WP3

New theranostic pharmaceuticals/surgery tools for personalised treatments of (ovarian) cancer

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UNIL | Université de Lausanne
Faculté de biologie et de médecine

Disclosure

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.

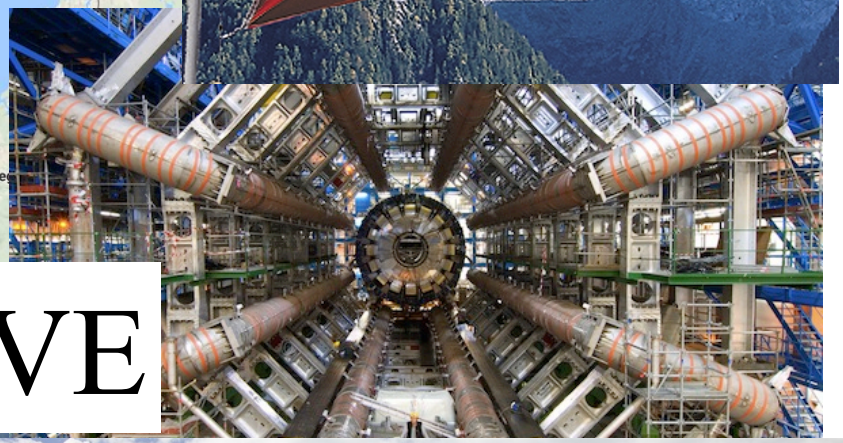
Summary of contents

- Team presentation
- Introduction to medical applications of radioactivity (not covering brachytherapy)
- Single projects of WP3

