



Actualités concernant les traceurs TEP/Anticorps en Oncologie : ImmunoTEP



Hôpitaux de Lyon

Réunion inter-régionale de médecine nucléaire

11 Avril 2015

TORDO Jérémie (IHL)

Introduction

- Démocratisation récente de l'utilisation de la TEP en imagerie
 - Permet une imagerie **métabolique**
- **Utilisation majoritaire 18-FDG (coût, disponibilité ...)**
 - Nombreuses indications en Oncologie
 - Staging, évaluation thérapeutique ...
 - Efficacité reconnue, mais ...

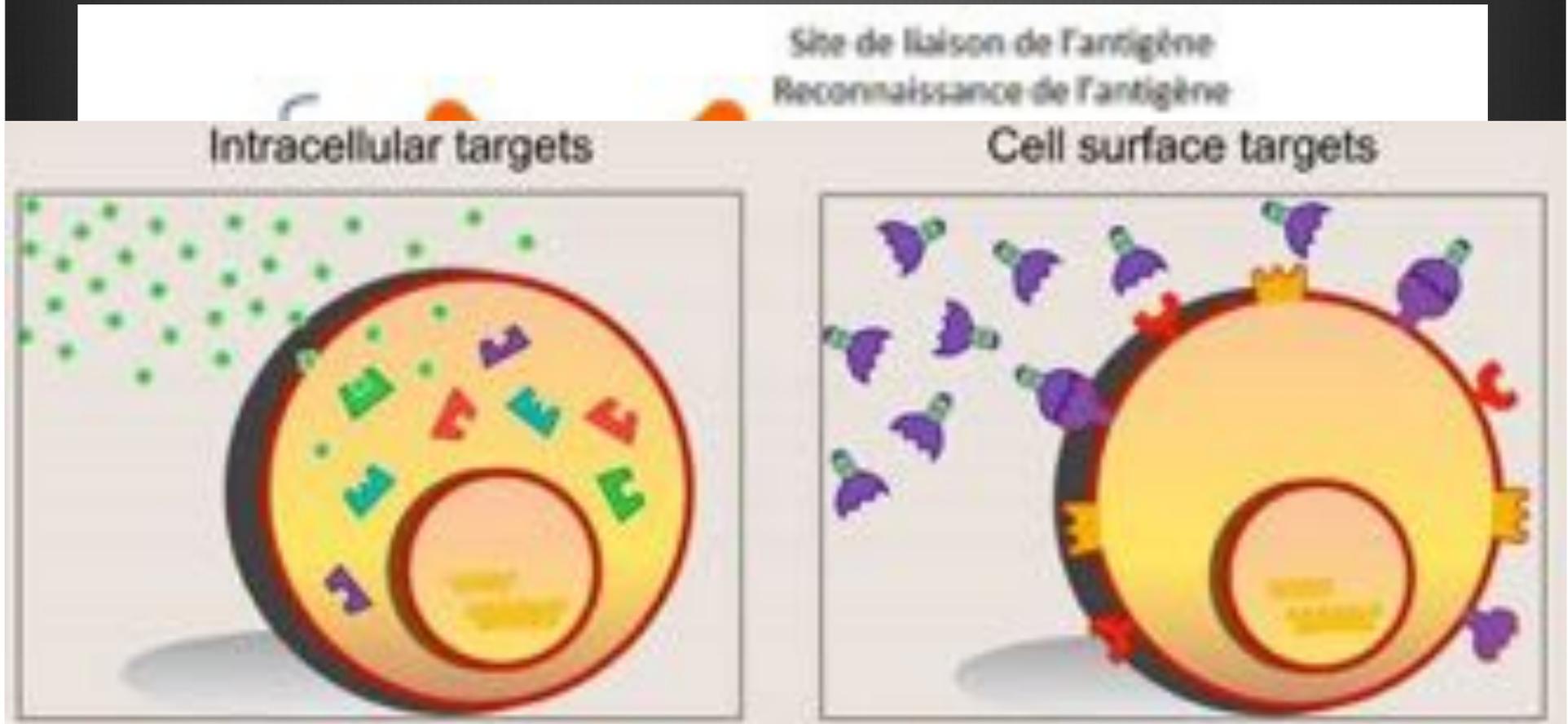
→ Peu de spécificité

Introduction

En parallèle :

- Nette augmentation du nombre et de l'utilisation des **thérapies ciblées** (Plan cancer 2014-2019).
- **Amélioration** constante des techniques:
 - Découverte de nouvelles cibles moléculaires
 - Progrès en chimie, ciblage.
- **Utilisation des Anticorps monoclonaux (AcM) ou fragments d'anticorps en tant que vecteurs pour l'imagerie métabolique ?**
 - **ImmunoTEP ou Imagerie phénotypique**

Anticorps monoclonaux



- Glycoprotéines de la famille des **immunoglobulines**
- 4 chaînes polypeptidiques : 2 chaînes lourdes + 2 chaînes légères



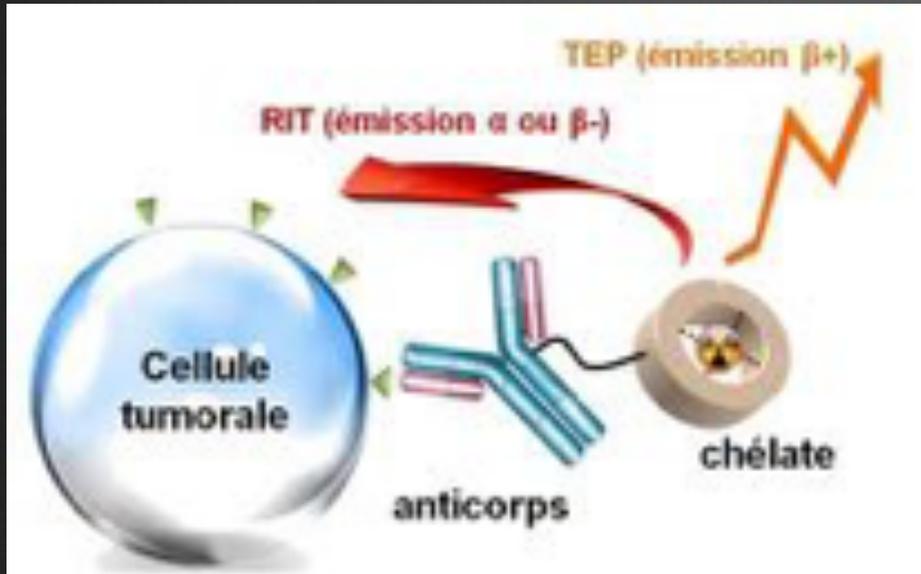
Hanahan D, Cell 2011

Liste actuelle des anticorps monoclonaux approuvés par la FDA en Oncologie

Drug Name	Year	Manufacturer	Indication
Trastuzumab	2006	Genentech	HER2-positive breast cancer
Ipilimumab	2011	Bristol-Myers Squibb	Recurrent melanoma
Pembrolizumab	2013	Merck	Metastatic melanoma, NSCLC
Nivolumab	2013	Ono Pharmaceuticals	Recurrent melanoma, NSCLC
Atezolizumab	2015	Roche	Metastatic NSCLC
Carbimab	2015	Genentech	Metastatic colorectal cancer
Bevacizumab	2004	Genentech	Metastatic colorectal cancer, NSCLC
Cetuximab	2004	Roche	Metastatic colorectal cancer
Ustekinumab	2013	Roche	Metastatic colorectal cancer
Secukinumab	2015	Novartis	Metastatic colorectal cancer
Adalimumab	2004	AstraZeneca	Metastatic colorectal cancer
Infliximab	2004	Roche	Metastatic colorectal cancer
Ipilimumab	2011	Bristol-Myers Squibb	Metastatic colorectal cancer
Pembrolizumab	2013	Merck	Metastatic colorectal cancer
Nivolumab	2013	Ono Pharmaceuticals	Metastatic colorectal cancer
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Atezolizumab	2015	Roche	Metastatic colorectal cancer
Carbimab	2015	Genentech	Metastatic colorectal cancer

Développement
exponentiel

Imagerie métabolique ciblée



Associer un vecteur d'une cible moléculaire spécifique à un radioélément TEP (non FDG)

Avantages de la TEP :

- Sensibilité
- Résolution
- Correction d'atténuation
- Possibilité de quantification



Imagerie métabolique ciblée

- Une idée pas si récente que ça :

