C. Bailly

# The theranostic approach « à la Nantaise »





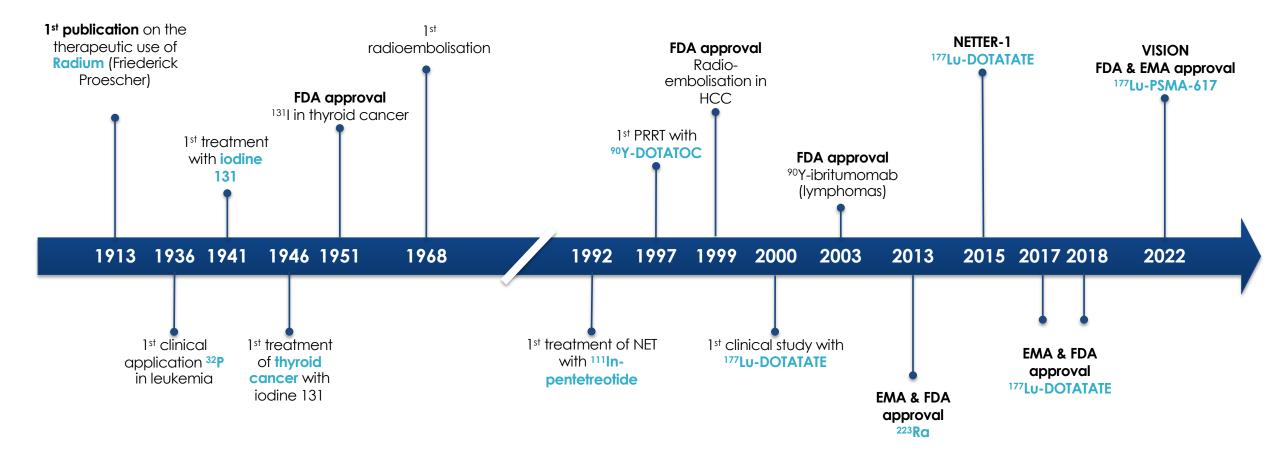








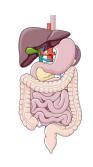
# Targeted radionuclide therapy

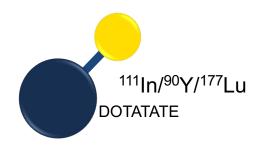


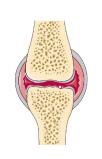
# TRT in daily practice















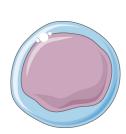


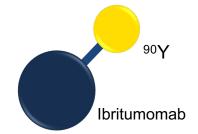




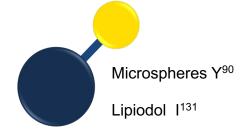












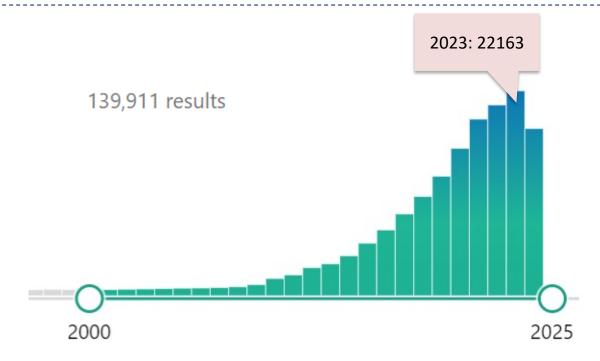
# Theranostics?

■ Combination of 2 words:

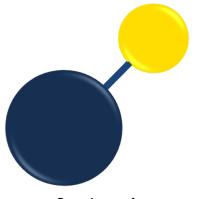
# **Diagnostics**

# **Therapeutics**

■ First used by John Funkhouser (Chief Executive Officer of PharmaNetics) in 2002 to describe one of his company's objectives: to develop **diagnostic tests** directly linked to **specific therapies**.