Team components of WP3

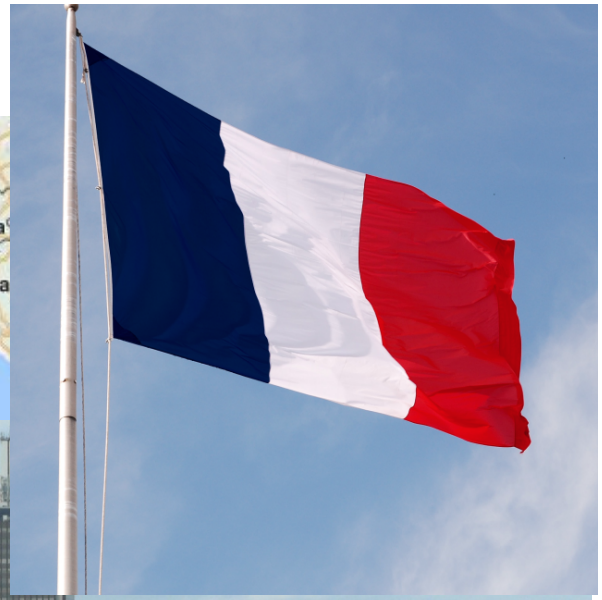
Medicis Promed

The Physicist



GENEVE

The Engineer



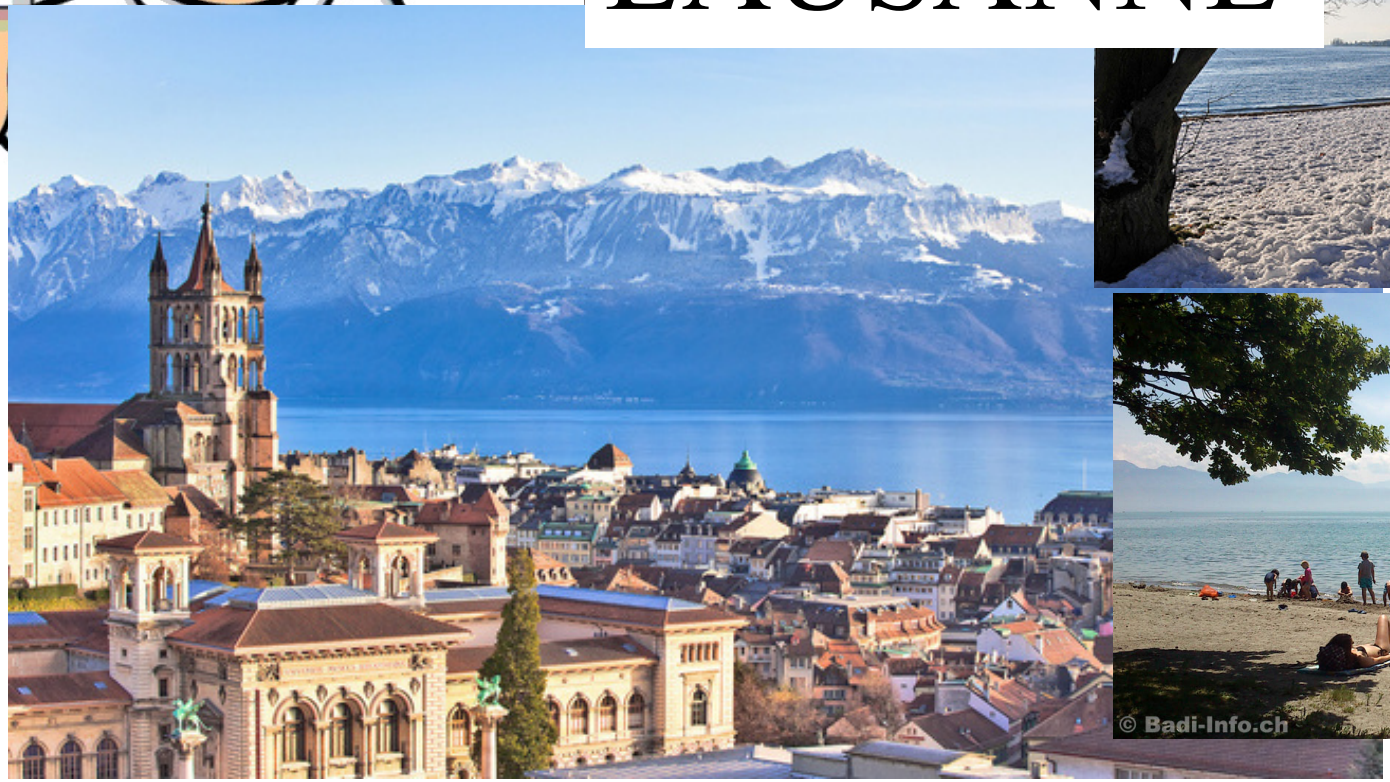
NANTES

The Chemist

LISBON

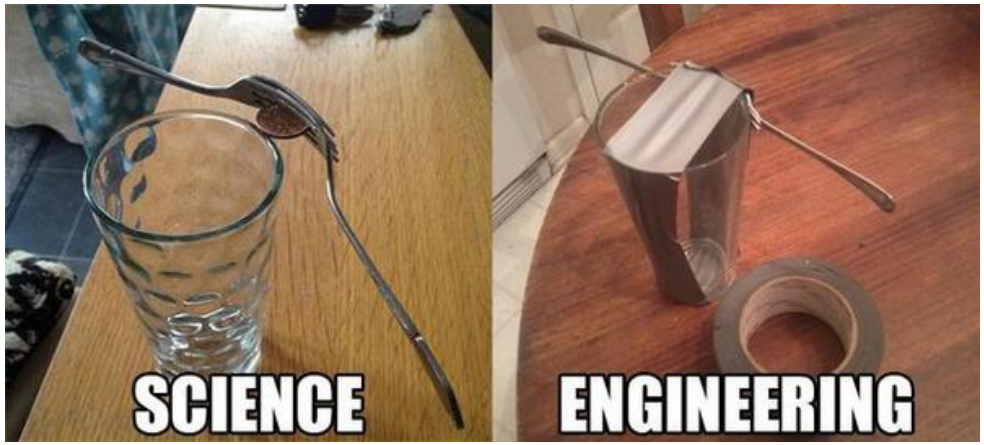
The Doctor

LAUSANNE

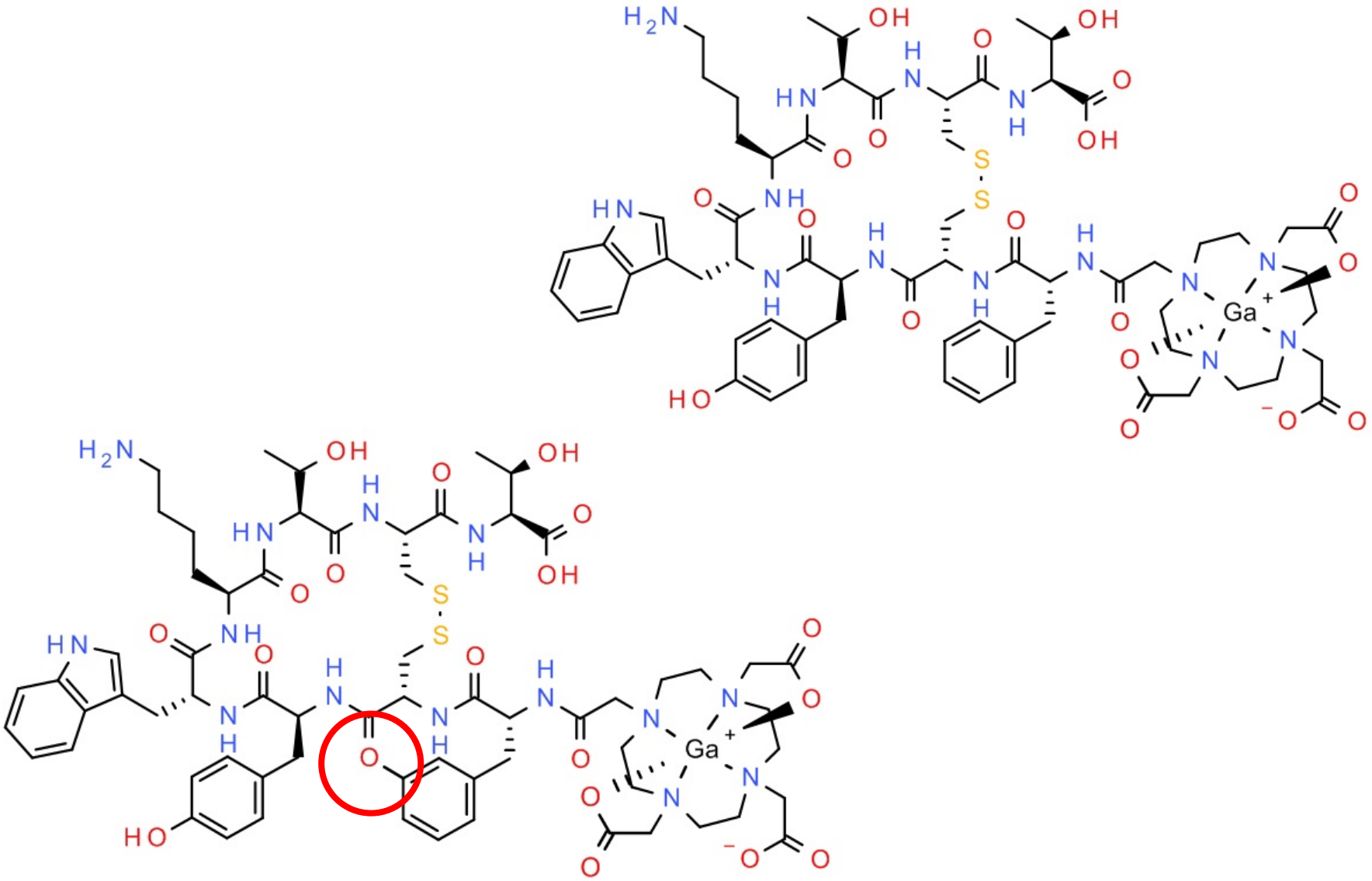


Physicist vs Engineer

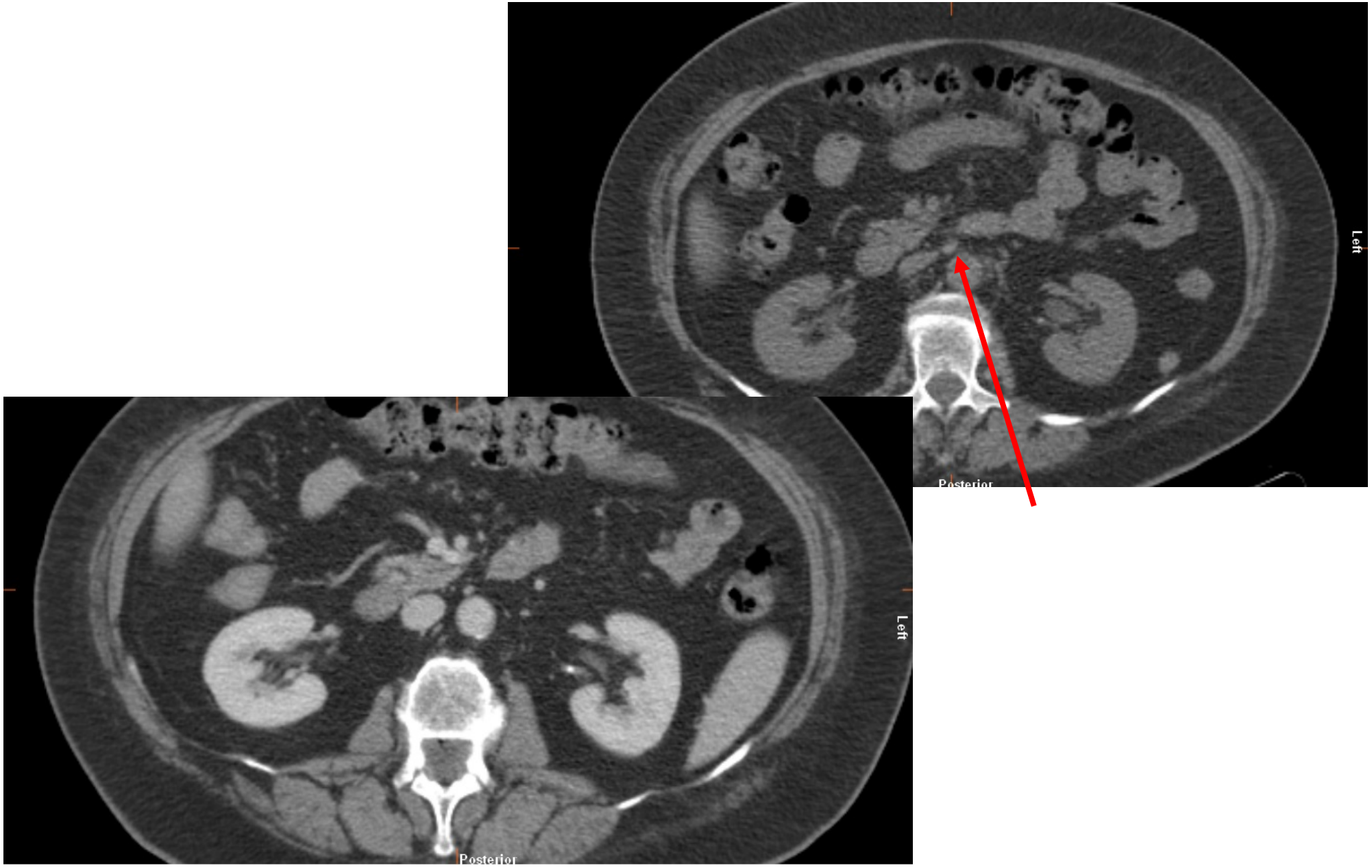
A **physicist** tries to understand the origin of natural phenomena, while it looks to me that the **engineer** is more concerned with understanding their functioning, in order to find possible practical applications



Chemically-minded people….