Copper-64-Labeled Antibodies for PET Imaging

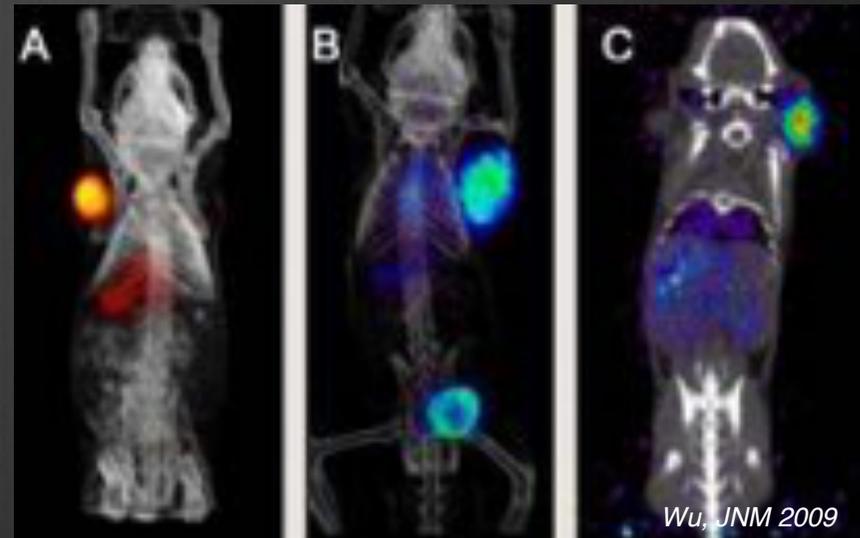
Carolyn J. Anderson, Judith M. Connett, Sally W. Schwarz, Pamela A. Rocque, Li Wu Guo, Gordon W. Philpott, Kurt R. Zinn, Claude F. Meares and Michael J. Welch

Division of Radiation Sciences, Washington University Medical School, St. Louis, Missouri; Department of Surgery, Jewish Hospital, St. Louis, Missouri; University of Missouri Research Reactor, Columbia, Missouri; and Department of Chemistry, University of California, Davis, Davis, California

In conclusion, we have developed and evaluated a ^{64}Cu -labeled anticolo-rectal antibody that appears very promising for utilization with PET for the evaluation of colon cancer. An amendment to our IND for ^{111}In -Br ϕ HBED-1A3 (23) to include ^{64}Cu -benzyl-TETA-1A3 administration in colorectal cancer patients is currently underway.

Received Jan. 22 1992; revision accepted Apr. 21, 1992.

For reprints contact: Michael J. Welch, PhD, Division of Radiation Sciences, Washington University School of Medicine, Box 8131, 510 S. Kingshighway Blvd., St. Louis, MO 63110.



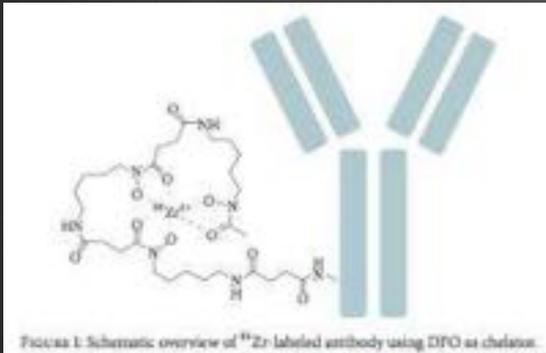
- Mais une utilisation uniquement en recherche pré-clinique ?

Delay Characteristics of Fluoride Emitters Used in Preclinical or Clinical Radiocarcinoma/lymphoma Studies*

Fluoride emitter	Fluoride	Half-life (hr)	Max. β^- energy†		Max. γ energy†		Effective source radius (cm)	Reference
			(keV)	(%)	(keV)	(%)		
¹⁸ F	Fluoride	110	1.00	97.0	—	—	10, 11	
¹⁸ F	Fluoride	110	—	—	—	—	12	
¹⁸ F	Fluoride	110	—	—	—	—	13	
¹⁸ F	Fluoride	110	—	—	—	—	14, 15	
¹⁸ F	Fluoride	110	—	—	—	—	16	
¹⁸ F	Fluoride	110	—	—	—	—	17	
¹⁸ F	Fluoride	110	—	—	—	—	18	
¹⁸ F	Fluoride	110	—	—	—	—	19	
¹⁸ F	Fluoride	110	—	—	—	—	20	
¹⁸ F	Fluoride	110	—	—	—	—	21	
¹⁸ F	Fluoride	110	—	—	—	—	22	
¹⁸ F	Fluoride	110	—	—	—	—	23	
¹⁸ F	Fluoride	110	—	—	—	—	24	
¹⁸ F	Fluoride	110	—	—	—	—	25	
¹⁸ F	Fluoride	110	—	—	—	—	26	
¹⁸ F	Fluoride	110	—	—	—	—	27	
¹⁸ F	Fluoride	110	—	—	—	—	28	
¹⁸ F	Fluoride	110	—	—	—	—	29	
¹⁸ F	Fluoride	110	—	—	—	—	30	
¹⁸ F	Fluoride	110	—	—	—	—	31	
¹⁸ F	Fluoride	110	—	—	—	—	32	
¹⁸ F	Fluoride	110	—	—	—	—	33	
¹⁸ F	Fluoride	110	—	—	—	—	34	
¹⁸ F	Fluoride	110	—	—	—	—	35	
¹⁸ F	Fluoride	110	—	—	—	—	36	
¹⁸ F	Fluoride	110	—	—	—	—	37	
¹⁸ F	Fluoride	110	—	—	—	—	38	
¹⁸ F	Fluoride	110	—	—	—	—	39	
¹⁸ F	Fluoride	110	—	—	—	—	40	
¹⁸ F	Fluoride	110	—	—	—	—	41	
¹⁸ F	Fluoride	110	—	—	—	—	42	
¹⁸ F	Fluoride	110	—	—	—	—	43	
¹⁸ F	Fluoride	110	—	—	—	—	44	
¹⁸ F	Fluoride	110	—	—	—	—	45	
¹⁸ F	Fluoride	110	—	—	—	—	46	
¹⁸ F	Fluoride	110	—	—	—	—	47	
¹⁸ F	Fluoride	110	—	—	—	—	48	
¹⁸ F	Fluoride	110	—	—	—	—	49	
¹⁸ F	Fluoride	110	—	—	—	—	50	
¹⁸ F	Fluoride	110	—	—	—	—	51	
¹⁸ F	Fluoride	110	—	—	—	—	52	
¹⁸ F	Fluoride	110	—	—	—	—	53	
¹⁸ F	Fluoride	110	—	—	—	—	54	
¹⁸ F	Fluoride	110	—	—	—	—	55	
¹⁸ F	Fluoride	110	—	—	—	—	56	
¹⁸ F	Fluoride	110	—	—	—	—	57	
¹⁸ F	Fluoride	110	—	—	—	—	58	
¹⁸ F	Fluoride	110	—	—	—	—	59	
¹⁸ F	Fluoride	110	—	—	—	—	60	
¹⁸ F	Fluoride	110	—	—	—	—	61	
¹⁸ F	Fluoride	110	—	—	—	—	62	
¹⁸ F	Fluoride	110	—	—	—	—	63	
¹⁸ F	Fluoride	110	—	—	—	—	64	
¹⁸ F	Fluoride	110	—	—	—	—	65	
¹⁸ F	Fluoride	110	—	—	—	—	66	
¹⁸ F	Fluoride	110	—	—	—	—	67	
¹⁸ F	Fluoride	110	—	—	—	—	68	
¹⁸ F	Fluoride	110	—	—	—	—	69	
¹⁸ F	Fluoride	110	—	—	—	—	70	
¹⁸ F	Fluoride	110	—	—	—	—	71	
¹⁸ F	Fluoride	110	—	—	—	—	72	
¹⁸ F	Fluoride	110	—	—	—	—	73	
¹⁸ F	Fluoride	110	—	—	—	—	74	
¹⁸ F	Fluoride	110	—	—	—	—	75	
¹⁸ F	Fluoride	110	—	—	—	—	76	
¹⁸ F	Fluoride	110	—	—	—	—	77	
¹⁸ F	Fluoride	110	—	—	—	—	78	
¹⁸ F	Fluoride	110	—	—	—	—	79	
¹⁸ F	Fluoride	110	—	—	—	—	80	
¹⁸ F	Fluoride	110	—	—	—	—	81	
¹⁸ F	Fluoride	110	—	—	—	—	82	
¹⁸ F	Fluoride	110	—	—	—	—	83	
¹⁸ F	Fluoride	110	—	—	—	—	84	
¹⁸ F	Fluoride	110	—	—	—	—	85	
¹⁸ F	Fluoride	110	—	—	—	—	86	
¹⁸ F	Fluoride	110	—	—	—	—	87	
¹⁸ F	Fluoride	110	—	—	—	—	88	
¹⁸ F	Fluoride	110	—	—	—	—	89	
¹⁸ F	Fluoride	110	—	—	—	—	90	
¹⁸ F	Fluoride	110	—	—	—	—	91	
¹⁸ F	Fluoride	110	—	—	—	—	92	
¹⁸ F	Fluoride	110	—	—	—	—	93	
¹⁸ F	Fluoride	110	—	—	—	—	94	
¹⁸ F	Fluoride	110	—	—	—	—	95	
¹⁸ F	Fluoride	110	—	—	—	—	96	
¹⁸ F	Fluoride	110	—	—	—	—	97	
¹⁸ F	Fluoride	110	—	—	—	—	98	
¹⁸ F	Fluoride	110	—	—	—	—	99	
¹⁸ F	Fluoride	110	—	—	—	—	100	

*Half-life, max. β^- energy (keV) and percentage, and max. γ energy (keV) and percentage as reported by International Commission on Radiological Protection (ICRP) and the National Cancer Institute (NCI).
 †Only energies with β^- are given.
 ‡Maximum energy.
 §Calculated according to Paper et al. (17).
 ¶Fluoride emitter with known half-life and energy.

