CANOA 2017

Breast cancer and immuno….PET

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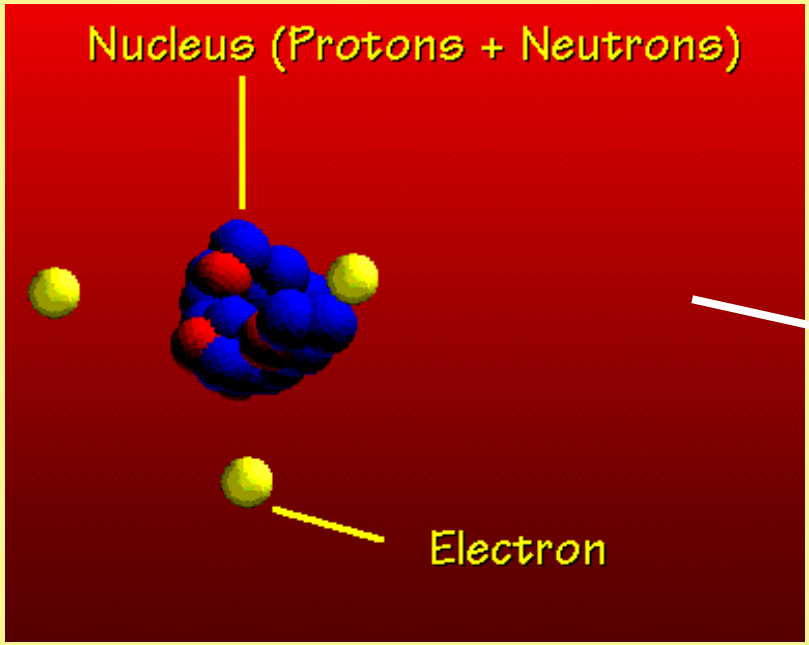
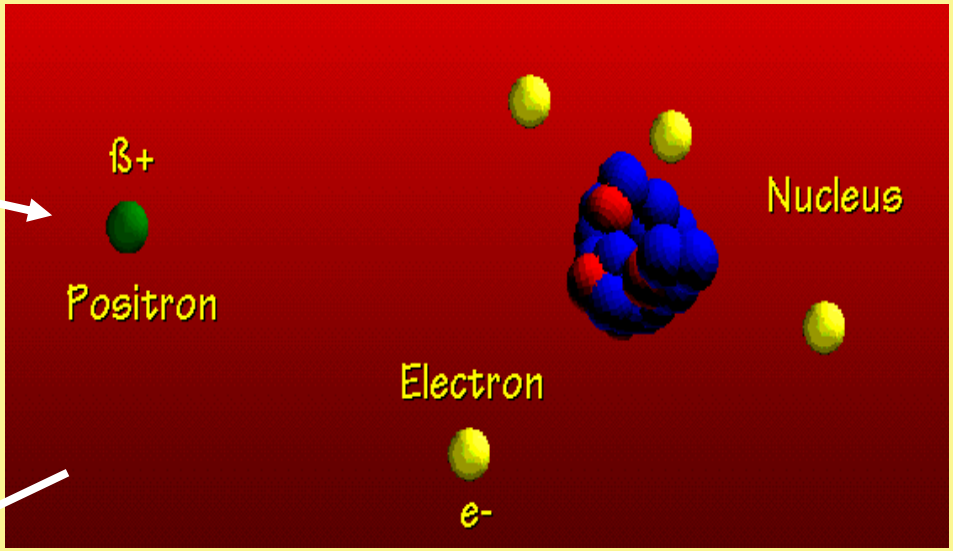
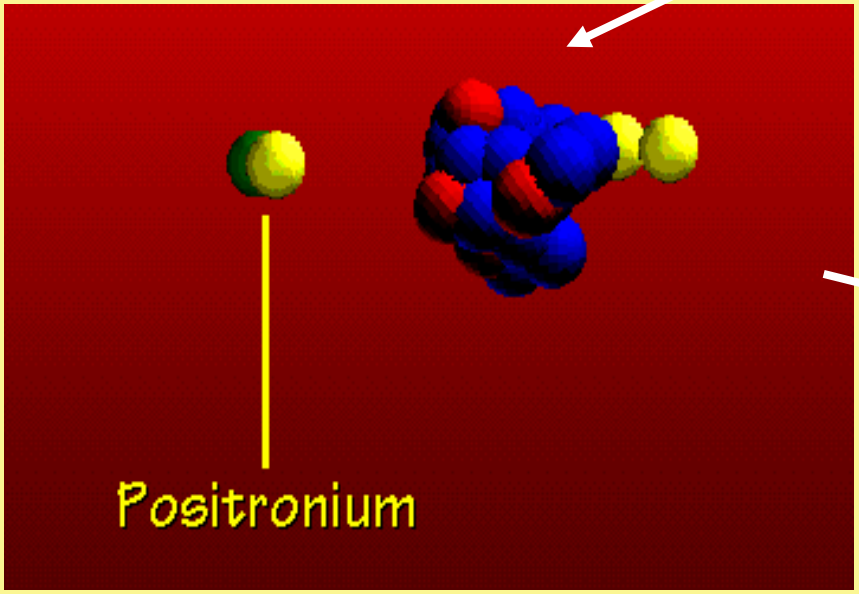
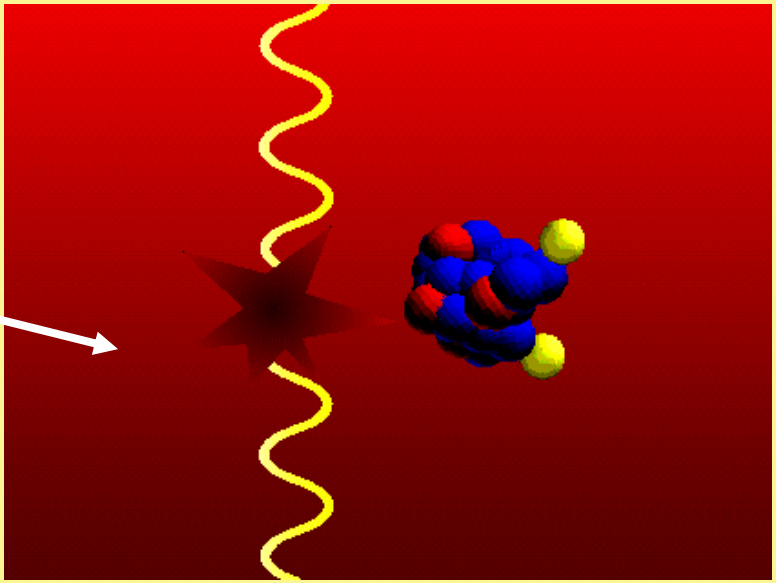
Annichilazione del positrone

