MEDICIS - PROMED project

MEDICIS-PROMED

Marie Curie training H2020

kick-off meeting - April 22, 2015

WP3: Theranostic radiopharmaceuticals for imaging

Pr. Leo Buhler
Pr. Osman Ratib
University Hospital of Geneva (HUG)

MEDICIS - PROMED project

Theranostic ?

MEDICIS - PROMED project

Published:
May 12th 1921
© The New York Times

The New York Times.

MME. CURIE PLANS TO END ALL CANCERS

Says Radium Is Sure Cure, Even in Deep-Rooted Cases, if Properly Treated.

MEDICIS - PROMED project

1921

2015

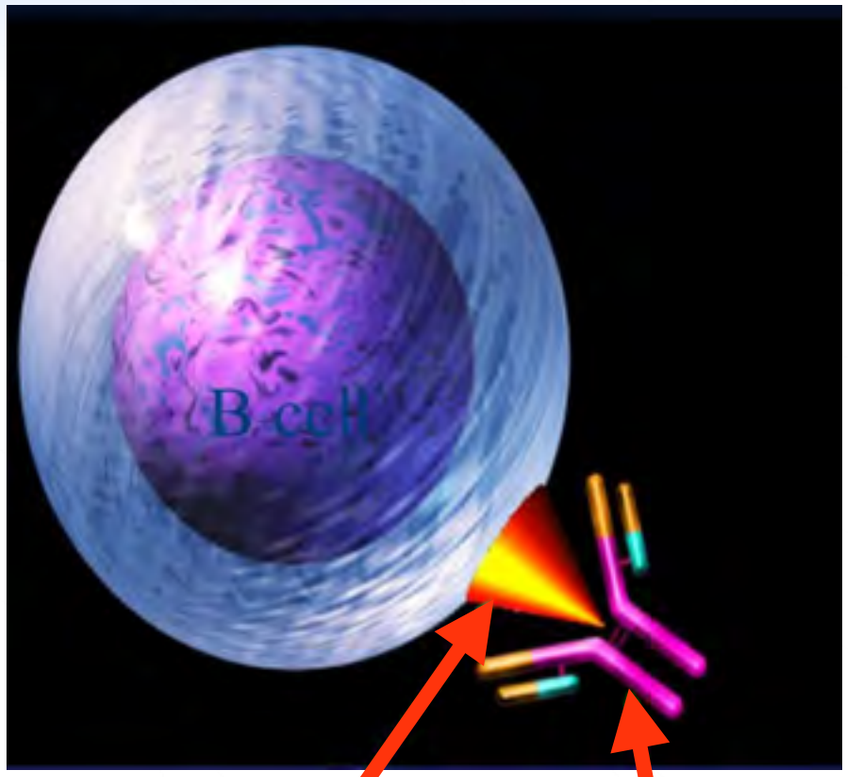
MEDICIS - PROMED project

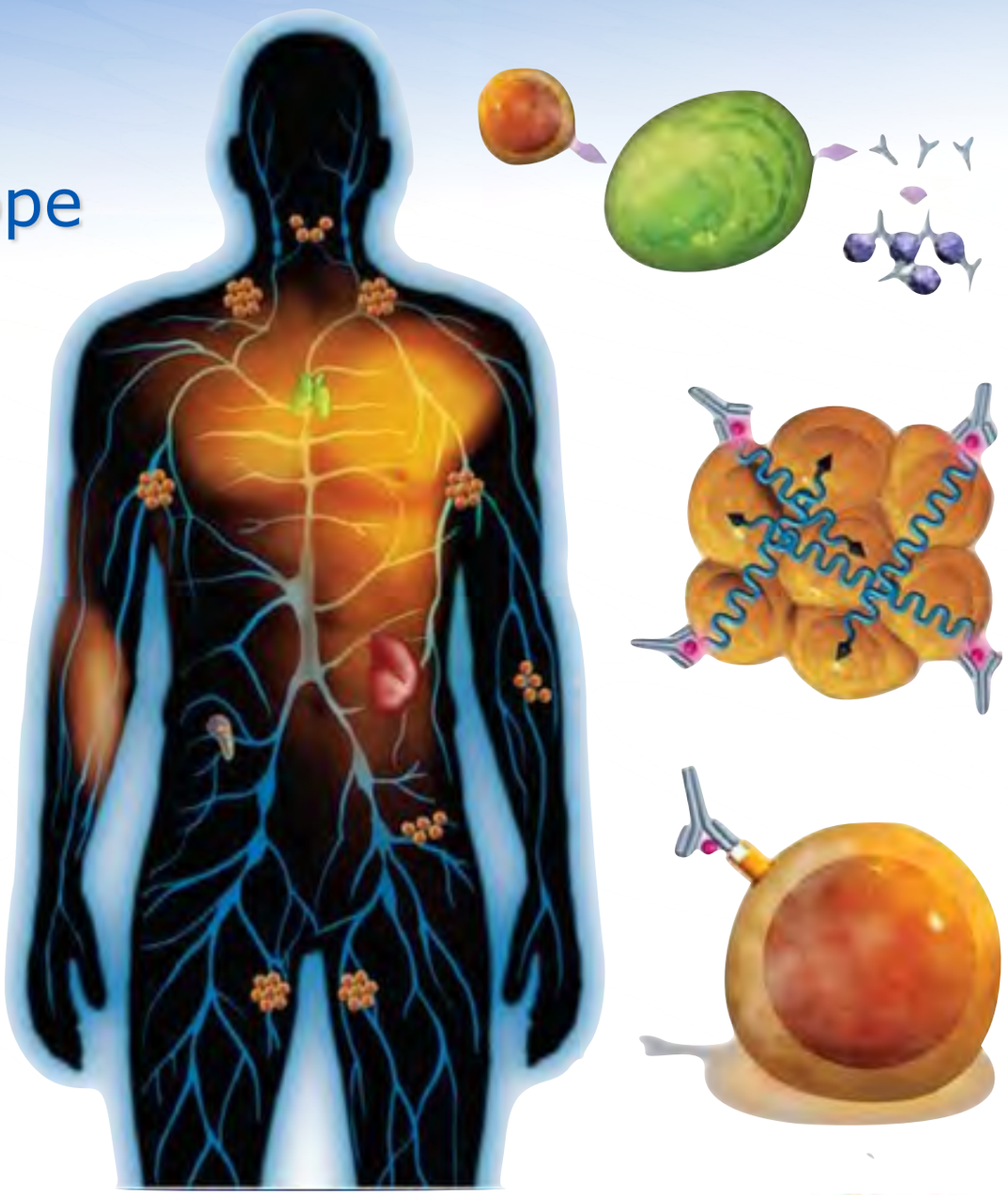
Examples

MEDICIS - PROMED project

$^{131}I/^{90}Y$ labelled antibody for NHL therapy

- Monoclonal antibody
- Labelled with Beta emitting isotope