Un des traceurs les plus utilisés : ⁸⁹Zirconium



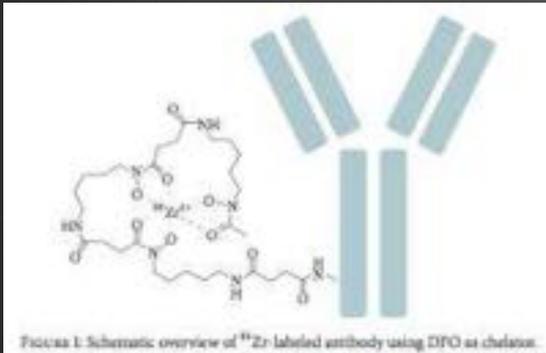
Decay data of ⁸⁹Zr.

Radiation type	Energy (keV)	Radiation Intensity (%)
β^{-}	395.5	22.74
Auger-L	1.91	79.00
Auger-K	12.7	19.47
γ -annihilation	511.0	45.48
γ	909.15	99.04
γ	1620.8	0.07
γ	1657.3	0.11
γ	1713.0	0.75
γ	1744.5	0.12

Un des radioéléments les plus utilisés en immunoTEP :

- Période de 78,4 heures
- Rendement énergétique suffisant pour l'obtention d'images avec contraste suffisant

⁸⁹Zirconium



Relevant Article

TABLE 1: Overview of the described preclinical and clinical studies using ⁸⁹Zr-labeled antibodies.

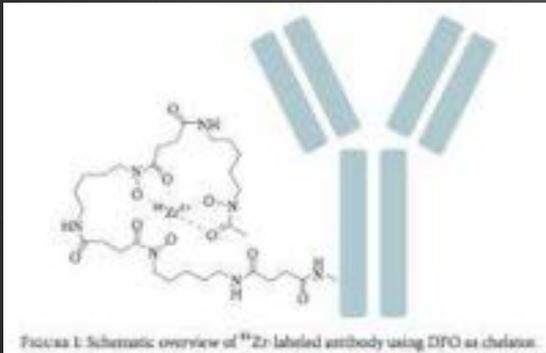
Target	Type of tumor	Targeting vector
CD44v6*	Non-Hodgkin's lymphoma	certumab
CD44v6*	Head and neck squamous cell carcinoma	cnAb U36
EGFR	Multiple	Cetuximab
EGF-1	Prostate	MD7
GPC3	Liver	αGPC3
HER1	Colorectal	Pertuzumab
HER2*	Breast and ovarian	Trastuzumab
IGF-1R	Triple negative breast cancer	81N7
MIT	Head and neck squamous cell carcinoma and gastric	DN39
MNCA IX	Renal cell carcinoma	αG250
PSMA	Prostate	7E11
VEGF	Liver	BC610344
VEGF*	Breast, head, and neck squamous cell carcinoma and ovarian	Bevacizumab

*Targets evaluated in clinical studies

- PSMA
- CD44V6 (cancer ORL : ganglions, métastases)
- VEGF (Bevacizumab)

⁸⁹Zirconium

IgG antiCD44v6

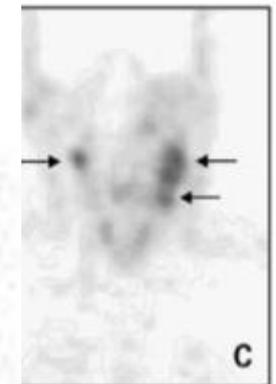


Performance of Immuno-Positron Emission Tomography with Zirconium-89 Labeled Chimeric Monoclonal Antibody U26

in the
Head
Pontus
Jan C.
Adriaan

Table 4. Correlation of preoperative findings with histopathologic findings per level in six patients who received FDG-PET

40 operated levels, 13 tumors involved	Sensitivity	Specificity	Accuracy
Palpation	7/13 (54%)	27/27 (100%)	34/40 (85%)
CT/MRI	10/13 (77%)	27/27 (100%)	37/40 (93%)
FDG-PET	8/13 (62%)	27/27 (100%)	35/40 (88%)
⁸⁹ Zr-immuno-PET	11/13 (85%)	27/27 (100%)	38/40 (95%)

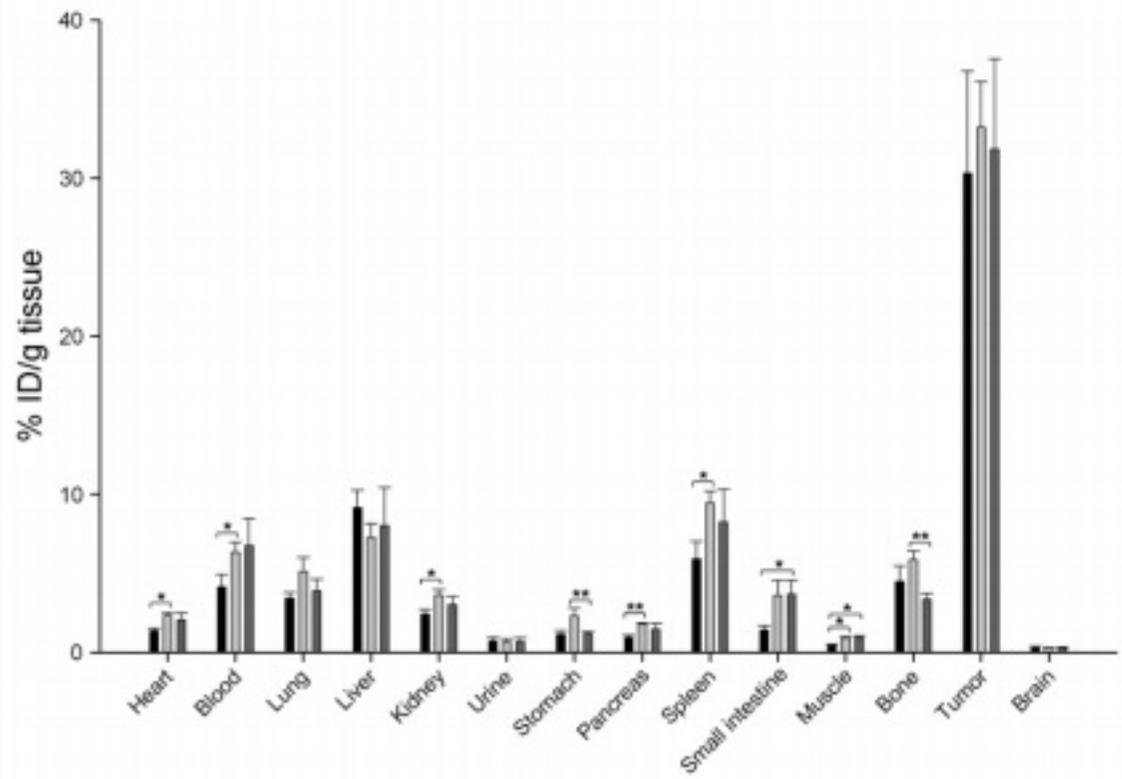
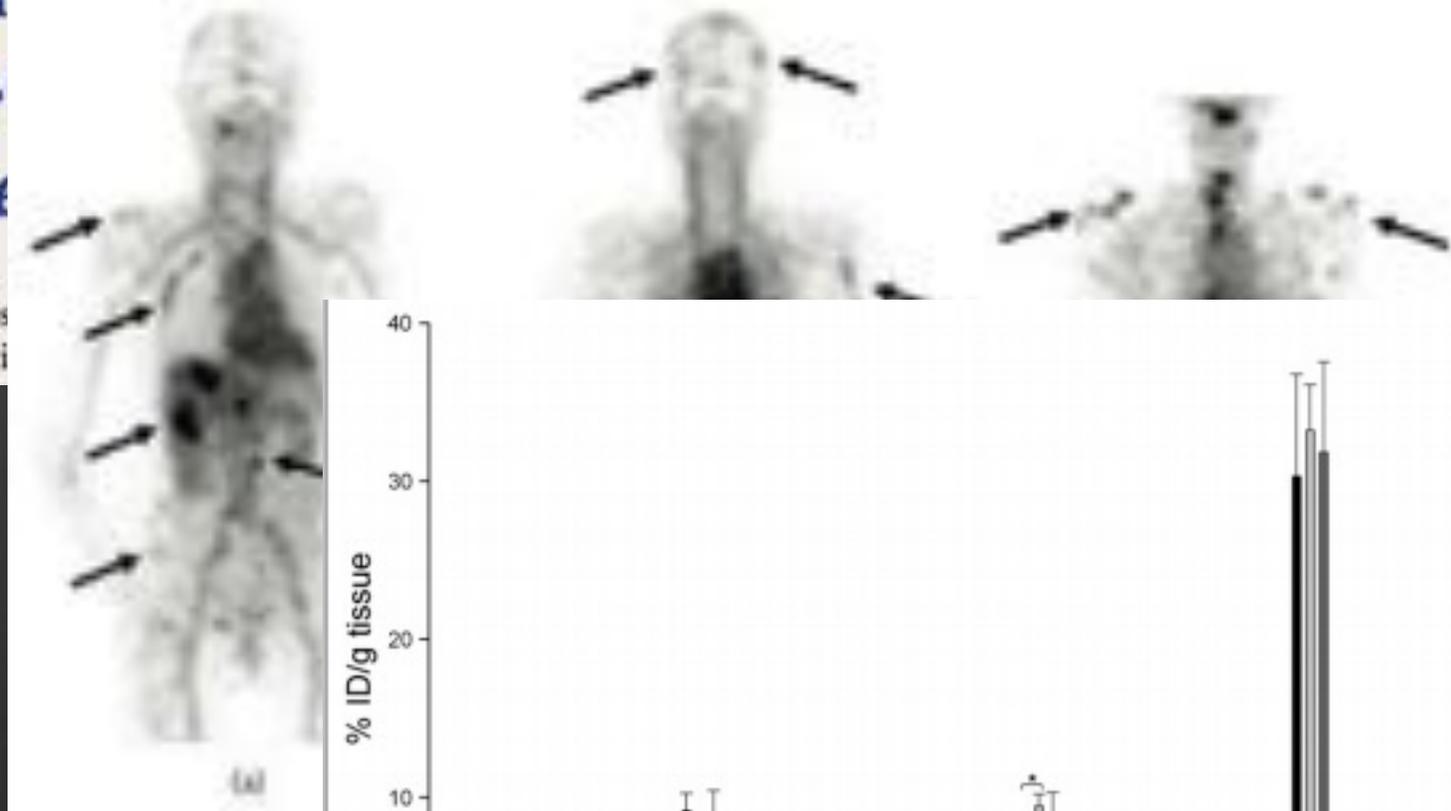