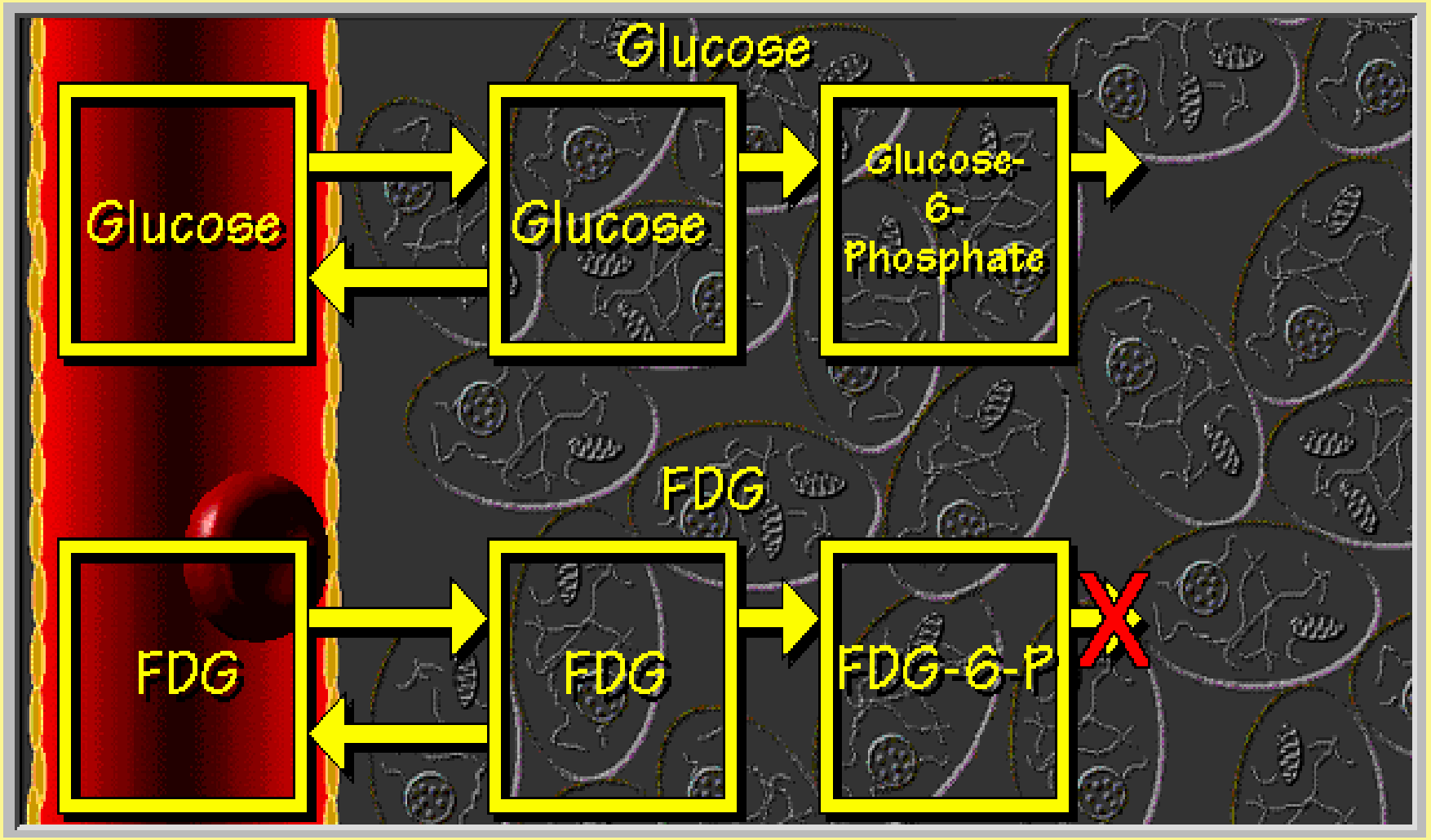




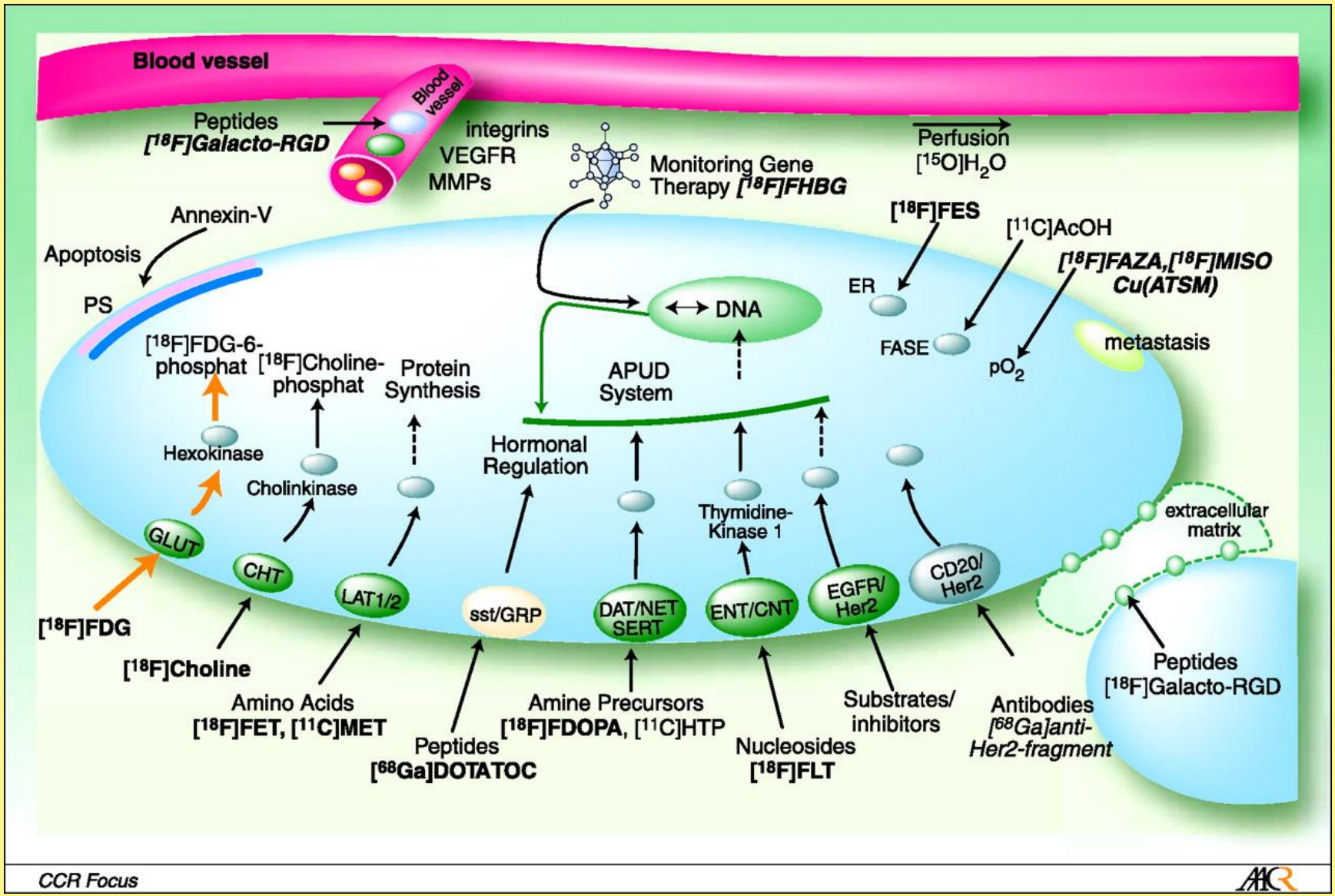




L’ FDG iniettato al paziente agisce come tracciante della glicolisi e si accumula maggiormente in sedi ove questa via metabolica è attivata in misura abnorme rispetto al consueto metabolismo aerobico, cosa che avviene in varie condizioni patologiche, come ad esempio nel contesto di tumori primitivi e di loro metastasi.



