Myélomes et Lymphomes: les nouveaux radiopharmaceutiques

Clément BAILLY

Caroline BODET-MILIN

Françoise KRAEBER-BODÉRÉ

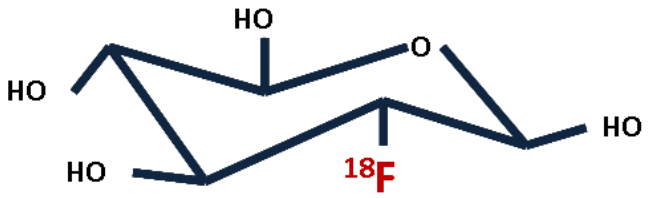
CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

CRCINA Centre de Recherche en Cancérologie et Immunologie Nantes Angers

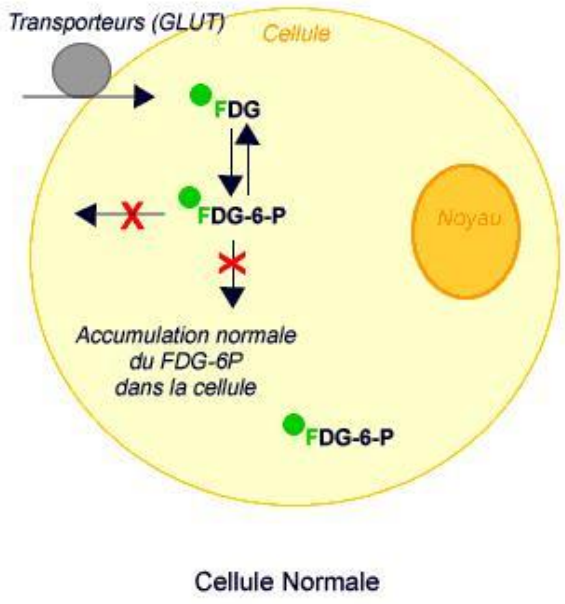
iron labex

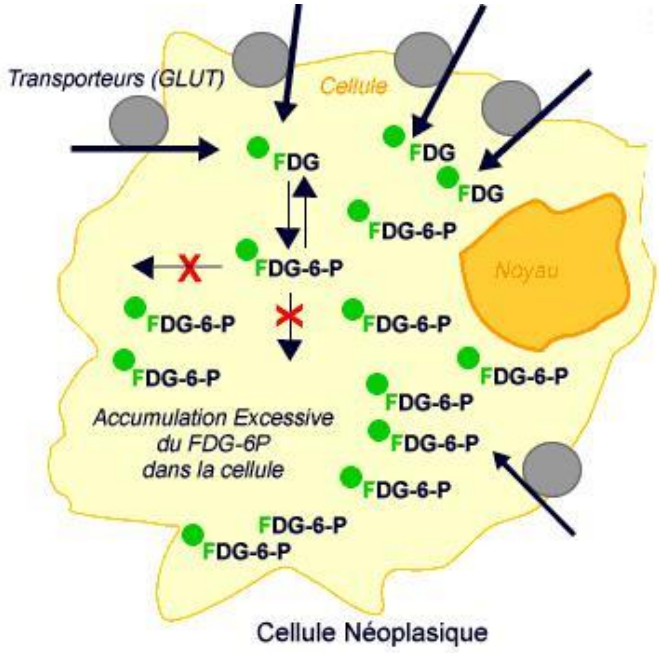
DHU ONCO-GREFFE

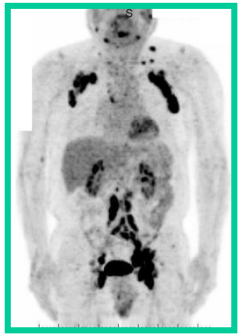
Integrated Center for Oncology Nantes / Angers - France



FDG: seul radiopharmaceutique recommandé en routine







2014

Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

See accompanying article doi: 10.1200/JCO.2013.53.5229

A B S T R A C T

Abstract

The purpose of this work was to modernize recommendations for evaluation, staging, and response assessment of patients with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). A workshop was held at the 11th International Conference on Malignant Lymphoma in Lugano, Switzerland, in June 2011, that included leading hematologists, oncologists, radiation oncologists, pathologists, radiologists, and nuclear medicine physicians, representing major international lymphoma clinical trials groups and cancer centers. Clinical and imaging subcommittees presented their conclusions at a subsequent workshop at the 12th International Conference on Malignant Lymphoma, leading to revised criteria for staging and of the International Working Group Guidelines of 2007 for response. As a result, fluorodeoxyglucose (FDG) positron emission tomography (PET)–computed tomography (CT) was formally incorporated into standard staging for FDG-avid lymphomas. A modification of the Ann Arbor descriptive terminology will be used for anatomic distribution of disease extent, but the suffixes A or B for symptoms will only be included for HL. A bone marrow biopsy is no longer indicated for the routine staging of HL and most diffuse large B-cell lymphomas. However, regardless of stage, general practice is to treat patients based on limited (stages I and II, nonbulky) or advanced (stage III or IV) disease, with stage II bulky disease considered as limited or advanced disease based on histology and a number of prognostic factors. PET-CT will be used to assess response in FDG-avid histologies using the 5-point scale. The product of the perpendicular diameters of a single node can be used to identify progressive disease. Routine surveillance scans are discouraged. These recommendations should improve evaluation of patients with lymphoma and enhance the ability to compare outcomes of clinical trials.

J Clin Oncol 32.

2014

International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma

S Vincent Rajkumar, Meletios A Dimopoulos, Antonio Palumbo, Joan Blade, Giampaolo Merlini, María-Victoria Mateos, Shaji Kumar, Jens Hillengass, Efstathios Kastritis, Paul Richardson, Ola Landgren, Bruno Paiva, Angela Dispenzieri, Brendan Weiss, Xavier LeLeu, Sonja Zweegman, Sagar Lonial, Laura Rosinol, Elena Zamagni, Sundar Jagannath, Orhan Sezer, Sigurdur Y Kristinsson, Jo Caers, Saad Z Usmani, Juan José Lahuerta, Hans Erik Johnsen, Meral Beksac, Michele Cavo, Hartmut Goldschmidt, Evangelos Terpos, Robert A Kyle, Kenneth C Anderson, Brian G M Durie, Jesus F San Miguel

Lancet Oncol 2014; 15: e538–48

Panel: **Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma**

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

FDG: intérêt pronostique certain

- Valeur pronostique démontrée
- Etudes prospectives multicentriques
- VPP et VPN imparfaites mais >>>>> CT dans le lymphome et IRM dans le myélome pour l'évaluation thérapeutique
- Un modèle d'harmonisation pour le lymphomes

FDG: des limites

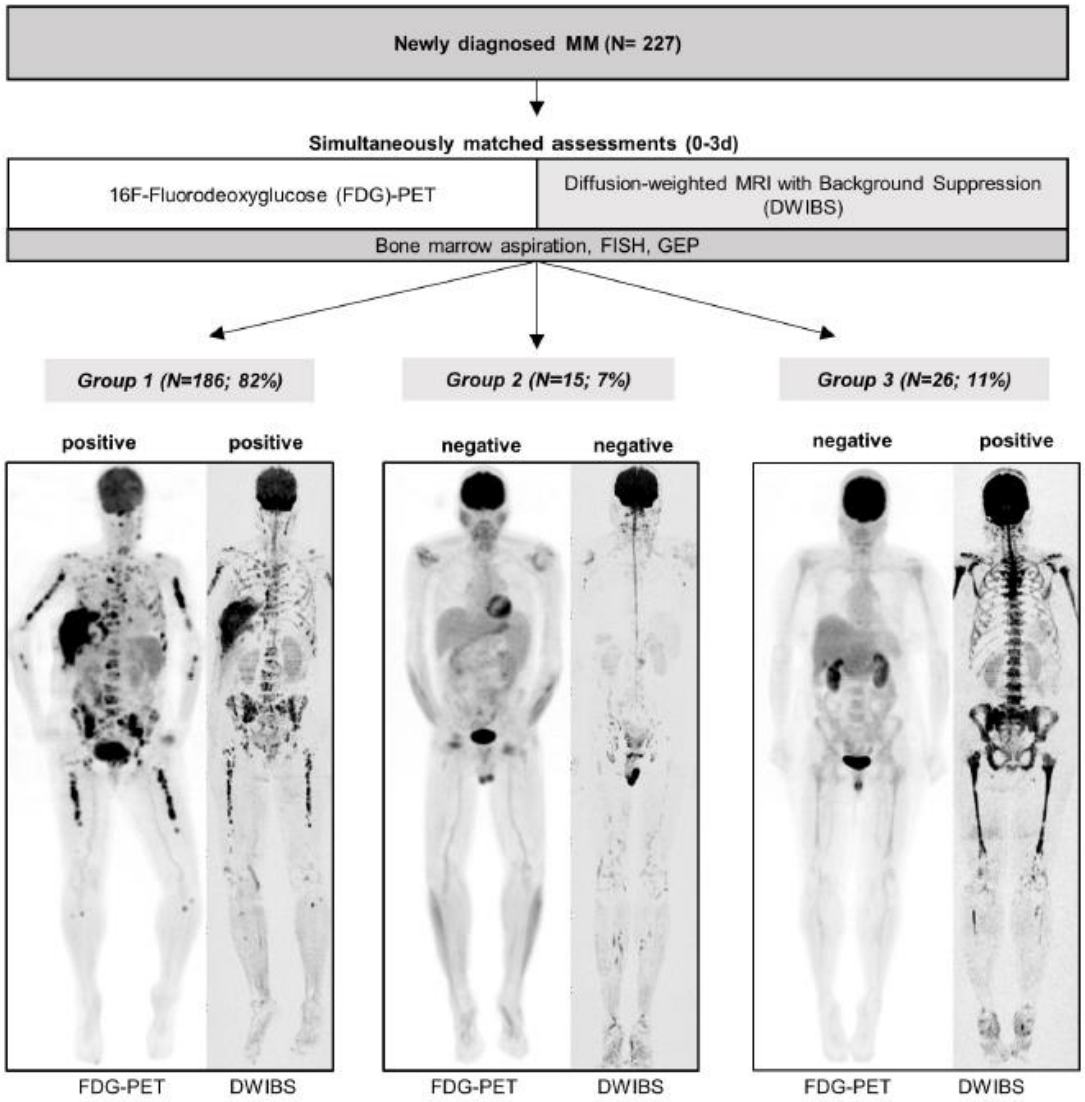
- Faux positifs liés aux fixations inflammatoires gênant le bilan initial ou la caractérisation des masses résiduelles
- Faux négatifs dans les pathologies peu avides de FDG (formes indolentes de lymphome, certaines formes de myélome) et pour la détection des infiltrations ostéo-médullaires
- Fixation cérébrale limitant la détection des atteintes du SNC
- Pas de prédiction de l'efficacité des traitements (théranostique)
- Pas de prédiction de la résistance

