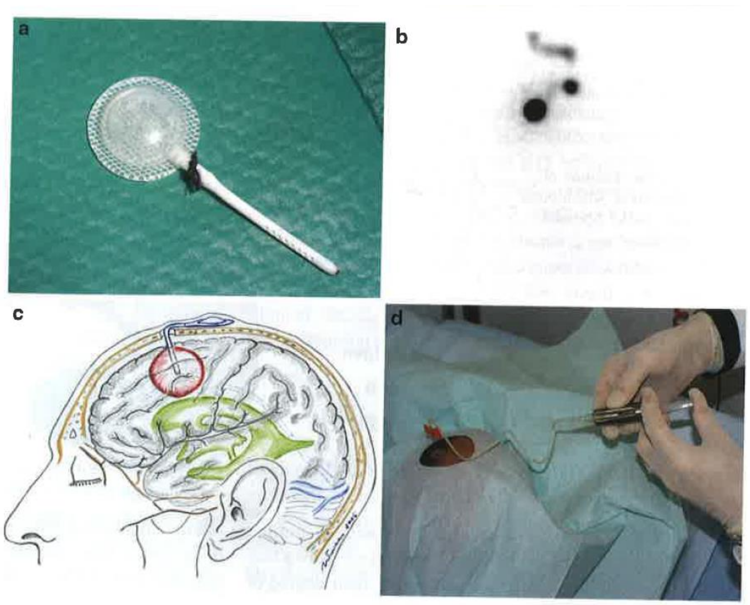
JRC Institutes
ITU

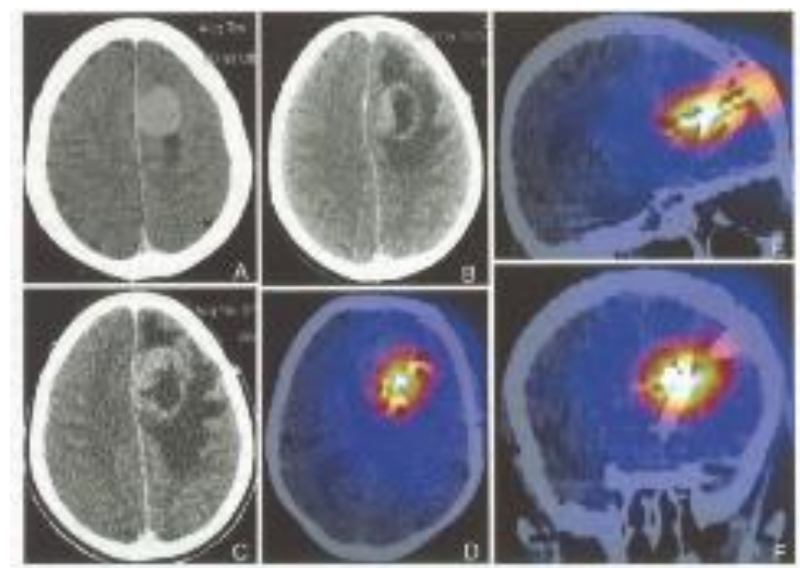

Targeted alpha-radionuclide therapy of functionally critically located gliomas with ^{213}Bi-DOTA-[Thi^{8},Met(O$_2$)^{11}]-substance P: a pilot trial