# Radiotheranostics



 $\gamma$  or  $\beta$ +: Imaging

# **Treatment Decision**

Individualized therapy

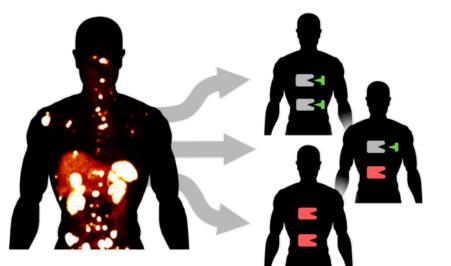
Molecular Imaging

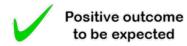
i.e. PET imaging

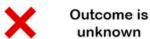


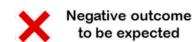
Cancer

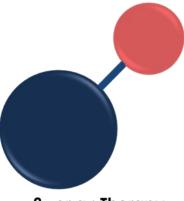
**Stratification** 



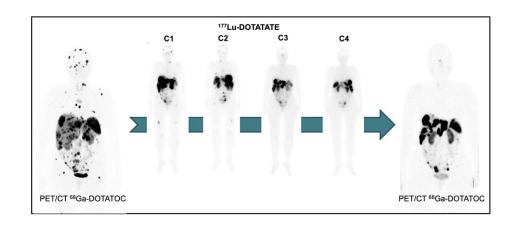






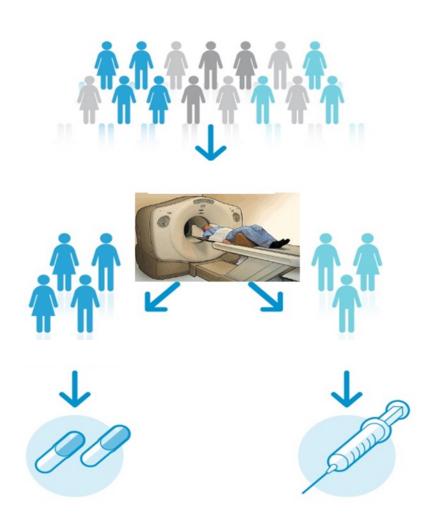


β- or a : Therapy

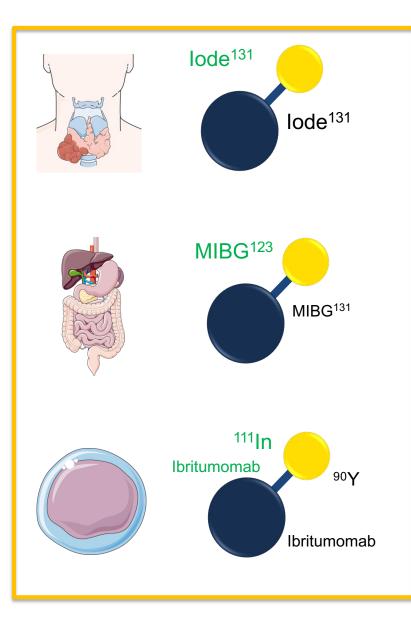


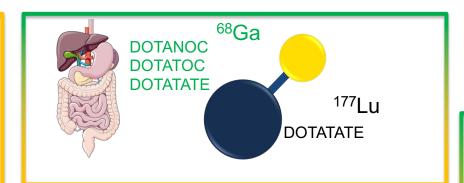
# Aims of Radiotheranostics?

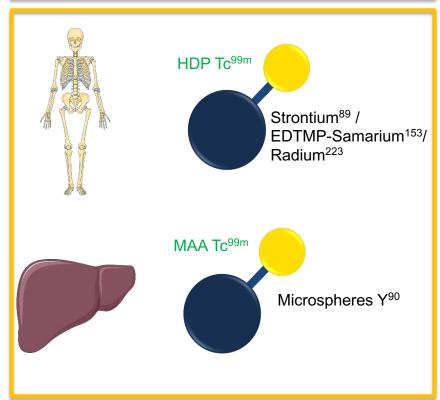
- To determine localization/accessibility in the site of disease state under study as a surrogate for contentia therapeutic agent with similar chemical properties
- To examine its biodistribution as invactive of off target (adverse) effects of the potential therapeutic agent
- To monitor the region to this treatment
- As an aid in determining the optimal therapeutic
  dose for activity to be administered, based on the
  anti-parted tumoricidal doses measured in the tumor
  site



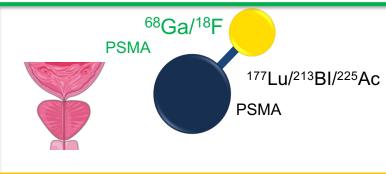
# TRT in daily practice





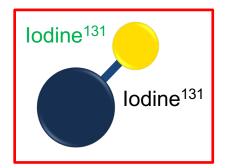


# SPECT/CT PET/CT





# Thyroid cancer: a historical application



RADIOACTI

RADIOACTIVE IODINE-SEIDLIN ET AL.

J. A. M. A. Dec. 7, 1946

autumn, a single month providing 5 per cent of the infections. Grassing, paving roads and runways and ultimately the use of highly refined oil on athletic areas were important dust control measures. This control reduced infection rates from one half to two thirds.

2330 Clay Street, San Francisco 15. 2330 Clay Street, San Francisco 15. 636 South Painter Street, Whittier, Calif. 2298 Durant Avenue, Berkeley 4, Calif.

838

#### ABSTRACT OF DISCUSSION

Dr. RUSSELL V. LEE, San Francisco: Dr. Smith and his associates know more about coccidioidomycosis than any one else, and this work with the Army Air Forces and Ground Forces was a most remarkable piece of combined epidemiology and curative medicine. They surveyed every was in that

#### RADIOACTIVE IODINE THERAPY

Effect on Functioning Metastases of Adenocarcinama of the Thyroid

S. M. SEIDLIN, M.D.
L. D. MARINELLI, M.A.
und
ELEANOR OSHRY, B.S.
New York

Therapy of neoplastic disease usually consists of two phases: first, the treatment of the primary focus and, second, that of metastases. Specifically, in adenocarcinoma of the thyroid, the primary site together with its immediate extensions is conventionally treated by surgery, radiation or both. Distant metastases, if treated, are usually subjected to palliative external

#### RADIOACTIVE IODINE THERAPY

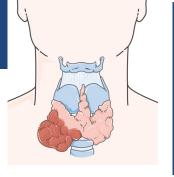
#### Effect on Functioning Metastases of Adenocarcinoma of the Thyroid

S. M. SEIDLIN, M.D.; L. D. MARINELLI, M.A.; ELEANOR OSHRY, B.S. *JAMA.* 1946;132(14):838-847.

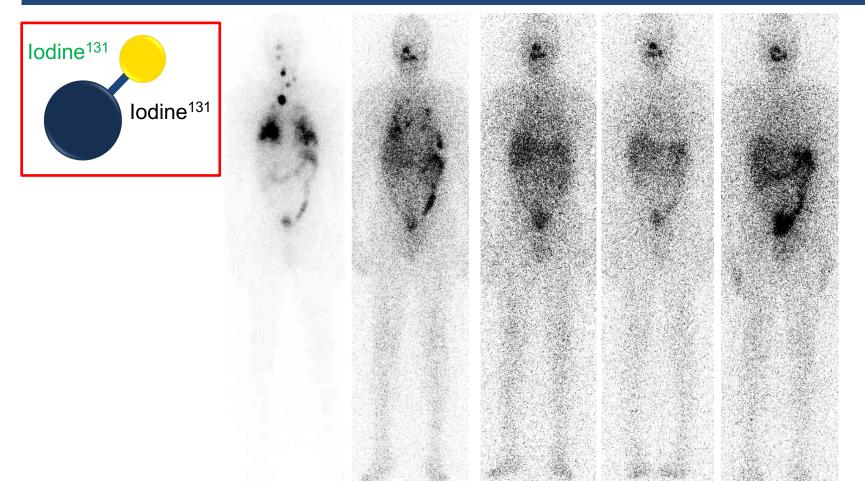
a lot of dust; soldiers around camps and marching in physical training kick up a lot of dust, and they have become infected at a terrific rate. There was a hospital at San Benito where when the fourth of the way of one datachness where because

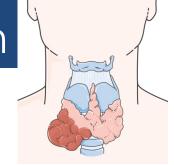
of the thyroid. In a patient with multiple lesions, Geiger counter measurements showed appreciable uptake of radioactive iodine in only one of the metas-

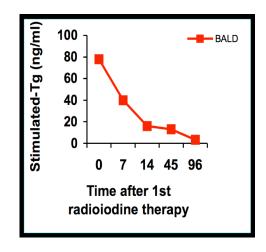
Diagnostic whole body scan with <sup>131</sup>I: first example of theranostics



# Thyroid cancer: a historical application



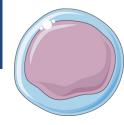




D.Taïeb 2007

Ability to detect iodine uptake in metastases of differentiated thyroid carcinoma and to identify patients who would benefit from therapeutic doses of <sup>131</sup>I.