Selected targets and corresponding nuclear imaging probes already established for nuclear molecular imaging in the clinic or currently under assessment in clinical studies

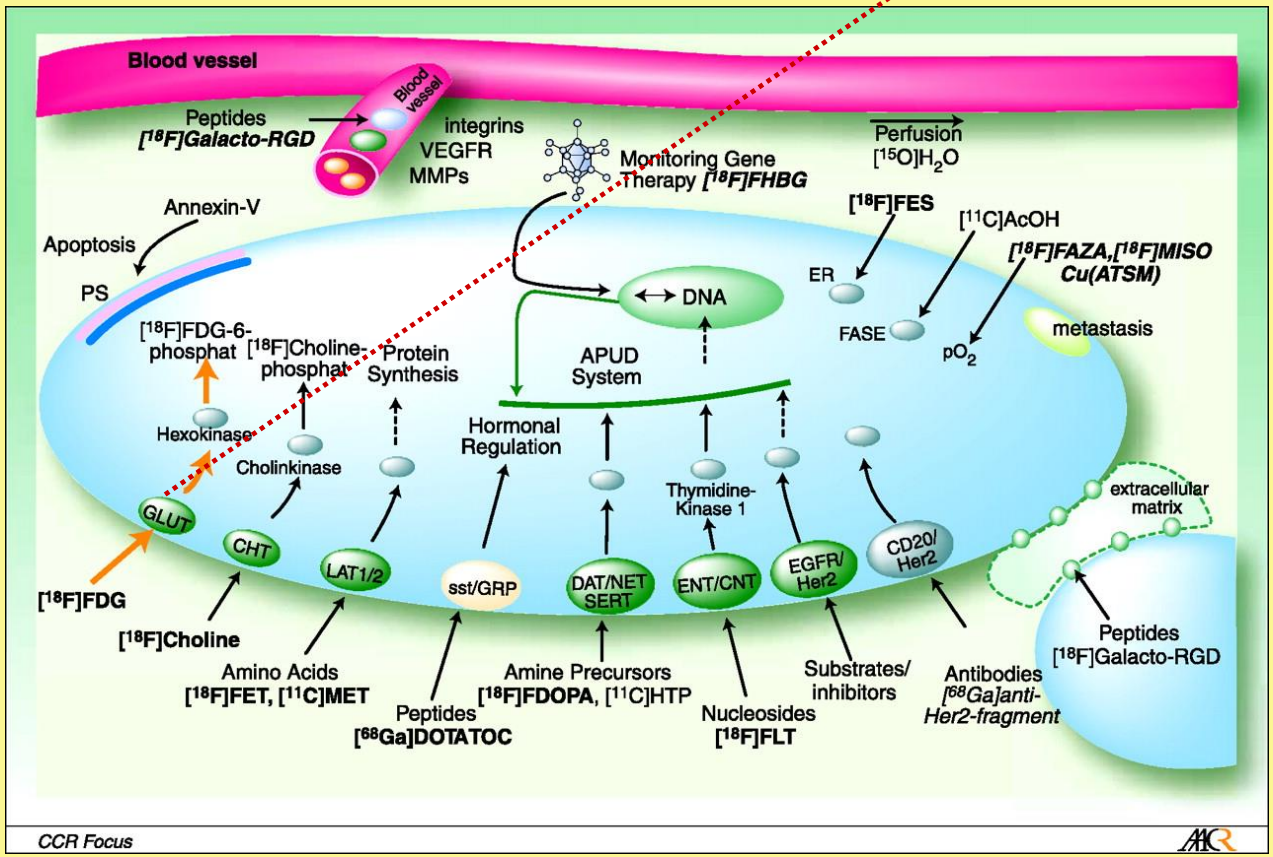


Wester H Clin Cancer Res 2007;13:3470-3481

Clinical Cancer Research

Selected targets and corresponding nuclear imaging probes already established for nuclear molecular imaging in the clinic or currently under assessment in clinical studies

E' veramente l'unica informazione oncologicamente rilevante?