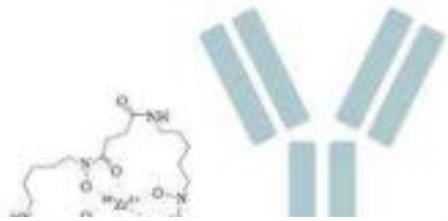
Clin cancer 2006

⁸⁹Zirconium

Development and Characterization of Clinical- HER2/neu

Eli C.F. Dijkers^{1,2}, Jos
Johan R. de Jong², Eli





⁸⁹Zirconium

⁸⁹Zr-Bevacizumab PET Imaging in Primary Breast Cancer

Sietske E.
Hetty T.
Joost B.

de Jong⁴,
R. de Jong²,
de Jong¹

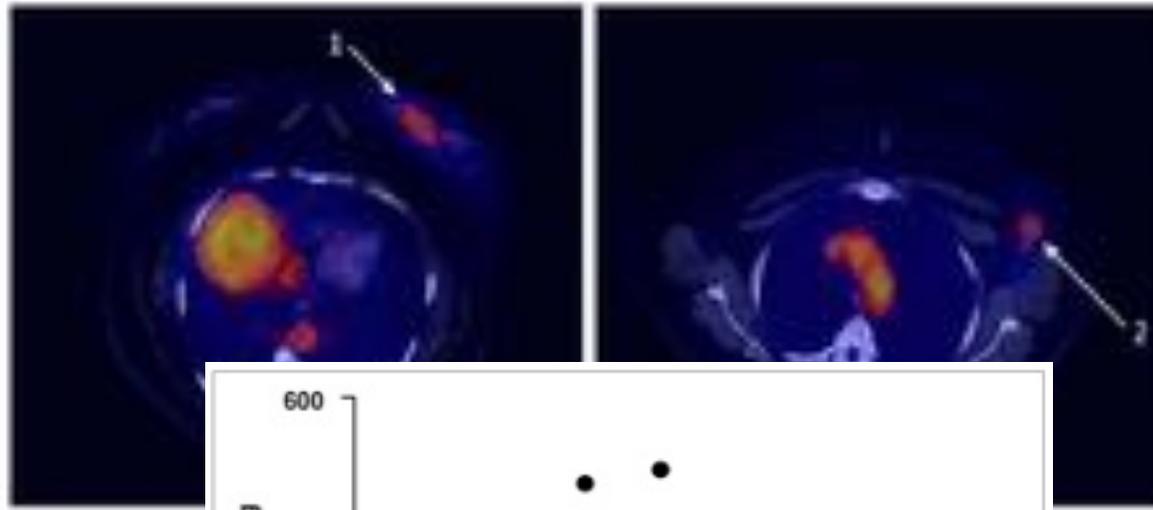
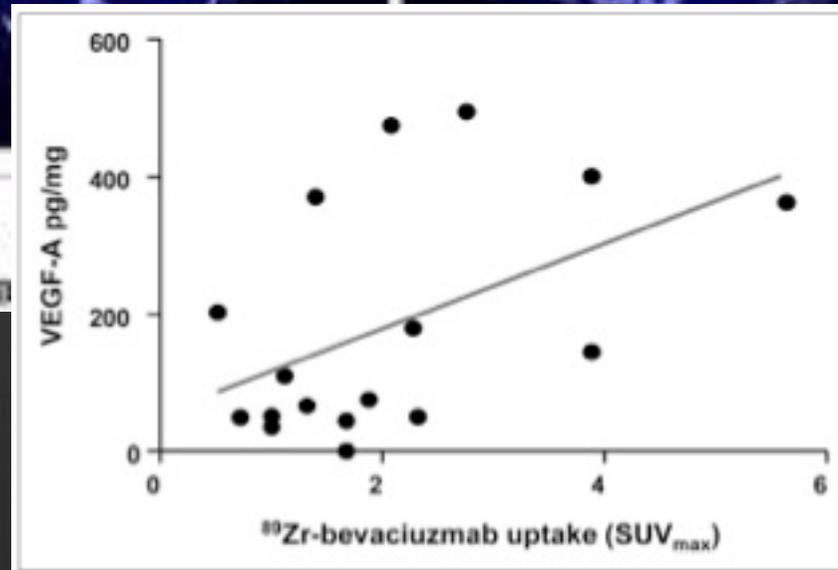


FIGURE 1.
primary breast

ient with





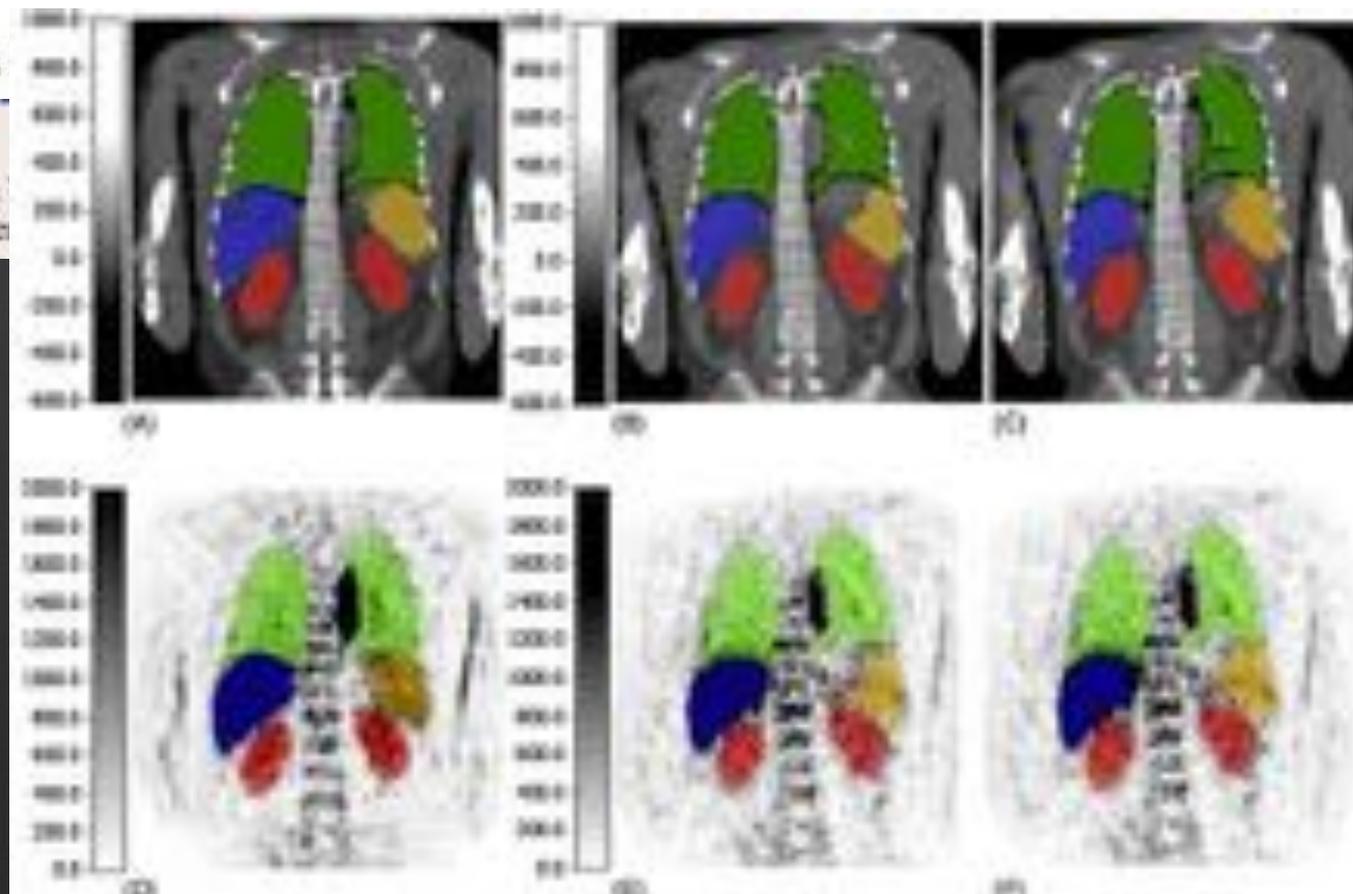
⁸⁹Zirconium

Validation of simplified dosimetry approaches in ⁸⁹Zr-PET/CT: The use of manual versus semi-automatic delineation methods to estimate organ absorbed doses