### Haematological diseases: whistles in the wind



■ Rituximab (Rituxan) is a chimeric (murine and human) monoclonal antibody targeting CD-20+ antique

# YET.... a commercial failure.

VOLUME 28 · NUMBER 18 · JUNE 20 2010

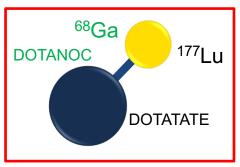
Journal of Clinical Oncology

COMMENTS AND CONTROVERSIES

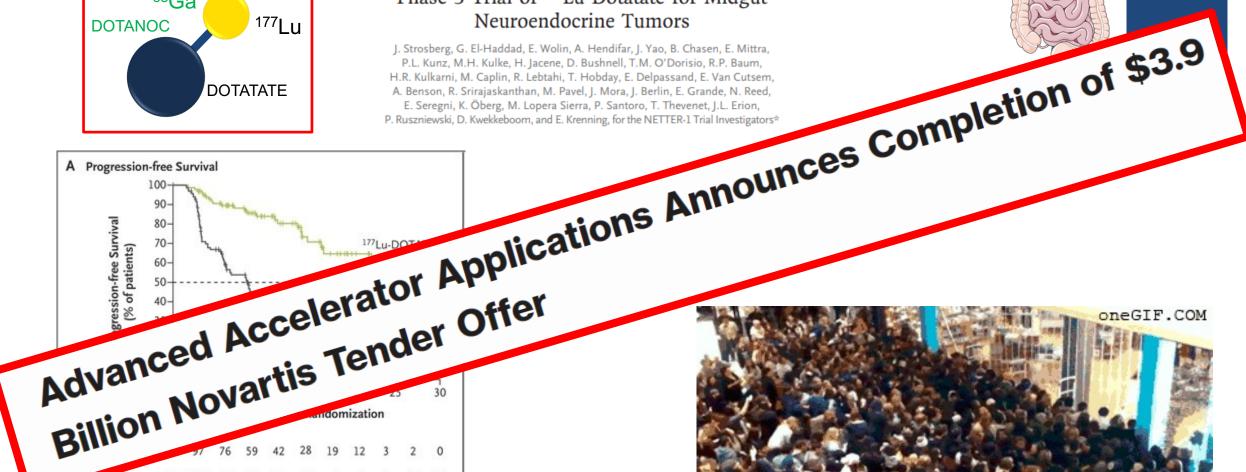
Radioimmunotherapy of Lymphoma: A Treatment Approach Ahead of Its Time or Past Its Sell-By Date?

Tim Martin Illidge, School of Cancer and Imaging Sciences, Manchester Academic Health Sciences, University of Manchester, Manchester, United Kingdom se

# Neuroendocrine tumors: the new "flagship"



#### Phase 3 Trial of <sup>177</sup>Lu-Dotatate for Midgut **Neuroendocrine Tumors**



113 80 47 28 17 10 4 3 1 0 0



### **Radiotheranostics**

« We treat what we see, we see what we treat »