Wester H Clin Cancer Res 2007;13:3470-3481

Clinical Cancer Research

Breast Cancer and Micad

Molecolar Imaging Contranst Agent Database

1: Human Studies: PET18F -> 16α-[18F]Fluoro-17β-estradiol

2: Background: PET64Cu -> HSDAVFTDNYTKLRKQ-NIe-AVKK-(3-OCH3,4-OH)-FLNSSV-GABA-L-(Dap-(BMA)2)-64Cu

3: Background: Multimodal64Cu, quantum dot (QD705) -> 64Cu-1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid-quantum dot-vascular endothelial growth factor

4: Background: PET64Cu -> 64Cu-DOTA hu4D5v8 (scFv-CH2-CH3)2

5: Human Studies: PET18F -> [18F]Fluorocholine

6: Background: PET64Cu -> 64Cu-N,N'-Bis(S-benzoyl-thioglycoloyl)diaminopropanoate-KRAS-PNA-d(Cys-Ser-Lys-Cys)

7: Human Studies: PET18F -> 3'-Deoxy-3'-[18F]fluorothymidine

8: Rodents: PET18F -> 16α-[18F]Fluoro-17β-estradiol -> Animal Studies

9: Background: SPECT99mTc -> 99mTc-N,N'-Bis(S-benzoyl-thioglycoloyl)diamidopropanoyl-KRAS-PNA-d(Cys-Ser-Lys-Cys)

10: Human Studies: PET18F -> [18F]Fluoro-2-deoxy-2-D-glucose

11: Rodents: PET64Cu -> 64Cu-1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-interleukin-18-binding protein-Fc -> Animal Studies

12: Rodents: PET68Ga -> 68Ga-Trastuzumab F(ab') fragment -> Animal Studies

13: Background: PET11C -> l-[methyl-11C]Methionine

14: Background: SPECT99mTc -> 99mTc-glutamate peptide 3-aminoethyl estradiol

15: Background: PET18F -> 5-[(E)-2-(4-[18F]Fluorophenyl)ethenyl]-1,3-benzenediol

16: Background: PET89Zr -> 89Zr-Labeled trastuzumab, a humanized monoclonal antibody against epidermal growth factor receptor 2

17: Background: PET64Cu -> 64Cu-1,4,7-Triazacyclononane-1,4-diacetate-8-aminooctanoic acid-Gln-Trp-Ala-Val-Gly-His-Leu-Met-NH2

18: Background PET11C -> [O-11C-methyl]4-N-(3-Bromoanilino)-6,7-dimethoxyquinazoline

19: Background: PET11C -> (S)-6-[(4-Chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-[11C]methyl-1H-benzotriazole

20: Background: PET64Cu -> 64Cu-1,4,7,10-Tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-interleukin-18-binding protein-Fc

21: Rodents: PET64Cu -> 64Cu-DOTA hu4D5v8 (scFv-CH2-CH3)2 -> Animal Studies

22: Background: PET18F -> [18F]Fluoro-2-deoxy-2-D-glucose

23: Rodents: PET11C -> N-[N-[(S)-1,3-Dicarboxypropyl]carbamoyl]-S-[11C]methyl-L-cysteine -> Animal Studies

24: Rodent an humans: PET11C -> [11C]Choline -> Animal Studies

25: Human Studies: PET18F -> 1-(2'-Deoxy-2'-[18F]-fluoro-β-D-arabinofuranosyl)thymine

NB) Possibilità di utilizzo del Na-18F, per la ricerca di metastasi ossee o per studi MIXED con FDG.

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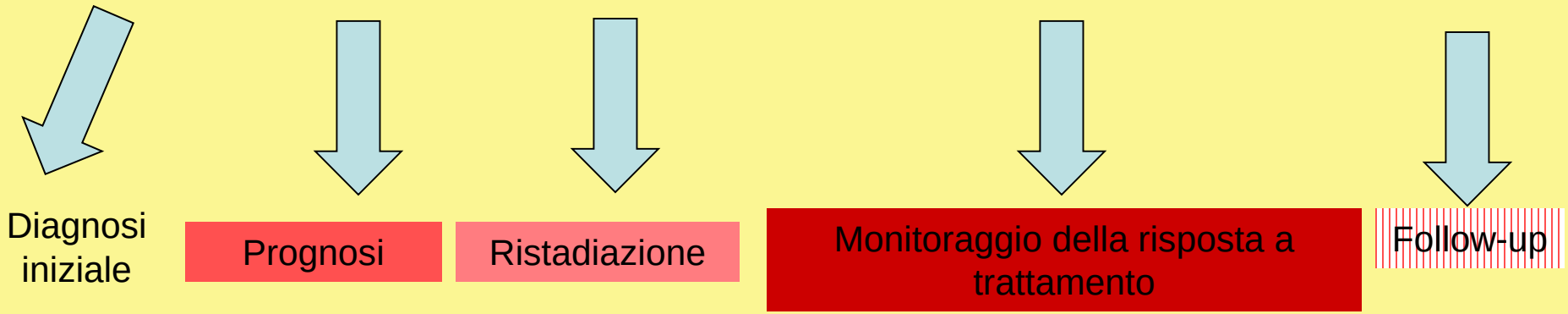
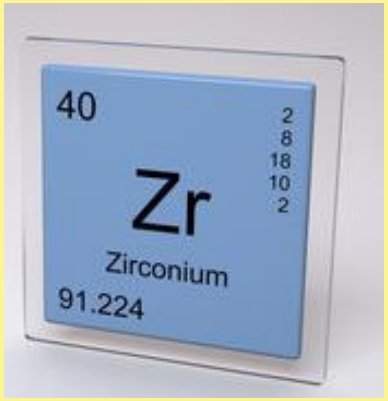
Fare la Pet?...Quando la PET?...Quale PET?

