CERN-MEDICIS:

Production d'isotopes selon l'approche « ISOLDE » pour la recherche médicale

Thierry Stora

Isolde Users Workshop

27th November 2013

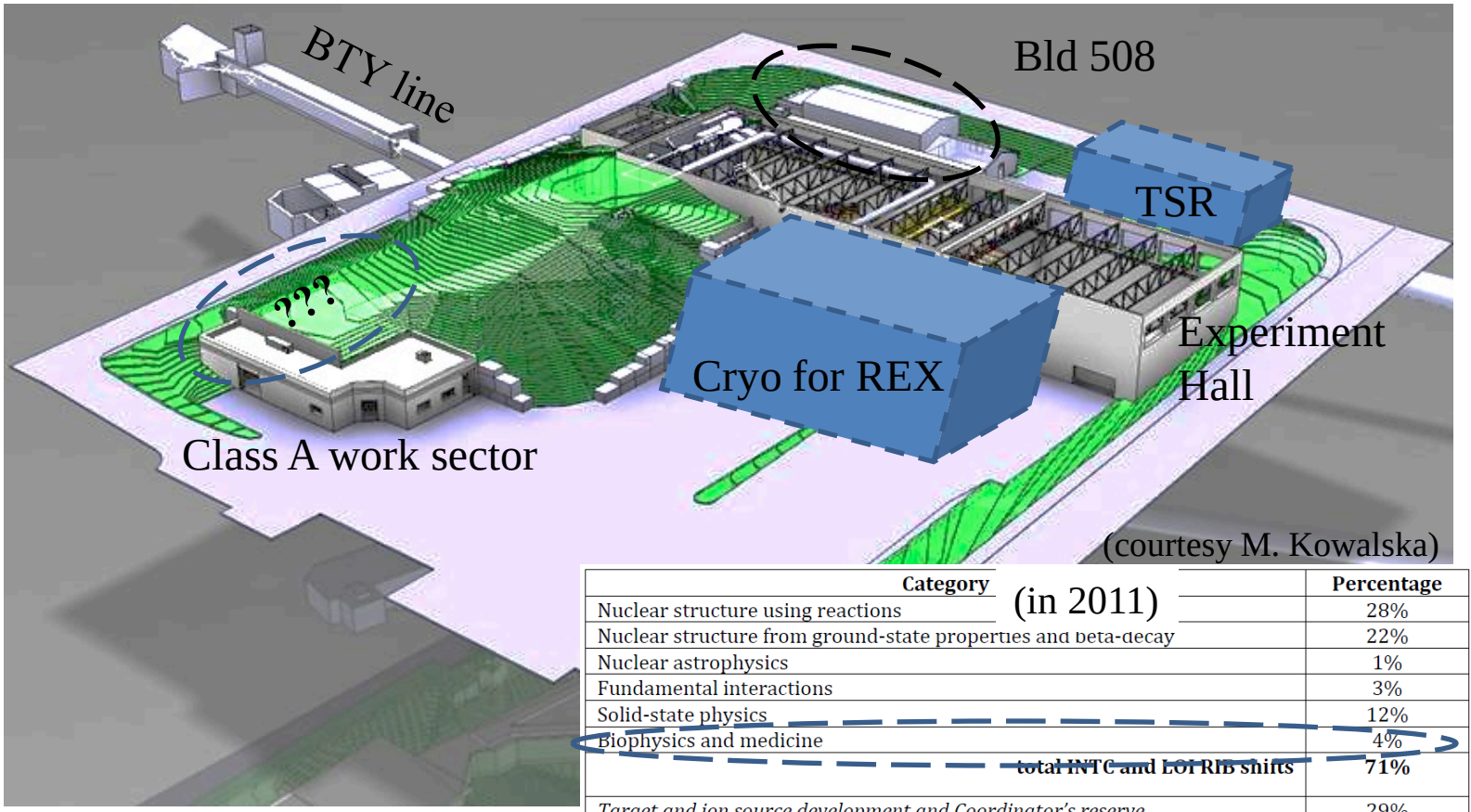
What's new since the last report at the Isolde workshop ?

The Philosophy behind

The ISOLDE facility

The On-Line Isotope Mass Separator ISOLDE is a facility dedicated to the production of a large variety of radioactive ion beams for a great number of different experiments, e.g. in the field of nuclear and atomic physics, solid-state physics, life sciences and material science

Up to 50% of total CERN proton are delivered to ISOLDE



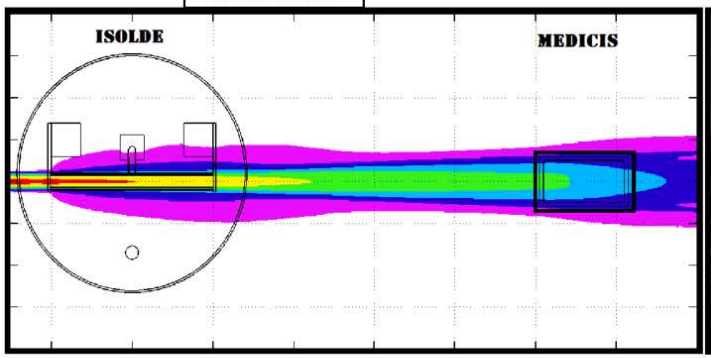
(in 2011)

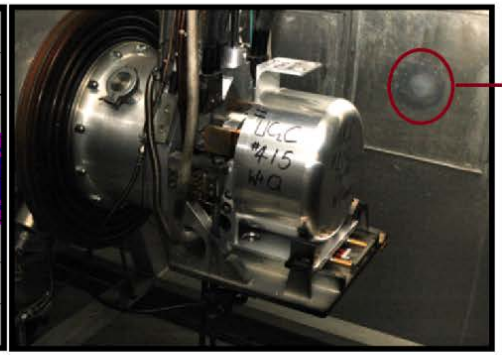
Category	Percentage
Nuclear structure using reactions	28%
Nuclear structure from ground-state properties and beta-decay	22%
Nuclear astrophysics	1%
Fundamental interactions	3%
Solid-state physics	12%
Biophysics and medicine	4%
total INTC and LOI RIB shifts	**71%**
Target and ion source development and Coordinator's reserve	29%