blood®
Leading the way in experimental and clinical research in hematology

Low expression of hexokinase-2 is associated with false-negative FDG-positron emission tomography in multiple myeloma

Leo Rasche, Edgardo Angtuaco, James E. McDonald, Amy Buros, Caleb Stein, Charlotte Pawlyn, Sharmilan Thanendrarajan, Carolina Schinke, Rohan Samant, Shmuel Yaccoby, Brian Walker, Joshua Epstein, Maurizio Zangari, Frits van Rhee, Tobias Meissner, Hartmut Goldschmidt, Kari Hemminki, Richard Houlston, Bart Barlogie, Faith E. Davies, Gareth J. Morgan and Niels Weinhold

Blood 2017 :blood-2017-03-774422; doi: https://doi.org/10.1182/blood-2017-03-774422



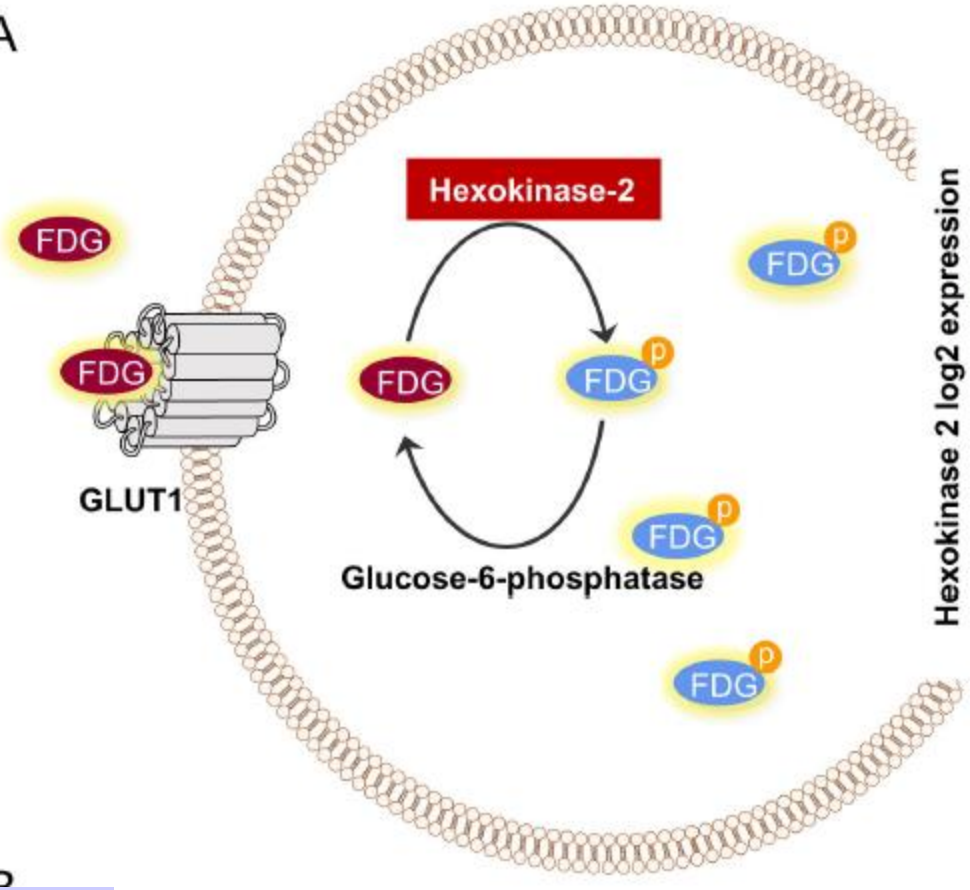
blood®
Leading the way in experimental and clinical research in hematology

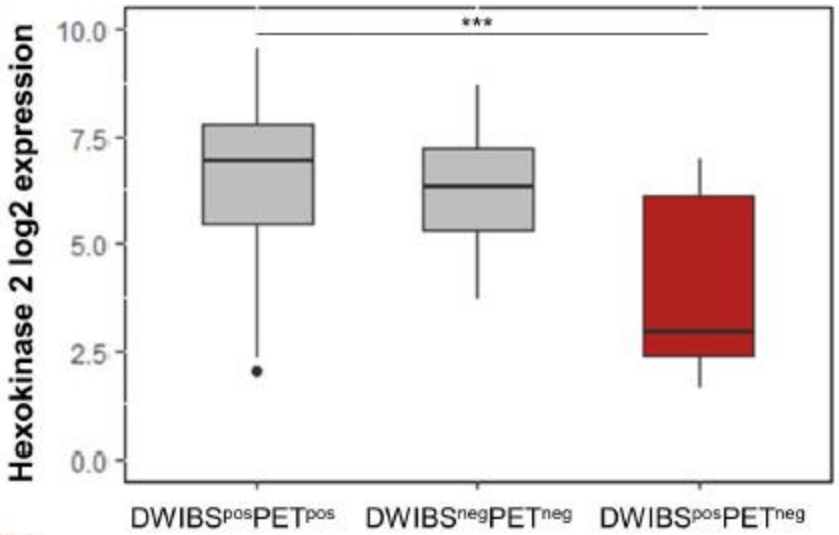
Low expression of hexokinase-2 is associated with false-negative FDG-positron emission tomography in multiple myeloma

Leo Rasche, Edgardo Angtuaco, James E. McDonald, Amy Buros, Caleb Stein, Charlotte Pawlyn, Sharmilan Thanendrarajan, Carolina Schinke, Rohan Samant, Shmuel Yaccoby, Brian Walker, Joshua Epstein, Maurizio Zangari, Frits van Rhee, Tobias Meissner, Hartmut Goldschmidt, Kari Hemminki, Richard Houlston, Bart Barlogie, Faith E. Davies, Gareth J. Morgan and Niels Weinhold

Blood 2017 :blood-2017-03-774422; doi: https://doi.org/10.1182/blood-2017-03-774422

A





B

Quels autres MRP?