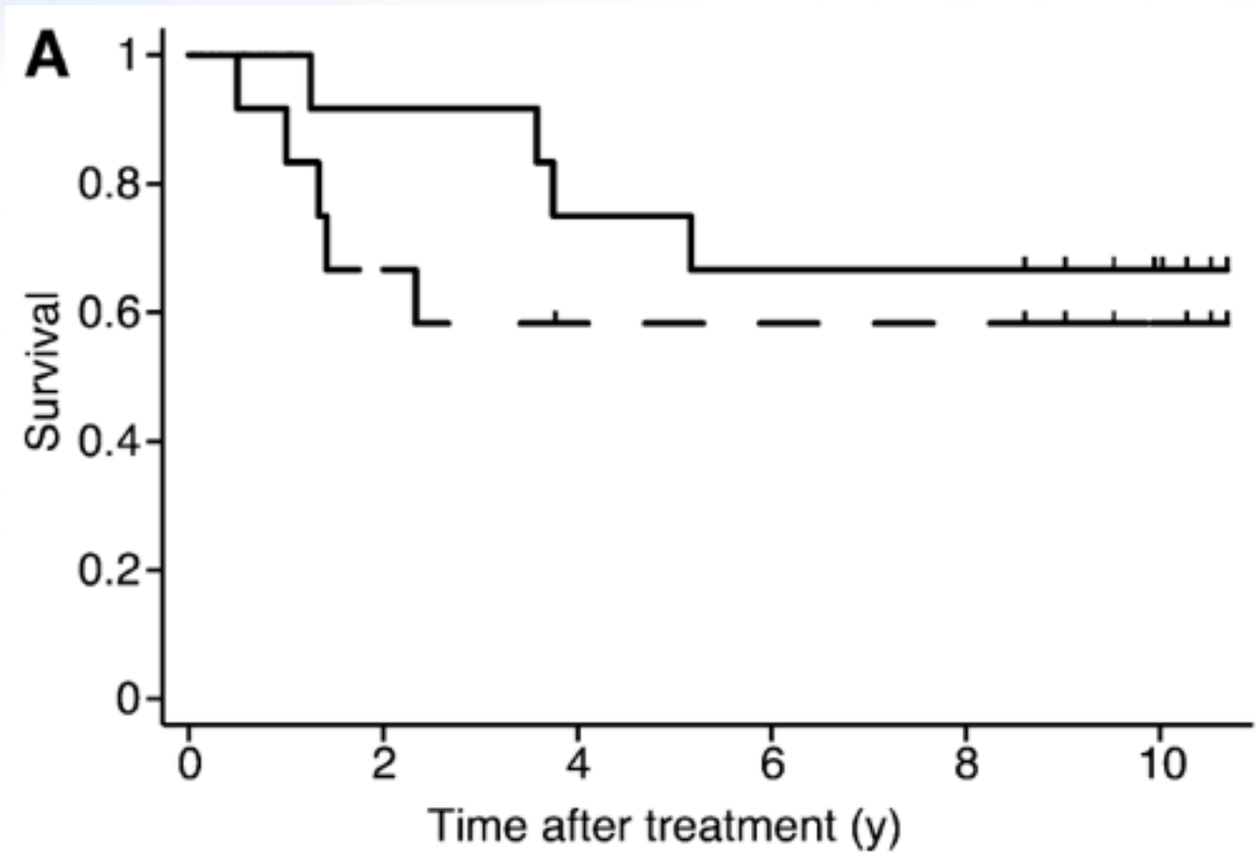


YEARS/ANS CERN

MEDICIS - PROMED project

$^{131}I/^{90}Y$ labelled antibody for NHL therapy

Treatment of indolent lymphoma with ^{131}I-tositumomab

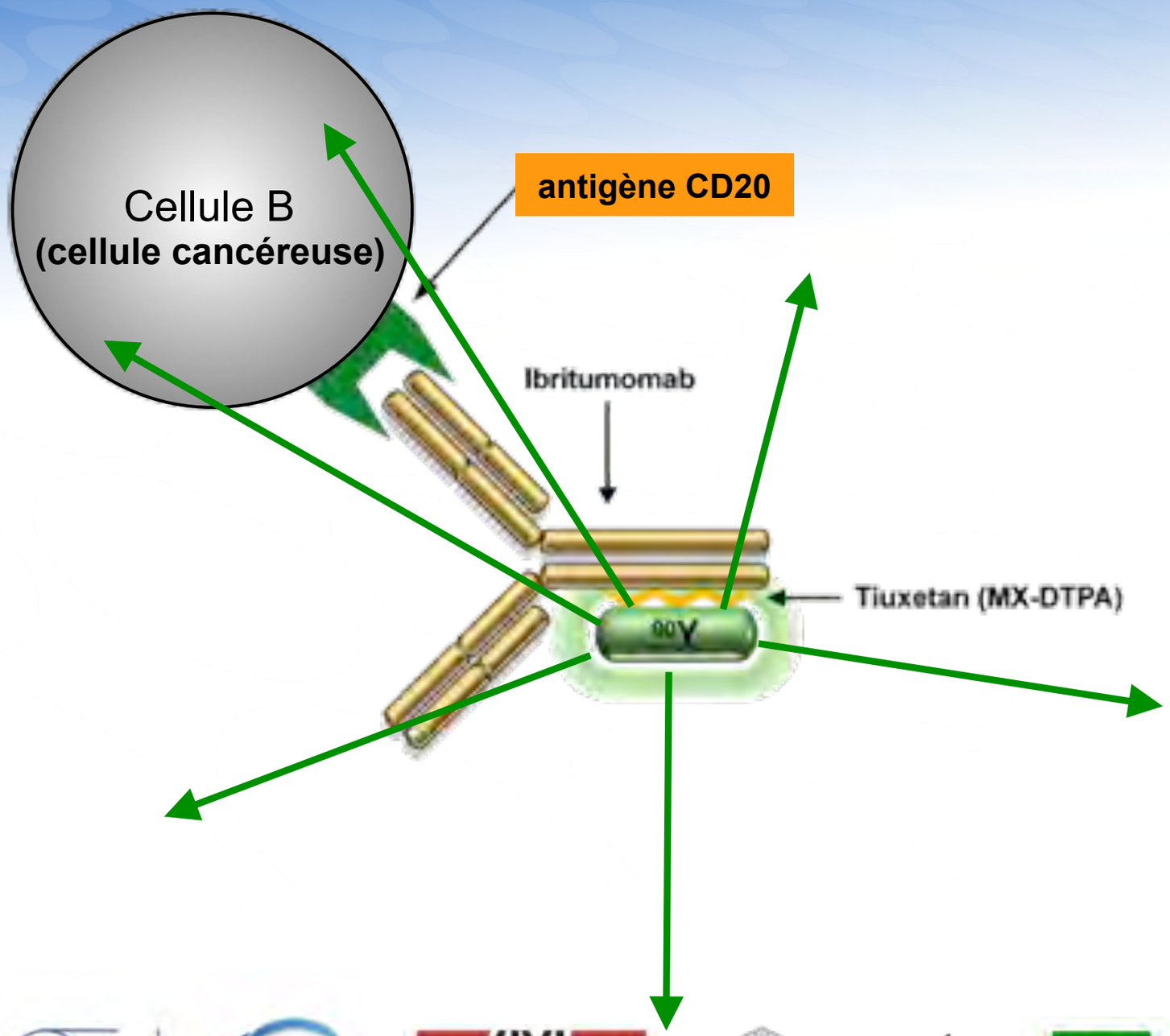


F. Buchegger et al British Journal of Cancer (2006) 94, 1770 – 1776 et J Nucl Med 2011; 52:896-900

CERN 60 YEARS/ANS CERN | EPFL ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE | UNIVERSITÉ DE GENÈVE FACULTÉ DE MÉDECINE | CHUV | HUG Hôpitaux Universitaires de Genève | Unil UNIL | Université de Lausanne Faculté de biologie et de médecine

MEDICIS - PROMED project

$^{131}I/^{90}Y$ labelled antibody for NHL therapy



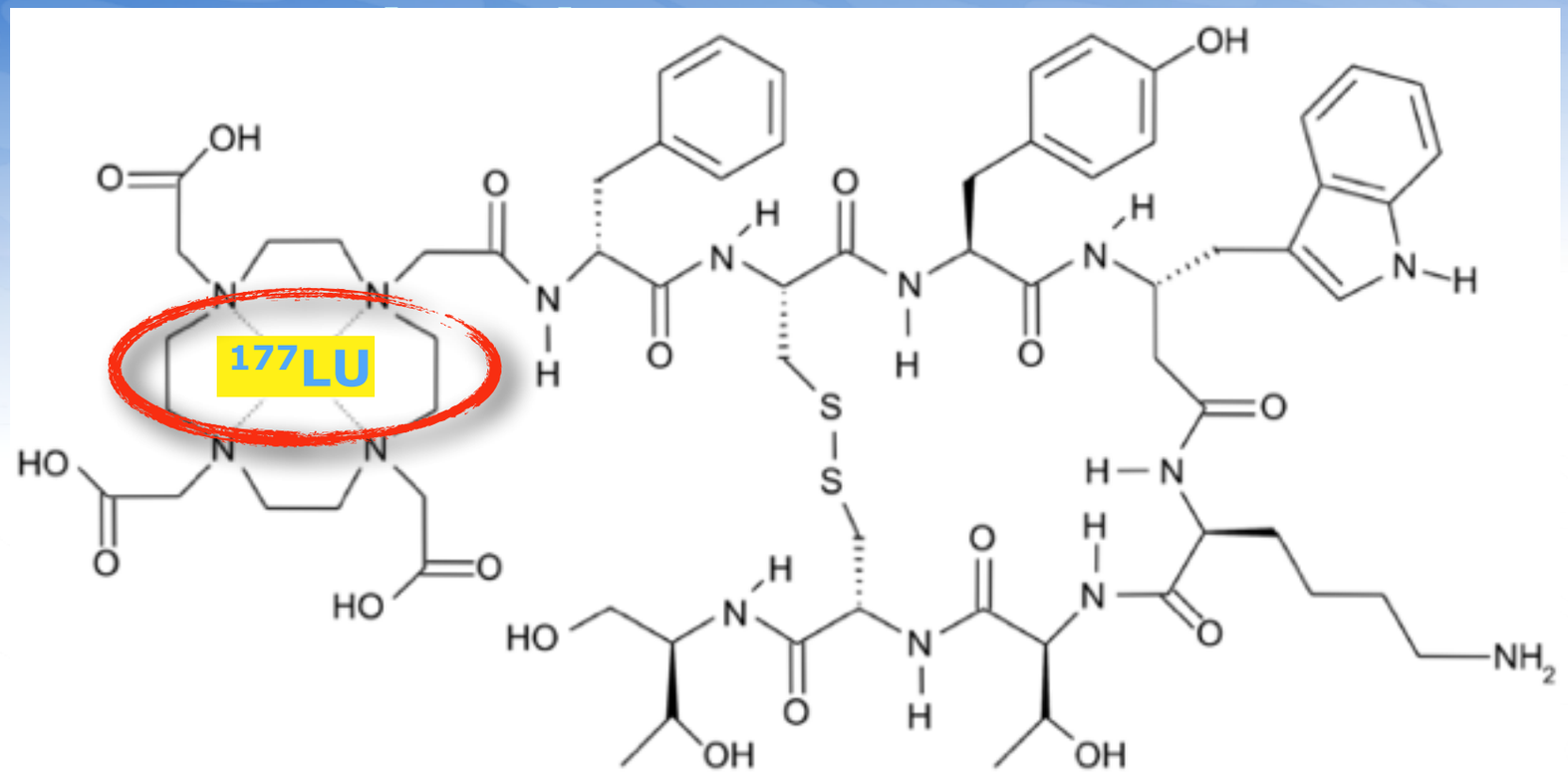
Anticorps monoclonal (ibritumomab), associé à un radioisotope (yttrium-90)