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

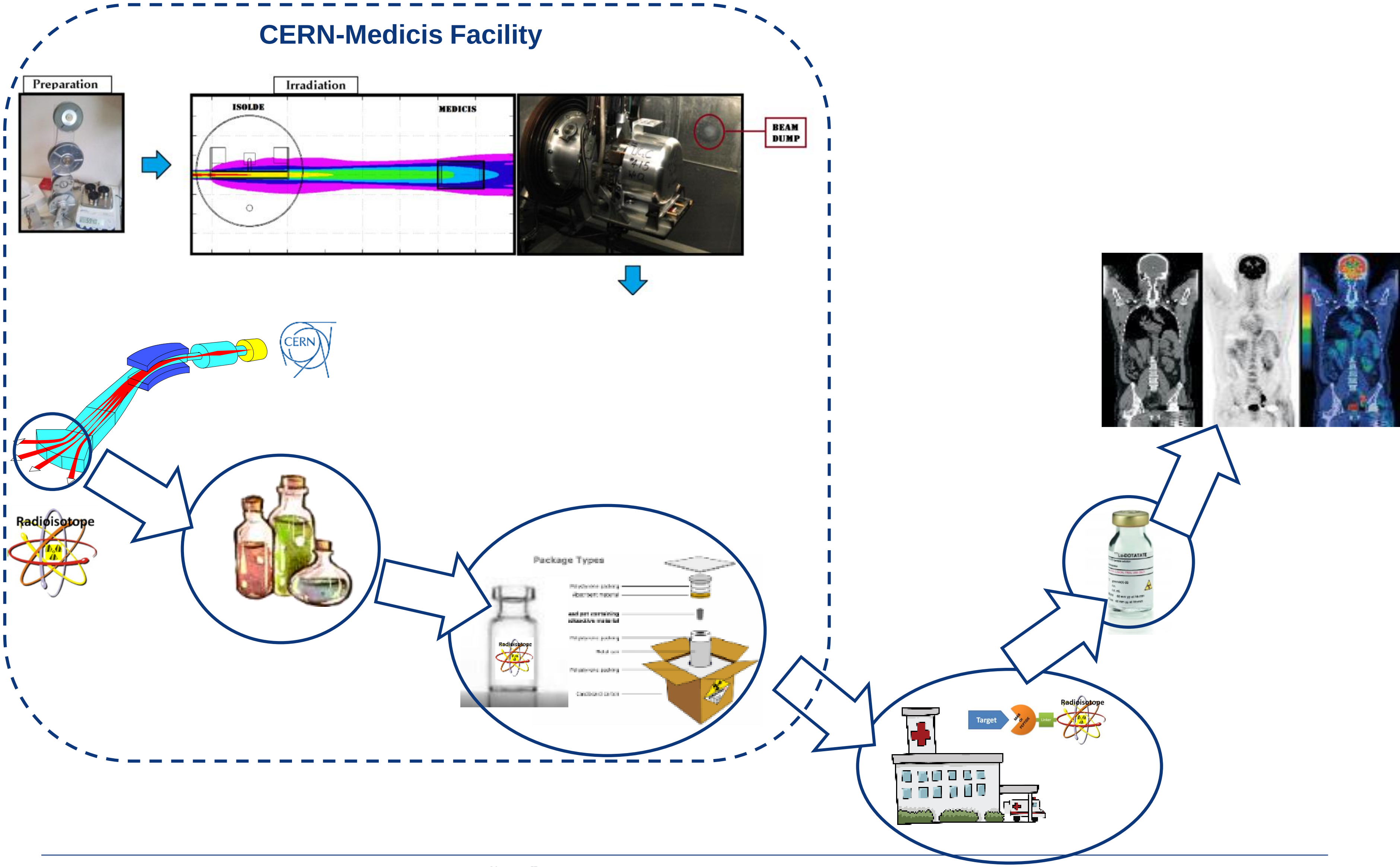
Eur J Nucl Med Mol Imaging (2010) 37:1335–1344
DOI 10.1007/s00259-010-1385-5

ORIGINAL ARTICLE





The complete cycle of MEDICIS



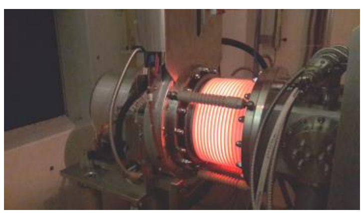
Take-home message

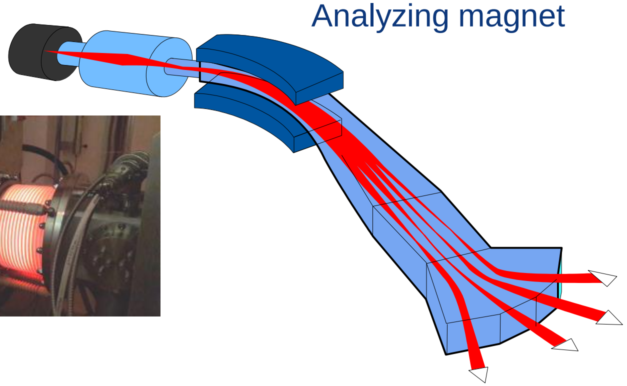
New isotopes can be delivered to
Partner biomedical institutes
where they synthesize new drugs
and test them for **precision imaging or treatment**


le dauphiné libéré
BELLEGARDE & PAYS DE GEX
GENEVOIS LE SAVOIR DES PHYSICIENS AU SERVICE DE LA MÉDECINE DE DEMAIN
La lutte anti-cancer se prépare au Cern

1st isotopes produced in ISOLDE HRS beam dump and separated in the lab during commissioning Dec 2017

Analyzing magnet





149/152/155/161Terbium ions collected in metal foils

Large Collaboration with regional and European Institutes

And now let's have a virtual tour !!