- Moins de résultats faux négatifs (meilleure Se) pour le myélome et les formes indolentes de lymphomes, pour les infiltrations ostéo-médullaires
- Moins de résultats faux positifs (meilleure VPP) pour les formes agressives de lymphomes

Eur J Nucl Med Mol Imaging (2016) 43:1995–2004
DOI 10.1007/s00259-016-3392-7

ORIGINAL ARTICLE

18F-fluorocholine versus 18F-fluorodeoxyglucose for PET/CT imaging in patients with suspected relapsing or progressive multiple myeloma: a pilot study

Thibaut Cassou-Mounat[1,2,3] · Sona Balogova[1,4] · Valérie Nataf[1,5] · Marie Calzada[1,2] · Virginie Huchet[1] · Khaldoun Kerrou[1] · Jean-Yves Devaux[2,3] · Mohamad Mohty[3,6,7] · Jean-Noël Talbot[1,3] · Laurent Garderet[3,6,7]

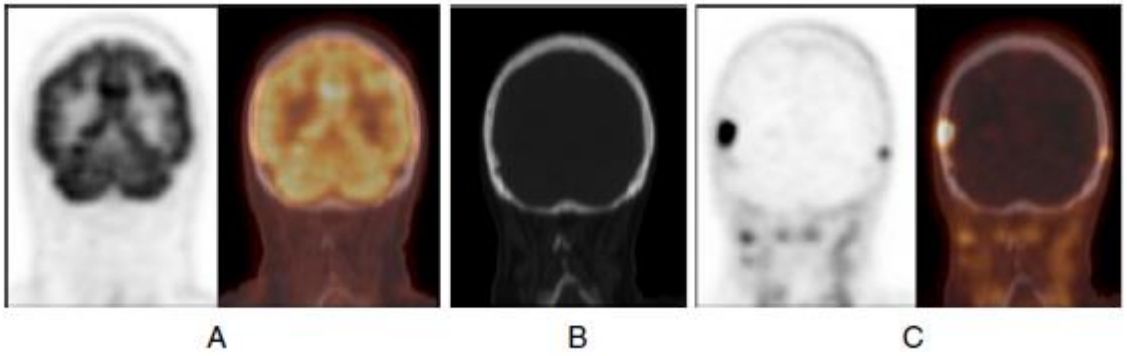


Fig. 3 Coronal slices of the same patient. Negative FDG PET/CT (a), small lytic lesions in the skull on CT (b), and positive FCH PET/CT (c) in patient #2

Eur J Nucl Med Mol Imaging (2016) 43:1995–2004
DOI 10.1007/s00259-016-3392-7

ORIGINAL ARTICLE

18F-fluorocholine versus 18F-fluorodeoxyglucose for PET/CT imaging in patients with suspected relapsing or progressive multiple myeloma: a pilot study

Thibaut Cassou-Mounat[1,2,3] · Sona Balogova[1,4] · Valérie Nataf[1,5] · Marie Calzada[1,2] · Virginie Huchet[1] · Khaldoun Kerrou[1] · Jean-Yves Devaux[2,3] · Mohamad Mohty[3,6,7] · Jean-Noël Talbot[1,3] · Laurent Garderet[3,6,7]

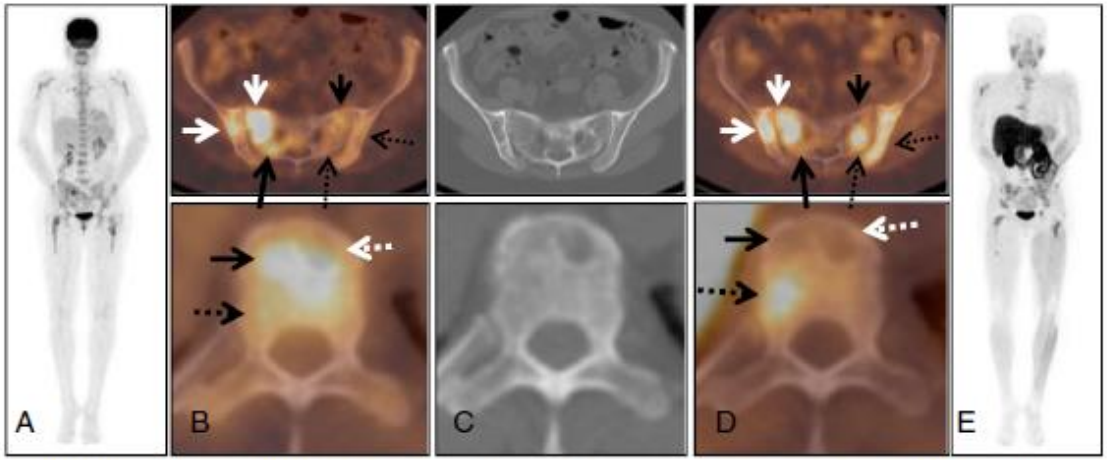


Fig. 1 Patient #19: FDG PET MIP (**a**), FDG PET/CT axial slices (sacrum, pelvis, and Th10) (**b**), CT (**c**), FCH PET/CT axial slices (sacrum, pelvis, and Th10) (**d**), and FCH PET MIP (**e**). Patient with innumerable bone foci on both FDG and FCH PET/CTs. The majority of foci are matched, taking-up both tracers (*white full arrow*). However, some foci appear more intense with FDG (*black full arrow*) and other with FCH (*black dotted arrow*). Furthermore, some lesions visible on CT take-up neither FDG nor FCH (*white dashed arrow*), probably as a consequence of the previous treatment

Exploration du métabolisme lipidique:
Complémentaire du FDG: Intérêt pour les TEP FDG neg?
Et la spécificité?
Valeur pronostique?
Etudes prospectives nécessaires

Theranostics 2016, Vol. 6, Issue 2 254

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2016; 6(2): 254-261. doi: 10.7150/thno.13921

Research Paper

^{11}C-Methionine-PET in Multiple Myeloma: Correlation with Clinical Parameters and Bone Marrow Involvement

Constantin Lapa[1,4✉], Stefan Knop[2,4], Martin Schreder[2,4], Martina Rudelius[3,4], Markus Knott[2,4], Gerhard Jörg[1,4], Samuel Samnick[1,4], Ken Herrmann[1,4], Andreas K. Buck[1,4], Hermann Einsele[2,4], Katharina Lückerath[1,4]

Métabolisme accru des acides aminés par les cellules de myélome

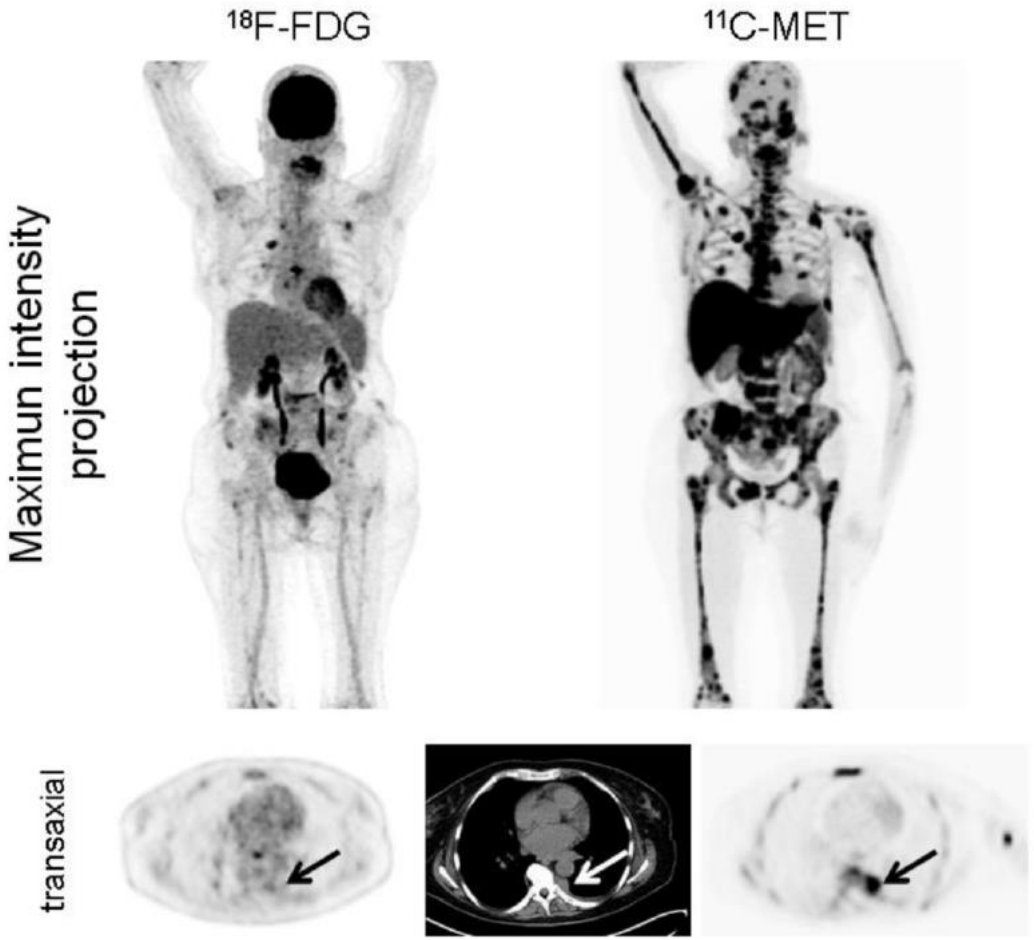


Figure 3: Display of a patient (patient #6) with MM Ig G κ. FDG depicts moderate uptake in the skeleton in contrast to highly intense lesions in MET (maximum intensity projection, upper row). Additionally, pleural extramedullary disease was exclusively detected by MET (arrows, transaxial slices, lower row). The patient deceased 5 months later.