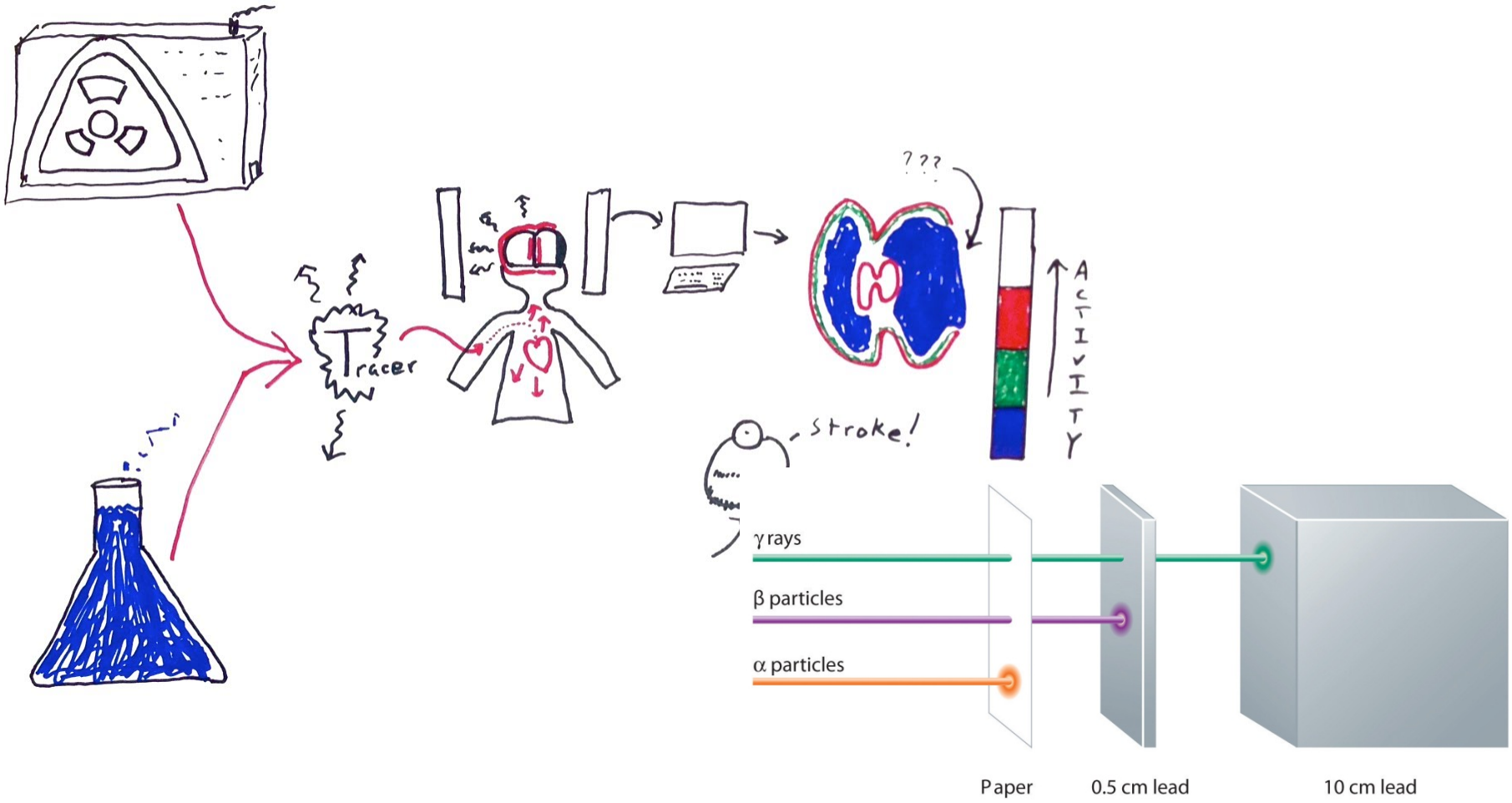
Medically-minded people….



Radioactivity for medical use (Nuclear Medicine)

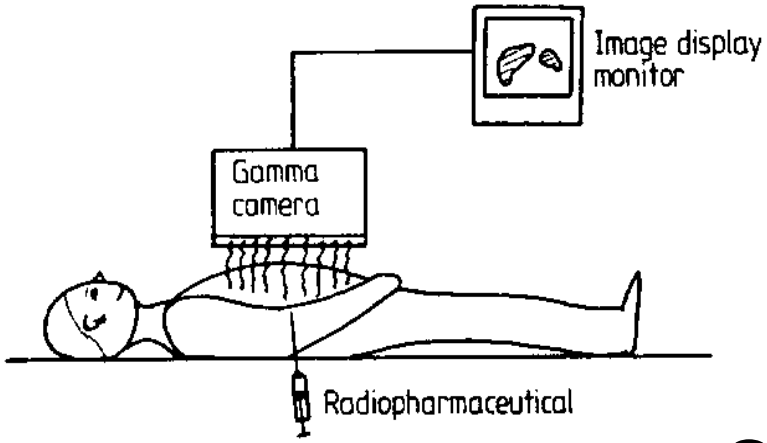
Medicis Promed

Radioactivity for medical use



Diagnosis: SPECT(γ), PET (β+)

Therapy: (β-) (α)



SPECT

PET/CT

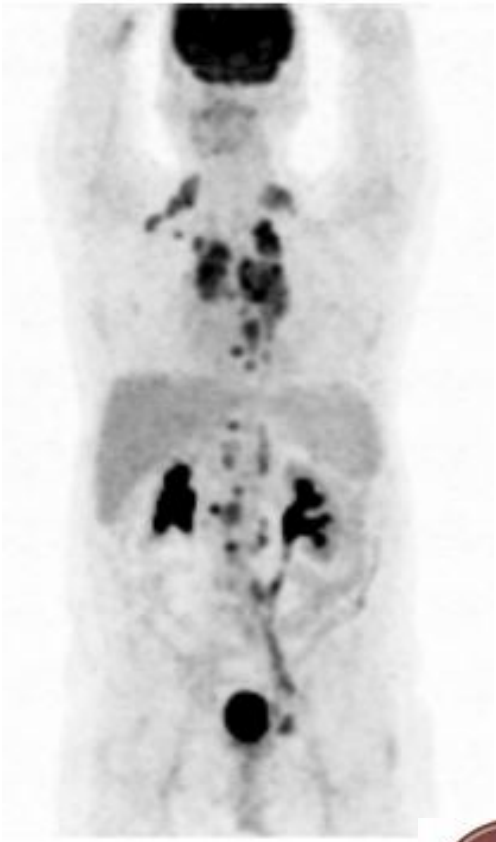
THERAPY

There is not only one PET!!

Prostate Adenok, raising PSA

^{18}F-Choline

^{68}Ga-DOTANOC



^{18}F-FDG

Principles of Thera/gnostic

1) You treat what you see (Treatment planning = Dosimetry) and

2) yo

of dose delivery)

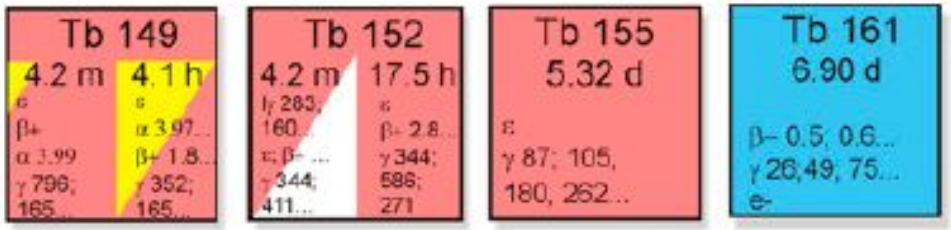
Same is

u) or α/γ (^{223}Ra)

Different

$^{123/124}$I; ^{86}Y/^{90}Y)

Surrogate



^{n}Tc/^{188}Re)

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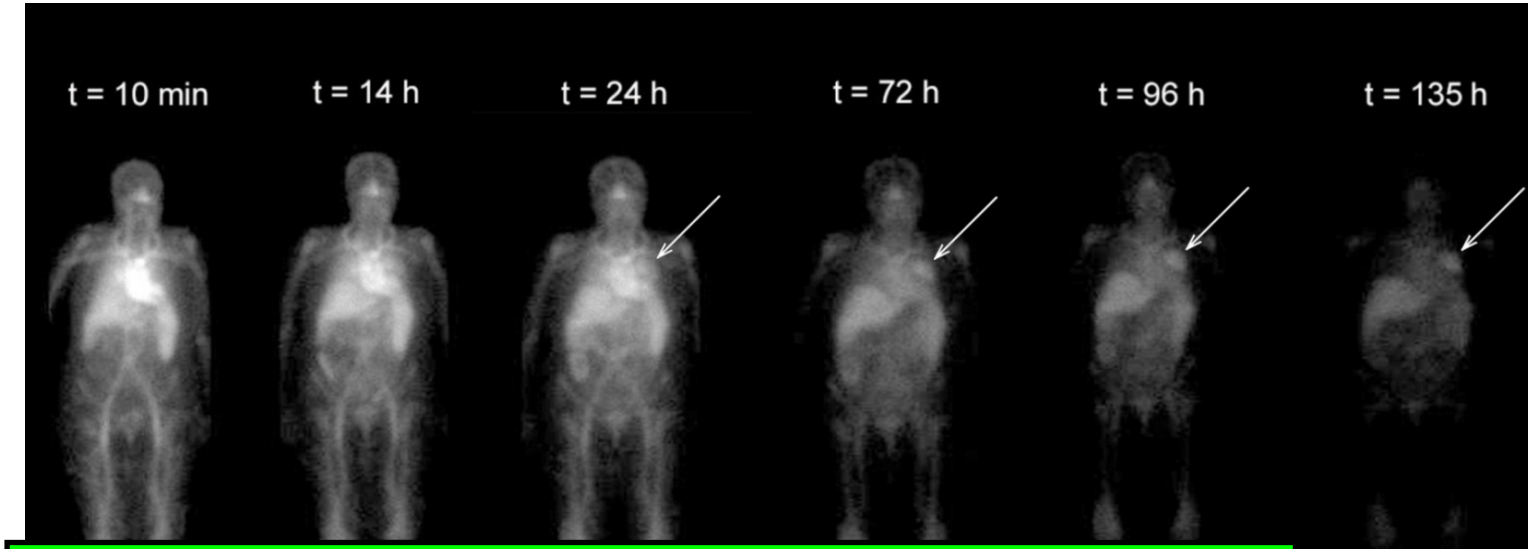
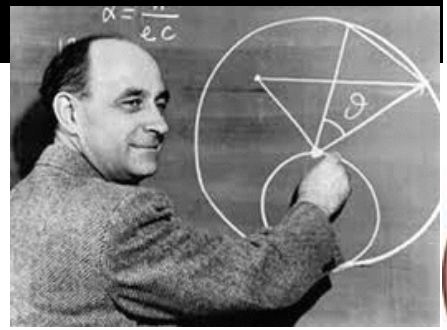
Organ / Tumor Dosimetry



$$\bar{D}(r_k \leftarrow r_h) = \sum_{h=0}^{N} \tilde{A}_h \cdot S(r_k \leftarrow r_h)$$