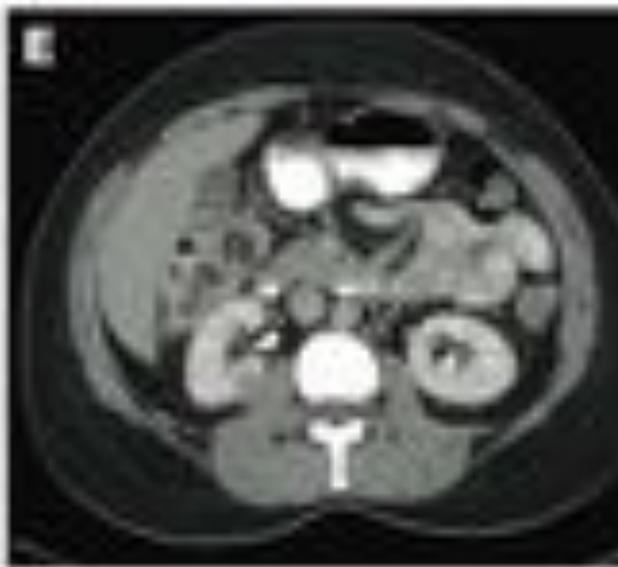
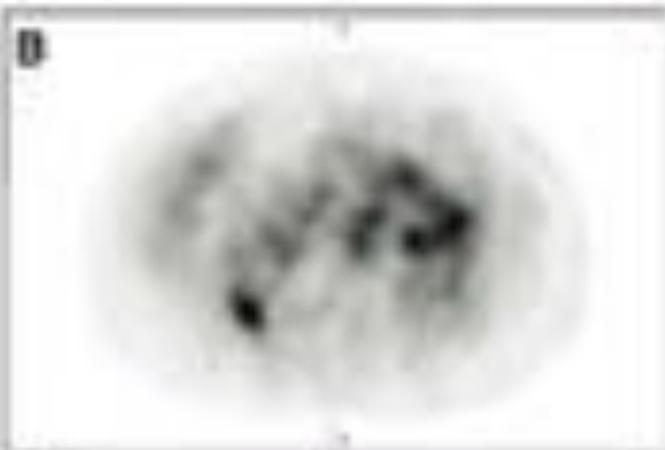
N. E. Makris, F. H. P. van Velden, M. C. Huisman, C. W. Menke, A. A. Lammertsma, and R. Boellaard