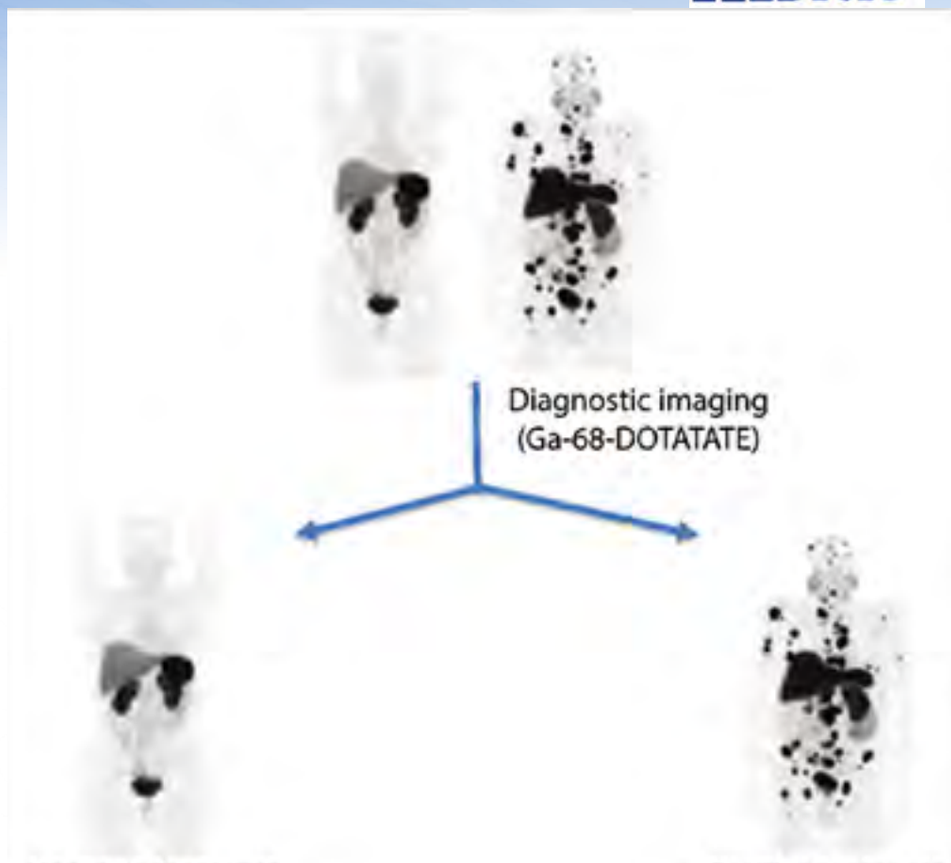
L'yttrium-90 se décompose en zirconium-90 stable, par l'émission des particules bêta riches en énergie (demi-vie: 2.67 jours).

La portée des rayons bêta de l'yttrium-90 dans le tissu est de 5 mm au maximum.

MEDICIS - PROMED project

^{68}GA/^{177}LU DOTATOC in Neuroendocrine tumors





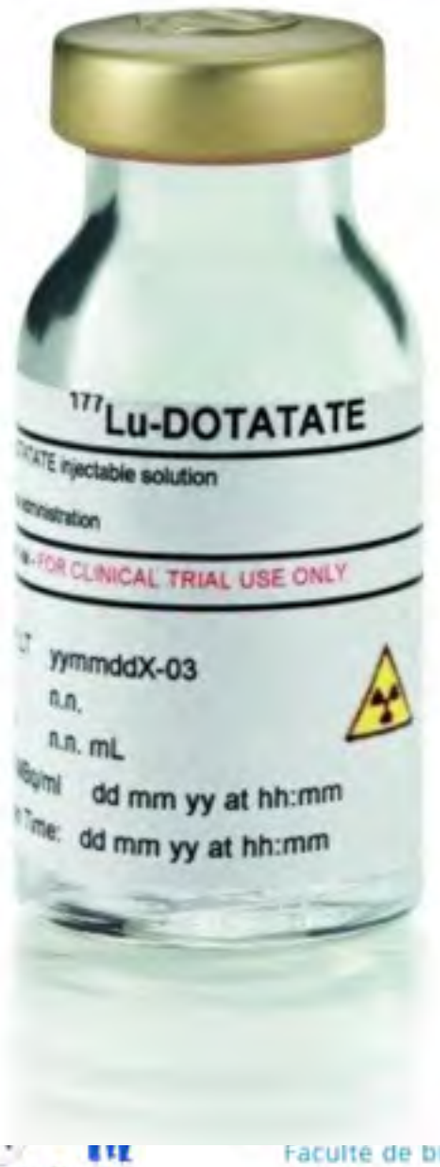
- ^{177}LU emits intermediate energy beta particles (133 KeV)
- Beneficial in small sized tumors (tissue range 2mm)
- Concomitant gamma emission enables imaging with gamma cameras

MEDICIS - PROMED project

Peptide Receptor Radionuclide Therapy (PRRT)

Lutathera®

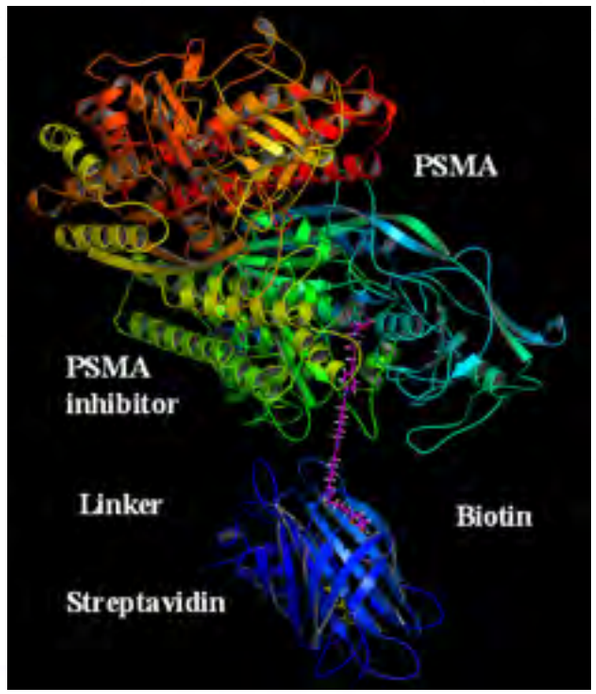
- Phase II results in progressive midgut carcinoid showed Progression-Free Survival of more than 44 months compared to the reported 14.6 months of Novartis' Sandostatin® LAR
- Lutathera® was shown to increase overall survival by between 3.5 and 6 years in comparison to current treatments, including chemotherapy.
- It was also shown to significantly improve quality of life