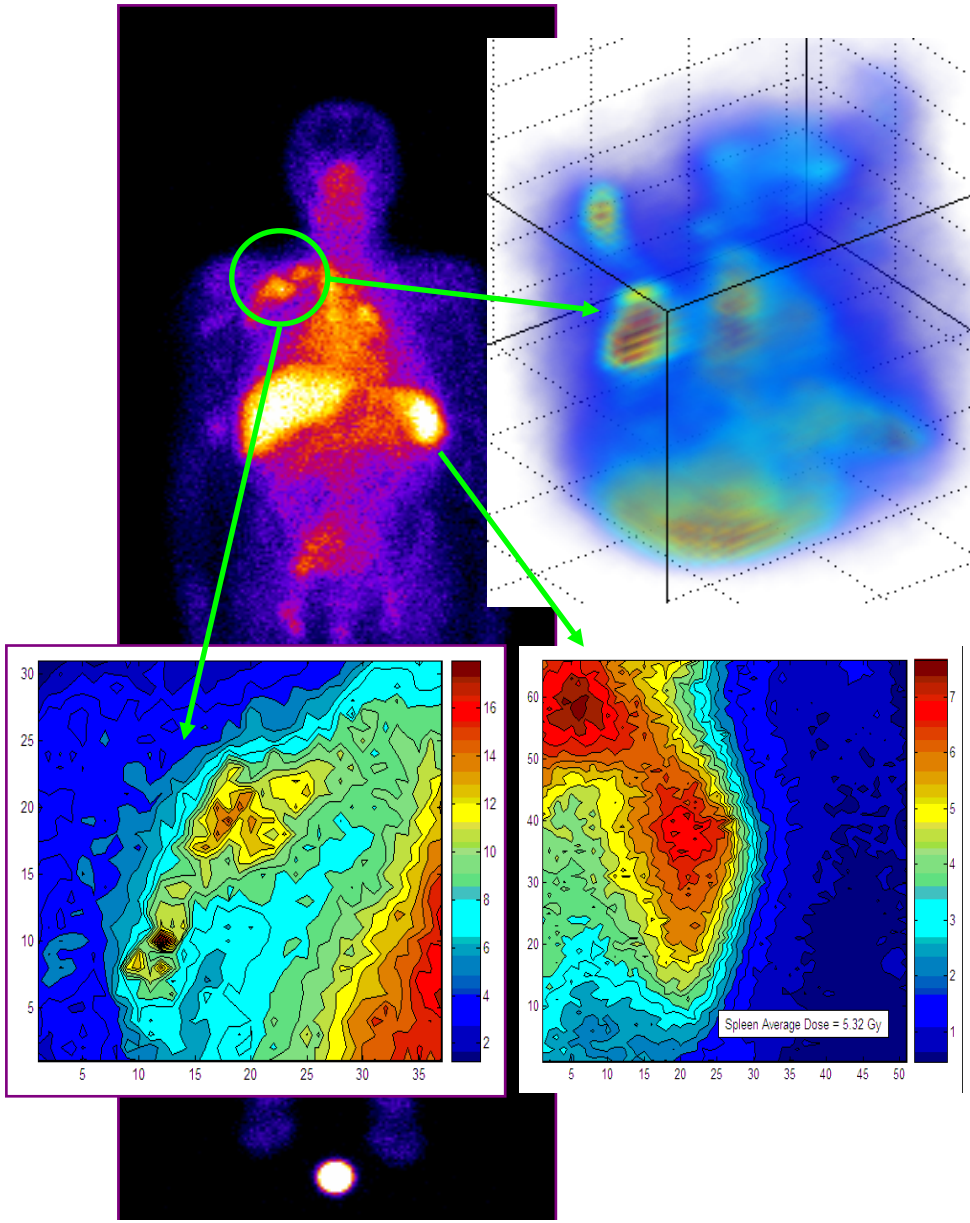
=

X



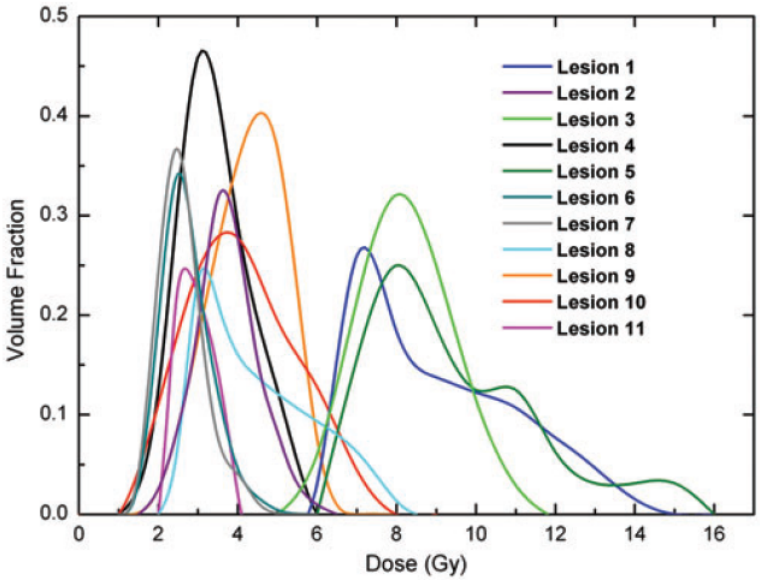
Cicone F, Scopinaro F 2013 In: Rituximab: Pharmacology, clinical use and health effects.

Voxel-based dosimetry



D'Arienzo M et al. 2012 Cancer Biother Radiopharm

Dose Volume Histograms (DVH)