Theranostics 2016, Vol. 6, Issue 2 254

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2016; 6(2): 254-261. doi: 10.7150/thno.13921

Research Paper

^{11}C-Methionine-PET in Multiple Myeloma: Correlation with Clinical Parameters and Bone Marrow Involvement

Constantin Lapa[1,4✉], Stefan Knop[2,4], Martin Schreder[2,4], Martina Rudelius[3,4], Markus Knott[2,4], Gerhard Jörg[1,4], Samuel Samnick[1,4], Ken Herrmann[1,4], Andreas K. Buck[1,4], Hermann Einsele[2,4], Katharina Lückerath[1,4]

Sur-expression du transporteur des AA LAT-1 par les cellules de myélome

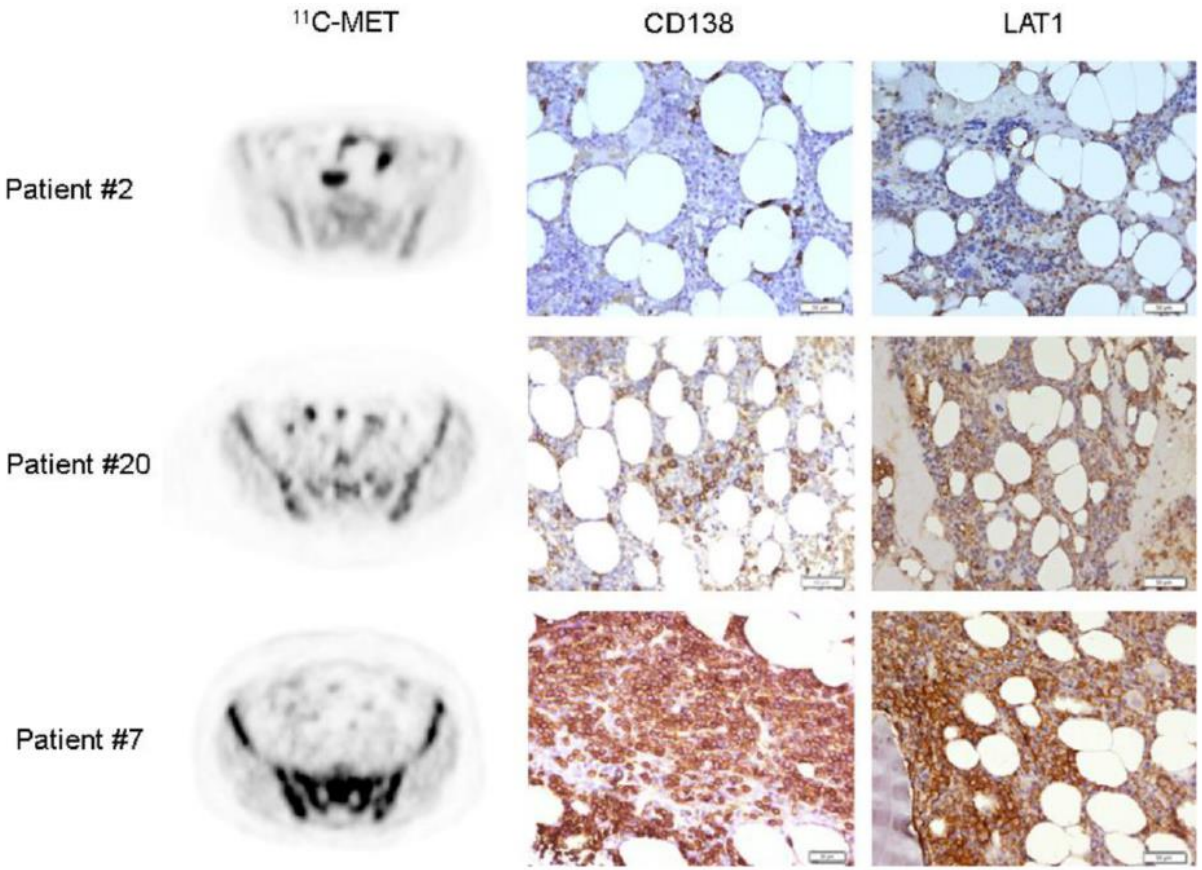


Figure 4: Histological assessment of LAT1 expression on MM bone marrow biopsies. LAT1 expression was detected in 13/15 samples using an anti-CD98 antibody. Sections were counterstained with H&E. Three exemplary cases are shown with corresponding anti-CD138 staining for comparison with the degree of MM-cell bone marrow infiltration (patient #2, 0%; patient #20, 15%; patient #7, 70%). Magnification 200x.

Theranostics 2016, Vol. 6, Issue 2 254

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

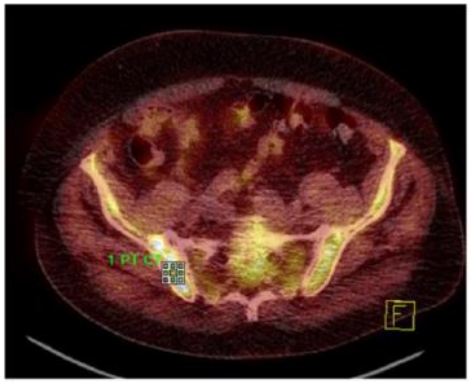
2016; 6(2): 254-261. doi: 10.7150/thno.13921

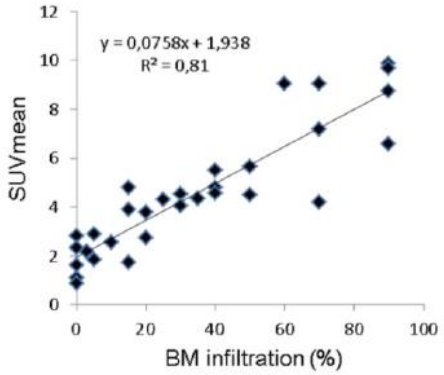
Research Paper

^{11}C-Methionine-PET in Multiple Myeloma: Correlation with Clinical Parameters and Bone Marrow Involvement

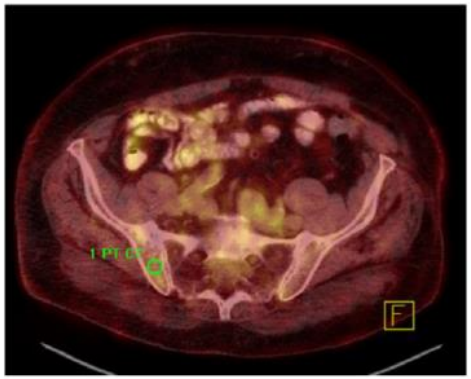
Constantin Lapa[1,4✉], Stefan Knop[2,4], Martin Schreder[2,4], Martina Rudelius[3,4], Markus Knott[2,4], Gerhard Jörg[1,4], Samuel Samnick[1,4], Ken Herrmann[1,4], Andreas K. Buck[1,4], Hermann Einsele[2,4], Katharina Lückerath[1,4]

MET





FDG



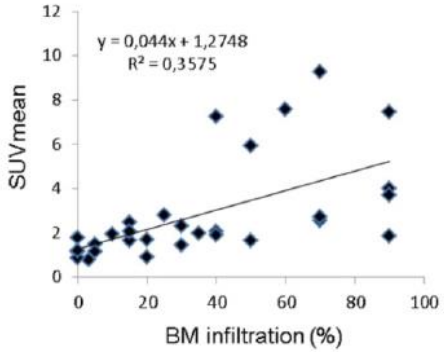


Figure 5: Correlation of radiotracer uptake with bone marrow infiltration. Assessment of iliac crest bone marrow involvement by FDG and MET-PET for a single patient (patient #31, transaxial fused PET/CT slices, left). Dot plots for SUV_{mean} for all individual patients (n=31) with a strong correlation for FDG (r=0.6) and a very strong correlation for MET (r=0.9).

bjh BRITISH JOURNAL OF HAEMATOLOGY

Explore this journal >

Correspondence

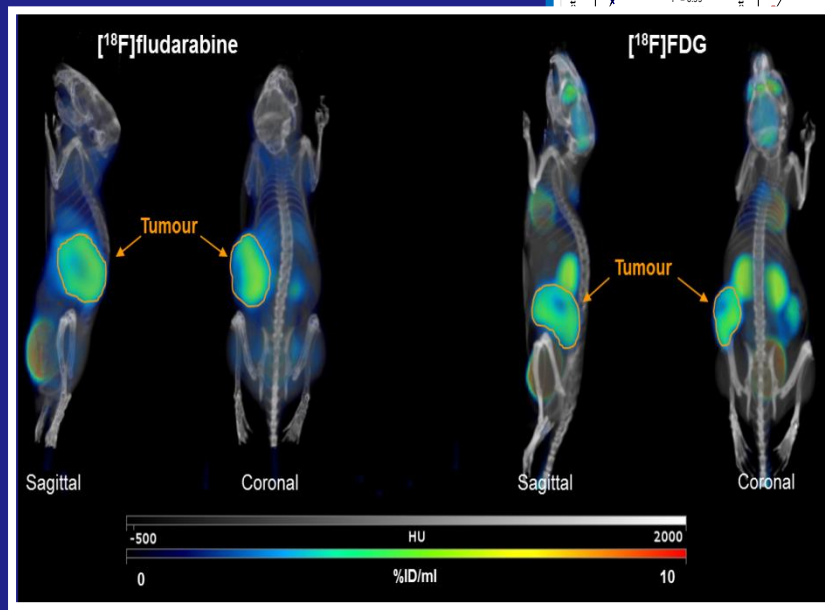
[^{11}C]Methionine emerges as a new biomarker for tracking active myeloma lesions