Citation: *Medical Physics*

Pontus K.E. Börjesson¹,
Guus A.M.S. van Dongen



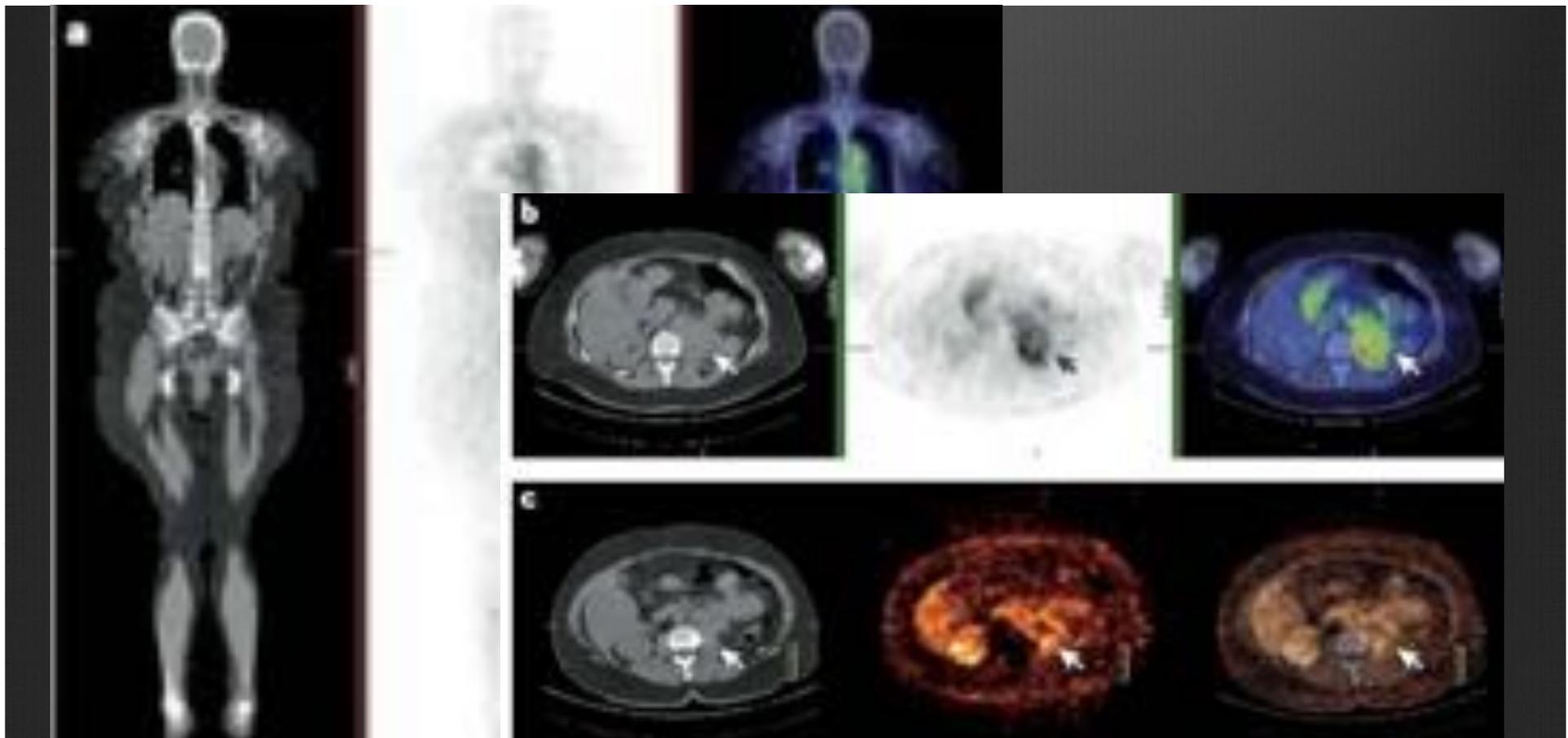
¹²⁴Iode



¹²⁴Iode
cG250 CAIX specific

Antibody therapy of cancer

Andrew M. Scott¹, Jedd D. Wolchok^{2,3,4,5} and Lloyd J. Old^{3,4,5}



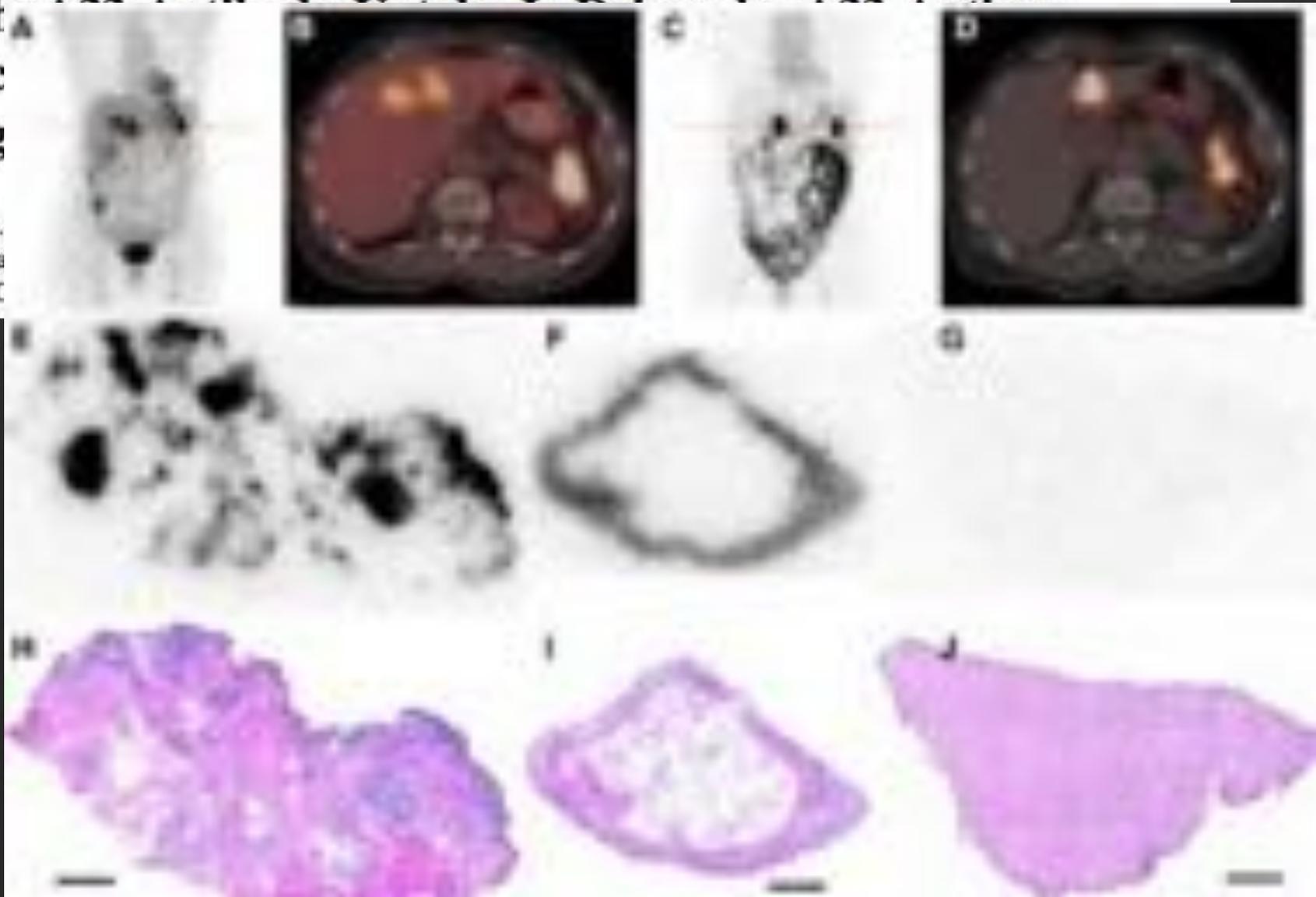
Nature 2012

¹²⁴Iode

AcM chimérique cG250 (anti-carbonic anhydrase-IX)

¹²⁴I-I
Conc
Imag

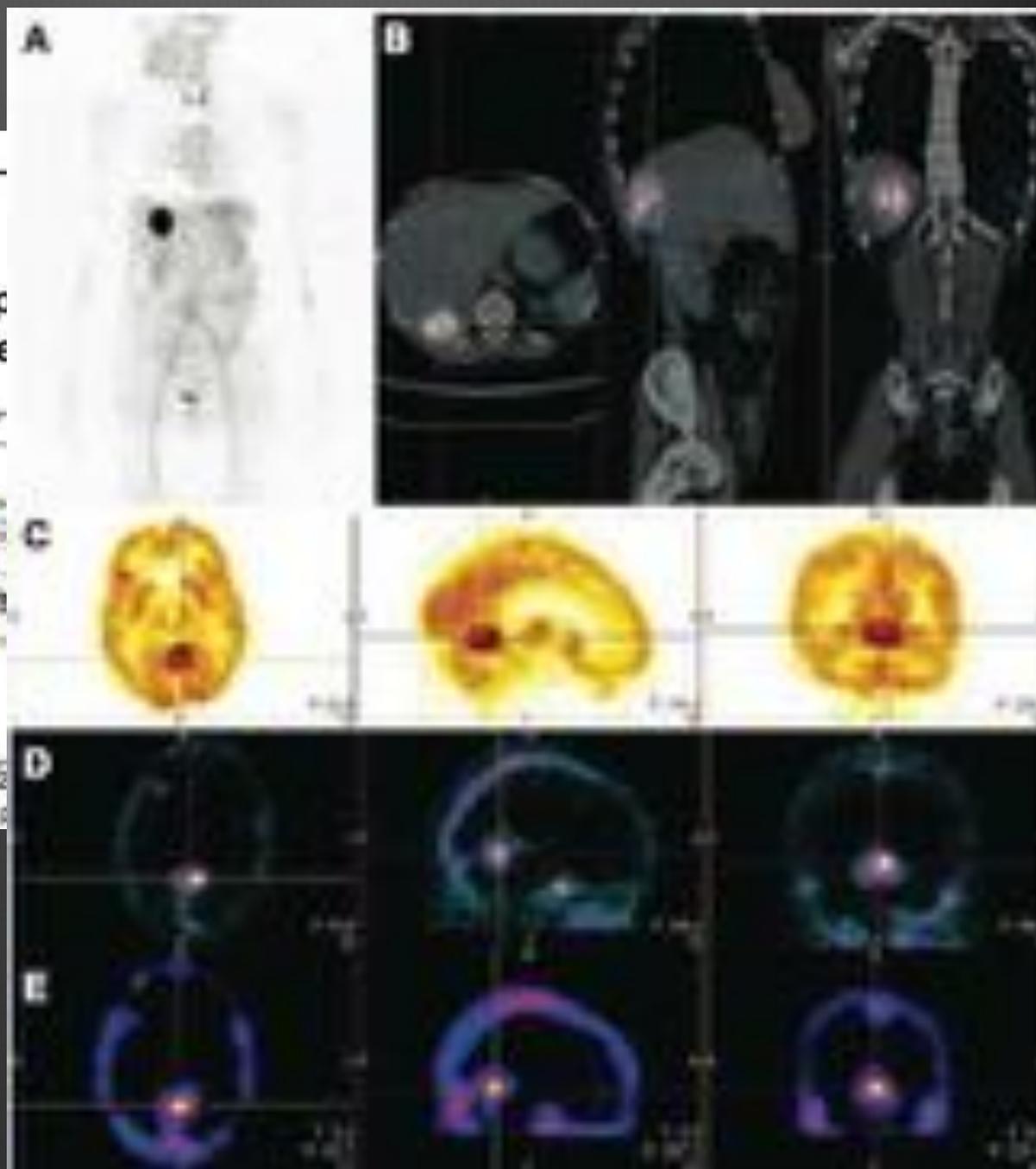
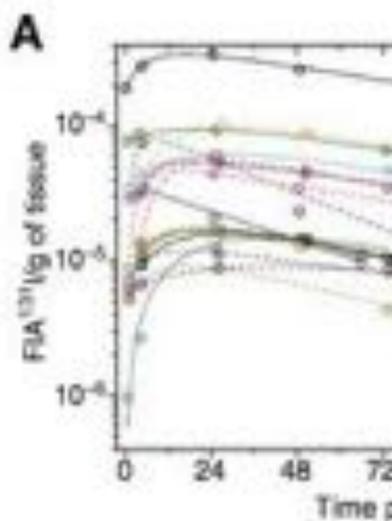
Joseph A.
Chaitanya
Lloyd J. C



Research Article

Radretumab Radioimmunotherapy Metastasis: A ^{124}I -L19SIP Dosime

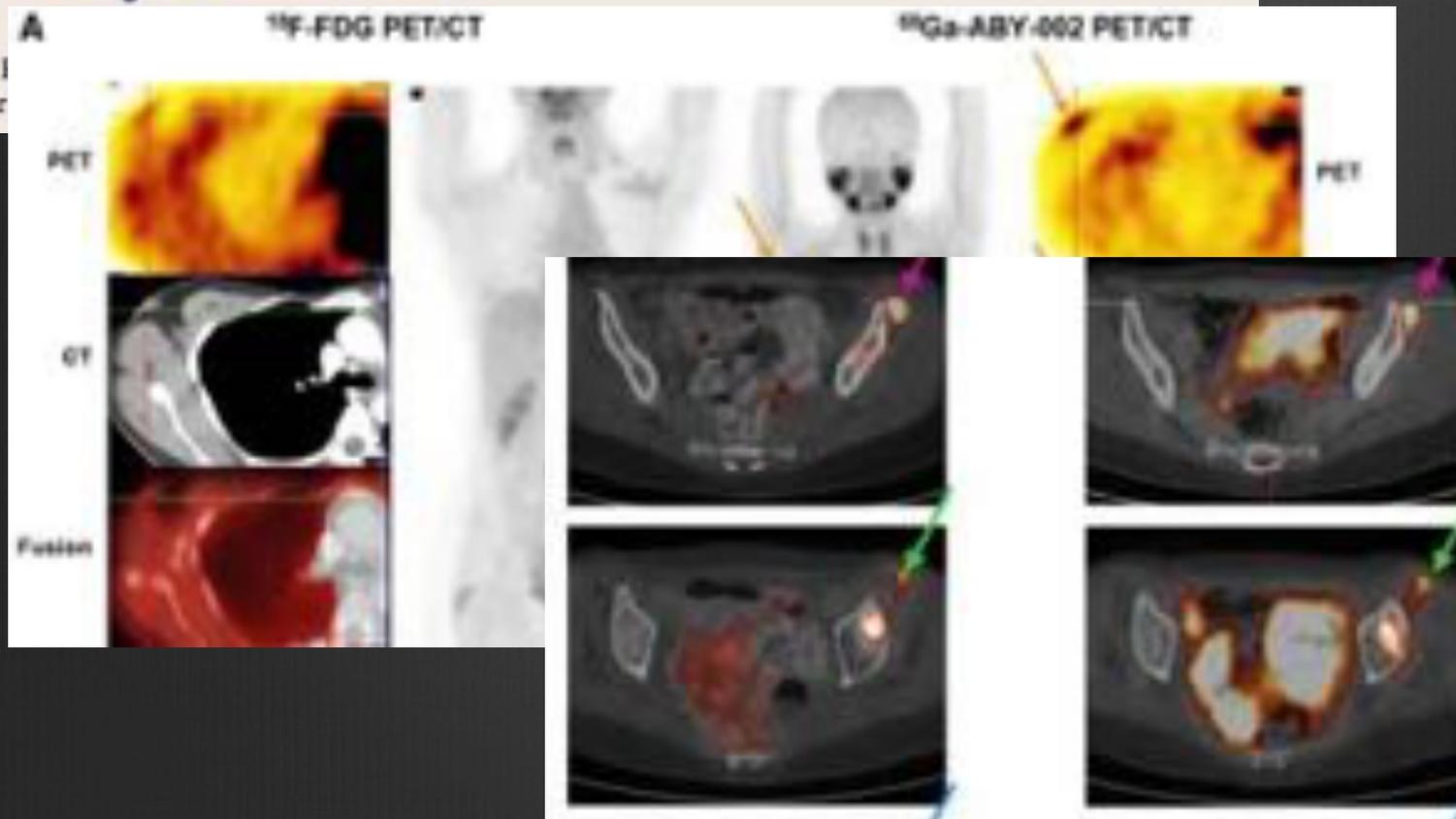
Gian Luca Poli¹, Cle
Giuliano Elia³, Leon