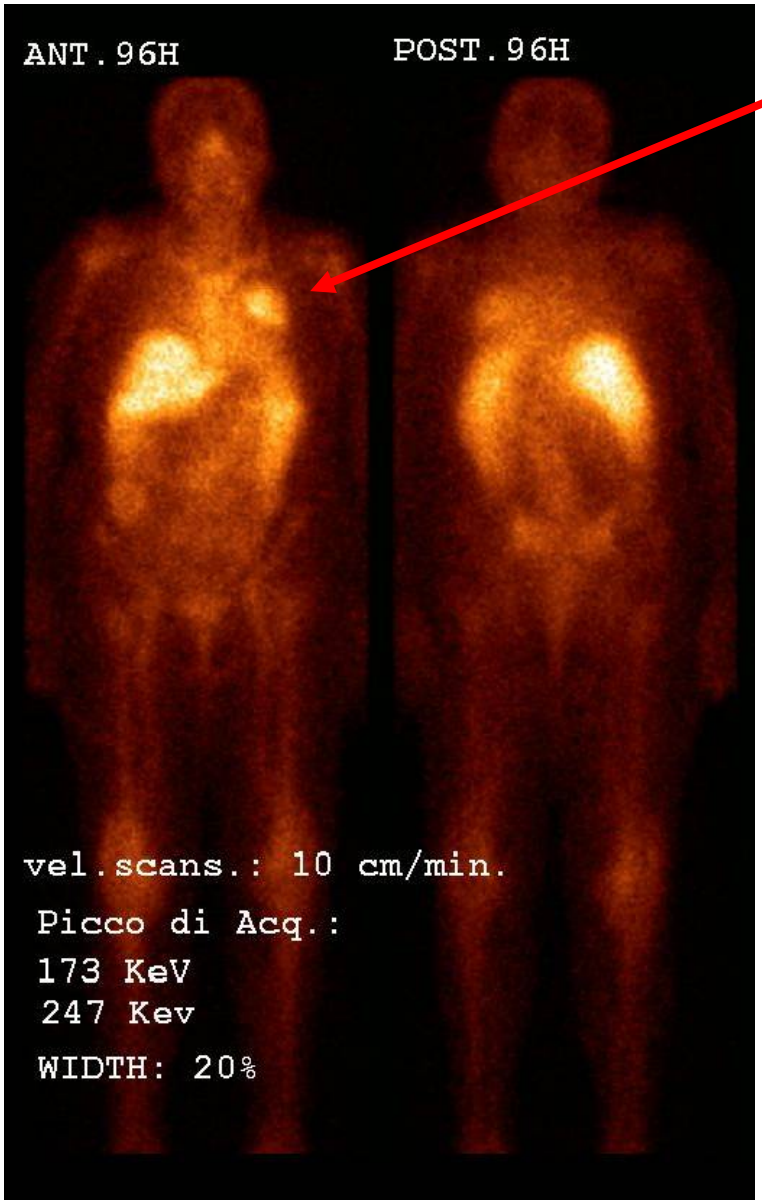


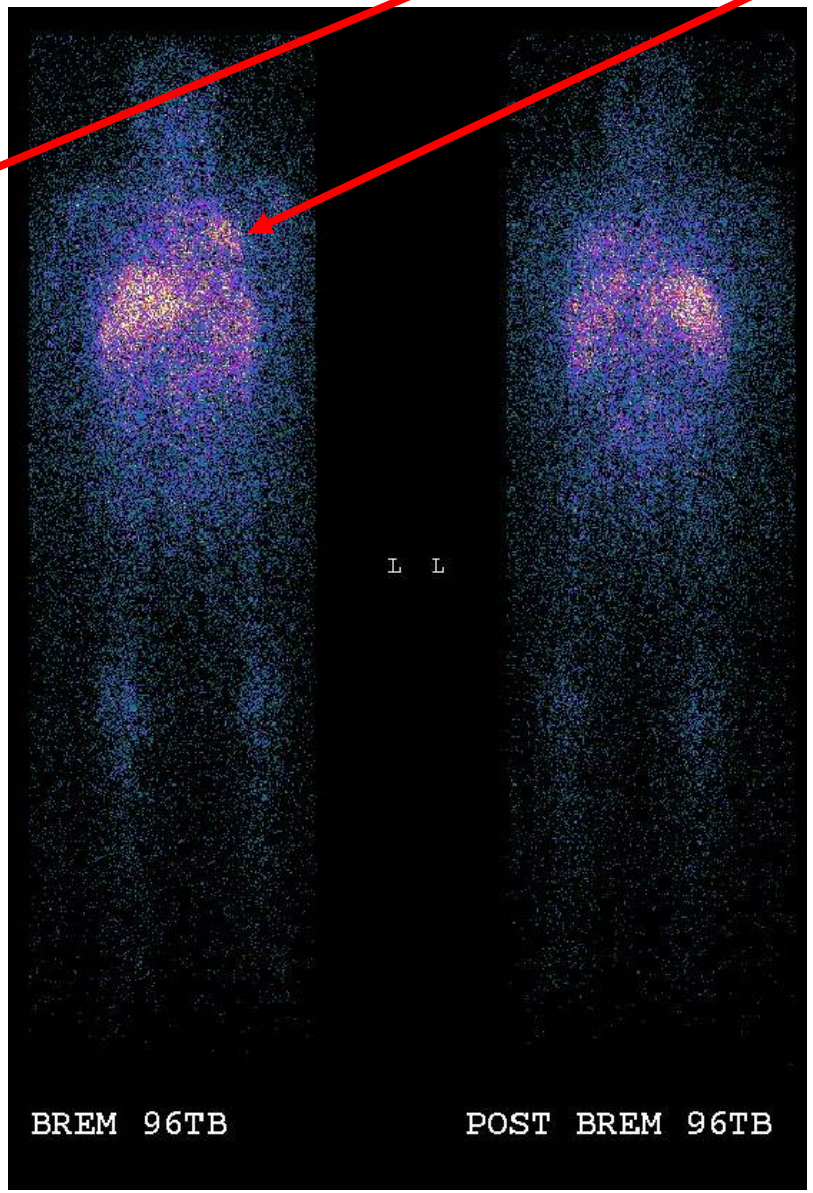
Equivalent Uniform Doses (EUD)

$$EUD = -\frac{1}{\alpha}\ln(S) = \frac{1}{\alpha}\ln\left[\int_0^\infty P(D)e^{-\alpha D}dD\right]$$

Cicone F et al. 2013 Cancer Biother Radiopharm

Planning vs verification of delivery: ^{111}In- vs ^{90}Y-Zevalin.

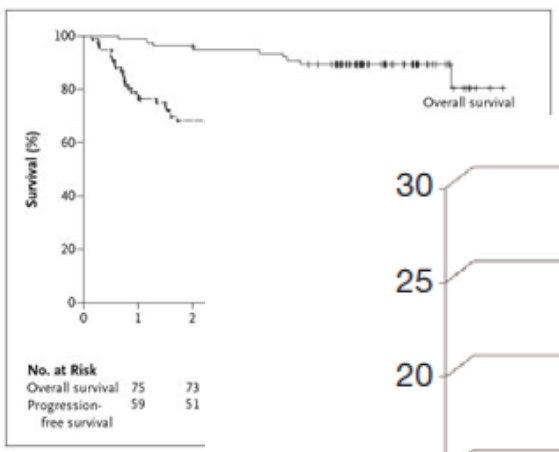




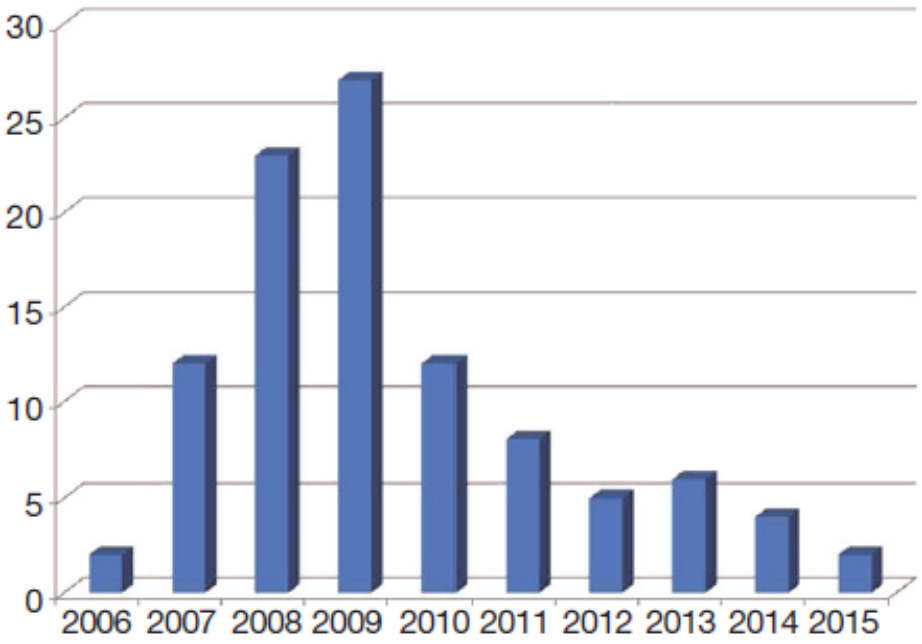
Bremmstrahlung !!!

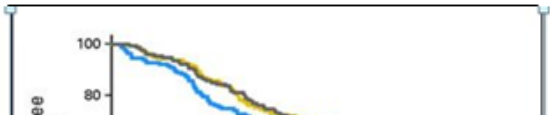
Cicone F, Scopinaro F 2013 In: Rituximab: Pharmacology, clinical use and health effects.

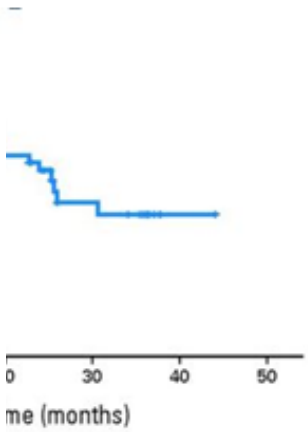
The failure of the Magic Bullet !



Kaminski MS et al.