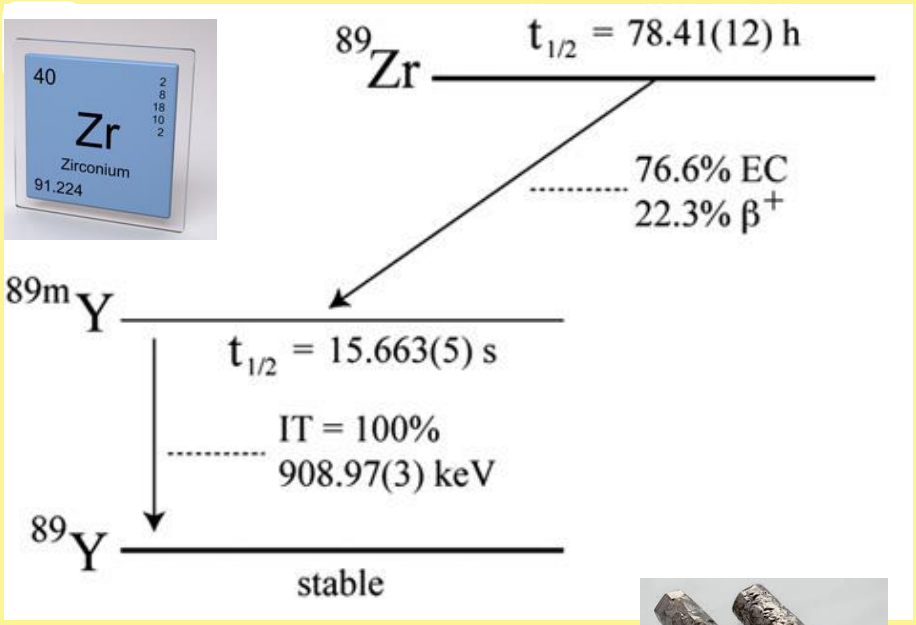




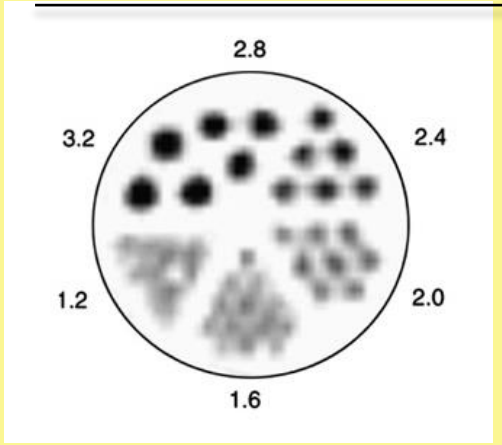
Nuova Agenda di lavoro

- ^{89}Zr Nuclear Propieties, Production
- ^{89}Zr Chemistry a Labelling
- ^{89}Zr Application

Zirconium-89 [^{89}Zr]



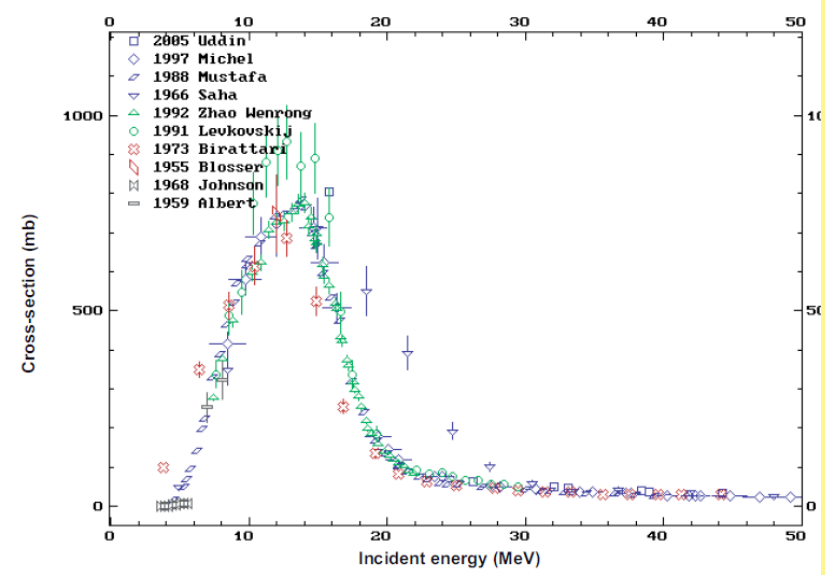
Half –life	78.4 h
Decay Mode	ε= 76.6% β^+= 22.3%
E(β^+)	395.5 kev
E(γ)	511 KeV 909.2 Kev
R_{ave} (β^+)	1.2 mm



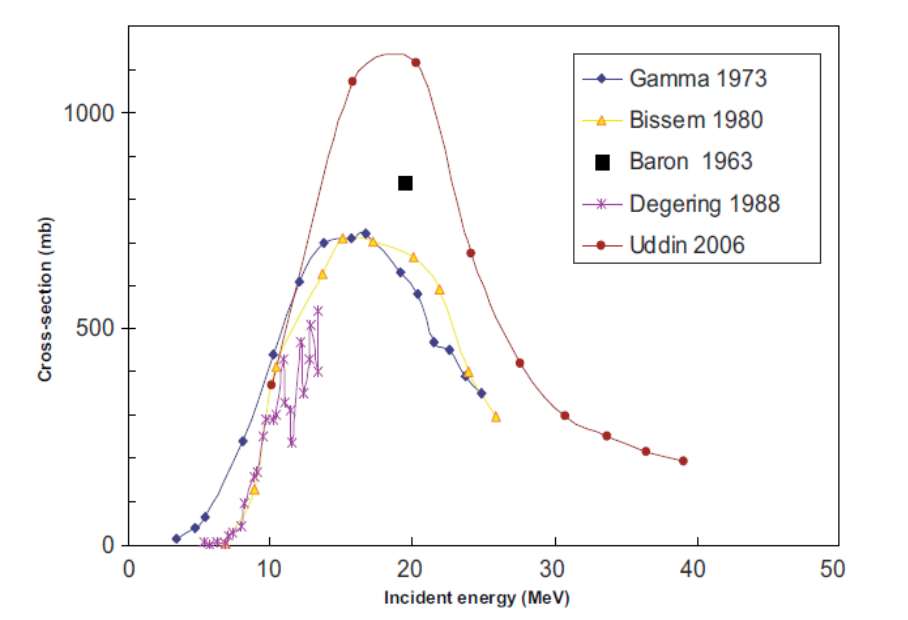
M.Deri *et al Nucl. Med. Biol.,2013,40,3-14*