Full MEDICIS principle

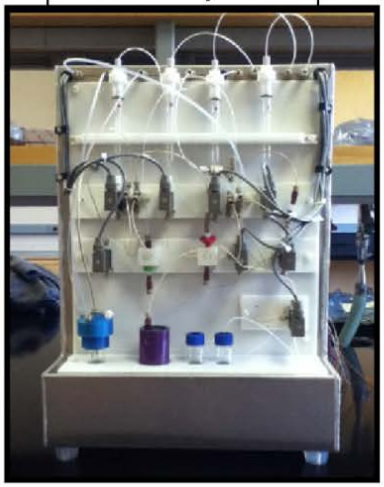
Preparation

Irradiation



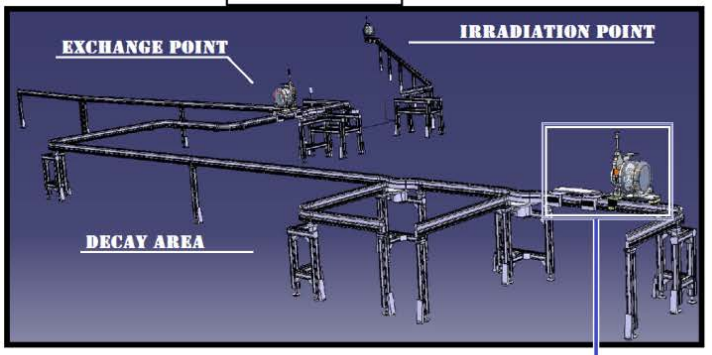


Chemical separation

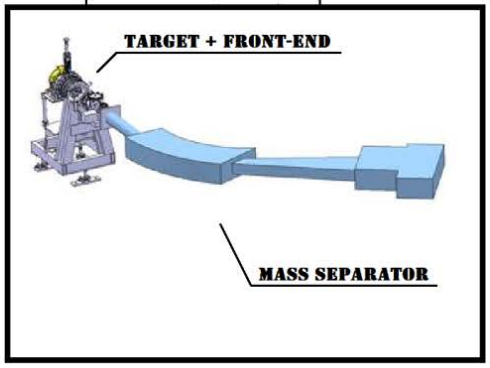


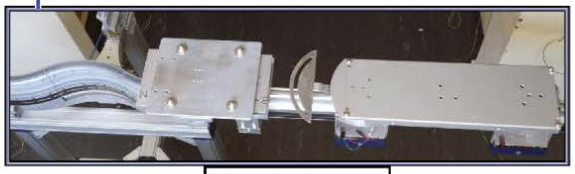
Pure isotope batch

Transfer



Online separation





Shuttle System

The Philosophy

- Scope : Life sciences, Medicine
- Innovative protocols (Surgery/brachytherapy/combination)
- Innovative isotopes

Field of Application	Radiation	Chemical elements	Half lives
PET	β^+	Alkaline earth Halogen Lanthanide Transition metals …	10's min. Hours Days Months
SPECT	γ		
TAT	α		
Beta therapy	β^-		
Auger therapy	e^-		

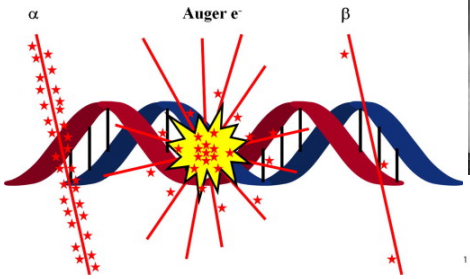
- Studies on cells, animals (« preclinical »)
  possibly extended to clinical phases
  (needs upgrades, but this can be reached)

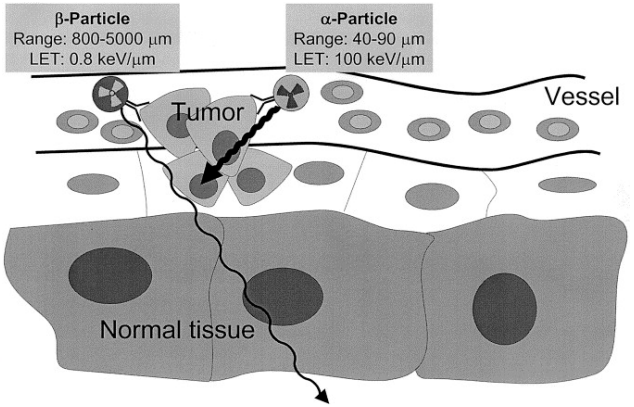
Drug development cycle

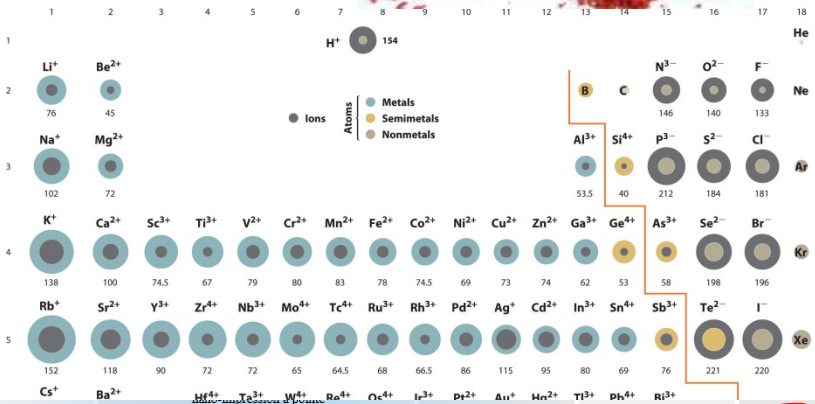
	Preclinical Testing	Phase I	Phase II	Phase III	FDA	Total Years	Phase IV
Years	3.5	1	2	3	2.5	12	Post-marketing
Test Population	Laboratory & animal studies	20 to 80 healthy volunteers	100 to 300 patient volunteers	1000 to 3000 patient volunteers	Review process/ Approval		
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate effectiveness, look for side effects	Verify effectiveness, monitor adverse reactions from long-term use			
Success Rate	5,000 compounds evaluated	5 enter trials				**1 Drug approved**	

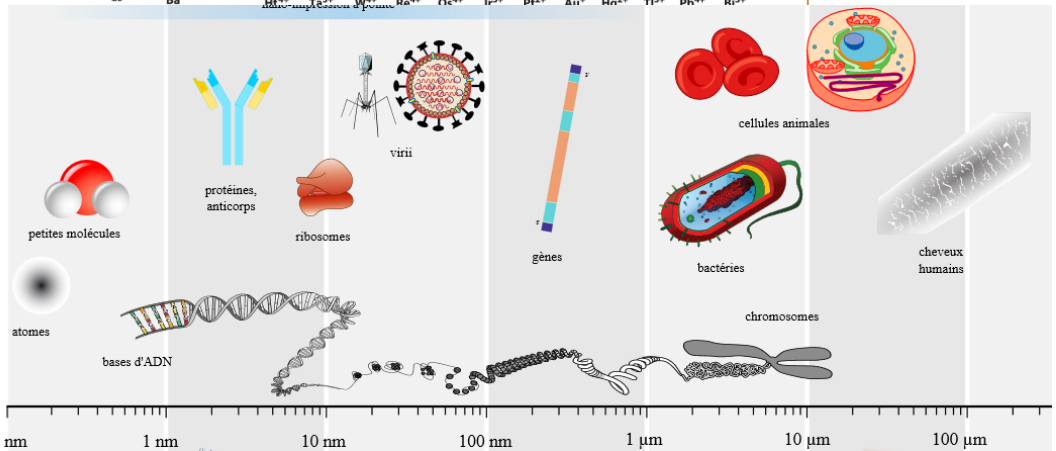
Source: www.allp.com

Chemical and radiation properties









The Project

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

Planning proposal*

**subject to modification…*

	Construction	2013-2015
PHASE I	Commissioning : No beam	end 2015
PHASE II	Commissioning with beam and light targets to gain operational experience	2016
PHASE II B	Isotope production with light targets	mid 2016
PHASE III	Extending to heavy targets up to Tantalum	end 2016
PHASE IV	Collection of short lived alpha emitters (e.g. 149Tb)	2017
PHASE IVB	Operation with Lasers	
PHASE V	Operation with Uranium targets/possible proton beam upgrade	2018