3;31:308-313

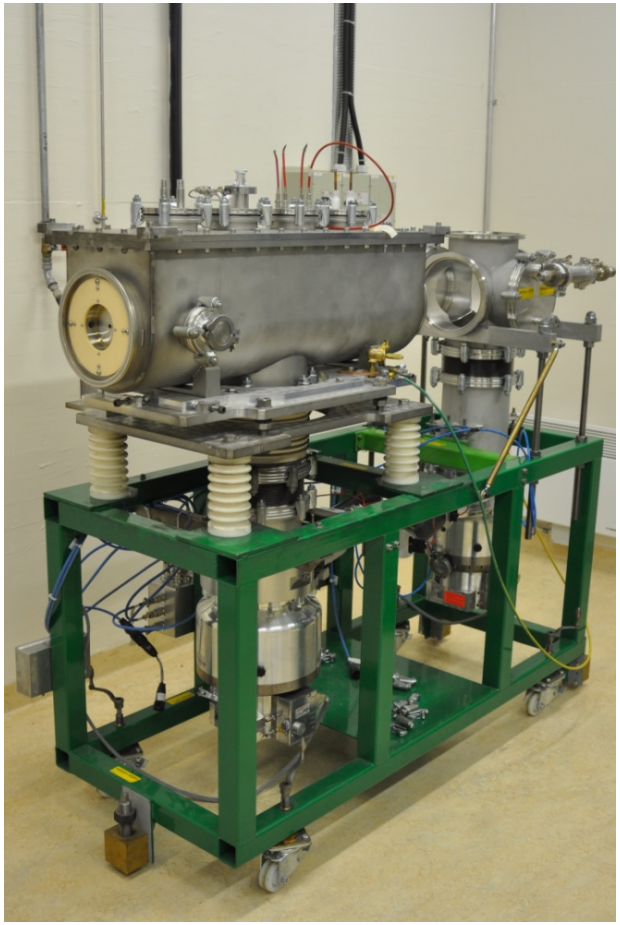
Figure 1 Distribution over time of a total of 101 radioimmunotherapy treatments with ^{90}Y-ibritumomab-tiuxetan (Zevalin®) performed at Sant'Andrea University Hospital of Rome, Italy, between July 2006 and October 2015.

Cicone F et al. Trans Canc Res 2016

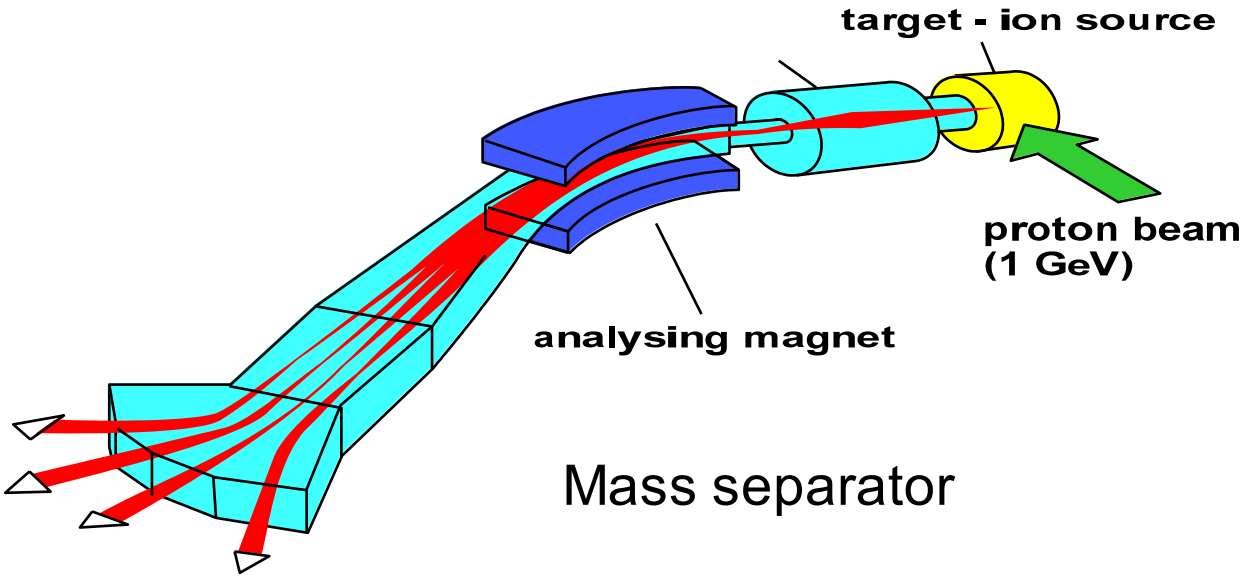
WP3/ Single projects

Medicis Promed

CERN: construction of Offline 2



RFQ Cooler



Mass separator

Development of ion sources

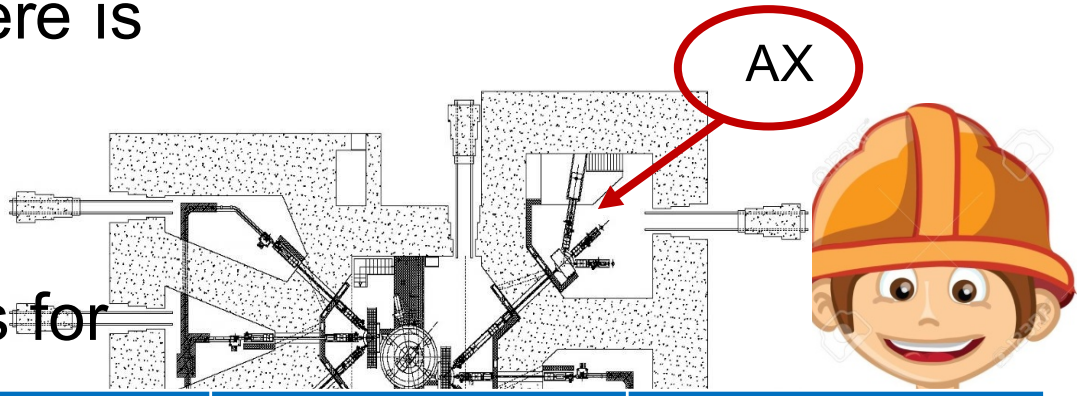
Beam manipulation (improvement of beam transmission, energy spread and divergence)

Industrial partner: AAA/Arronax

Aims:

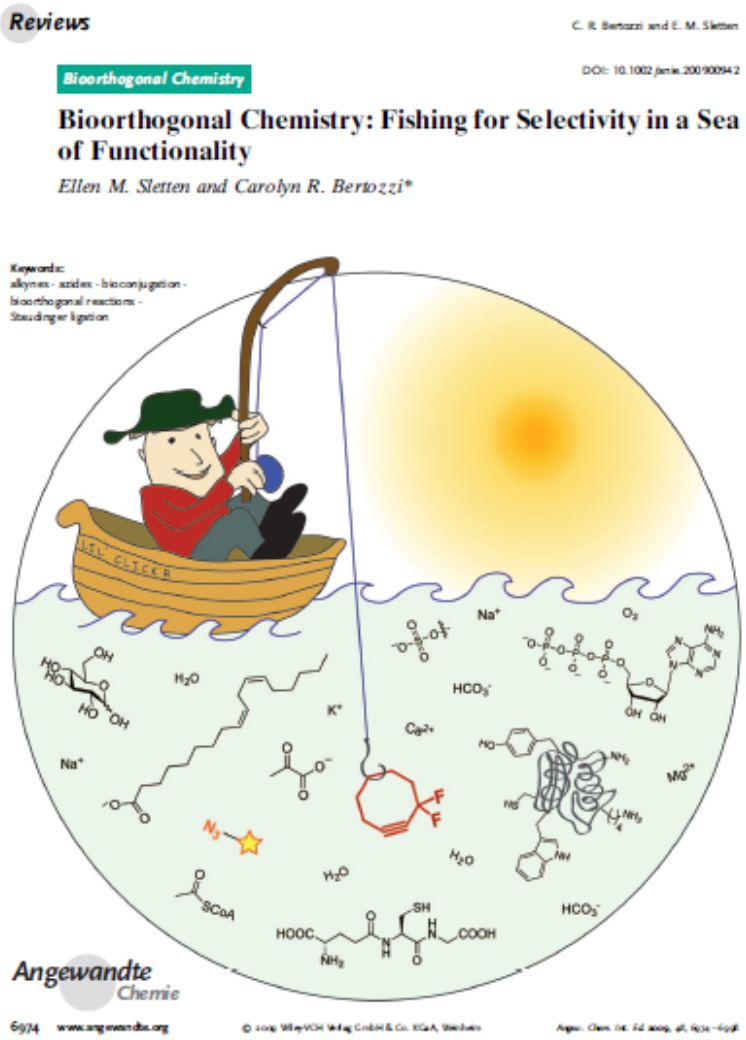
To study feasibility of applying mass separator tecqnique to commercial cyclotrons (there is none at the moment)

Selection and testing of innovative targets/isotopes for the market



Element	Radionuclide	Application	Comments
Scandium	Sc43	PET	15 MeV cycl
	Sc44	PET/ 3γ	15 MeV cycl
	Sc47	Therapy	reactor and 70 MeV cycl
Copper	Cu61	PET	15 MeV cycl
	Cu64	Therapy / PET	15 MeV cycl
	Cu67	Therapy / SPECT	reactor and 70 MeV cycl

Bioorthogonal Chemistry



Bio-orthogonal = no interference with biological processess

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 chemist[illegible] do not.