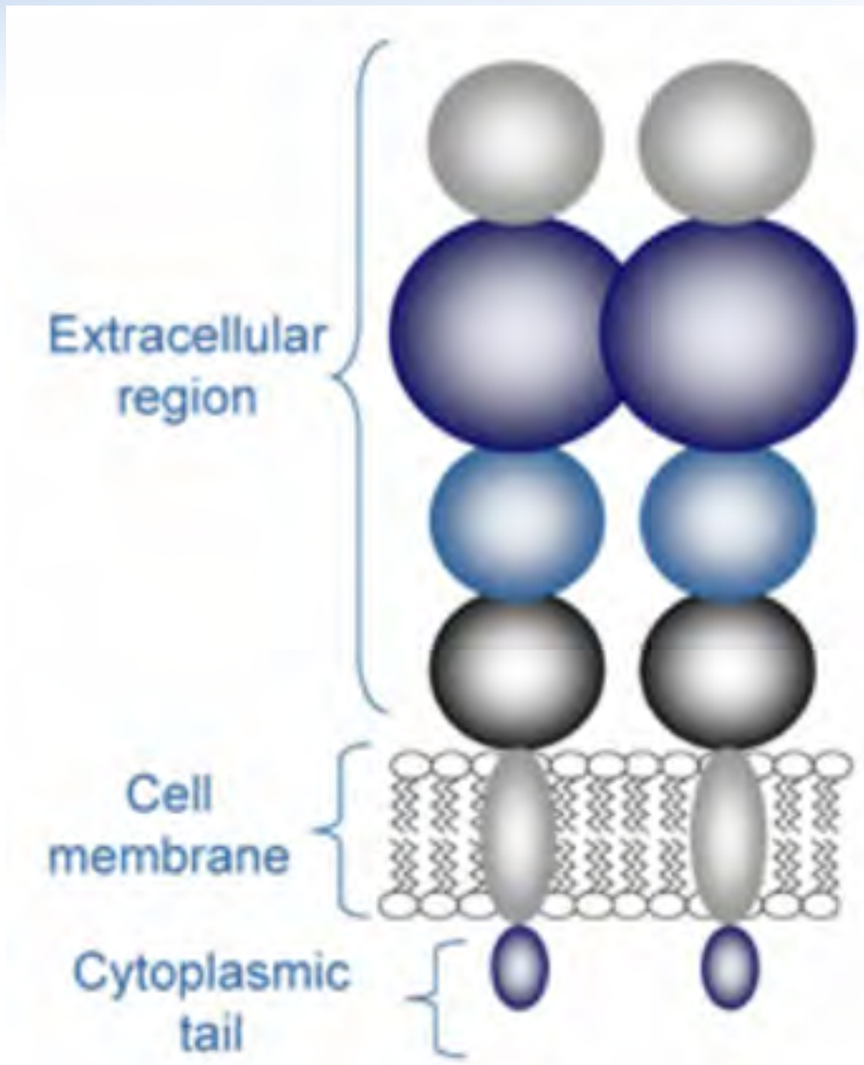


MEDICIS - PROMED project

Prostate-Specific Membrane Antigen

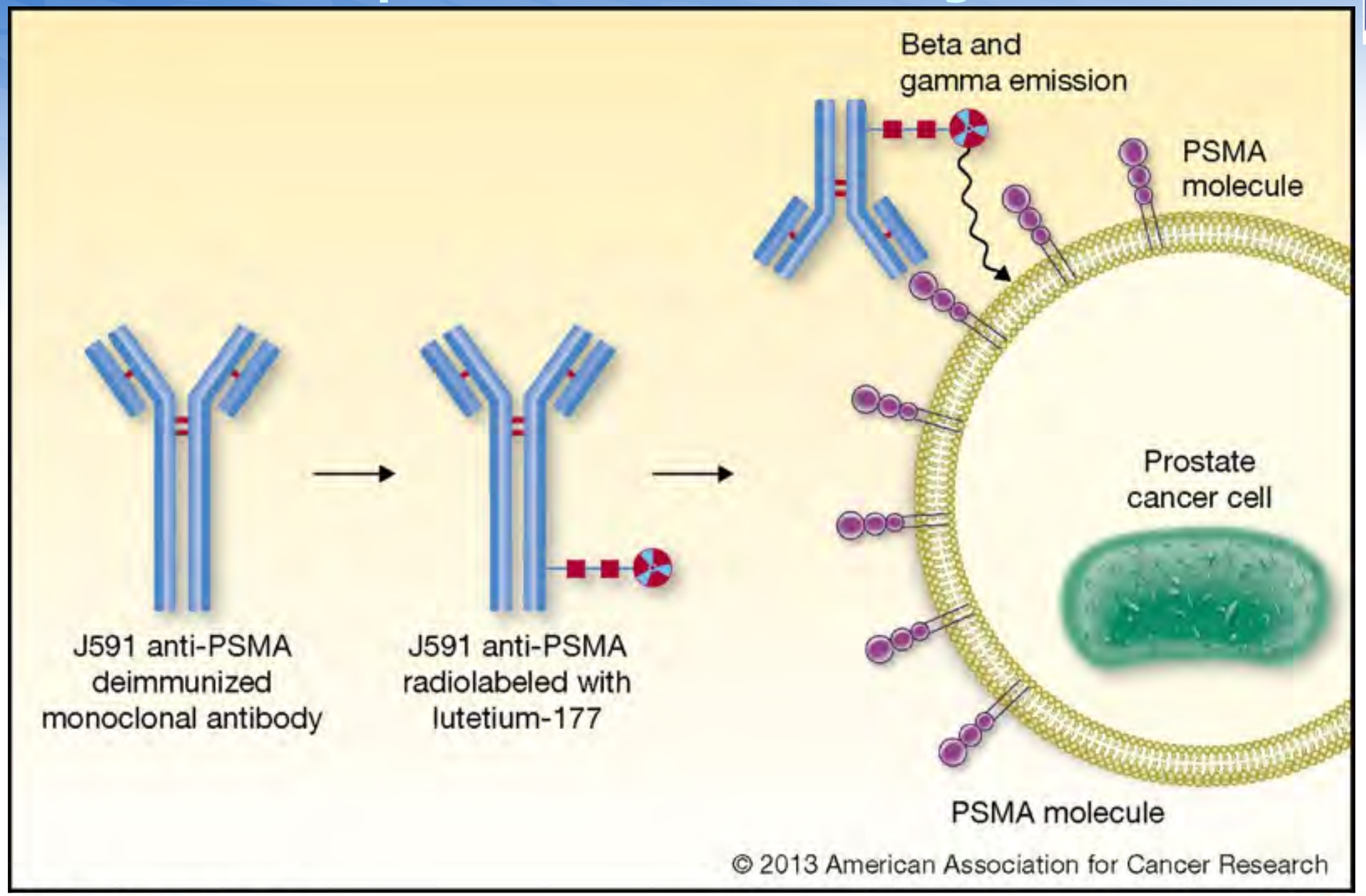
- Type II membrane bound glycoprotein
- Expressed in all forms of prostate tissue
- Over-expressed in carcinoma
- Also found in the neovasculature of most solid tumors