Multidisciplinary board



Oncologist

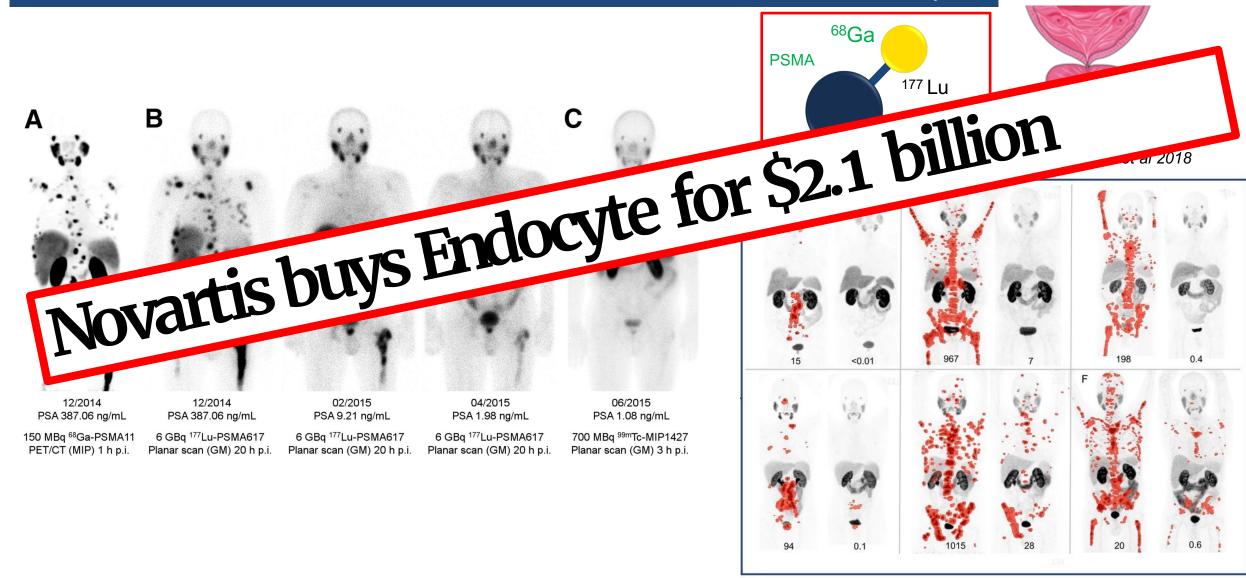
**Tumor** 



**Patient** 

**Treatment** 

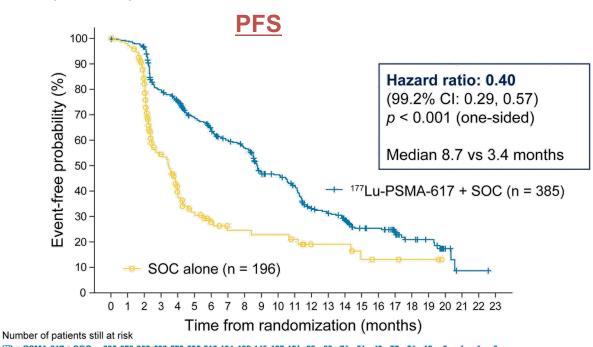
# 177Lu-PSMA: future "success story"?

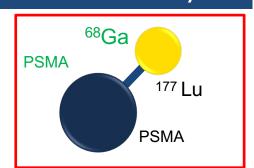


<sup>68</sup>Ga-PSMA11 PET maximum intensity projection (MIP) images at baseline and 3 months after <sup>177</sup>Lu-PSMA617 in 6 patients with PSA decline >98%. Any disease with SUVmax over 3 in red.

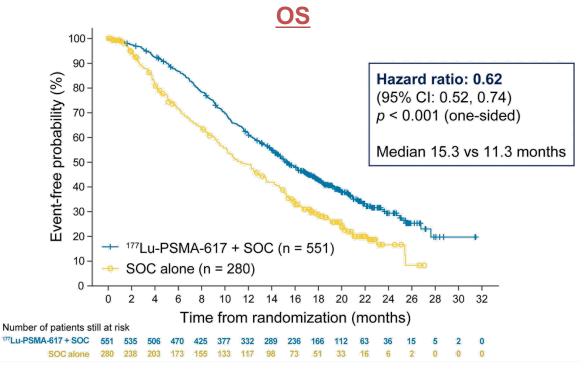
## 177Lu-PSMA: future "success story"?

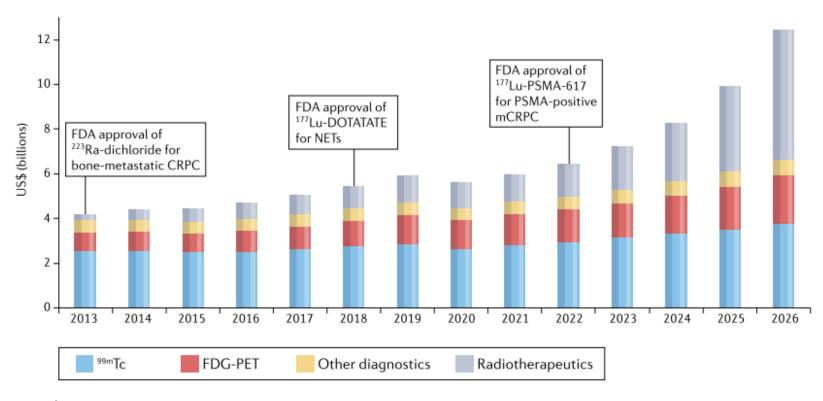
ASCO 2021: Phase III Study of Lutetium-177-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer (VISION)











**Nuclear Medicine Department** First real-life data on [177Lu]Lu-**CHU de Nantes PSMA-617**: Descriptive analysis on the largest metastatic castration-resistant prostate cancer (mCRPC) cohort treated TOTALITE DES TRAITEMENTS in early access in France 500 Anne-Laure Giraudet 1, Pierre Olivier 2, Vincent Massard 3, Aude Fléchon 4 Sylvie Girault 5, Sophie Abadie 6, François Somme 7, Philippe Barthélémy 8, Clément Bailly 9. Caroline Viala 10. Yann Godbert 11 and Guilhem Roubaud 12 450 400 Nuclear Medicine Department, Centre Léon Bérard, Lyon, France; <sup>2</sup> Nuclear Medicine Department, Brabois Hospital, Vandœuvre-lès-Nancy, France; <sup>3</sup> Oncology Department, Institut de Cancérologie de Lorraine, Vandœuvre-lès-Nancy, France; <sup>4</sup> Medical Oncology Department, Centre Léon Bérard, Lyon, France; 350 Suclear Medicine Department, ICO Paul Papin, Angers, France; Department of Medical Oncology, ICO Paul Papin, Angers, France; Nuclear Medicine and Molecular Imaging Department, Institut de ncérologie Strasbourg Europe, Strasbourg, France; 8 Medical Oncology Department, Institut de 300 ogie Strasbourg Europe, Strasbourg, France; 9 Nuclear Medicine Department, University Hospital, Nantes, France; <sup>10</sup> Digestive Oncology Department, University Hospital, Nantes, France; <sup>11</sup> Nuclear Medicine Department, Institut Bergonié, Bordeaux, France; 12 Medical Oncology Department, Institut 233 lode<sup>131</sup> 250 200 medicalcongressposters.com Default.aspx?doc=fe99a 150 Quick Response (QR) code are for personal use only and may not be 8676 100 50 2010 2011 2013 2015 2016 2017 2018 2019 2012 2014 ■ TOTAL TRAITEMENTS ■ TOTAL HOSPIT EN RIV MAA Tc99m Microspheres Y90 DOTANOC **PSMA** DOTATATE

### **Nuclear Medicine in Nantes**

2008

2009

2012

2015

2017

2018

2019

2022

2023











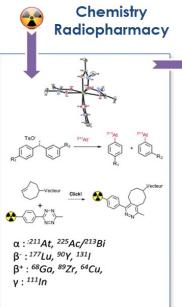


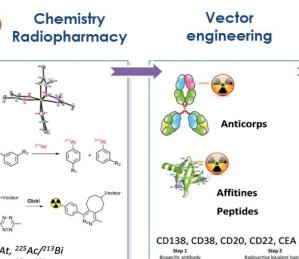




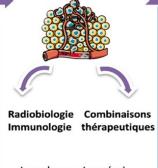






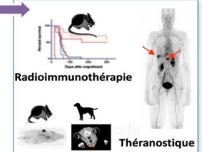






Lymphome, Leucémie, Myélome Multiple, CMT, Colon, sein, poumon, Prostate, mélanome