Team overview

MEDICIS' team @CERN:

T. Stora (MEDICIS), S. Marzari (Building), R. Catherall (HIE-DS coord), A.P. Bernardes (g-al safety), Z. Lawson (Biological&KTT aspects)

M. Vagnoni (RCS), R. Augusto (Fluka), A. Polato (Ventilation, cooling), E. Perez-Duenas (Bld), V. Barozier (Integration), R. Necca (EL), J.L. Grenard (Robot), K. Kershaw (Robot), M. Stachura (Bio R&D), J. Vollaire (RP), A. Dorsival (RP), F. Loprete (doors), Y. Martinez (isotope separator), tbcont'd

A new office for biomedical applications at CERN

About CERN | Students & Educators | Scientists | CERN

Announcements | Opinion | Official communications | Updates

Streamlining the path from physics to medicine

Rolf Heuer

We all know them: the well-established cases of knowledge transfer from physics to medicine in which CERN has played an important role. From technology for PET scanners to dedicated accelerator designs for cancer therapy, we have contributed a lot over the years. But until

Interview with Steve Myers

Oct 20 2013

Medical applications play an important role at CERN and recently the DG has decided to structure them under a common umbrella. Steve Myers, CERN's Director of Accelerators and Technology has been appointed as the first Head of CERN's Office for Medical Applications. We have decided to dedicate October's issue of the PH Newsletter to this interesting field and asked Steve Myers for an interview. Following his long-standing career on accelerators and his experience from LEP and the LHC, Steve discusses about his future ambitions and the challenges of his new role.

What do you think about your new role and what is your greatest ambition?

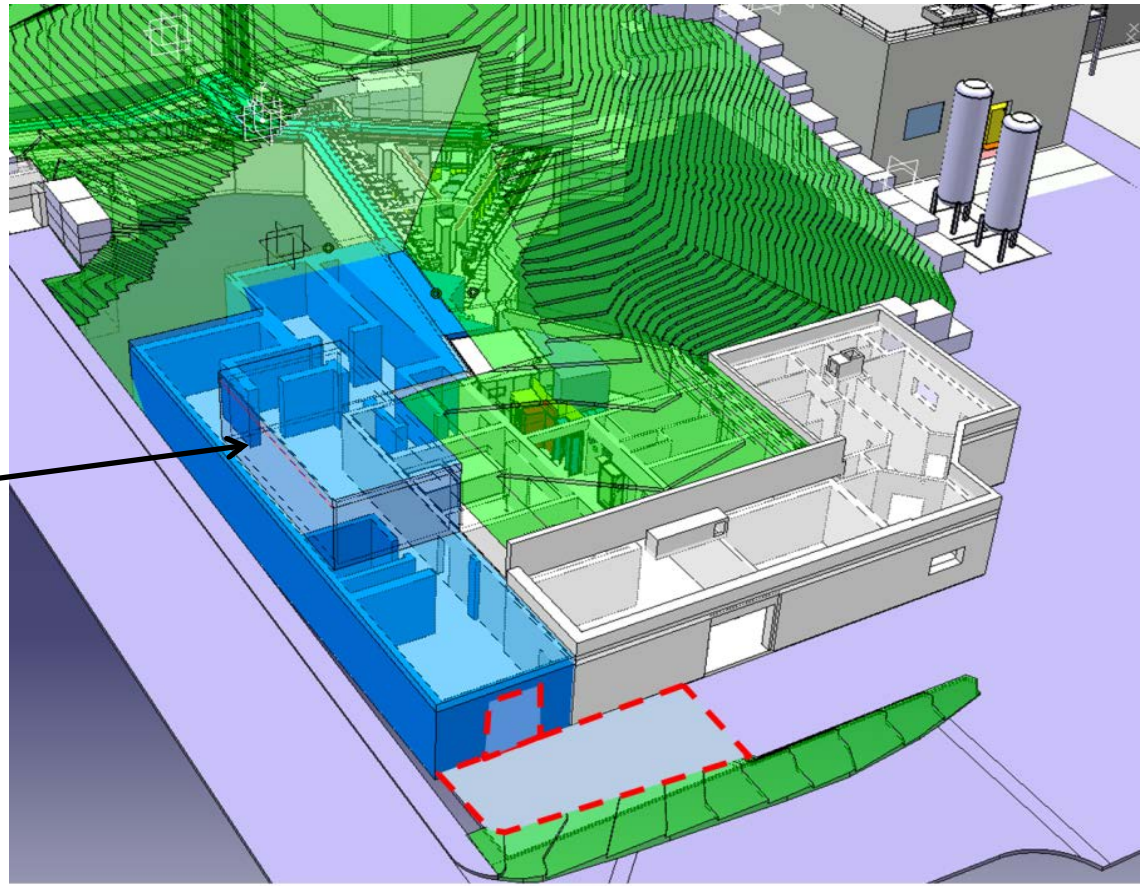
This is the first time that CERN has put (into its medium-term) a budget line for medical applications. It is a small budget line but can be the seed for important projects. Over the last years, many medical activities have been going on at CERN; however these efforts were not focused. There are several activities related to CERN's technologies including the design of specialized accelerators for cancer therapy, the conversion of the Low Energy Ion Ring (LEIR) into a biomedical facility, radio-isotope production using ISOLDE, medical imaging and applications to improve dosimetry for patients and finally large scale computing applications. The DG thought that the time had come to put these projects under one umbrella and asked me to be the coordinator.

I want to set a common goal and try to coordinate these

Kick-off meeting last Friday (22 Nov) !