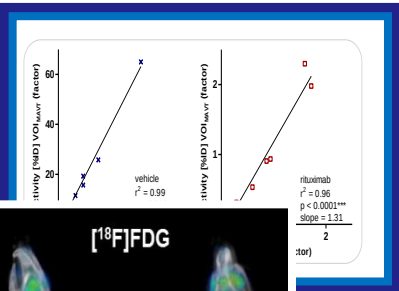
Constantin Lapa, Martin Schreder, Katharina Lückerath, Samuel Samnick, Martina Rudelius, Andreas K. Buck, Klaus M. Kortüm, Hermann Einsele, Andreas Rosenwald, Stefan Knop

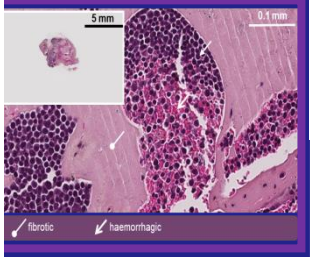
First published: 3 May 2017 Full publication history

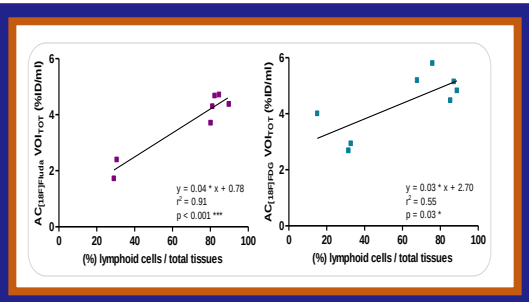
DOI: 10.1111/bjh.14696 View/save citation

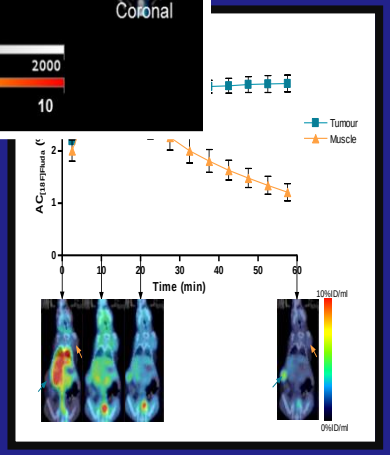
Exploration du métabolisme des aa: intérêt probable dans le MM, notamment avec un traceur fluoré
Probable meilleure Se que le FDG
Probable meilleure Sp que le FDG (moins de fixation dans les cellules inflammatoires)
Biodistribution favorable (infiltration médullaire)
Valeur pronostique?
Etudes prospectives nécessaires











specificity
robustness during therapy

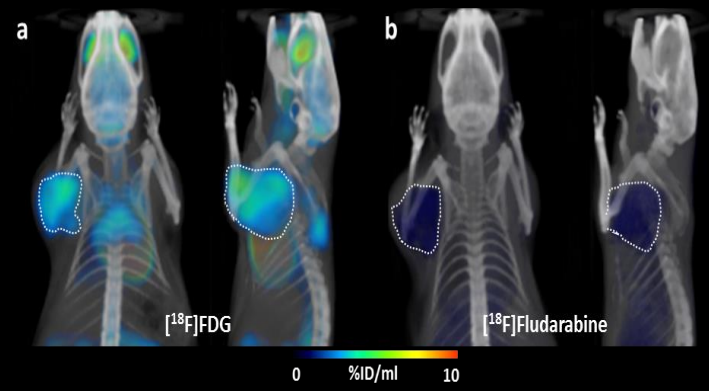
EJNMMI Research
a SpringerOpen Journal

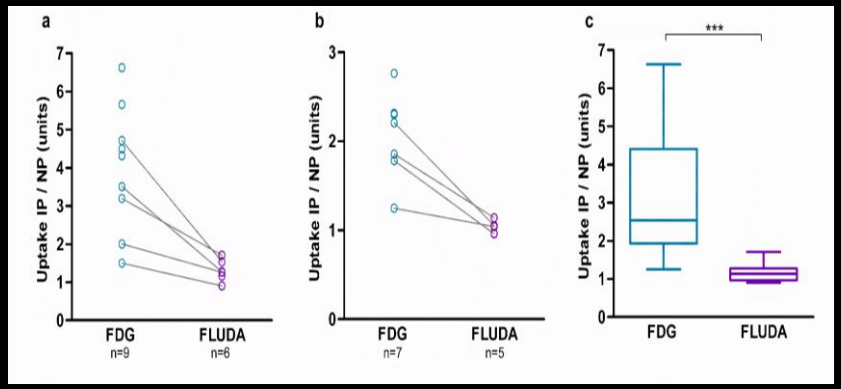
ORIGINAL RESEARCH Open Access

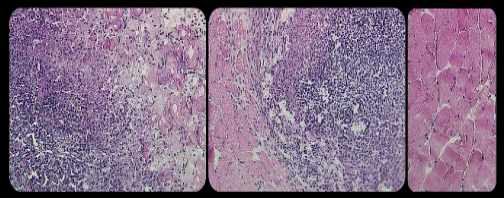
Evaluation of the specificity of [18F]fludarabine PET/CT in a xenograft model of follicular lymphoma: comparison with [18F]FDG and impact of rituximab therapy

Narinée Hovhannisyan[1,2,3*], Stéphane Guillouet[1,2,3], Fabien Fillesoye[1,2,3], Martine Dhilly[1,2,3], Delphine Patin[1,2,3], Françoise Galateau[4], Michel Leporrier[1,2,3] and Louisa Barré[1,2,3]

18Fludarabine: fixation dans les tissus lymphoïdes, indépendante du cycle cellulaire







specificity
in the case of inflammation

molecular pharmaceutics

Brief Article

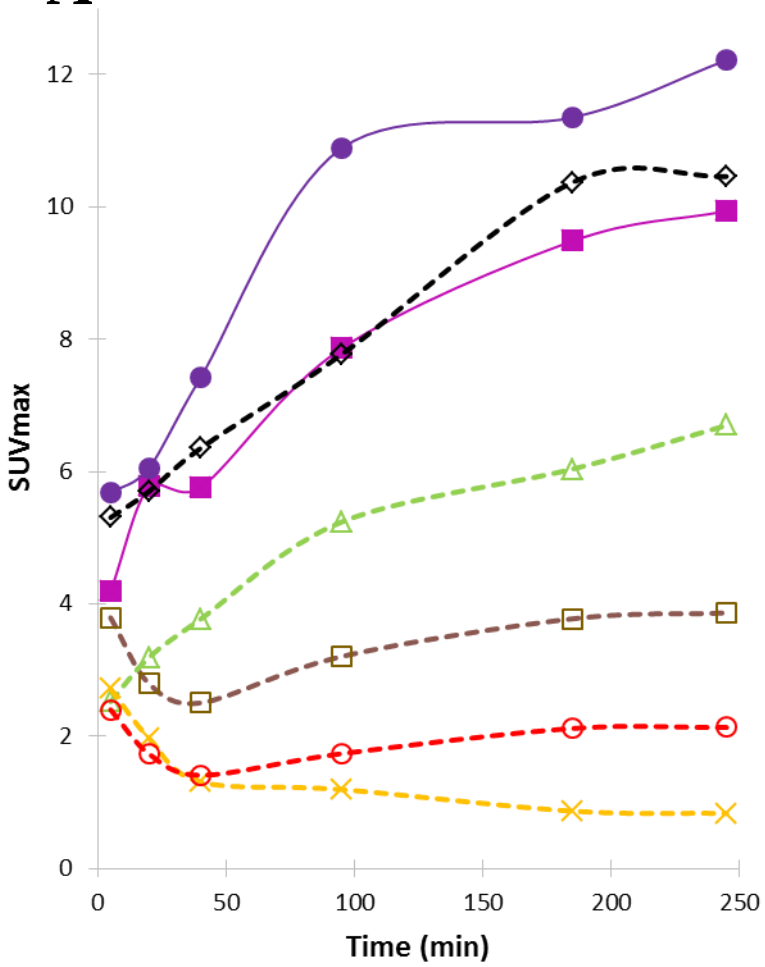
pubs.acs.org/molecularpharmaceutics

Comparative Analysis between [18F]Fludarabine-PET and [18F]FDG-PET in a Murine Model of Inflammation

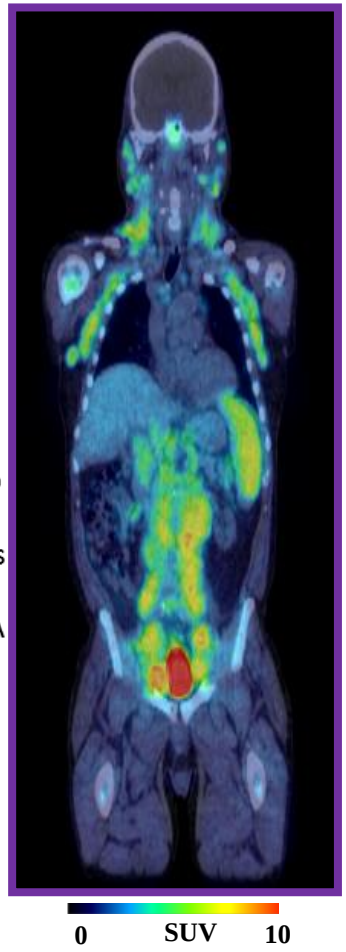
Narinée Hovhannisyan,*[†,‡,§] Martine Dhilly,[†,‡,§] Stéphane Guillouet,[†,‡,§] Michel Leporrier,[†,‡,§] and Louisa Barré[†,‡,§]