#### **Preclinical** experimentation and clinical research



#### **Imagerie**

Pharmacocinétique Dosimétrie Analyse d'image Modélisation Evaluation clinique













- Optimising/standardising/improving current applications/therapies
- Search for new targets

■ Development of new molecules

- Technological inovations
- Alphatherapy

### Normalization ??

ing

Annals of Nuclear Medicine (2018) 32:512–522 https://doi.org/10.1007/s12149-018-1291-7

#### **REVIEW ARTICLE**



# Molecular imaging reporting and data systems (MI-RADS): a generalizable framework for targeted radiotracers with theranostic implications

Molecular Imaging
Reporting and Data System

Rudolf A. Werner<sup>1,2,3</sup> · Ralph A. Bundschuh<sup>4</sup> · Lena Bundschuh<sup>4</sup> · Mehrbod S. Javadi<sup>1</sup> · Takahiro Higuchi<sup>2,5</sup> · Alexander Weich<sup>3,6</sup> · Sara Sheikhbahaei<sup>1</sup> · Kenneth J. Pienta<sup>7</sup> · Andreas K. Buck<sup>2,3</sup> · Martin G. Pomper<sup>1</sup> · Michael A. Gorin<sup>1,7</sup> · Constantin Lapa<sup>2,3</sup> · Steven P. Rowe<sup>1,7</sup>

1	1A	Benign lesion, characterized by biopsy or anatomic imaging without abnormal uptake	n/a	1	N
	1B	Benign lesion, characterized by biopsy or anatomic imaging with abnormal uptake	n/a	2-3	N
2		Soft-tissue site or bone lesion atypical for metastatic PCa or NET	n/a		N
3	3A	Equivocal uptake in soft-tissue lesion typical of PCa or NET	B, F/U	1-2	N
	3B	Equivocal uptake in bone lesion not atypical of PCa or NET	B, F/U	1-2	$N^b$
	3C	Intense uptake in site highly atypical of all but advanced stages of PCa or NET (i.e., high likelihood of nonprostatic/non-NET malignancy or other benign tumor)	В	3	N
	3D	Lesion suggestive of malignancy on anatomic imaging but lacking uptake. For SSTR-RADS: 2-deoxy-2-[ <sup>18</sup> F]-fluoro-D-glucose [ <sup>18</sup> F]-FDG is recommended to rule out potential dedifferentiation of a single lesion	B, F/U	Not available	N <sup>b</sup>
4		Intense uptake in site typical of PCa or NET but lacking definitive findings on conventional imaging	n/a	3	Y
5		Intense uptake in site typical of PCa or NET but with definitive findings on conventional imag-	n/a	3	Y

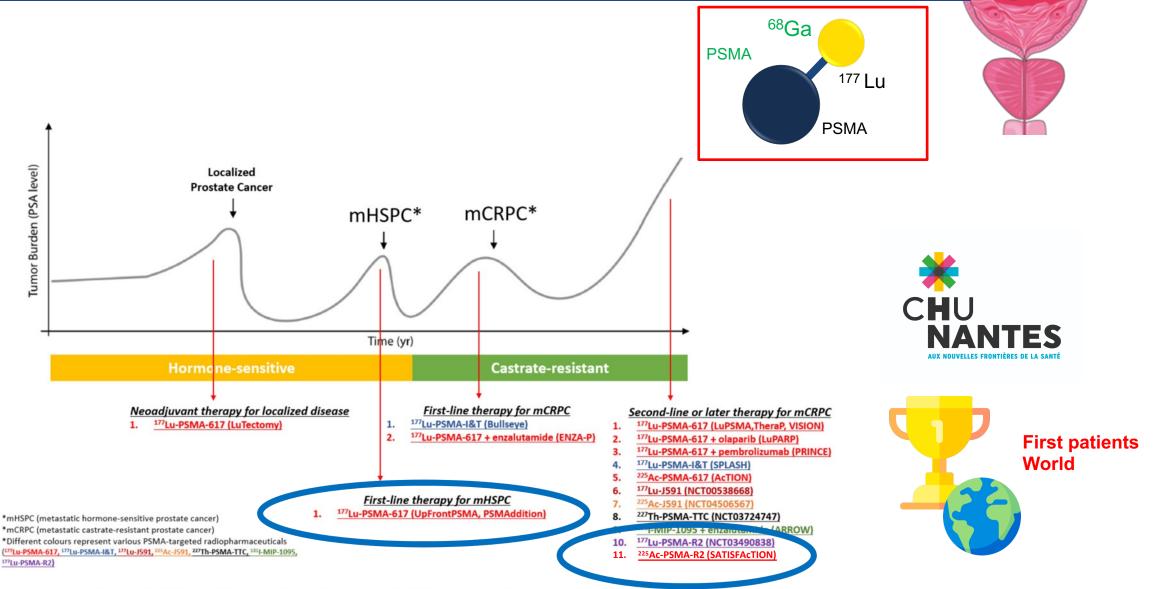
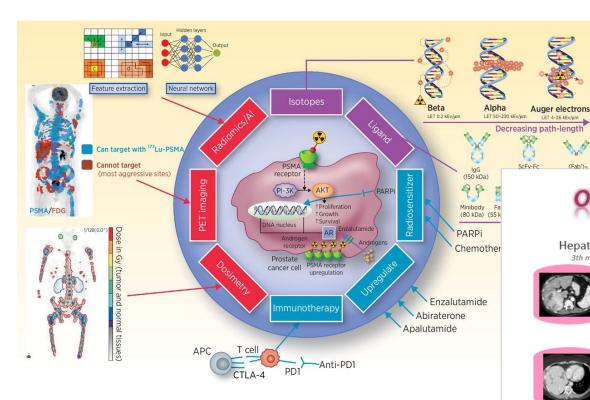


Figure 1. Schematic overview of selected PSMA theranostics clinical trials as of June 2021.