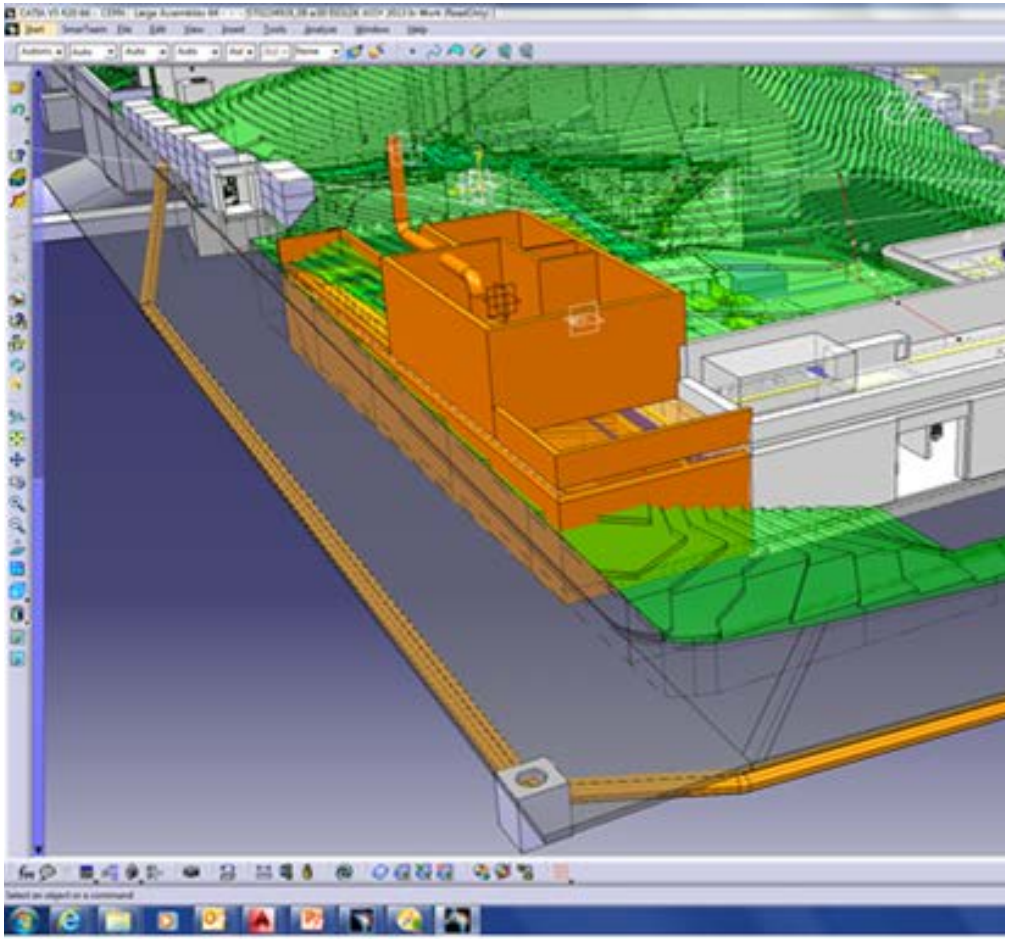
Some Progress(es)