MEDICIS - PROMED project

Prostate-Specific Membrane Antigen



MEDICIS - PROMED project

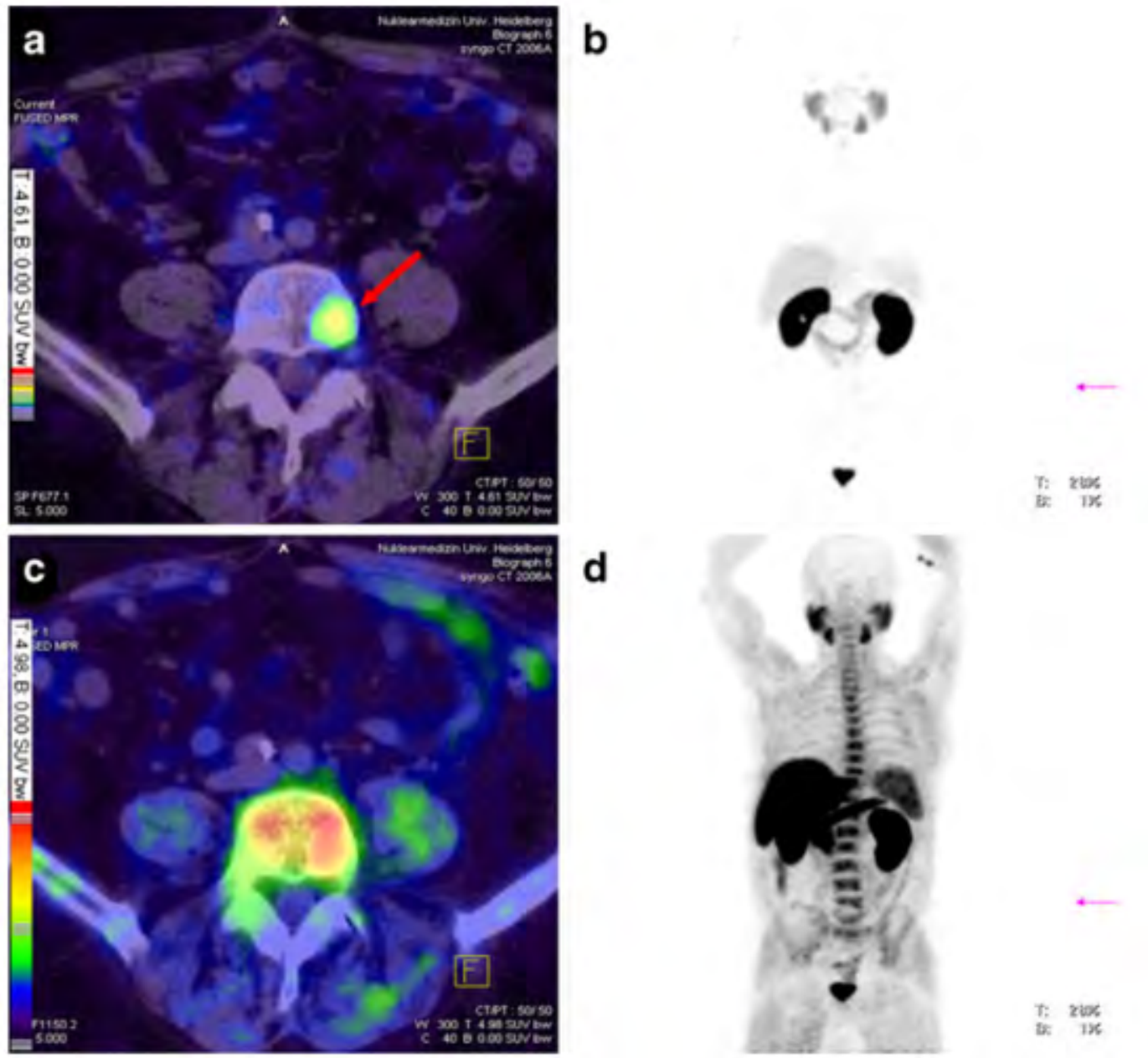
Prostate-Specific Membrane Antigen

Eur J Nucl Med Mol Imaging (2012) 39:1085–1086
DOI 10.1007/s00259-012-2069-0

IMAGE OF THE MONTH

[^{68}Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with ^{18}F-FECH

A. Afshar-Oromieh · U. Haberkorn · M. Eder · M. Eisenhut · CM. Zechmann



Glu-NH-CO-NH-Lys-(Ahx)-[68Ga(HBED-CC)]
Compared to
18F-Fluorocholine

MEDICIS - PROMED project

Prostate-Specific Membrane Antigen

Phase II trial of ^{177}lutetium radiolabeled anti-PSMA antibody J591 (^{177}Lu-J591) for metastatic castrate-resistant prostate cancer (metCRPC): Survival update and expansion cohort with biomarkers

Scott T. Tagawa, Naveed H. Akhtar, Joseph Osborne, Paul Christos, Shankar Vallabhajosula, Stanley J. Goldsmith, Renee Kahn, Caryn Ecker, Michael J. Morris, Matthew I. Milowsky, Neil H. Bander, David M. Nanus,
Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center, New York, NY

BACKGROUND

- J591 is a deimmunized anti-PSMA monoclonal antibody that binds to the extra-cellular domain of viable PSMA+ cells with rapid internalization
  Liu et al. Cancer Res 1997; Liu et al. Cancer Res 1998
- ^{177}Lu is a low energy β particle; gamma emission allows imaging
  The short range of β emission is ideal for 1-3 mm tumor masses (may be suboptimal for bulky tumors) [O'Donoghue et al. J Nucl Med 2005]
- A phase I study of ^{177}Lu-J591 demonstrated safety and defined the MTD as 70 mCi/m^2, with good targeting and preliminary evidence of efficacy
  [Bander et al. J Clin Oncol 2005]
- Initial results of the phase II trial of single-dose ^{177}Lu-J591 demonstrated efficacy with a possible dose-response and confirmed the excellent ability (94%) of the radiolabeled mAb to target known sites of disease
  Tagawa et al. ASCO 2008

METHODS

Entry Criteria (summary)
- Adenocarcinoma of prostate with radiographically evident metastases
- Progression despite medical/surgical castration (testosterone < 50)
- Adequate bone marrow and organ function
  (including ANC ≥ 2000, platelet count ≥150)
- ECOG performance status 0-2
- No prior β-emitting radioisotopes (e.g. strontium, samarium)

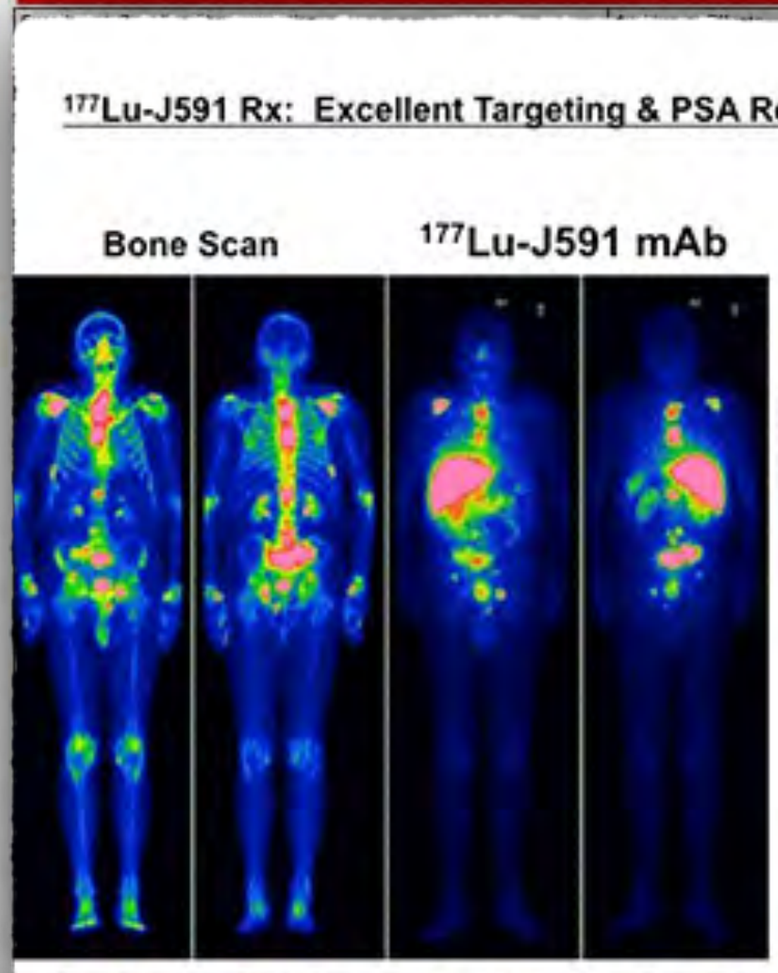
Treatment
- Single infusion of ^{177}Lu-J591
  Initial study = 2 cohorts: 15 pts 65 mCi/m^2, 17 pts 70 mCi/m^2 (Ph I MTD)
- Expansion cohort
  15 pts received ^{111}In-J591 and imaging to prospectively study imaging biomarker, followed by a single dose of 70 mCi/m^2 of ^{177}Lu-J591
- No pre-medications given

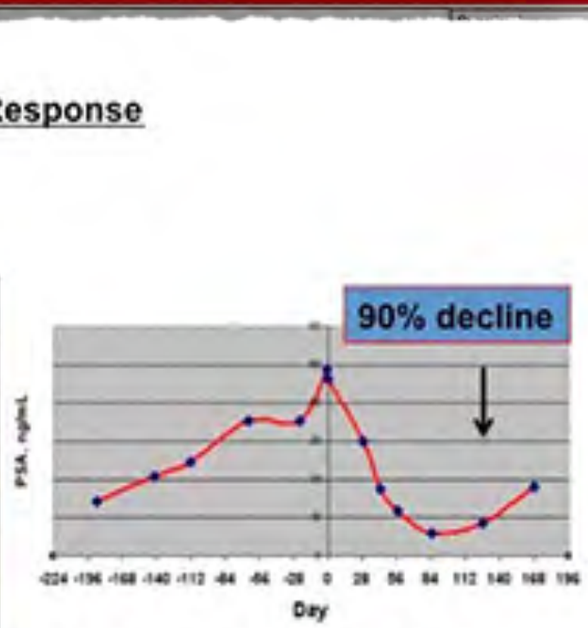
Imaging (Figure 1)
- Planar gamma camera imaging was performed 6-8 days after ^{177}Lu-J591 (2-4 days after ^{111}In-J591)
- Images were scored by 2 independent radiologists blinded to outcome retrospectively in the initial cohorts, prospective in expansion cohort:
  Visual score
  0 (no uptake), 1 (weakly positive), 2 (definitely positive), 3 (equal intensity to liver), 4 (greater uptake than liver)
  Tumor Targeting Index (novel metric to semi-quantitatively score images)
  Calculated for the most prominent lesions using the ratio of lesion count density (corrected for background) to whole body count density.
  TTI = (lesion ROI count – background) / (total body count)

Efficacy measures
- Bone scans and cross-sectional imaging q 3 mo until progression, serum PSA at least monthly, progression-free and overall survival
- CTC counts (CellSearch) at baseline and after 4-6 wks in expansion cohort

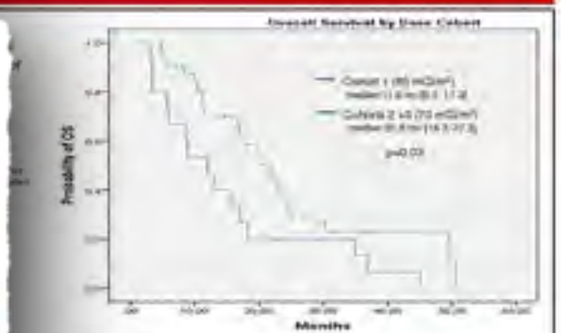
RESULTS

^{177}Lu-J591 Rx: Excellent Targeting & PSA Response





Pre-treatment PSADT=3.9 mo.