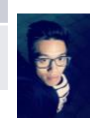


1	RINGVALL-MOBERG	Annie	SWE	CERN	EU	Academic	01.06.2016	29.03.2019	7	University of Gothenburg June 2016
2	VUONG	Nhât-Tân	CH	CERN	EU	Academic	01.01.2016	01.01.2019	12	EPFL May 2016
3	PITTERS	Johanna	AT	CERN	EU	Academic	01.10.2015	01.10.2018	15	TU Vienna October 2016
4	NAZAROVA	Marina	RU	UNIMAN	UK	Academic	12.11.2015	12.11.2018	13.5	UNIMAN November 2015
5	GADELSHIN	Vadim	RU	JGU Mainz	DE	Academic	15.01.2016	15.01.2019	11.5	JGU Mainz August 2016
6	FORMENTO	Roberto	IT	AAA	FR	Non-academic	08.02.2016	08.02.2019	11	Uni. Nantes May 2016
7	CHOWDHURY	Sanjib	IN	C2TN	PT	Academic	01.01.2016	01.01.2019	12	IST January 2016
8	D'ONOFRIO	Alice	FR	C2TN	PT	Academic	02.11.2015	02.11.2018	14	IST February 2016
9	CHOI	KyungDon	KR	CNAO	IT	Academic	12.11.2015	12.11.2018	13.5	Uni. Pavia October 2016
10	MAIETTA	Maddalena	IT	LEMER PAX	FR	Non-academic	20.10.2015	20.10.2018	14.5	Uni. Nantes January 2016
11	STEGEMANN	Simon	DE	KULeuven	BE	Academic	01.06.2016	29.03.2019	7	KULeuven June 2016
12*	LITVINENKO	Alexandra	RU	UNIGE/HUG	CH	Academic	01.12.2016	29.03.2019*	1	UNIGE 2017
13*	CICONE	Francesco	IT	CHUV	CH	Academic	15.10.2015	15.10.2018*	14.5	UNIL November 2015
14*	PRIONISTI	Ioanna	GR	UNIGE/HUG	CH	Academic	01.01.2017	29.03.2019*	0	UNIGE 2017
15*	FAM	Thhe Kyong	UA	EPFL	CH	Academic	01.08.2015	01.08.2018*	17	EPFL August 2015

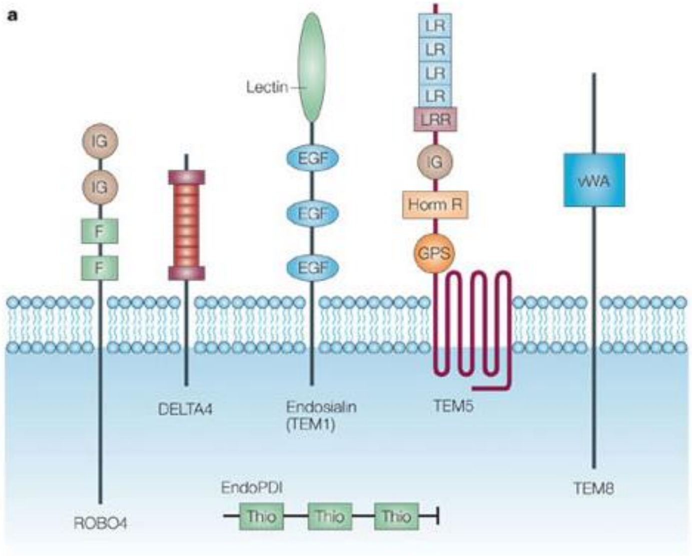






The Target : Tumor Endotelial Marker-1 (TEM1)



Overexpressed by:

Tumor Vessels

Tumor cells

Host microenvironment (fibroblasts, pericytes)