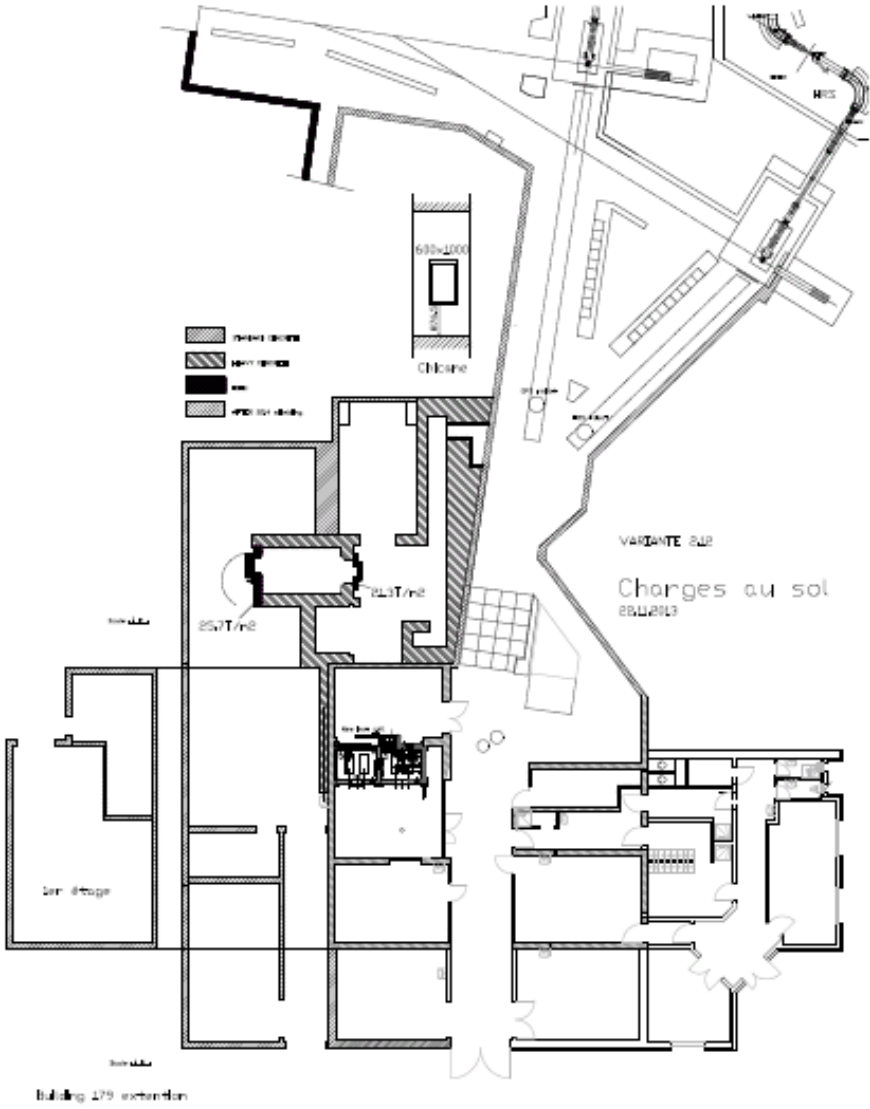
3D Building layout and integration



Positive safety review in summer 2013

“Cold building” in 2014





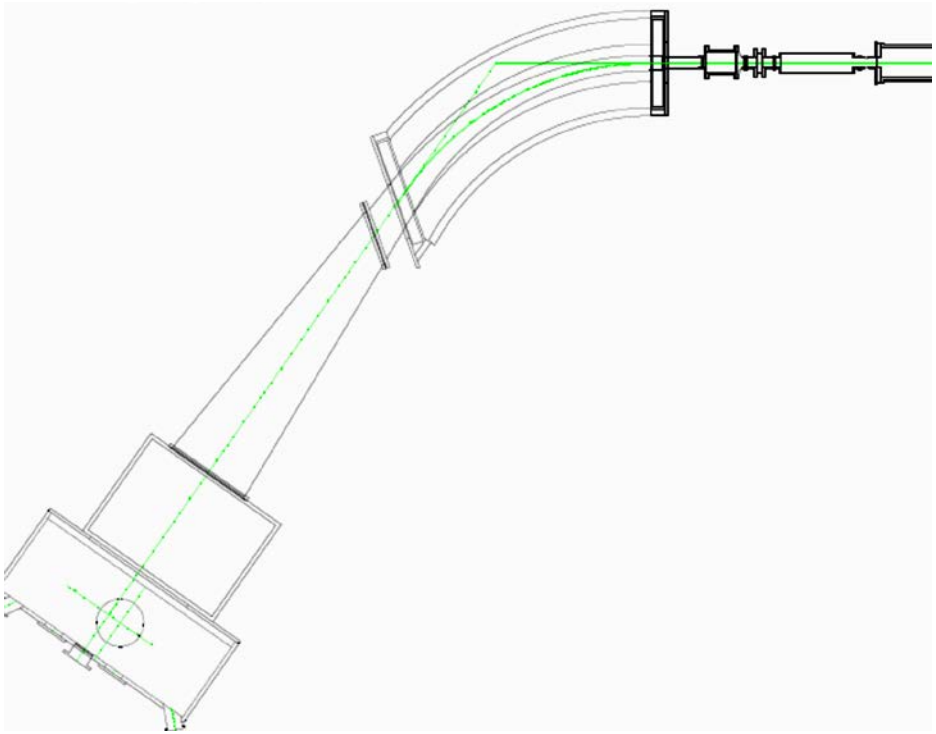
Civil Engineering has started

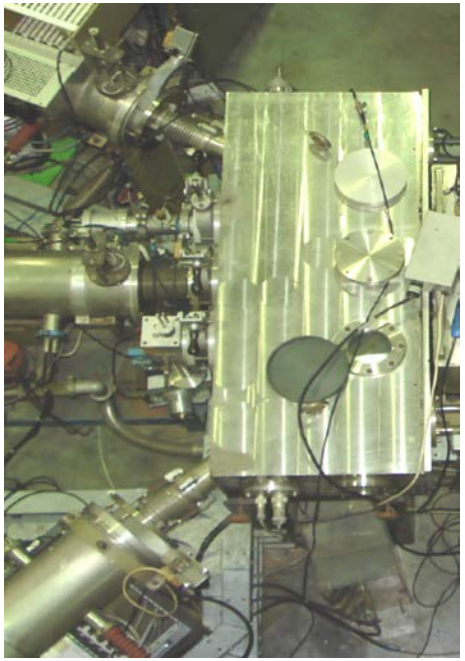
Have you ever made your own garden shed ?