Nuclear reaction for ^{89}Zr production

- ^{89}Y(p,n)^{89}Zr
- ^{89}Y(d,2n)^{89}Zr
- ^{nat}Sr(α,xn)^{89}Zr



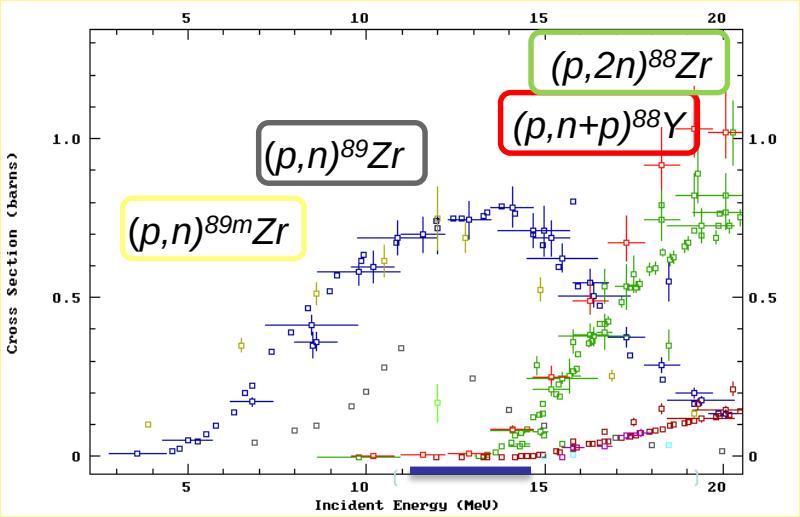
Excitation function for ^{89}Y(d,2n)^{89}Zr reaction



Excitation function for ^{89}Y(p,n)^{89}Zr reaction

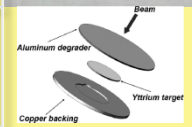
^{89}Zr with medical cyclotron

^{89}Y(p,n)^{89}Zr



Competitive Nuclear Reaction:
^{89}Y(p,n)^{89m}Zr (>3.8 MeV, 4.2 m)
^{89}Y(p,2n)^{88}Zr (>13.076 MeV, 83.4 d)
^{89}Y(p,pn)^{88}Y (>11.609 MeV, 106.6 d)

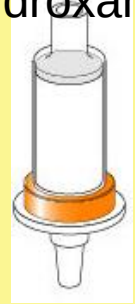
Target for ^{89}Zr production

		Beam Energy (MeV)	Y foil thickness (mm)	Beam parameter	Yield (MBq/μAh)	Radionuclidic Purity	
DeGrado*	2016	14	2M $Y(NO_3)_3$	2h@40μA	4.4	99%	 Mayo Clinic
Wooten	2013	14.7	0.64	4h@15μA	55.5	99.998%	 Washington Univeristy
Cicoria	2011	12.6	0.30	1h@20μA	70.5	99.9995%	 S.Orsola Hospital
Holland	2005	15	0.10	5h@15μA	55	99.9%	 Memorial Sloan Kattering Center
Verel	2003	14	0.035 sputtered	1h@20μA	80.5	99.99%	 Negrar Hospital
Kandil	2007	12.6	13 ($Y_2O_{3)}$	5h@2μA	27.9	99.9%	 Julich Center

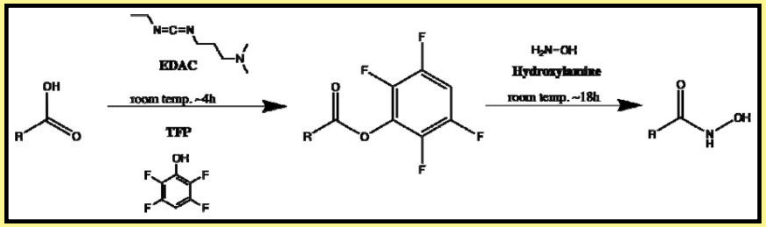
^{89}Zr Recovery

Negrar EZAG module used for processing
Target material and riformulation of ^{89}Zrsolution

Cation exchange resin funzionalized to hydroxamic groups

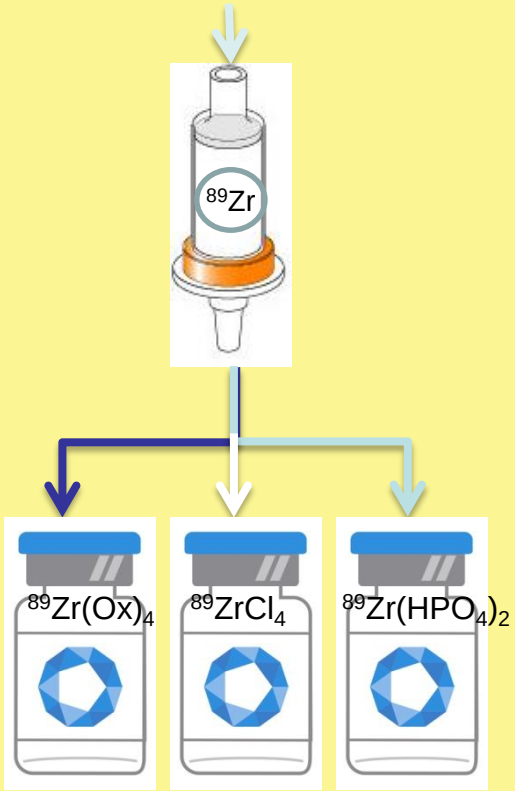


- Irradiated Y target
- Target dissolution
- ^{89}Zr trapping on purification column
  - Washing ^{88}Y removal
  - Recovery solution



^{89}Zr Formulation

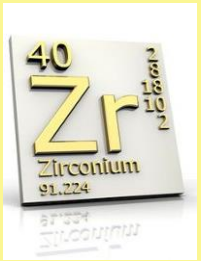
HOX 1M / HCl 1M /PBS 1.2 M



- **Oxalic** in large amounts can lead to decalcification of blood and acute kidney falure, by precipitation of solid Ca. EMA (tox Ox 25 mg/Kg).
- The **Oxalic** concentration (usually 1M) are **close to saturation** (1.1 M) than it will be difficult to evaporate or reconstitute in a more concentrate solution.
- **Cloridric** precursor, **no standard procedure** to labelling Antibody are available.
- Cloridric, **need to be removed** before Mab labelling.
- **PBS ideal** for labelling Antibody.
- **Low recovery 80%.**
- **All the eluent solution** need to be evalueted by SA and **ICPMass** to minimize the metal contaminants.