Clin Cancer Res (2020) 26 (12): 2774-2776.



Optimisation and imProved Efficacy of targeted RAdioNuclide therapy in Digestive cancers by Imagomics

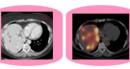
#### Hepatocellular Carcinoma (HCC)









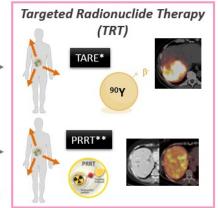


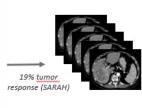


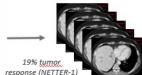
low incidence - high prevalence



- Morphological and clinical similarities
- Heterogenous tumors > Lack of relevant and reproducible imaging markers
- Major targets of TRT → Lack of personalized treatment strategy







**PROPOSE**: New diagnostic and follow up approaches

**DEVELOP**: New therapeutic concepts to treat more efficiently

**RESULTING**: Better outcome + Reduced healthcare costs

\* Transarterial Radioembolisation \*\* Peptide Receptor Radionuclide Therapy



FRANCE











# To do or not to do dosimetry....













- Administered like any other drug on a fixed or weight basis.
- Management of adverse events as they occur over the course of therapy.

MBq

### Systemic radiotherapy.

- Dose-dependent delivery to a target tissue.
- Anticipating adverse effects.

Gy



# To do or not to do dosimetry....









# Dosimetry for targeted radionuclide therapy in routine clinical practice: experts advice vs. clinical evidence

Arnaud Dieudonné<sup>1,2</sup> · Clément Bailly<sup>3</sup> · Florent Cachin<sup>4</sup> · Agathe Edet-Sanson<sup>1</sup> · Françoise Kraeber-Bodéré<sup>3</sup> · Sébastien Hapdey<sup>1</sup> · Charles Merlin<sup>4</sup> · Philippe Robin<sup>5</sup> · Pierre-Yves Salaun<sup>5</sup> · Paul Schwartz<sup>6</sup> · David Tonnelet<sup>1</sup> · Pierre Vera<sup>1</sup> · Frédéric Courbon<sup>7</sup> · Thomas Carlier<sup>3</sup>

European Journal of Nuclear Medicine and Molecular Imaging (2024) 51:947–950



Né-e le

Calcul de durée de restriction des contacts après radiothérapie interne vectorisée RIV



établi le lundi 2 septembre 2024

Nom Date du traitement
Prénom Opérateur

#### Eléments obligatoires à préciser (en jaune)

Radiopharmaceutique (menu déroulant)

lode-131-25%-fixation

Débit de dose à 1m (μSv/h) en sortie de chambre

Taille du patient(e) (cm)

Eléments optionnels (en bleu)

Période effective (j) imposée par l'utilisateur (laisser vide sinon)

Scénario utilisateur (éventuel) Temps (h) Distance (m)

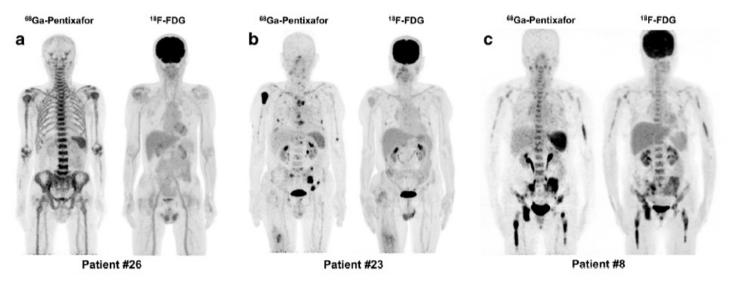
Durás à la distance V

- Optimising/standardising/improving current applications/therapies
- Search for new targets

■ Development of new molecules

- Technological inovations
- Alphatherapy

## <sup>68</sup>Ga-PENTIXAFOR (CXCR4)



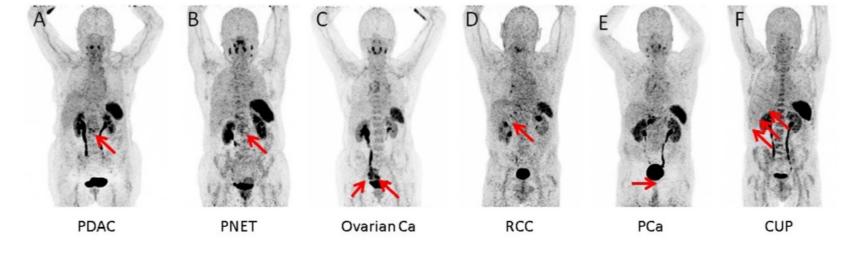
Pentixafor

177Lu

Pentixather

European Journal of Nuclear Medicine and Molecular Imaging Doi: 10.1007/s00259-019-04605-z

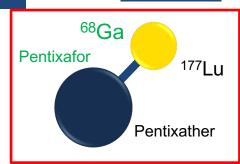
Front. Oncol. 9:770. doi: 10.3389/fonc.2019.00770

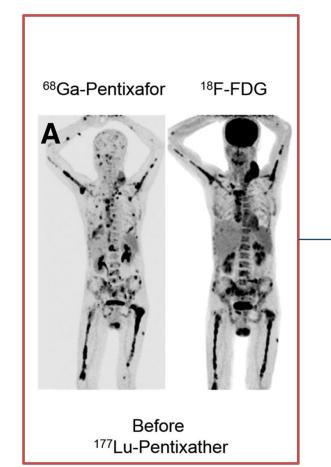


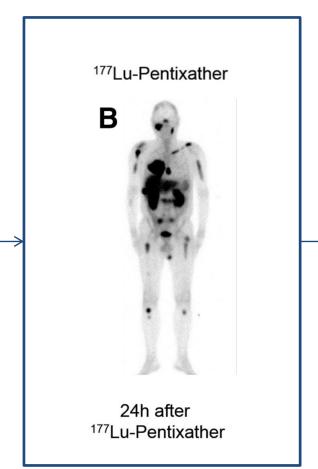
First-in-Human Experience of CXCR4-Directed Endoradiotherapy with <sup>177</sup>Lu- and <sup>90</sup>Y-Labeled Pentixather in Advanced-Stage Multiple Myeloma with Extensive Intra- and Extramedullary Disease