September 4th 2013

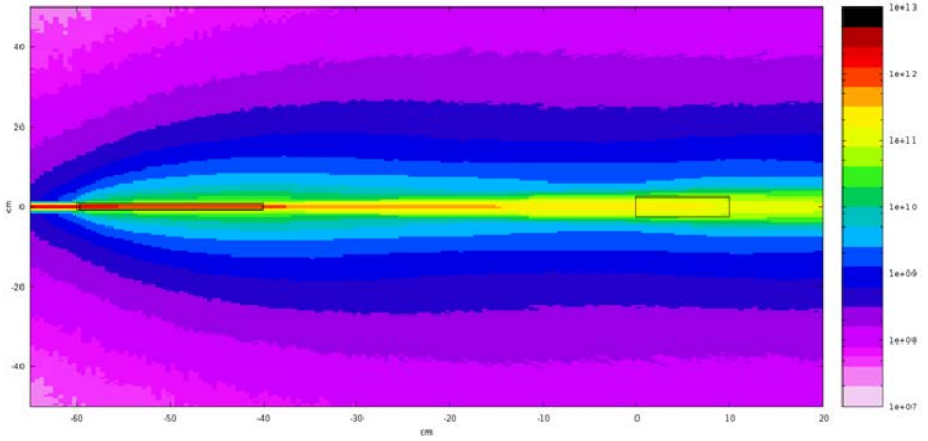
A big hole next to the Class A building

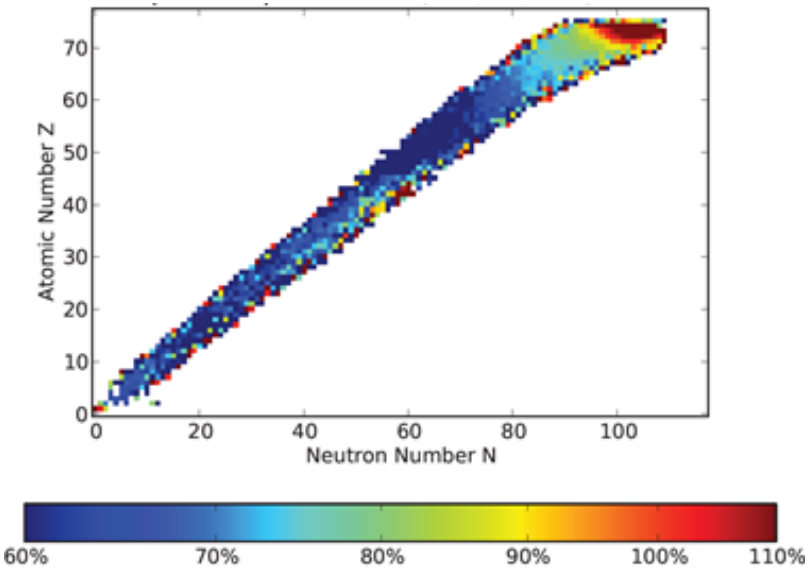
LISOL mass separator: A second life



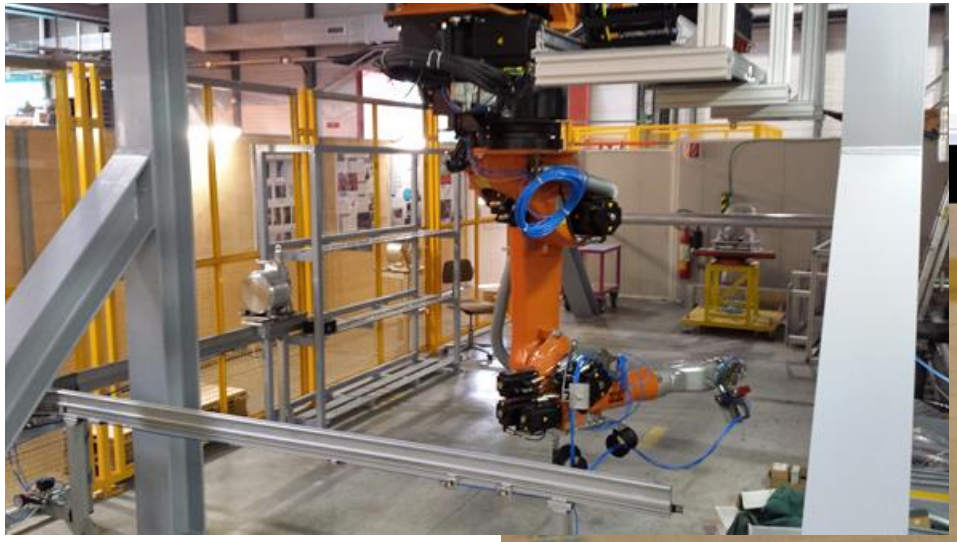


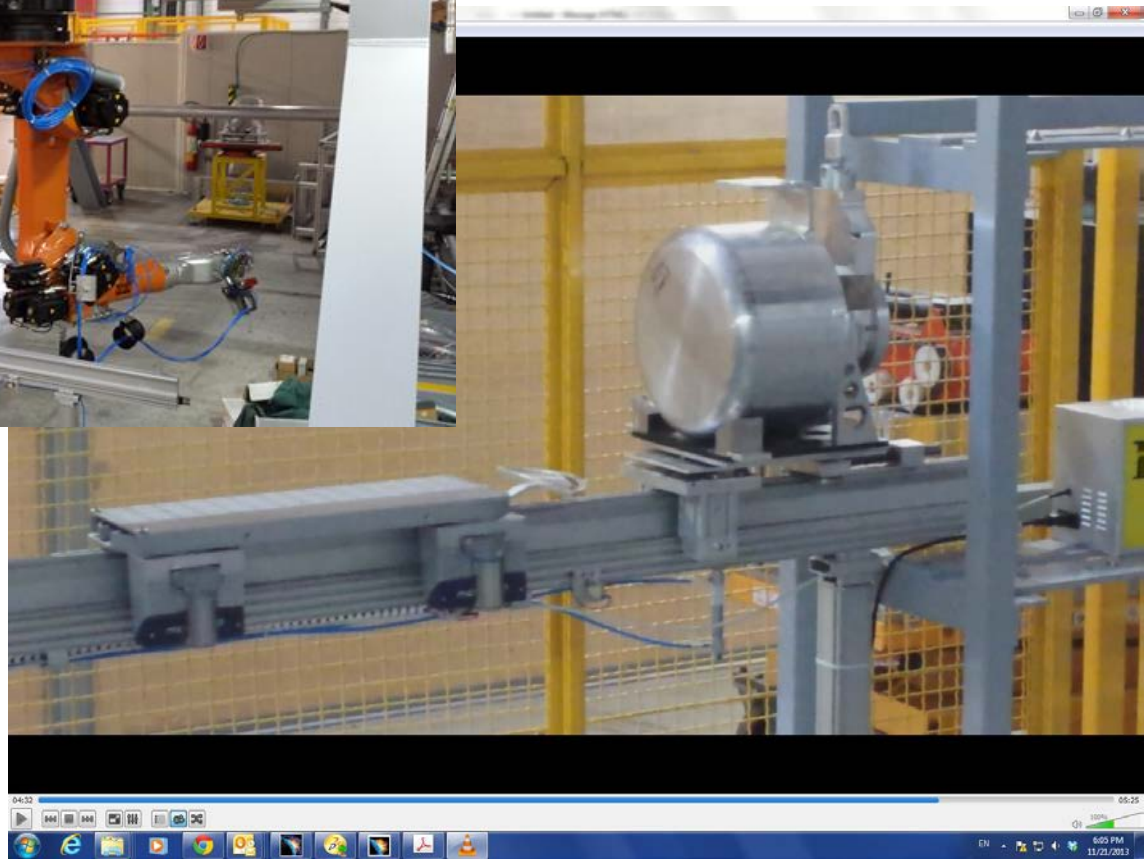
Adaptation of targets





The Rail Conveyer System and Kuka Robot





Tested for 5 years of operation during the CERN open days last September

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
β- 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
α,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
β- 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
β 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
α 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

The Scientific case

External partners

Dr. Forni (Clin. Carouge, Geneve)

Prof. Morel, Prof. Buehler, Prof. Y. Seimbille, Prof. Ratib (HCUGE, Geneve)

Prof. D. Hanahan (ISREC, EPFL, Lausanne)

Prof. F. Buchegger, Prof. J. Prior (CHUV, Lausanne)

Prof M. Huyse, prof. P. van Duppen (KUL, Univ. Leuven)

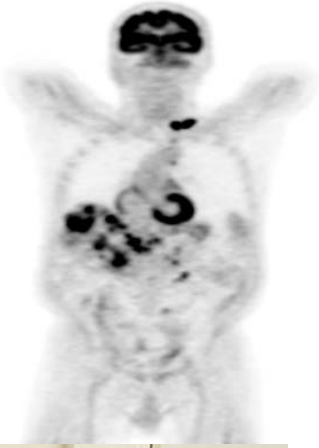
Prof. S. Lahiri (SINP, Kolkata)

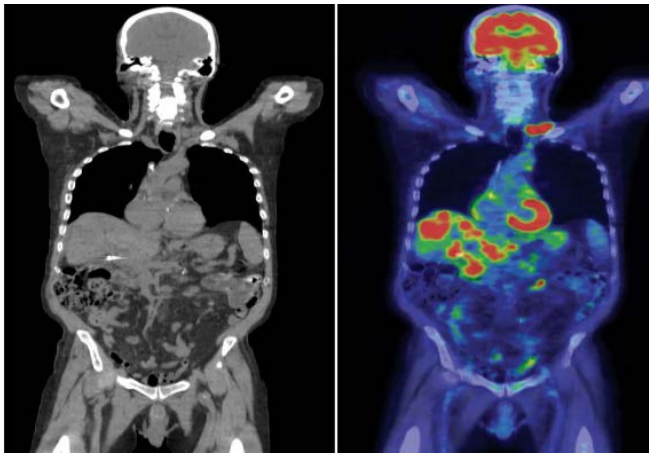
Prof. I. dos Santos (CT2N, Lisbon)

Prof. E. Piperkova (Nucl. Medicine, Sofia)