Nevertheless, carbonyl-based reac[illegible] profoundly appealing to students and[illegible] chemistry. It is our contention that[illegible] ducted, as it has been, in imitatio[illegible] chemistry is ill-suited for the rapid dis[illegible] with desired properties.

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

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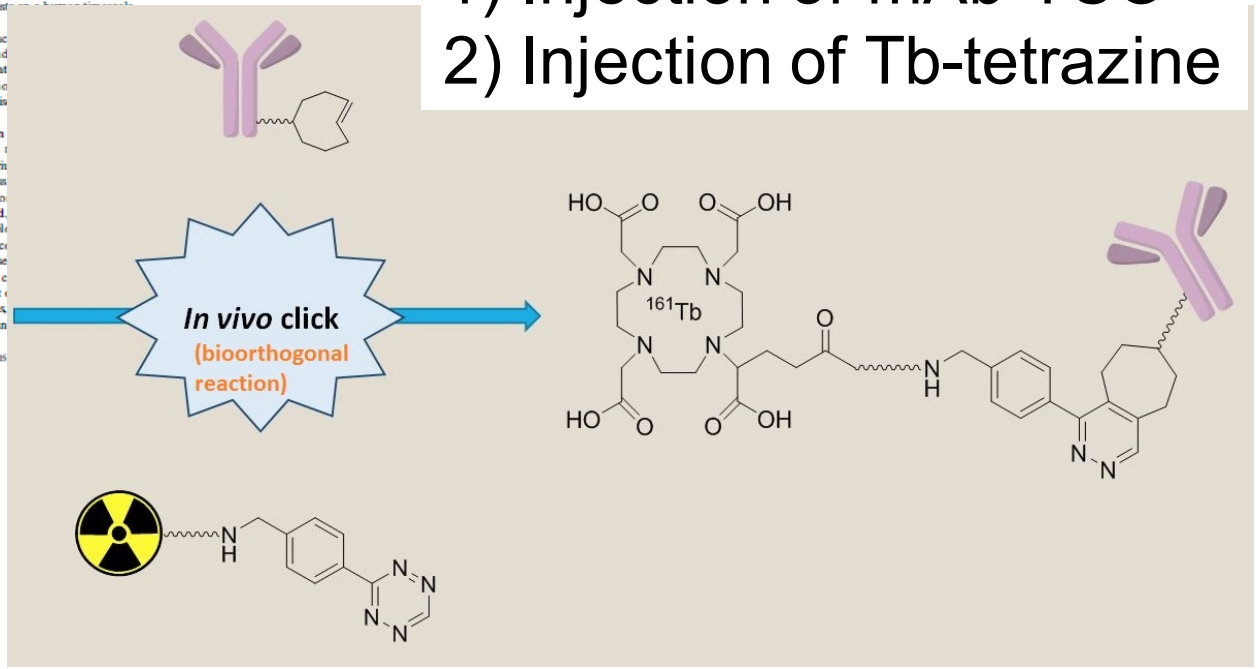
Angew. Chem. Int. Ed. **2001**, *40*, 2004–2021 1433-7851/01/4011-2005

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

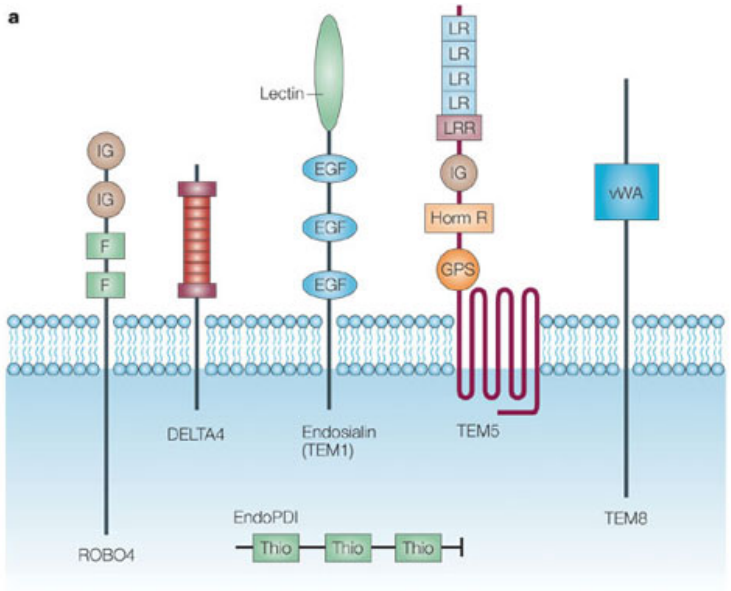
1) Injection of mAb-TCO
2) Injection of Tb-tetrazine



[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

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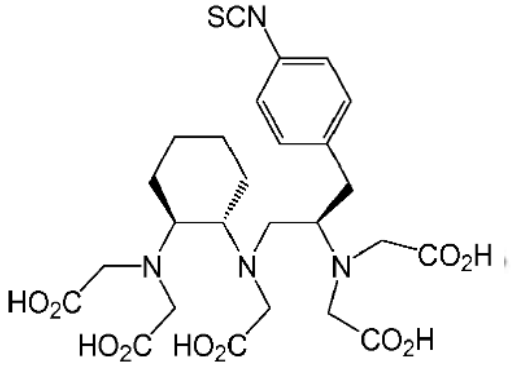
Labelling of 78Fc anti-TEM1 with radiometals



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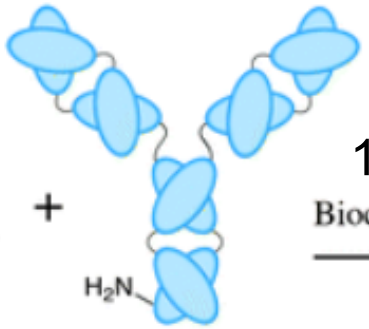
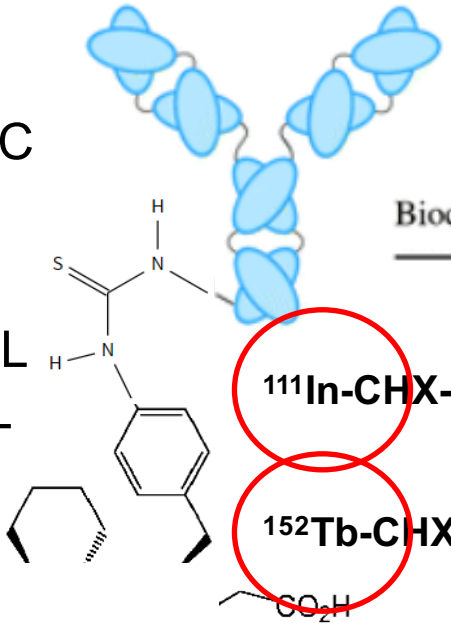


1 h 42 °C

Bioconjugation



Bioconjugation

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

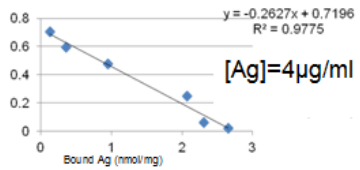
^{111}In-CHX-A"-DTPA-FcTEM1

and

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

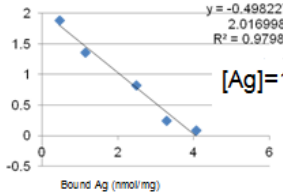
In Vitro Testing / Immunoreactivity

Scatchard plot



[Ag]=4µg/ml

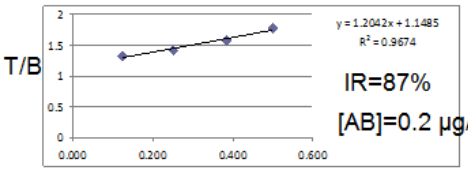
Kd = 3.8 nM
Bmax = 2.7 nmol/mg Ag



[Ag]=1µg/ml

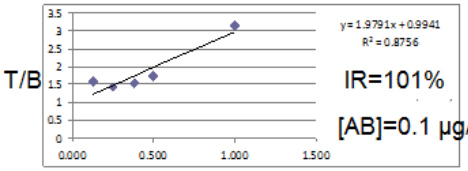
Kd = 2 nM
Bmax = 4 nmol/mg Ag

Lindmo plot



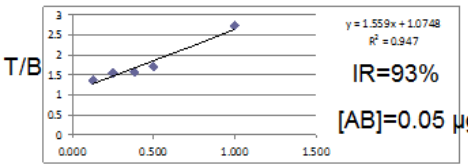
IR=87%

[AB]=0.2 µg/ml



IR=101%

[AB]=0.1 µg/ml



IR=93%

[AB]=0.05 µg/ml

1/[Ag]