Lin et al Appl.Rad.,2016,107,317-322
DeGrado et al JNM&B.,2016,43,97-100

^{89}Zr Coordination Chemistry



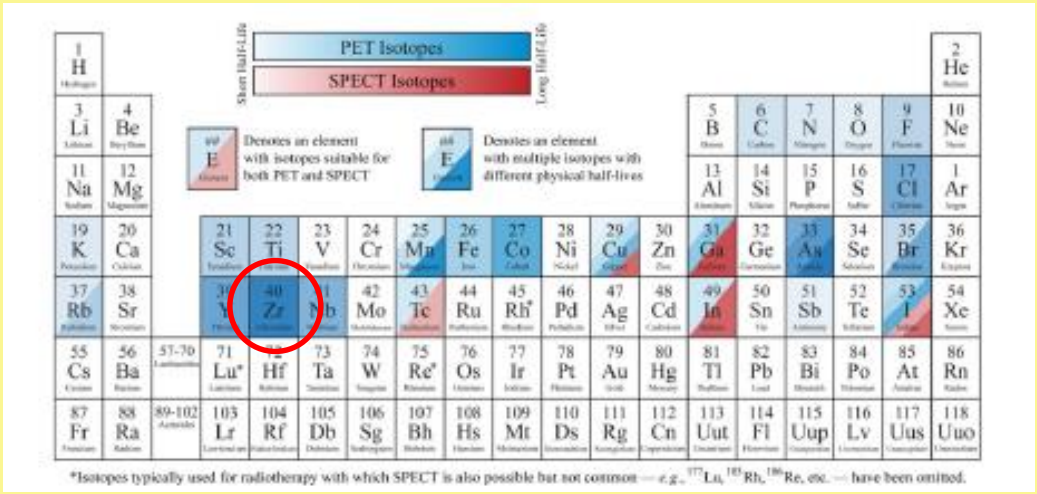
Zr is a **IV group metal**.

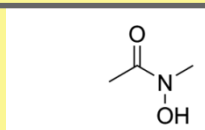
Zr exist on **water solution on Zr^{+4}**.

Cation relatively large , highly charged ion "**Hard ion"**

Complexes with **high coordination numbers**

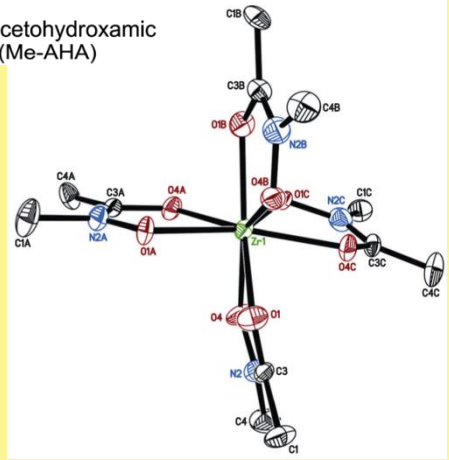
Prefer **Ligands** wit **Oxygen donors** (charged or not)





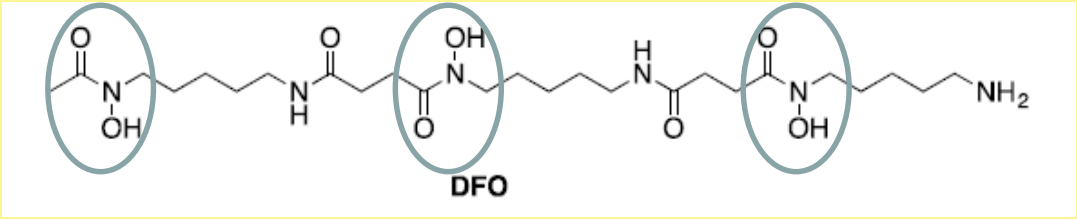
N-methyl acetohydroxamic acid (Me-AHA)

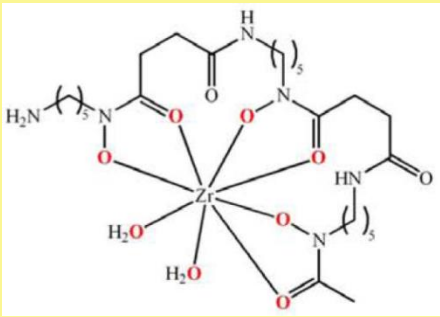
$Zr(Me\text{-}AHA)_4$



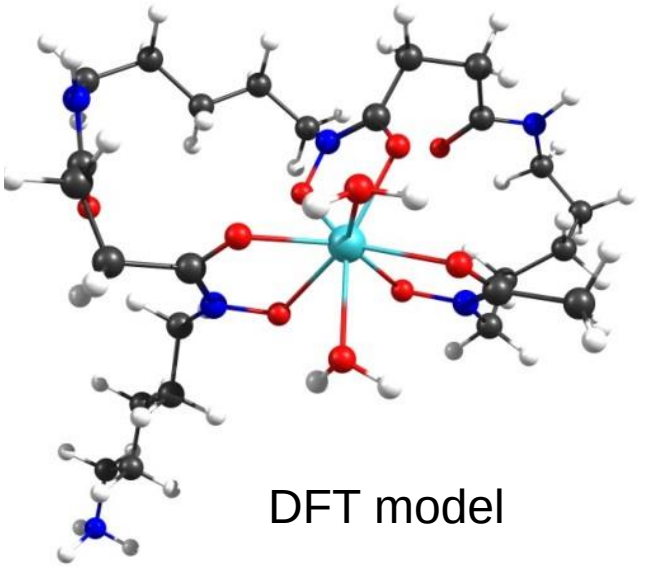
Guerard et al Chem.Comm.,2013,49,1002-1004

Desferrioxamine B (DFO)





$[Zr(DFO)(H_2O)_2]^{2+}$



DFT model

DFO is a chelant wich contain hydroxamate groups hexadentate three anion chelator.