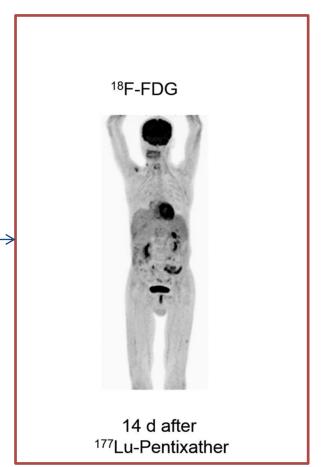
Ken Herrmann\*1-3, Margret Schottelius\*4, Constantin Lapa¹, Theresa Osl⁴, Andreas Poschenrieder⁴, Heribert Hänscheid¹, Katharina Lückerath¹, Martin Schreder⁵, Christina Bluemel¹, Markus Knott⁵, Ulrich Keller⁵,¹, Andreas Schirbel¹, Samuel Samnick¹, Michael Lassmann¹, Saskia Kropf<sup>8</sup>, Andreas K. Buck¹, Hermann Einsele⁵, Hans-Juergen Wester¹⁴, and Stefan Knon¹⁵

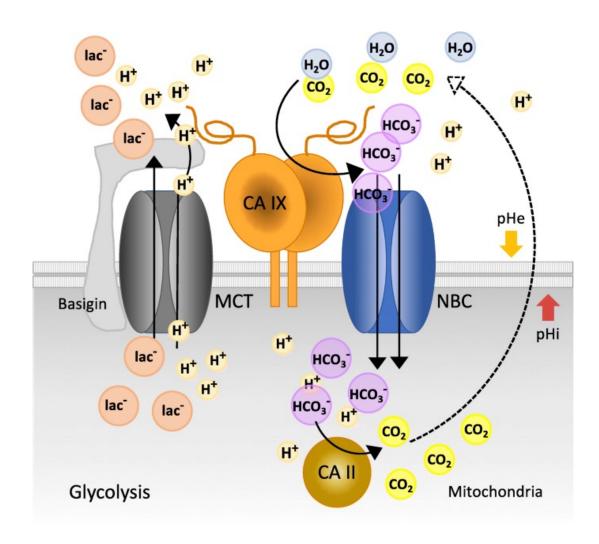










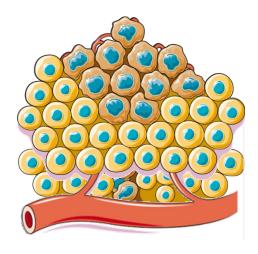


- CA IX is a cell-surface glycoprotein
- Contributes to pH regulation
- Can also behave as an adhesion molecule through its proteoglycan-like domain

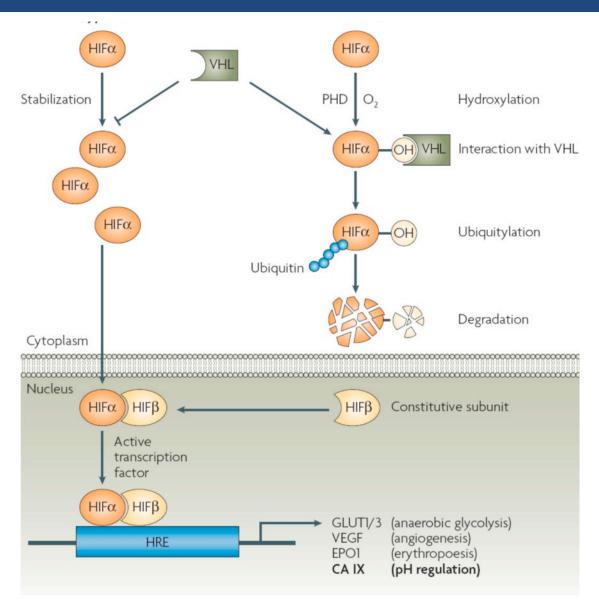
**Proliferation** 

**Neoangiogenesis** 

Dissemination



- CA IX is a cell-surface glycoprotein
- Contributes to pH regulation
- Can also behave as an adhesion molecule through its proteoglycan-like domain
- CA IX expression in non-cancerous
   tissues is rare and generally confined to
   epithelia of the stomach, gallbladder,
   pancreas, and intestine
- Involved in diverse aspects of cancer development



- CA IX is a cell-surface glycoprotein
- Contributes to pH regulation
- Can also behave as an adhesion molecule through its proteoglycan-like domain
- CA IX expression in non-cancerous
   tissues is rare and generally confined to
   epithelia of the stomach, gallbladder,
   pancreas, and intestine
- Involved in diverse aspects of cancer development
- Expression notably induced by hypoxia



# Targeting CA IX







 Prospective feasibility pilot study, assessing imaging performance of 89Zr-labelled Girentuximab PET-C in **metastatic triple negative breast cancer** patients





#### PERTINENCE project



 A Pilot Open-label, Feasibility Study to Assess safety, Tolerability, Radiation Dosimetry, and Imaging Properties of 89Zr-labeled giRenTuximab in patlents With Non-musclE-iNvasive Bladder CancEr



 ClinicalTrials.gov Identifier: NCT04897763 Sponsor: ICO



■ OPERANDI RHU (Optimisation and imProved Efficacy of targeted RAdioNuclide therapy in Digestive cancers by Imagomics)

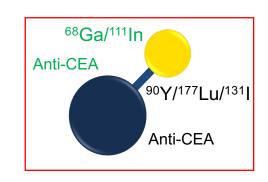
 An Open-label, Pilot Study to Assess Safety, Tolerability, Radiation Dosimetry, and Imaging Properties of 89Zr-labelled Girentuximab for in Vivo Detection of HCC and aggressive or refractory GEP-NENs by PET