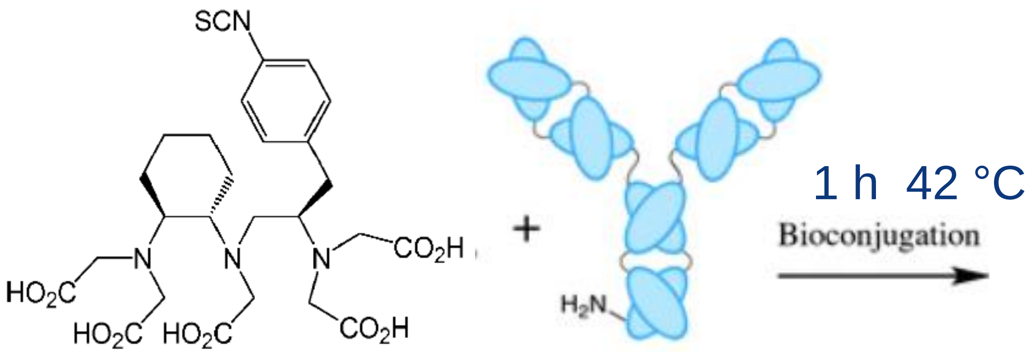
Morab 0004 (Clinical phase 2)

scFv78-Fc (78Fc)

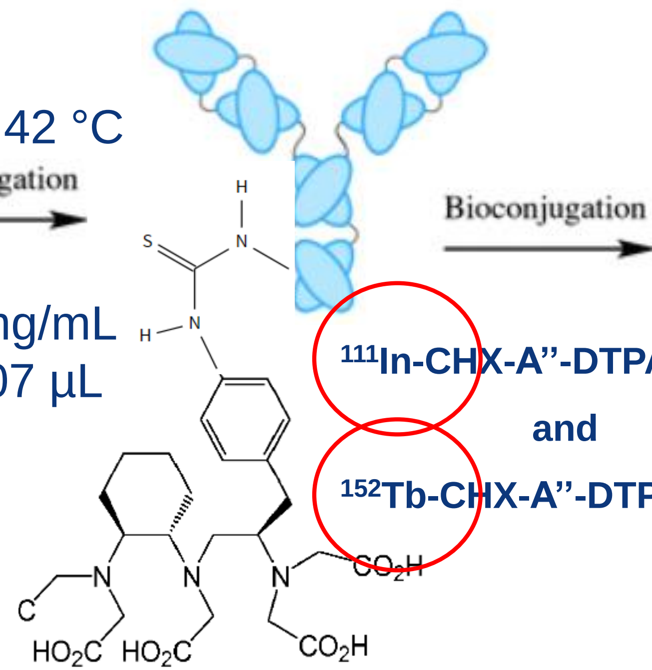
full IgG anti-TEM1

Cicone F et al.