⁶⁸Gallium

Molecular Imaging of *HER2*-Expressing Malignant Tumors in Breast Cancer Patients Using Synthetic ¹¹¹In- or ⁶⁸Ga-Labeled Affibody Molecules

Richard I
Vladimir



JNM 2010

Avantages imagerie métabolique ciblée

- Utilisation d'un vecteur **spécifique** de la cible recherchée
:
 - information obtenue plus **pertinente**
 - étude du processus moléculaire
- Permet de **prédire** et **d'évaluer l'efficacité** des thérapies ciblées
- Possibilité de développer des "**traceurs compagnons**" aux thérapies ciblées
→ Approche **théragnostique** de la médecine nucléaire
- Association RIV et ImmunoTEP

Association RIV et ImmunoTEP :

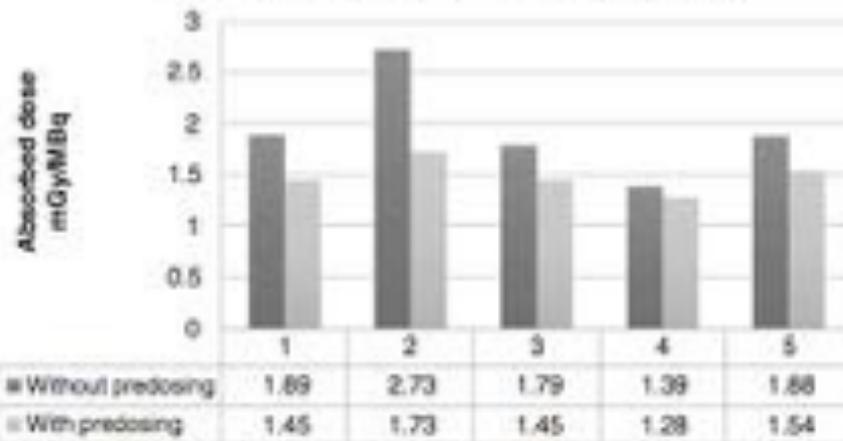
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00219-015-3021-6

ORIGINAL ARTICLE

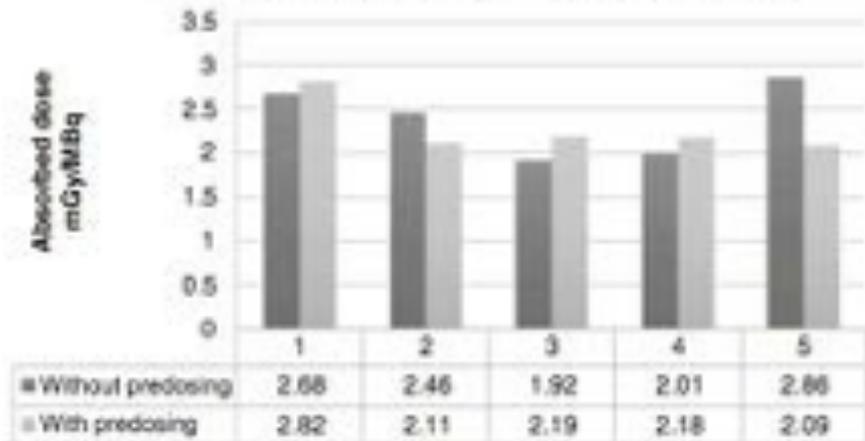
Tumour targeting and radiation dose of radioimmunotherapy with ^{90}Y -rituximab in CD20+ B-cell lymphoma as predicted by ^{89}Zr -rituximab immuno-PET: impact of preloading with unlabelled rituximab

NU
TI
PI
G
M

Bone Marrow ^{90}Y -rituximab

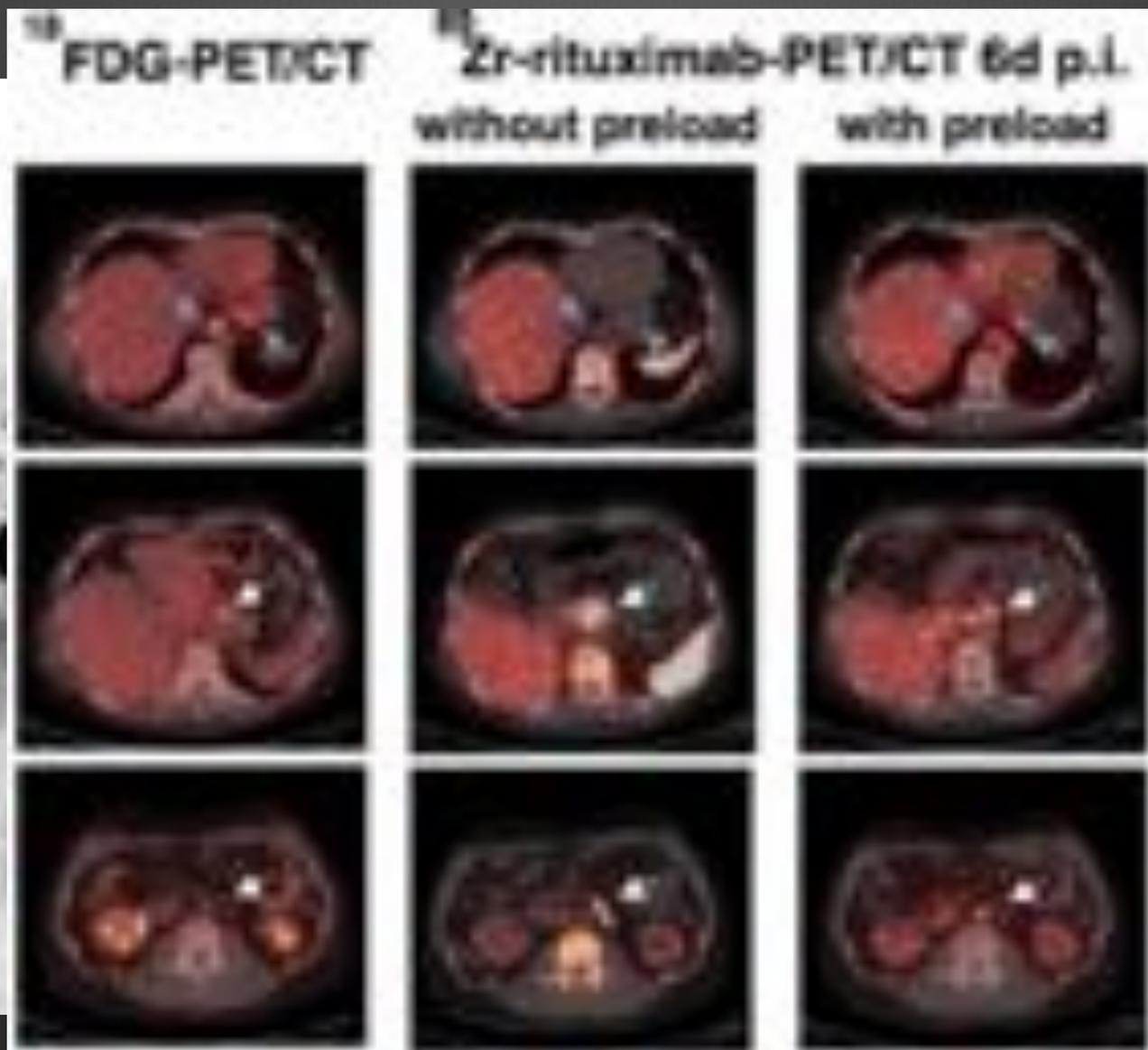


Liver dosimetry ^{90}Y -rituximab



Associé au pré-ciblage

Association RIV – ImmunoTEP et Pré-ciblage :



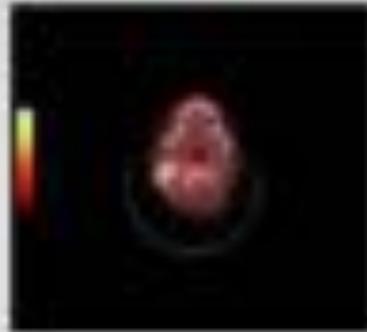
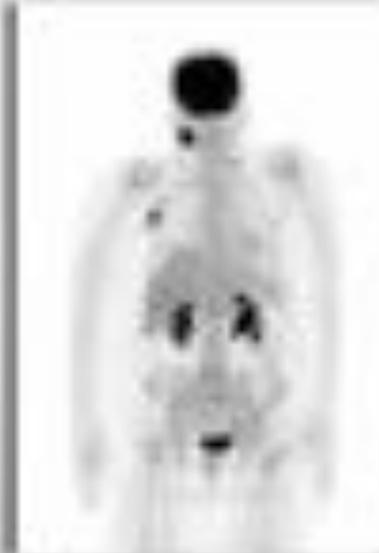
Association RIV et ImmunoTEP :

Immuno-PET imaging with ^{89}Zr -rituximab in patients with CD20+ B-cell lymphoma

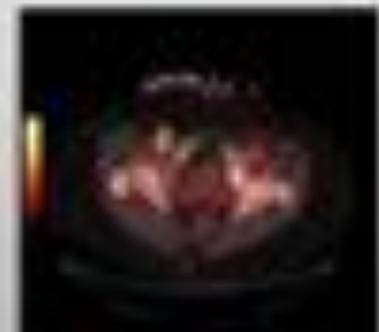
Single Centre Pilot Study (YZIPIT): objectives

Accuracy: comparison with FDG-PET/CT

^{18}F FDG-PET/CT



Immuno-PET/CT with ^{89}Zr -rituximab
6 days p.i.