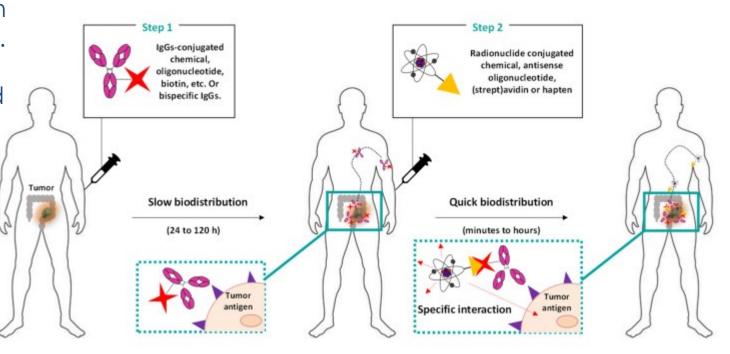


CEA expressed by numerous tumors: MCT (100%), colorectal cancer, lung cancer, breast cancer...

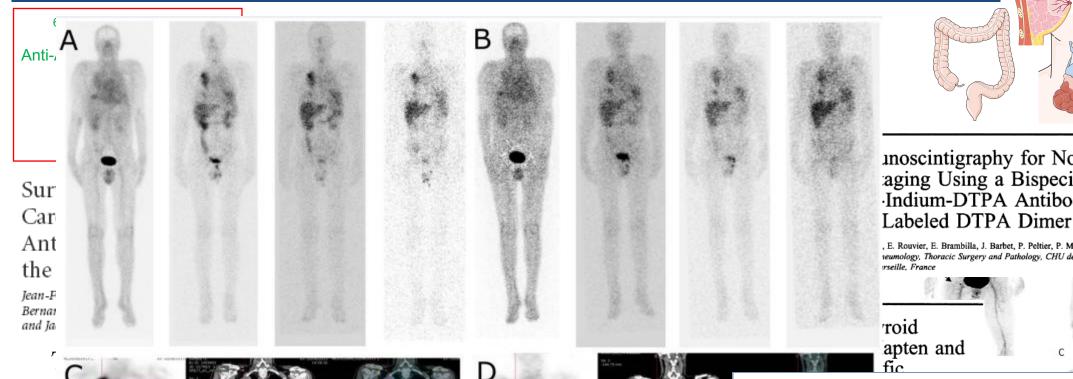
<u>Direct targeting:</u> Insufficient tumor contrast in imaging and too low tumor doses in therapy.

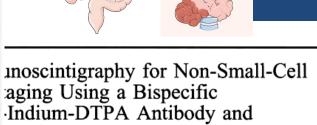
<u>Solution:</u> decouple injection of antibody and radionuclide to improve contrast.





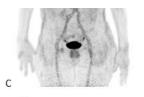
# Pretargeting of CEA expressing tumors





, E. Rouvier, E. Brambilla, J. Barbet, P. Peltier, P. Meyer, R. Sarrazin and Ch. Brambilla neumology, Thoracic Surgery and Pathology, CHU de Grenoble, Centre Catherine de rseille, France

roid apten and





Front Med (Lausanne), 2015; 2: 84.

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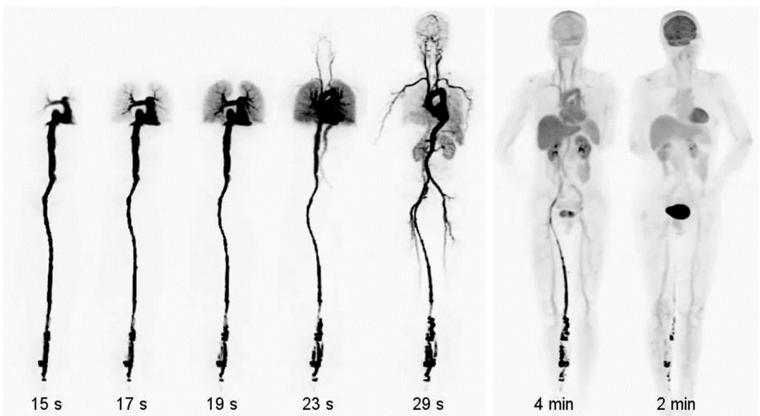
Caroline Bodet-Milin, 1,2,\* Ludovic Ferrer, 2,3,4 Aurore Rauscher, 2,3 Damien Masson, 5 Latifa Rbah-Vidal, 2 Alain Faivre-Chauvet, 1.2 Evelyne Cerato, 1 Caroline Rousseau, 2.3 José Hureaux, 6 Olivier Couturier, 7 Pierre-Yves Salaün, 8 David M. Goldenberg, 9,10 Robert M. Sharkey, 10 Françoise Kraeber-Bodéré, 1,2,3 and Jacques Barbet 2,11

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# Theranostic and technological inovations?

# First Human Imaging Studies with the EXPLORER Total-Body PET Scanner\*

Ramsey D. Badawi<sup>1,2</sup>, Hongcheng Shi<sup>3</sup>, Pengcheng Hu<sup>3</sup>, Shuguang Chen<sup>3</sup>, Tianyi Xu<sup>4</sup>, Patricia M. Price<sup>5</sup>, Yu Ding<sup>4</sup>, Benjamin A. Spencer<sup>1</sup>, Lorenzo Nardo<sup>1</sup>, Weiping Liu<sup>4</sup>, Jun Bao<sup>4</sup>, Terry Jones<sup>1</sup>, Hongdi Li<sup>4</sup>, and Simon R. Cherry<sup>1,2</sup>



# Our Evolution, their Revolution!!

Rapid growth of precision medicine

 Rapid growth in diagnostic, predictive and prognostic molecular imaging



- Image-guided targeted therapies
- Growth ++ of TRT via
   theranostic approaches

What's next?

- Optimisation of actual applications
- Development of new molecules

Revolution or evolution?



