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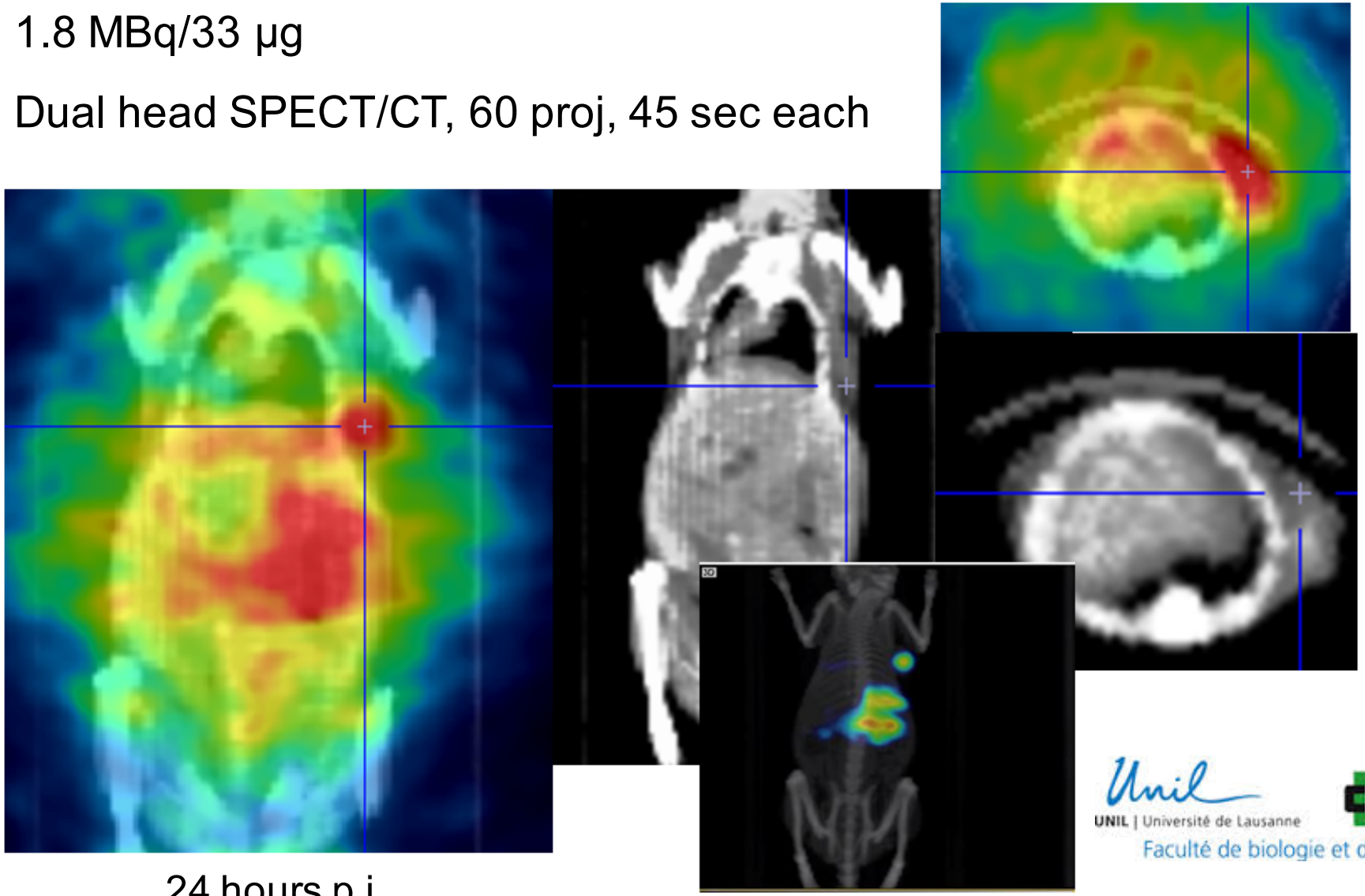
First SPECT imaging of ^{111}In-CHX-A''-DTPA-ScFv78Fc

Ewing Sarcoma cell line A673

1.8 MBq/33 µg

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



24 hours p.i.

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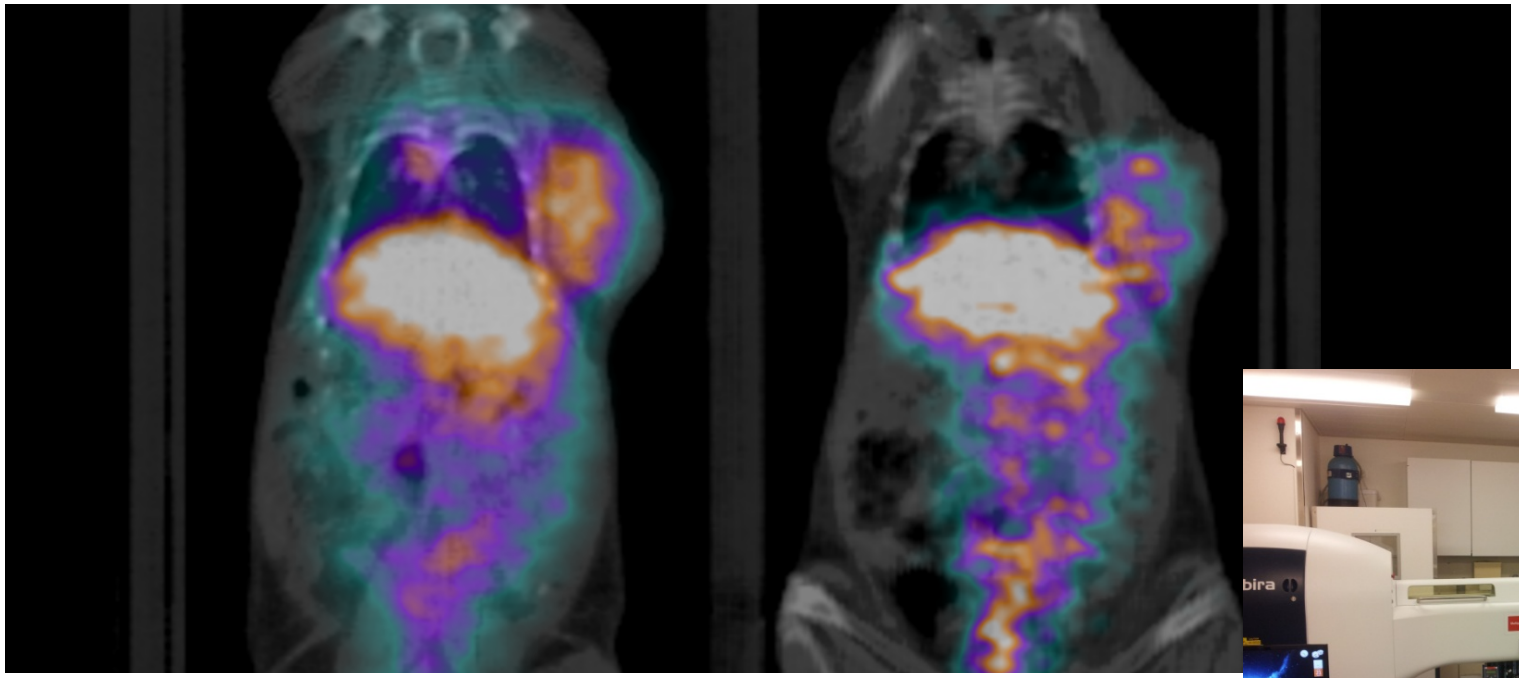
Cicone F et al. IRIST Conference, Lausanne 2016

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. 23rd IRIST Conference, 27-28 May 2016, Lausanne

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Thanks for your attention