…

Protocols



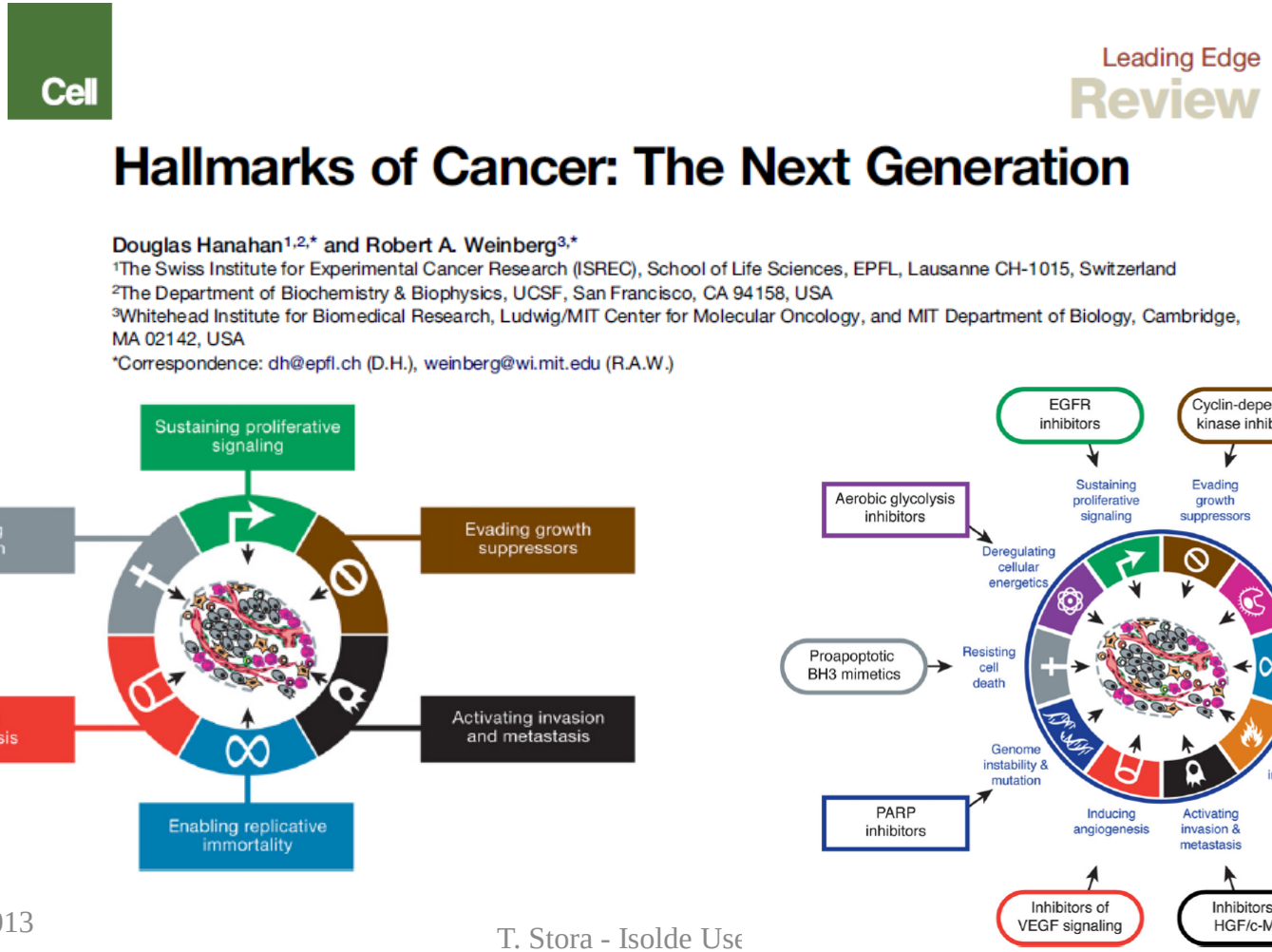


Hôpitaux Universitaires de Genève

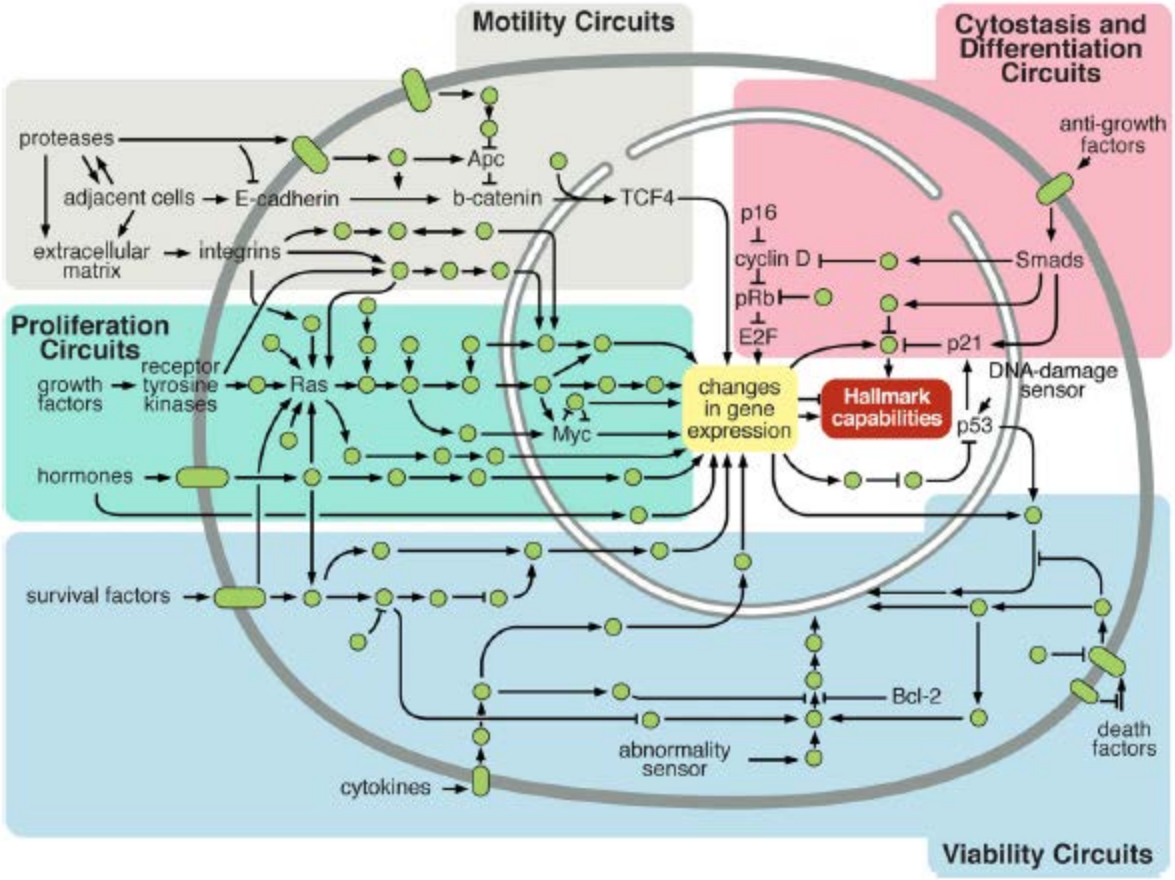
Translational approach

Cited >5000 times since 2011 (previous article cited 17000 times)