Un intérêt croissant global :

Int. J. Mol. Sci. **2015**, *16*, 3932-3954; doi:10.3390/ijms16023932

Review

Tumor Immunotargeting Using Innovative Radionuclides

Françoise Kraeber-Bodéré ^{1,2,3,*}, Caroline Rousseau ^{1,3}, Caroline Bodet-Milin ^{1,2},
Cédric Mathieu ², François Guérard ¹, Eric Frampas ^{1,4}, Thomas Carlier ^{1,2}, Nicolas Chouir
Ferid Haddad ⁶, Jean-François Chatal ⁶, Alain Faivre-Chauvet ^{1,2}, Michel Chérel ^{1,3}
and Jacques Barbet ^{1,6}

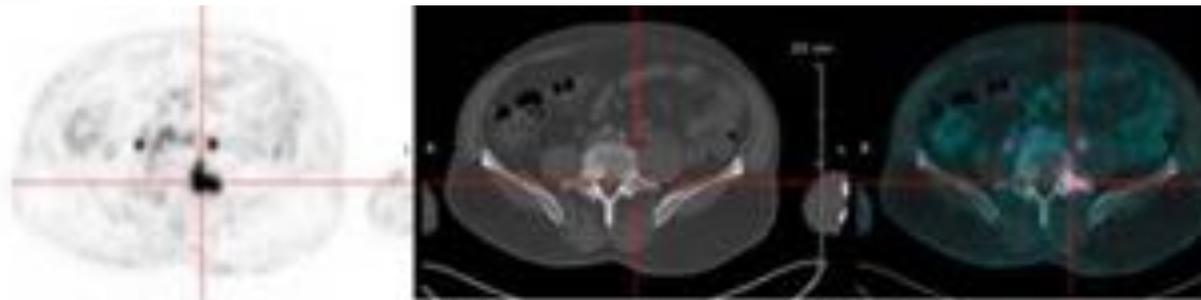
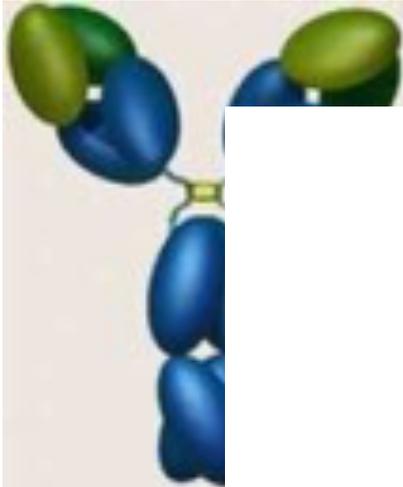


Figure 3. Positron emission tomography (PET) in a patient with a relapse of medullary thyroid carcinoma recorded after injection of the TF2 anti-carcino-embryonic antigen (CEA) bispecific antibody and the ⁶⁸Ga-IMP-288 peptide. Image shows a good detection of a bone lesion.

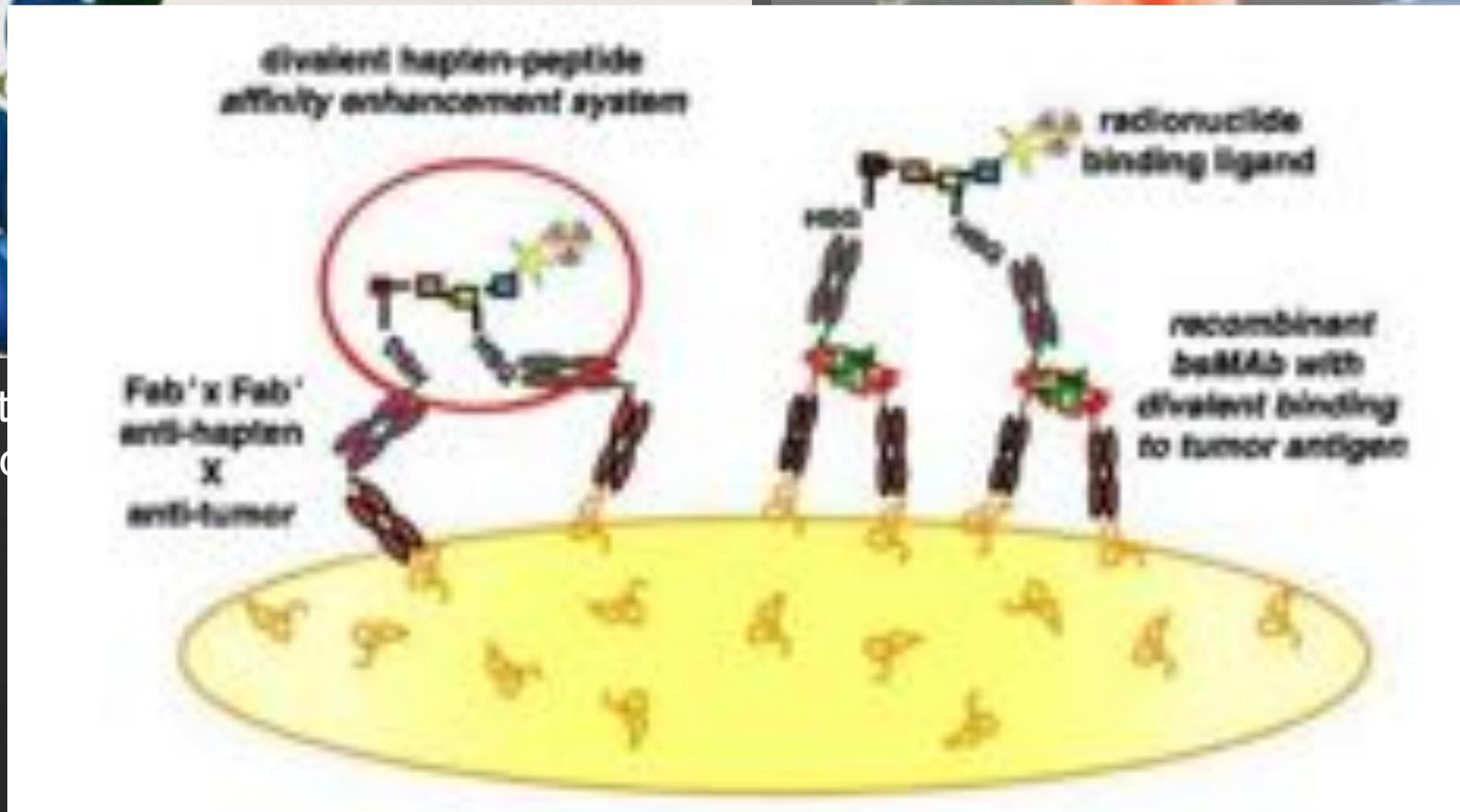
Figure 4. Imaging performed in a patient with a metastatic breast carcinoma. (A) Immuno-PET performed using the TF2 anti-CEA bispecific antibody and the ⁶⁸Ga-IMP-288 peptide detects a more diffuse bone marrow involvement than FDG-PET (B).



Amélioration de l'immunociblage



Réduct
clairanc



Pré-ciblage (pré-targeting)

Kidney

Tumor

Applications cliniques de l'imagerie ciblée :

- **Diagnostique :**
 - Détection
 - Caractérisation
 - Staging
 - Intérêt pronostique du ciblage
- **Thérapeutique :**
 - Sélection des patients à traiter :
 - *Exemple : HER2 et Herceptin*
 - Evaluation de l'étendue des lésions à traiter → Evaluation pré-dose
 - Possibilité de quantification et de dosimétrie si RIV associée envisagée
 - Concept de médecine personnalisée
- **Surveillance et évaluation post-thérapeutique**

Conclusion

[¹⁸F]FDG-PET/CT
before treatment with
⁹⁰Y-rituximab



MIP

Immuno-PET/CT
6 days p.i. of
⁹⁰Zr-rituximab



MIP

[¹⁸F]FDG-PET/CT 6 months after
treatment with ⁹⁰Y-rituximab
(0,4 mCi/kg) showing a com-
plete remission



MIP



Coronal Slice



Coronal Slice



Coronal Slice

*Aspect fondamental et avenir de la médecine nucléaire
? Concept de médecine personnalisée.*

Merci de votre attention