CLINICAL TRIAL • phase 1 • chronic lymphocytic leukemia

A



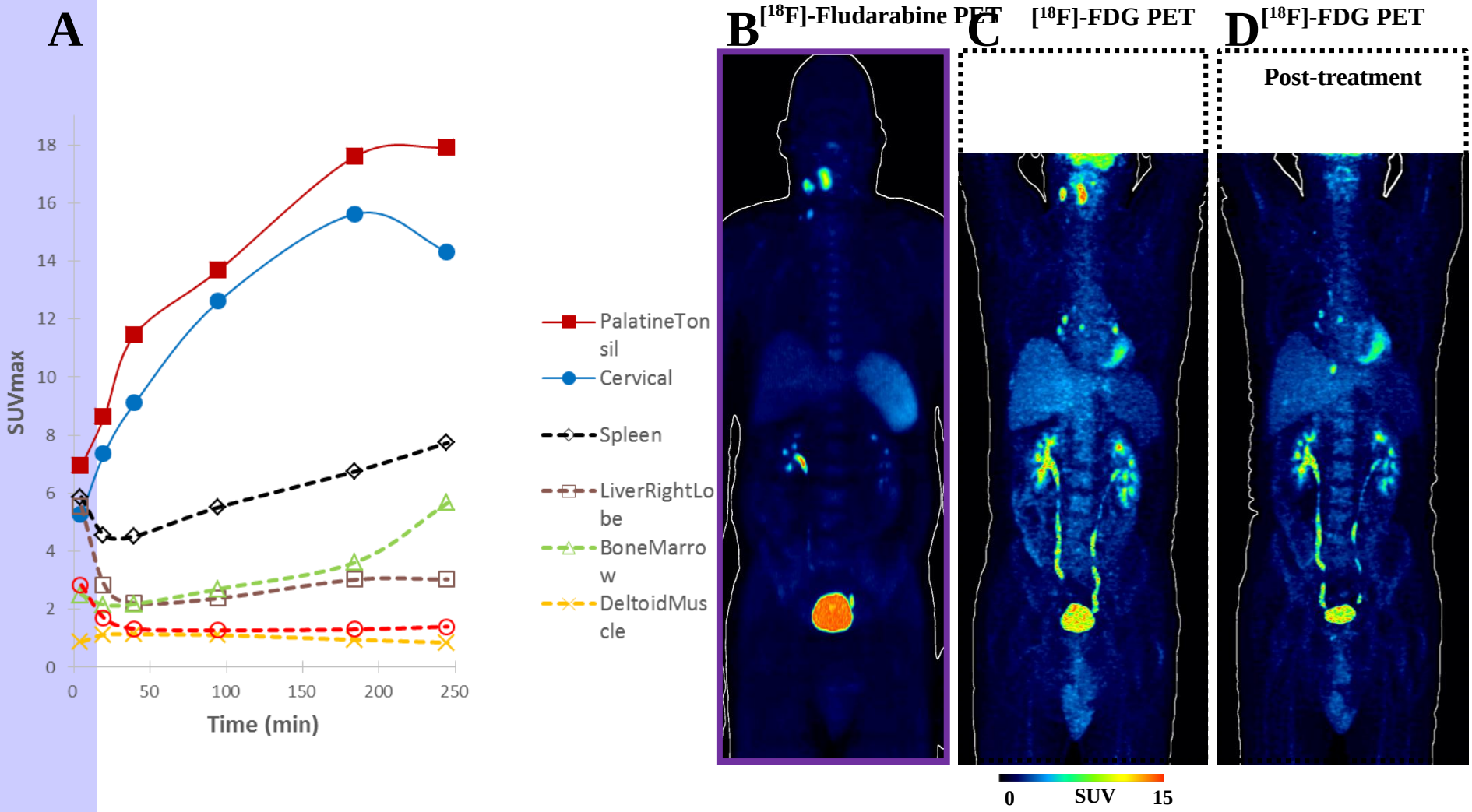
B [18F]-Fludarabine PET/CT



A. [18F]-Fludarabine uptake for 250 min post injection. **B.** Illustration of typical [18F]-fludarabine PET/CT scan (30-50 min, scan period surrounded by a border on the chart) of a CLL patient.

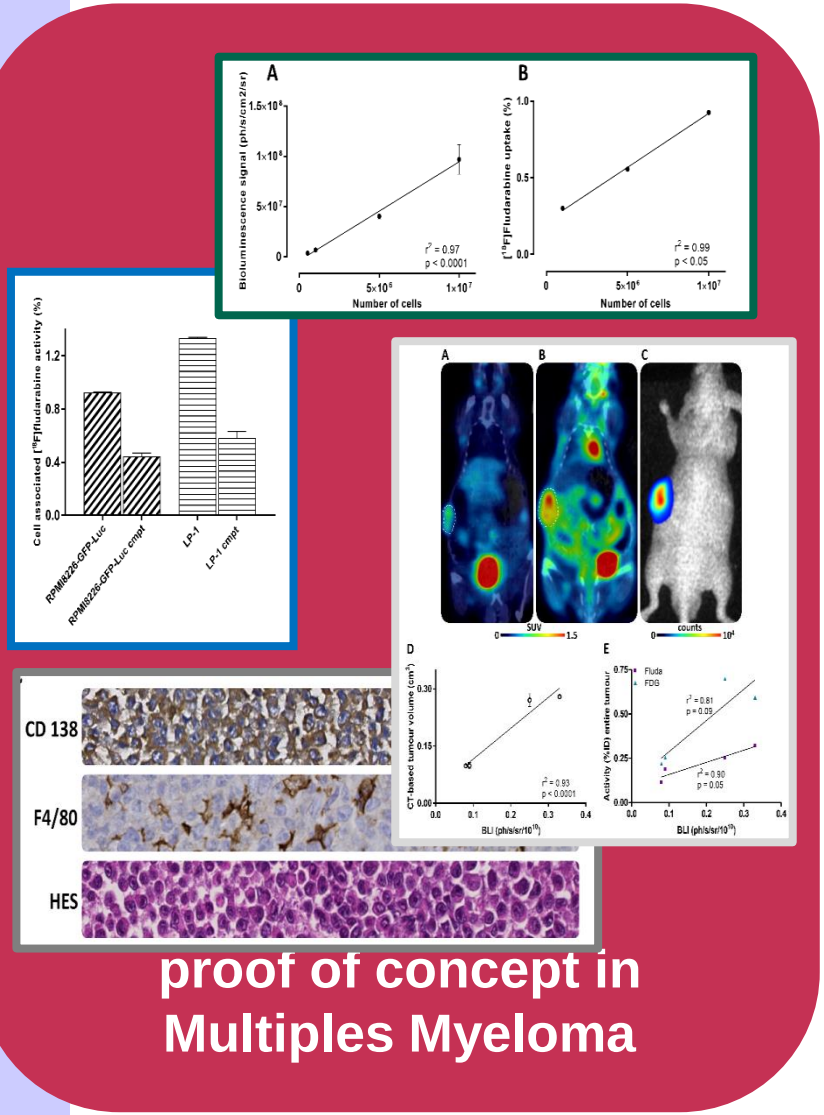
L. Barré, Cycéron, Caen

CLINICAL TRIAL • phase 1 • non-Hodgkin lymphoma (DLBCL)



Etude multicentrique financée par le PHRC 2016, CHU Caen

L. Barré, Cycéron, Caen



proof of concept in Multiples Myeloma

PLOS ONE *in press*

[^{18}F]Fludarabine-PET in a murine model of multiple myeloma

Narinée Hovhannisyan, Martine Dhilly, Martin Fidalgo, Fabien Fillesoye, Stéphane Guillouet, Brigitte Sola, Louisa Barré

Prospective Study of 3′-Deoxy-3′-^{18}F-Fluorothymidine PET for Early Interim Response Assessment in Advanced-Stage B-Cell Lymphoma

J Nucl Med 2016; 57:728–734
DOI: 10.2967/jnumed.115.166769

Heiko Schöder[1], Andrew D. Zelenetz[2], Paul Hamlin[2], Somali Gavane[1], Steven Horwitz[2], Matthew Matasar[2], Alison Moskowitz[2], Ariela Noy[2], Lia Palomba[2], Carol Portlock[2], David Straus[2], Ravinder Grewal[1], Jocelyn C. Migliacci[3], Steven M. Larson[1], and Craig H. Moskowitz[2]