CONCLUSIONS

-J591 was generally well tolerated with reversible myelosuppression
rgeting was seen with evidence of anti-tumor activity
nce of a dose-response (and toxicity) relationship was verified
asurement of PSMA expression may be a promising predictive
PSMA-based radioimmunotherapy

Supported by: Prostate Cancer Foundation; NIH (J.J.) R01CA94096, 1-KL2-RR024997

Disclosures: NHB has a financial relationship with BZL biologics, Inc.

YEARS/ANS CERN

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

CHUV

HUG
Hôpitaux Universitaires de Genève

UNIL | Université de Lausanne
Faculté de biologie et de médecine

MEDICIS - PROMED project

Prostate-Specific Membrane Antigen

Proposal Evaluation Form

EUROPEAN COMMISSION

Horizon 2020 - Research and Innovation Framework Programme

Evaluation Summary Report

Call: H2020-MSCA-ITN-2014
Funding scheme: Training Networks
Proposal number: 642889
Proposal acronym: MEDICIS-PROMED
Duration (months): 48
Proposal title: MEDICIS-produced radioisotope beams for medicine
Activity: ENG

N.	Proposer name	Country	Total Cost	%	Grant Requested	%
1	EUROPEAN ORGANIZATION FOR NUCLEAR RESEARCH	CH	795,680	28.12%	0	-
2	THE UNIVERSITY OF MANCHESTER	UK	273,288	9.66%	0	-
3	JOHANNES GUTENBERG UNIVERSITAET MAINZ	DE	249,216	8.81%	0	-
4	Advanced Accelerator Applications	FR	262,876	9.29%	0	-
5	INSTITUTO SUPERIOR TECNICO	PT	476,713	16.85%	0	-
6	Fondazione Centro Nazionale di Adroterapia Oncologica - Fondazione CNAO	IT	258,061	9.12%	0	-
7	KATHOLIEKE UNIVERSITEIT LEUVEN	BE	250,560	8.86%	0	-
8	LEMER PAX	FR	262,876	9.29%	0	-
	Total:		2,829,270		0	

WP3: Theranostic radiopharmaceuticals for imaging

MEDICIS - PROMED project

WP No	Work Package Title	Activity Type	Lead Participant No	Lead Participant Short Name	Start Month	End month	ESRs involvement
1	Mass separation of innovative medical isotopes using CERN-MEDICIS	Research	3	JOGU	4	48	2,4,5,7,10
2	^{11}Carbon PET-aided hadron therapy	Research	6	CNAO	4	48	3,9,11 + CH1,4
3	**Theranostic radiopharmaceuticals for imaging/ treatment of ovarian cancers**	**Research**	**4**	**AAA**	**4**	**48**	**1,6,8 + CH2,3**
4	Training	Training	1	CERN	4	48	1-11 +CH1-4
5	Management	Management	1	CERN	1	48	N/A
6	Communication	Communication	5	C2TN	6	48	1-11 +CH1-4

MEDICIS - PROMED project

Training	Knowledge gained	Institution	WP	
Mass separators	isotope mass separation isotope production targets and ion sources Hands-on training	**Isolde, CERN**	1,2	
Materials and radiation	2D materials Graphene Material performance and degradation	**Materials for demanding environments** **New CDT school/ Univ.**	1,2	
Fluka Monte-Carlo Code	Multiple particle tracking code Radiation protection Hadron therapy treatment planning	**INFN, CERN**	1,2,3	
Radiobiology	Biological radiation dose-response curve DNA damage and repair	**Univ. Pavia, CNAO**	2,3	
High power Lasers	Laser spectroscopy Atomic transitions Laser physics	**JOGU**	1,3	
5f intermetallic phase diagram	Inorganic synthesis of intermetallic alloys Handling of actinide materials Characterization techniques	**C2TN-IST**	1	
Molecular oncology	Molecular biology of normal and cancer cells Hallmarks of cancer Drug resistance mechanisms	**EPFL-ISREC**	2, 3	
Radiopharmaceuticals synthesis	Solid phase peptide synthesis principles Chelators for radiometals Automated synthesis	**C2TN-IST**	2,3	
Radioisotope production	Production cross-sections Energy deposition Irradiation facilities	**ARRONAX**	1,2	
Nuclear spectroscopy	Properties of exotic nuclei Optical techniques Combining atomic traps and lasers	**KUL**	1,2,3	
Ionization in plasma	Classification of plasmas Atomic phenomena Ionization mechanisms	**EPFL**	1	
Robotics and automation	Process definition Programed vs remote controlled Basic robotics	**EPFL**	1,2,3	
CERN Accelerator School	Basic physics of accelerators Accelerator components Beam dynamics	**CERN**	1,2,3	
Nuclear engineering	Basics of materials for nuclear environments Radiation damage Neutron irradiation	**Univ. Manchester**	1,2	
Functional imaging	**Principle of PET-SPECT imaging** **Image treatment softwares**	**HUG/CHUV**	**2,3**	

MEDICIS - PROMED project

	Affiliation	Project & secondment
ESR1	*CERN*	*Molecular break up* *Lemer Pax – 5 m – Industrial Magnet design*
ESR6	*AAA*	*Industrial production of therapy isotope using mass separation* *CERN-MEDICIS – 6m – Sc mass separated beams*
ESR8	*C2TN*	*Multifunctional 161Tb complexes for cell DNA targeting* *CHUV – 2m –mPET of ovarian cancers in mice* *EPFL – 8m – fluorescent / radioligand synthesis*
ESRCH2	*CHUV*	*Preclinical imaging and animal models – Clinical translation* *EPFL – 3m – tests on pancreatic cancer in mice*
ESRCH3	*HUG*	*New robot assisted instruments and delivery methods for brachytherapy* *C2TN – 3m – brachytherapy in small animals*

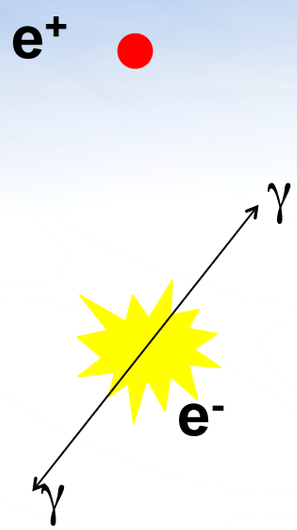
MEDICIS - PROMED project

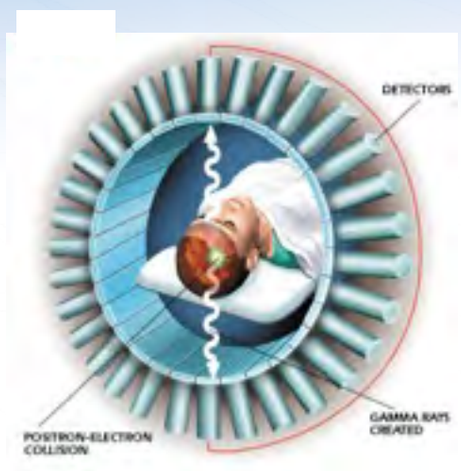
	Affiliation	Deliverables
ESR1	*CERN*	*D3.2 Laser molecular break-up in RFQ cooler for beam purification – M30*
ESR6	*AAA*	*D3.3 Cyclotron production and mass-separation of*
ESR8	*C2TN*	*D3.1 Cell-nucleus targeting with bioligands for Auger-therapy – M36*
ESRCH2	*CHUV*	*D3.CH1 Preclinical Imaging and Animal Models – Clinical Translation on ovarian cancer – M36*
ESRCH3	*HUG*	*D3.CH2 New robot-assisted instruments and delivery methods for brachytherapy – M32*