Prof D. Hanahan, Swiss Inst. For Exper. Cancer Research



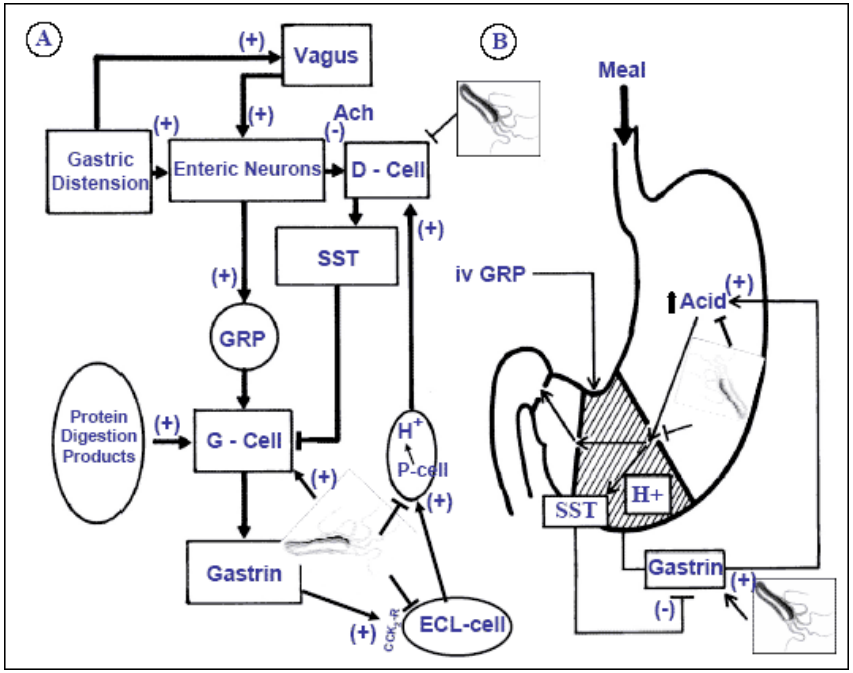
Let's take one example



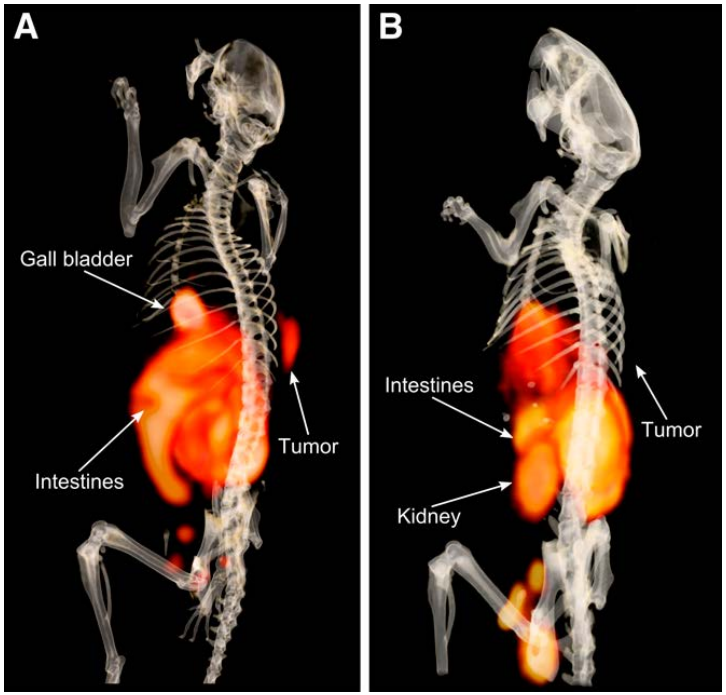
Disruptions of Negative-Feedback Mechanisms that Attenuate Proliferative Signaling

Yet another example involves the mTOR kinase, a coordinator of cell growth and metabolism that lies both upstream and downstream of the PI3K pathway. In the circuitry of some cancer cells, mTOR activation results, via negative feedback, in the inhibition of PI3K signaling. Thus, when mTOR is pharmacologically inhibited in such cancer cells (such as by the drug rapamycin), the associated loss of negative feedback results in increased activity of PI3K and its effector Akt/PKB, thereby blunting the antiproliferative effects of mTOR inhibition (Sudarsanam and Johnson, 2010; O'Reilly et al., 2006). It is likely that compromised negative-feedback loops in this and other signaling pathways will prove to be widespread among human cancer cells and serve as an important means by which these cells can achieve proliferative independence. Moreover, disruption of such self-attenuating signaling may contribute to the development of adaptive resistance toward drugs targeting mitogenic signaling.

GRPr : Gastrin Releasing Protein receptor



Sits within the stomach walls

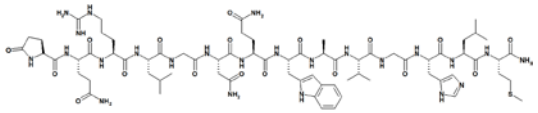


And is overexpressed in some cancers, ie Prostate cancers

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

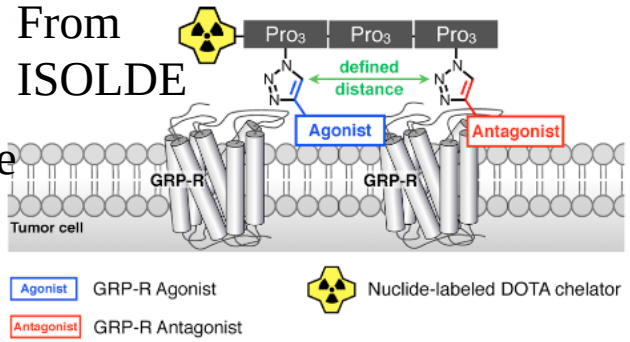
Test experiment

Bombesin analog from *Bombina bombina*



152Tb From ISOLDE

Prostate Cancer cells



- Peptide analog that specifically binds to prostate cancer tissues
- Batch collected at ISOLDE and exported to CHUV
- Tests on mice already showed better biodistribution (less toxicity to healthy tissues) than same peptide + 68Ga
  → Candidate for next therapeutic trials with 149Tb/161Tb

(A. Gottberg, K. Johnston, RP, GS)

And a first scientific report

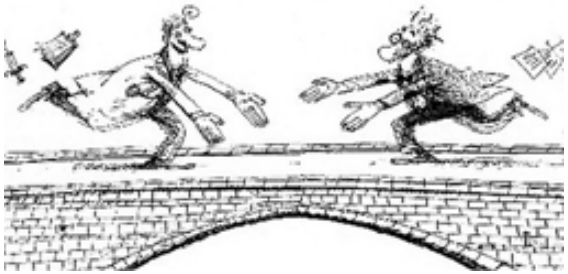
ICTR-PHE 2014

Session : Nuclear medicine

Keywords: Targeted radiotherapy, prostate cancer, Terbium isotopes

152/161Tb-DOTA-RM6 biodistribution studies in prostate cancer bearing SCID mice and 149Tb sources from CERN-MEDICIS

Franz Buchegger (CHUV), Thierry Stora (CERN), Leo Bühler (HUG), Cristina Müller (PSI), Roger Schibli (PSI), Marek Kosinski (CHUV), Emmanuel Deshayes (CHUV), Sébastian Baechler (CHUV), Alexander Gottberg (CERN), John O. Prior (CHUV), Helmut R. Maecke (UNIKLINIK-FREIBURG) and Rosalba Mansi (UNIKLINIK-FREIBURG)



New ideas

Critical mass

The (un)expected breakthrough

Yearly MEDICIS collaboration meetings/lectures has just found a generous sponsor:
The first one will be organized in summer 2014

Thank you !