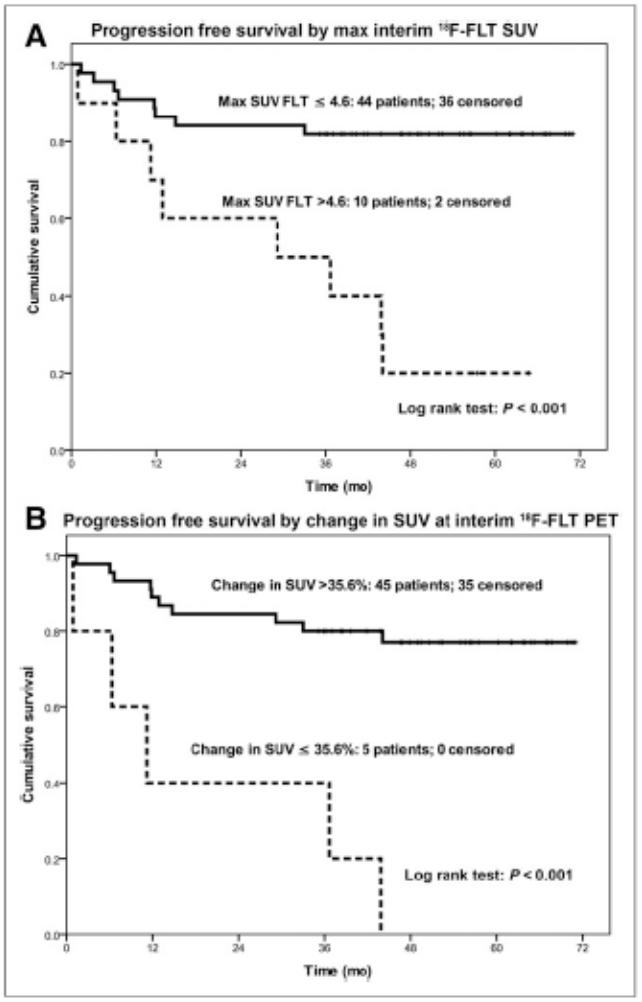


FIGURE 3. PFS as stratified by SUV_{max} on ^{18}F-FLT iPET (A) and by ^{18}F-FLT ΔSUV (B).

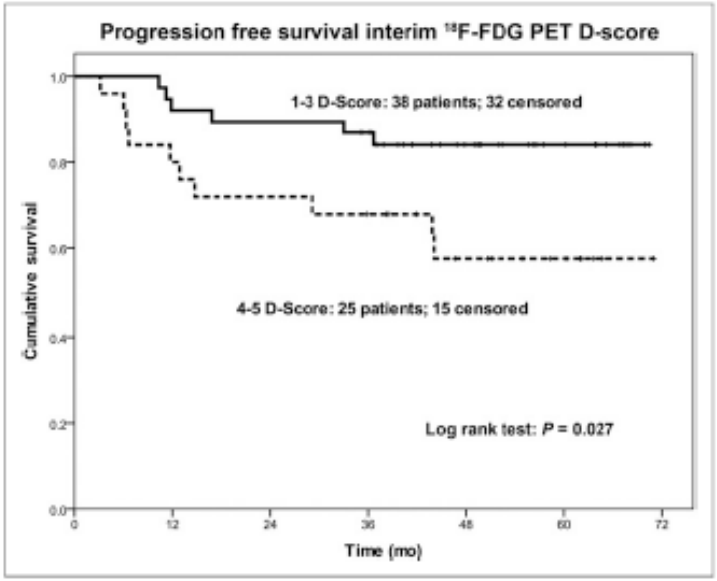


FIGURE 4. PFS as stratified by 5-point score on ^{18}F-FDG iPET.

! FDG à C4 versus FLT à C1-2
Intérêt par rapport au FDG?

Ciblage du CXCR4: théranostique

68Ga-Pentixafor/177Lu-Pentixather

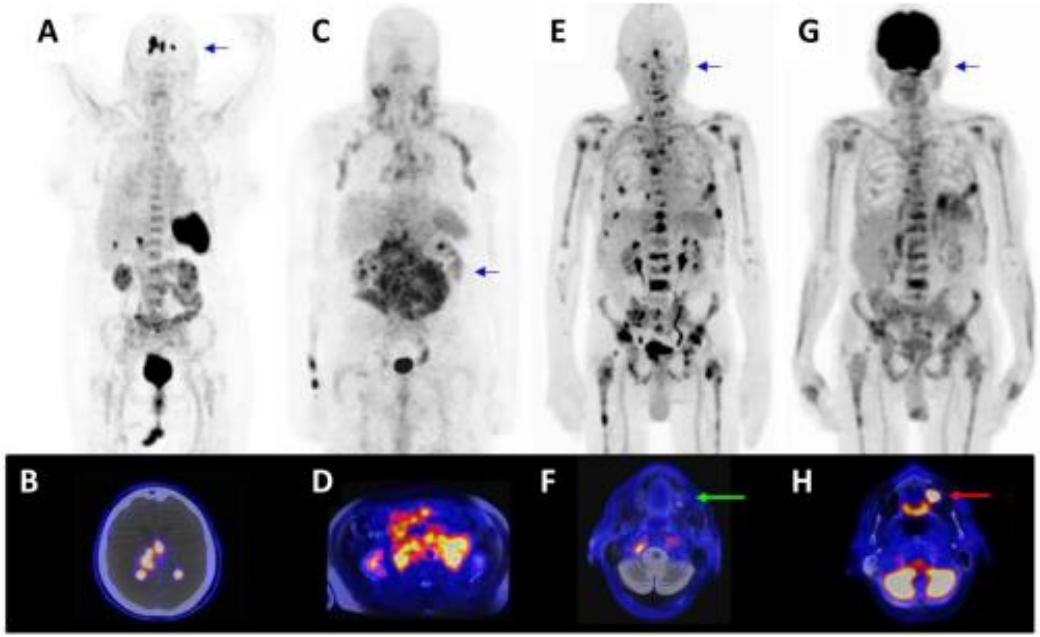


Figure 6: [^{68}Ga]Pentixafor-PET/CT in patients with lymphoproliferative malignancies. A) [^{68}Ga]Pentixafor- PET/CT in a patient with relapsed diffuse large B-cell lymphoma (PET MIP) with B) transaxial PET/CT image at the level of the brain. C) [^{68}Ga]Pentixafor-PET/MR in a patient with chronic lymphocytic leukemia and suspected transformation into aggressive B-cell lymphoma (PET MIP) with D) transaxial PET/MR image at the level of the kidneys. E) [^{68}Ga]Pentixafor PET/MR in a patient with multiple myeloma (PET MIP) with F) transaxial image at the level of the maxilla demonstrated no uptake in the maxilla (green arrow). G) Corresponding [^{18}F]FDG PET/MR (PET MIP) of the patient depicted in E) and F) with corresponding H) [^{18}F]FDG PET/MR transaxial image at the level of the maxilla (red arrow, same region as depicted in F) showed [^{18}F]FDG uptake in the maxilla/ floor of the maxillary sinus, most likely caused by a dental infection.

Imagerie de la résistance?