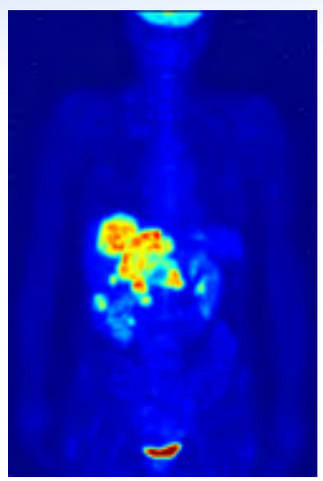
MEDICIS - PROMED project

Targeted Radionuclide Therapy

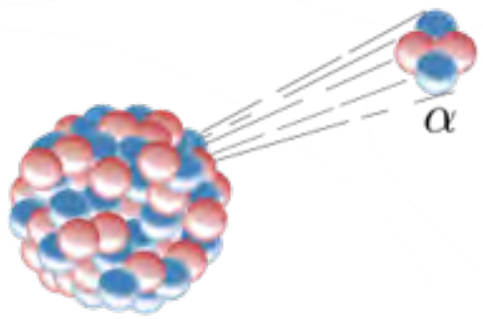
^{152}Tb-NOGADA-NT







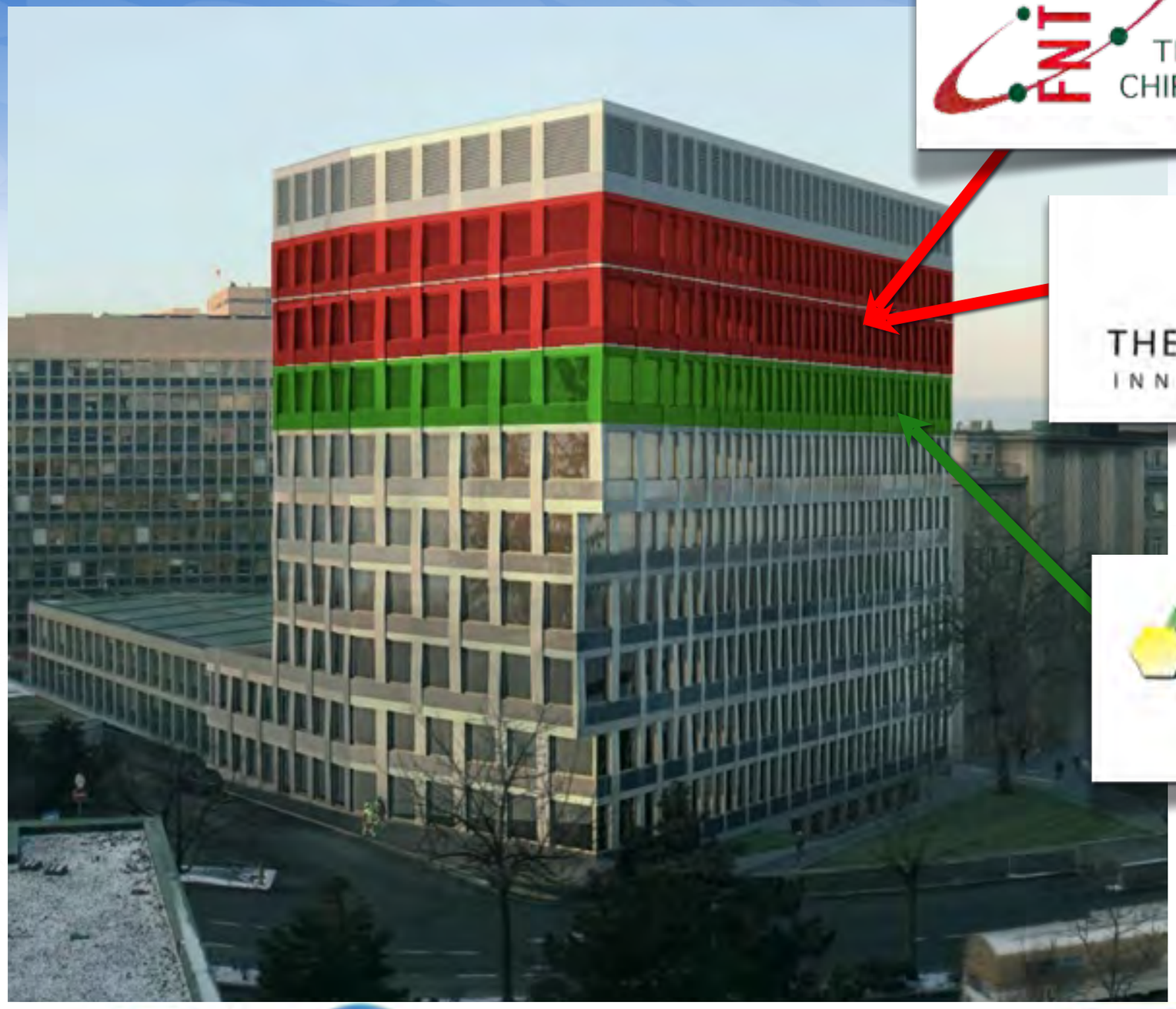
^{149}Tb-NOGADA-NT



2x p+
2x n°

Highly ionizing particle and low penetration depth

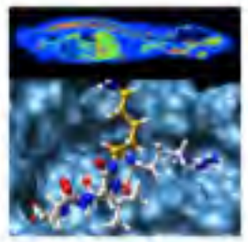
MEDICIS - PROMED project



FONDATION POUR LES NOUVELLES TECHNOLOGIES CHIRURGICALES

THE GENEVA INSTITUTE
INNOVATIONS IN SURGERY

ITMI
Institute of Translational Molecular Imaging



YEARS/ANS CERN

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

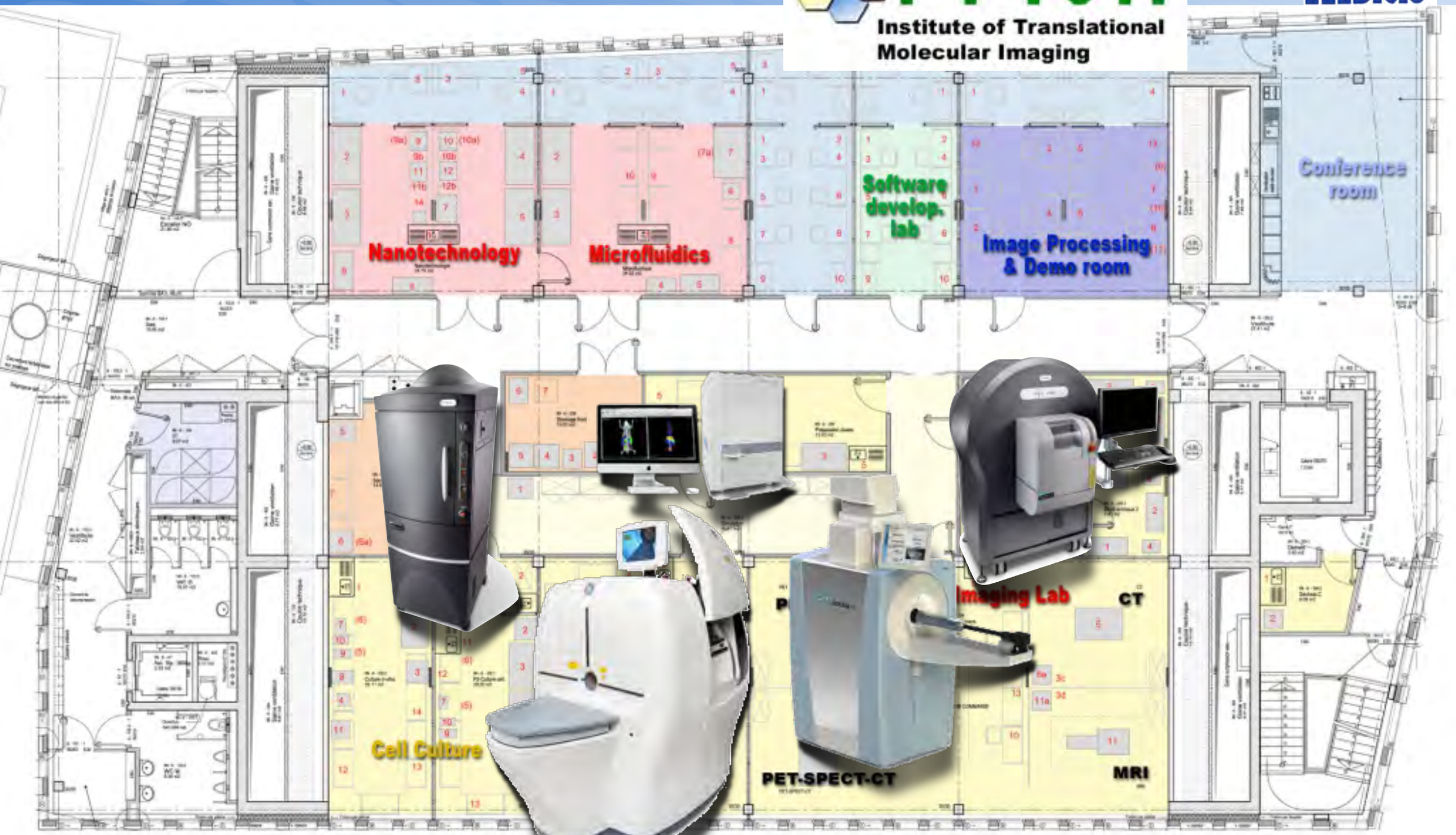
Hôpitaux Universitaires de Genève