Labelling of 78Fc anti-TEM1 with radiometals



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

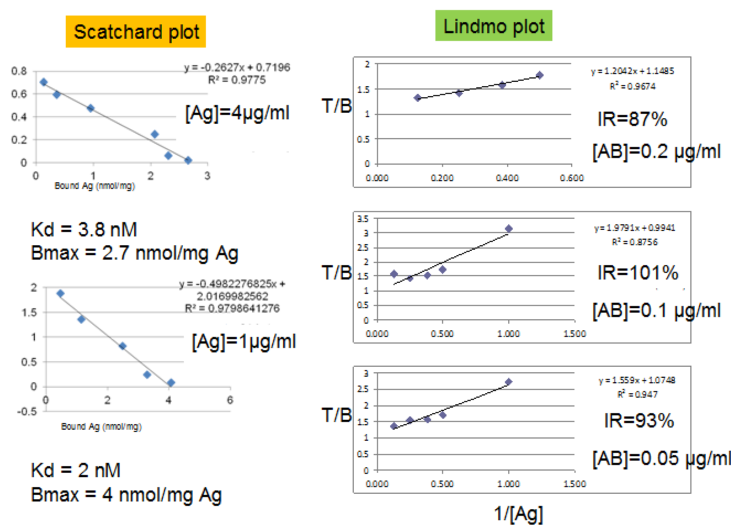


^{111}In-CHX-A''-DTPA-FcTEM1

and

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

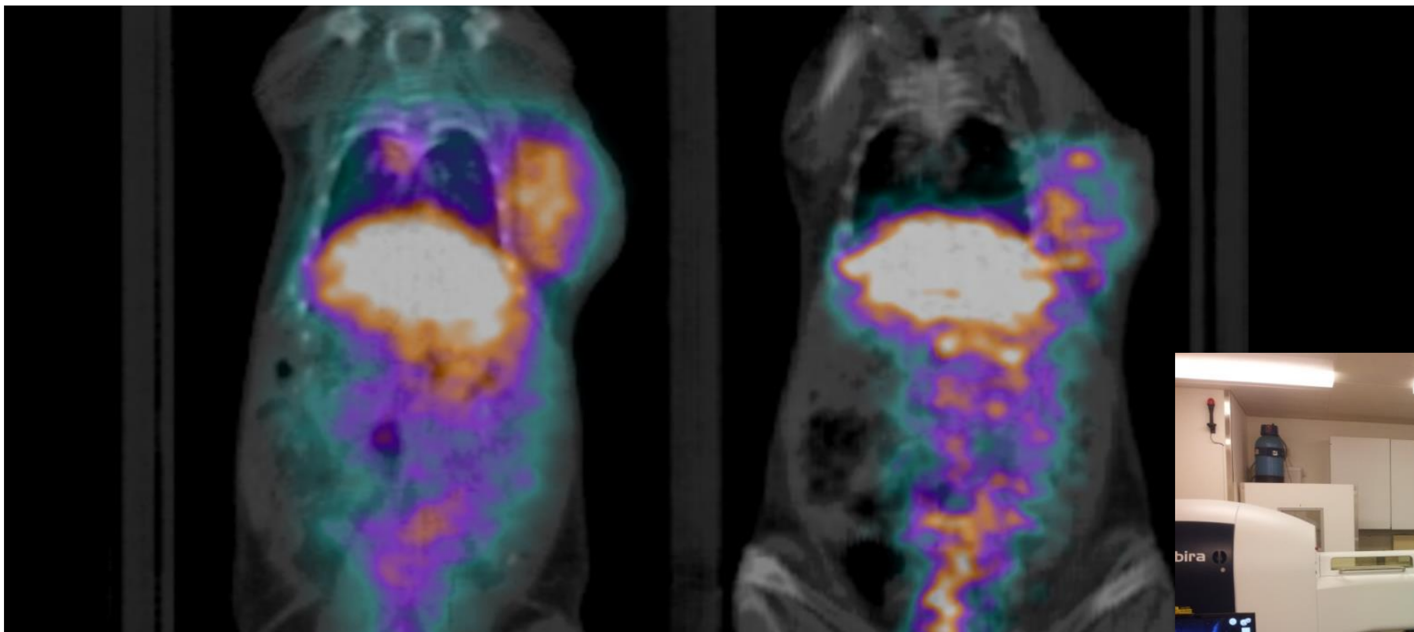
In Vitro Testing / Immunoreactivity



Cicone F et al.

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

Ewing Sarcoma cell line A673

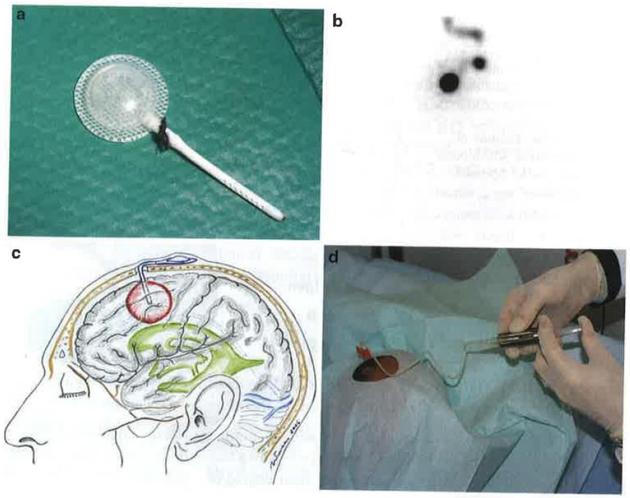


24 hours p.i. 60 hours p.i.

Cicone F et al. IRIST Conference, Lausanne 2016

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Intracavity injection +resection of Glioblastoma



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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)

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

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[2]The Department of Biochemistry & Biophysics, UCSF, San Francisco, CA 94158, USA
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