Immuno-TEP: imagerie spécifique

compagnon/théranostique

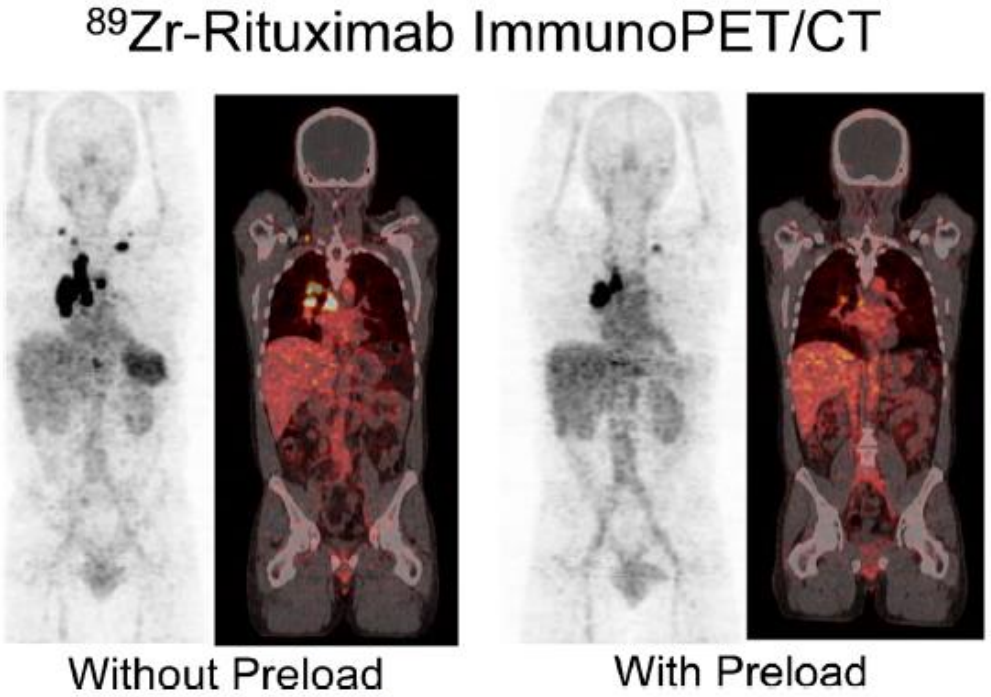
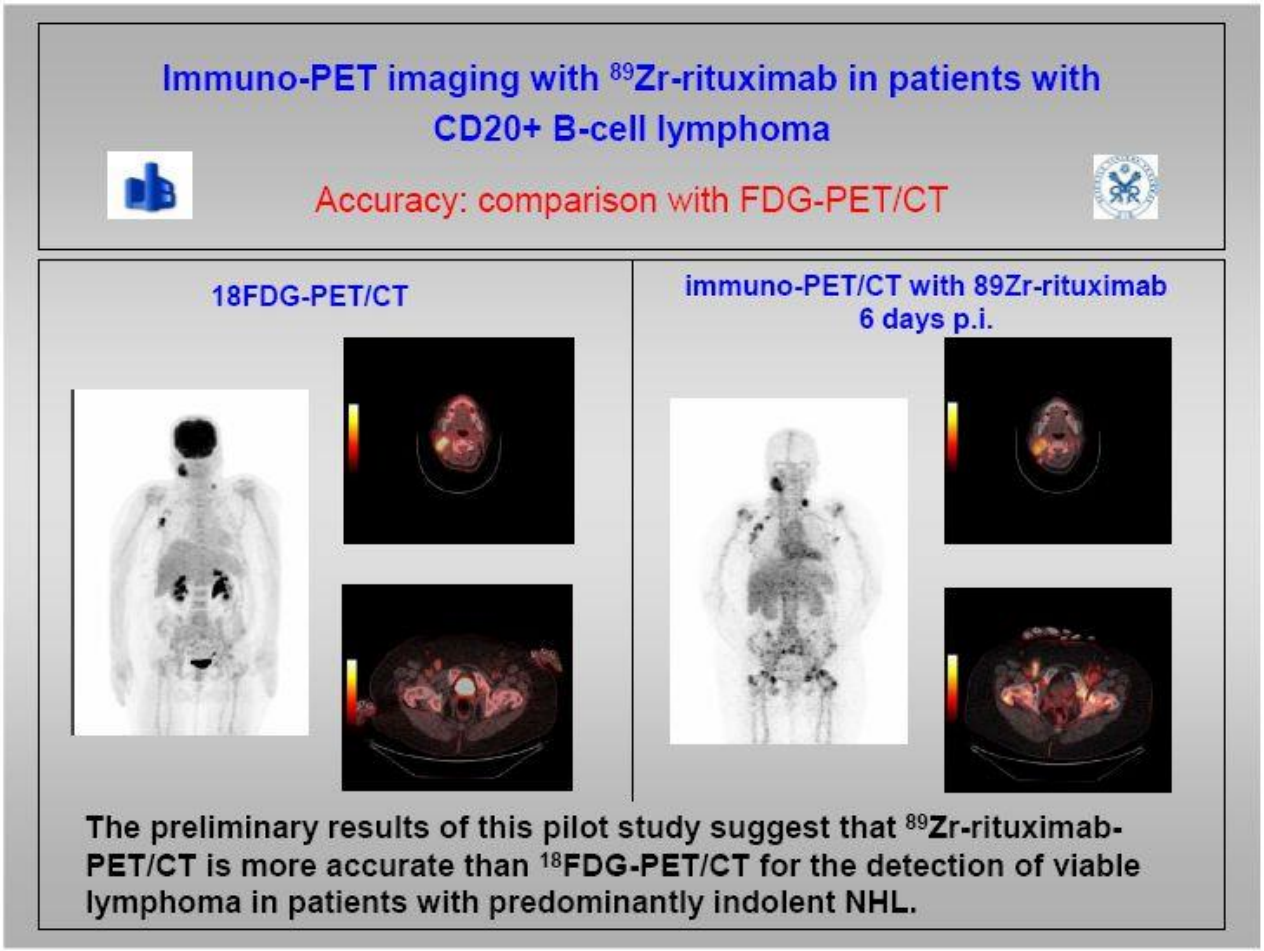


Fig. 6 Biodistribution of ^{89}Zr-rituximab in an adult male with B cell-depleted grade II follicular lymphoma. PET/CT imaging was performed 6 days after injection of ^{89}Zr-Rituximab with or without a preload of unlabeled rituximab. Tumor targeting is higher without a preload of unlabeled rituximab. Reprinted with permission [119]

England, Eur J Nucl Med 2017

Immuno-TEP: imagerie plus sensible que la TEP-FDG?



Muylle, Menton, 2011

Anti-CD30-89Zr et Hodgkin

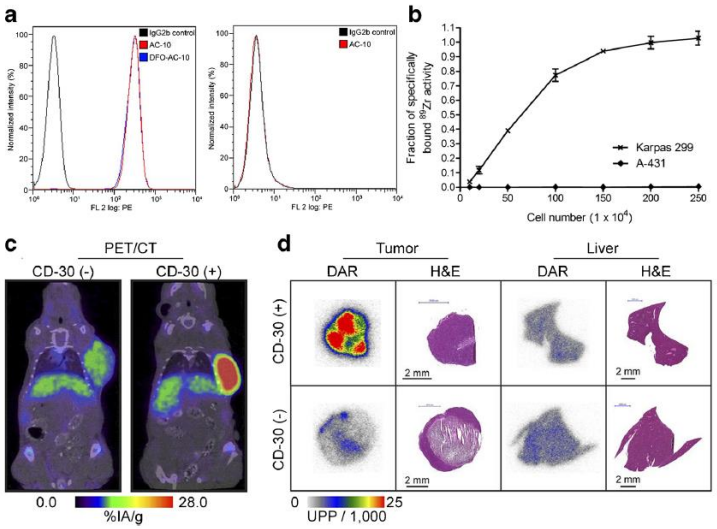
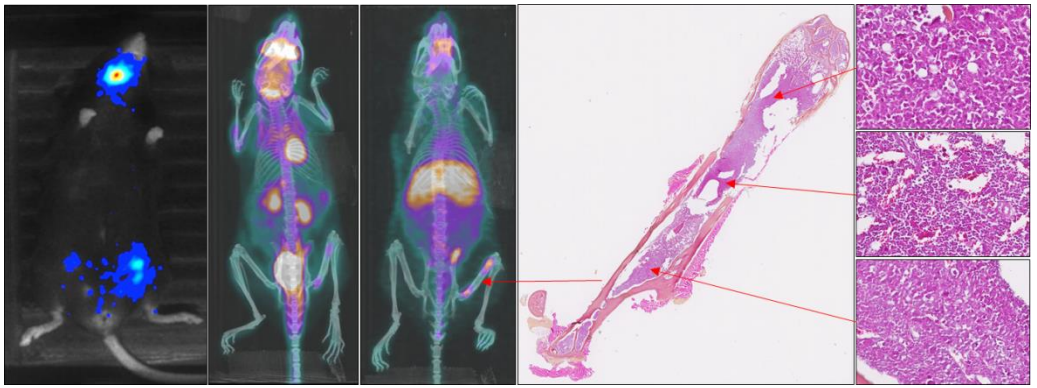


Fig. 4 PET imaging of ^{89}Zr-DFO-AC-10 in CD30 expression in xenograft mice. **a** Flow cytometry was used to determine the binding specificity of AC-10 and DFO-AC-10 to CD30-positive Karpas 299 cells. The x-axis denotes that detector (FL2) was used to detect the dye (PE) and the data are shown in a log plot. **b** In vitro saturated binding assay of ^{89}Zr-DFO-AC-10 to CD30-positive Karpas 299 cells and CD30-negative A-431 cells. **c** PET/CT images of two representative mice bearing CD30-positive Karpas 299 and CD30-negative A-431 tumors at 144 h after injection. **d** Digital autoradiography and immunohistochemistry were used to evaluate the biodistribution of ^{89}Zr-DFO-AC-10 in tumor and liver of both mouse models (*H&E* hematoxylin and eosin, *DAR* digital autoradiography, *UPP* units per pixel). Reprinted with permission [114]

England, Eur J Nucl Med 2017

Anti-CD138-64Cu et Myélome



Bailly, Oncotarget soumis

Conclusion

- FDG seul traceur recommandé en clinique
- Amélioration de la sensibilité de la TEP dans le myélome: 18F-choline, 11C-MET
- Amélioration de la sensibilité de la TEP dans les lymphomes indolents et exploration des atteintes du SNC: 18F-Fludarabine
- Amélioration de la spécificité de la TEP: 18F-Fludarabine
- Intérêt potentiel de la 18FLT dans l'évaluation thérapeutique des lymphomes
- Traceurs théranostiques pour une imagerie de haute sensibilité et spécifique mais technologie plus complexe: immuno-TEP, ciblage CXCR4
- Essais cliniques nécessaires
- Validation des approches « dual-tracers » et des nomogrammes pronostiques