UNIL | Université de Lausanne
Faculté de biologie et de médecine

MEDICIS - PROMED project

Infrastructure, labs, facilities

ITMI
Institute of Translational Molecular Imaging



MEDICIS - PROMED project

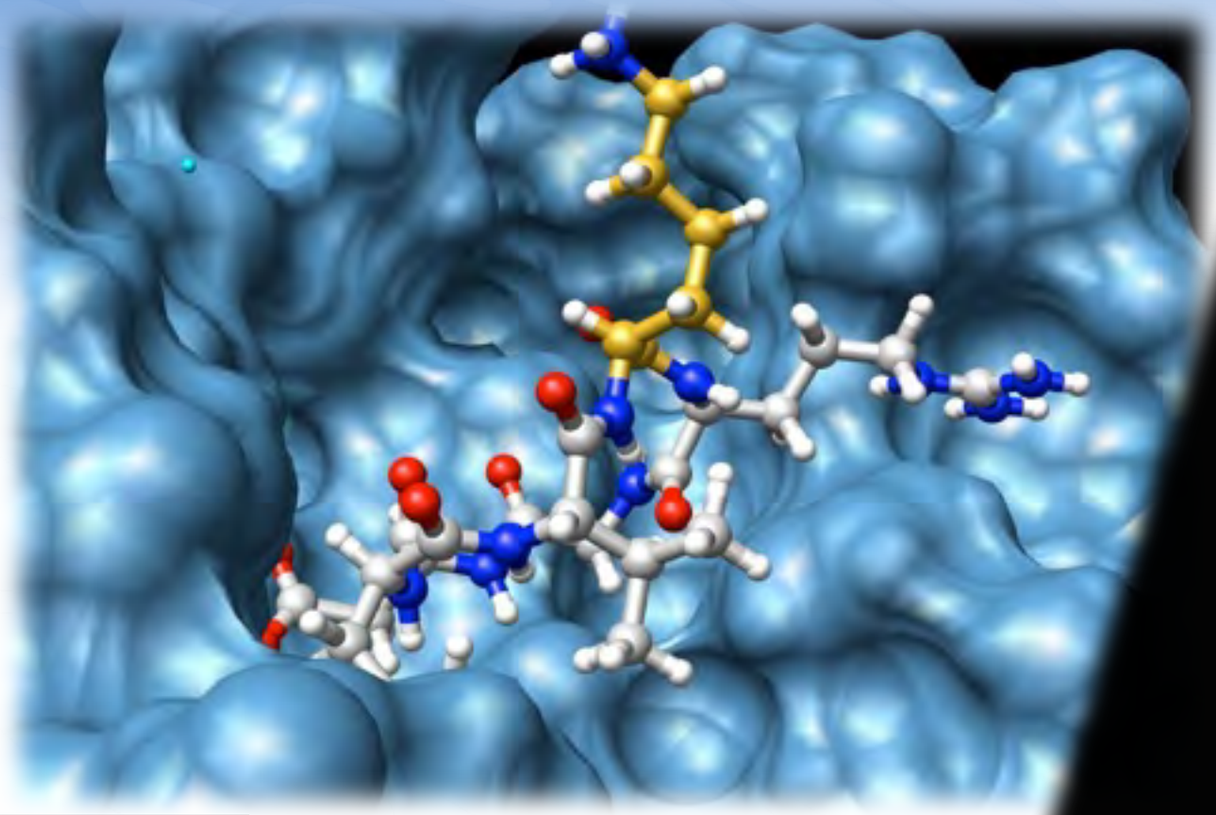
BATLAB (HUG)

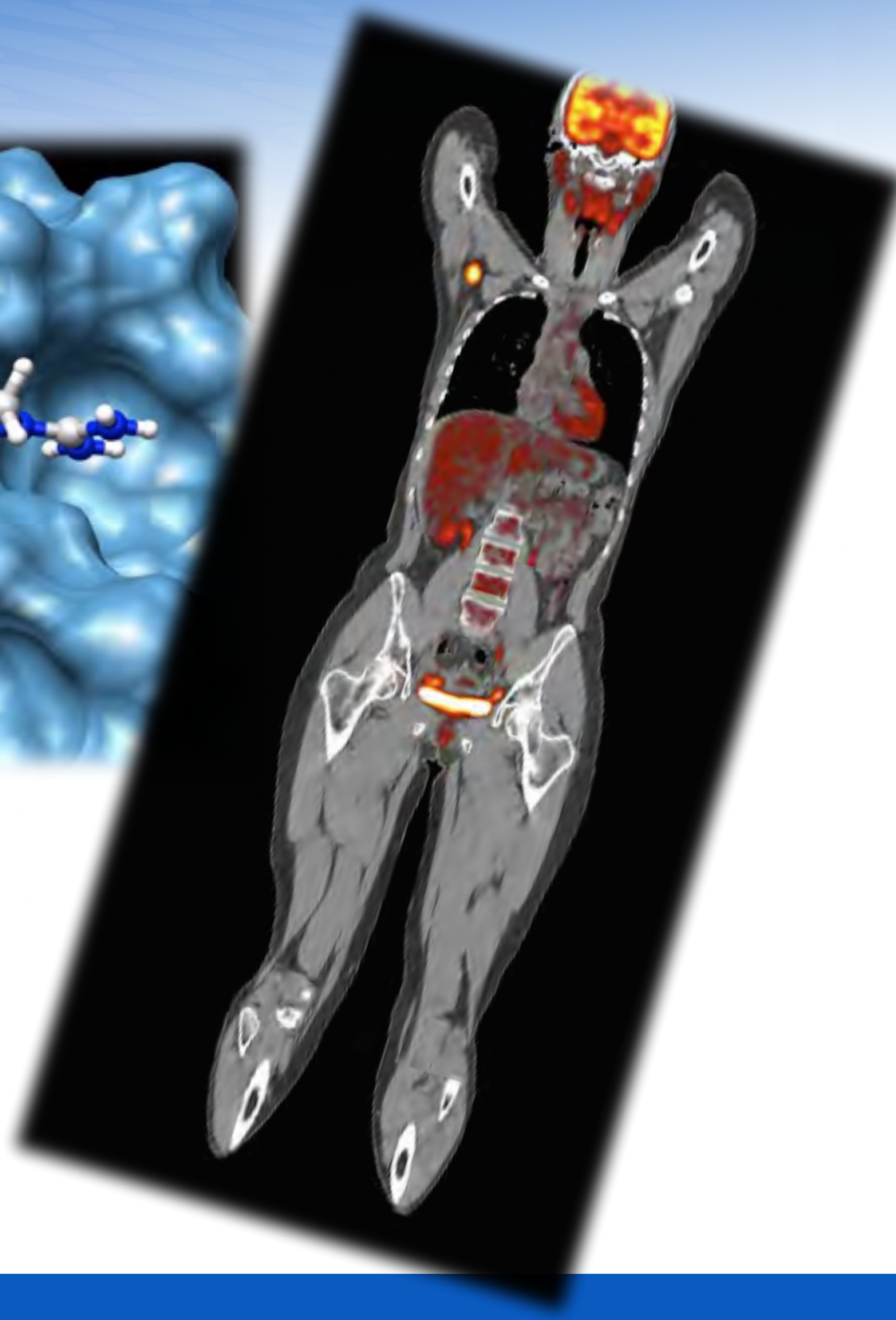
Campus Biotech

ITMI
Institute of Translational Molecular Imaging

CERN | 60 YEARS / ANS CERN | EPFL ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE | UNIVERSITÉ DE GENÈVE FACULTÉ DE MÉDECINE | CHUV | HUG Hôpitaux Universitaires de Genève | UNIL Université de Lausanne Faculté de biologie et de médecine

Thank you !





MEDICIS

CERN

60 YEARS/ANS CERN