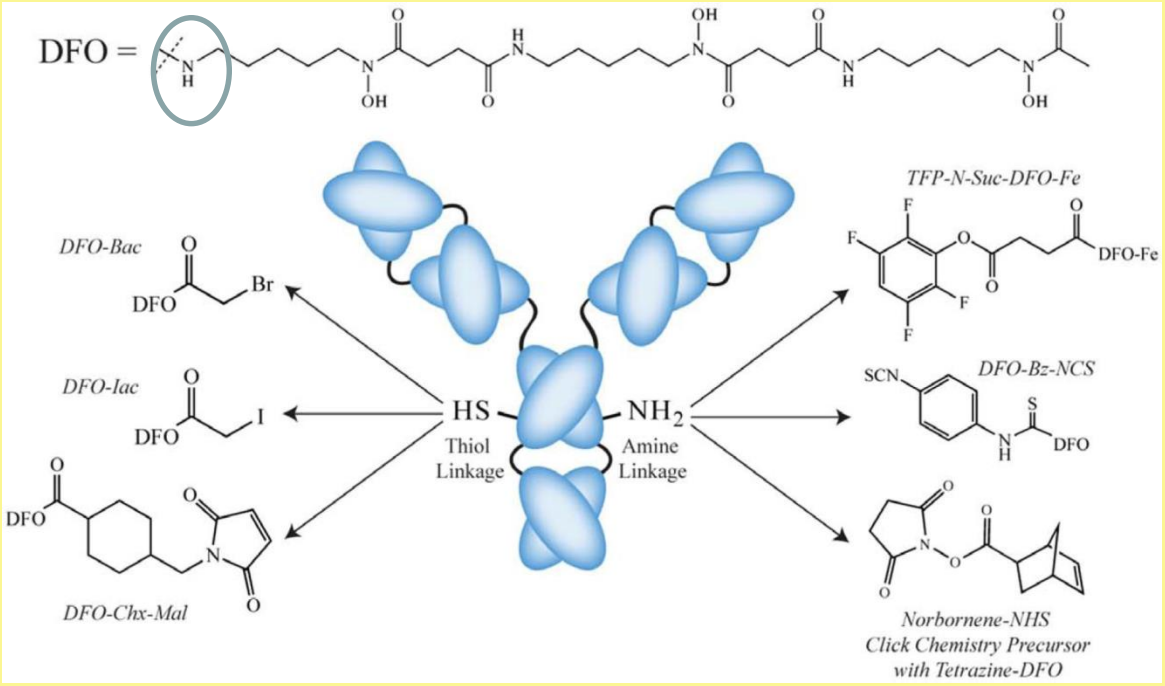
Deprotonation of hydroxy groups result hexadentate ligand.

Are naturally created from Streptomyces bacteria. FDA aprroved DFO like a drug for acute iron intoxication.

Make less concerns if it will be dissociated from mAb.

Holland et al Nucl.Med,2010,51,1293

DFO Conjugation



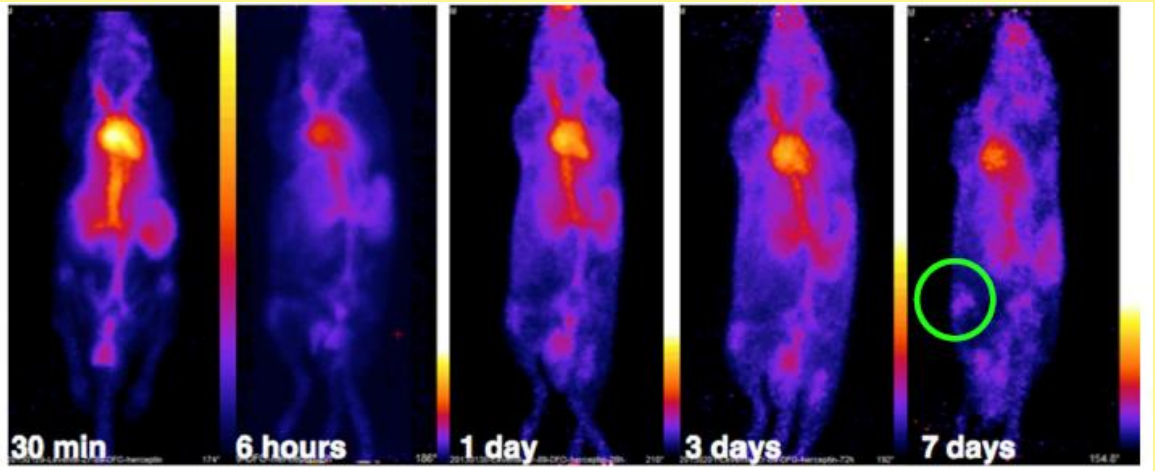
- DFO present a primary ammino group can be functionalizated.
- The modify DFO can be used to linkage Thiol goup or Amine goups present on biological molecules.

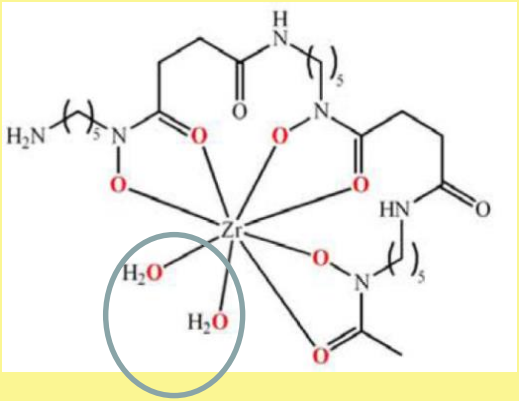
Typical reaction condition:

- DMSO solvent
- 3-10 fold excess of ligand
- 30-37 °C
- PD10 purification

M.Deri et al Nucl.Med.&Biol,2013,40,3-14

DFO Stability





[^{89}Zr]ZrDFOTrastuzumab

$^{89}Zr^{4+}$ high bone affinity.

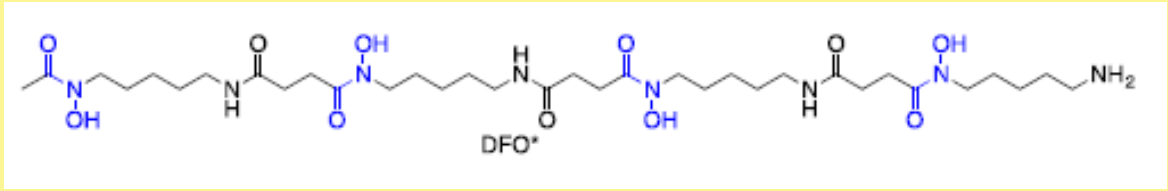
^{89}Zr can be also accumulated on liver and spleen due to the colloidal form.

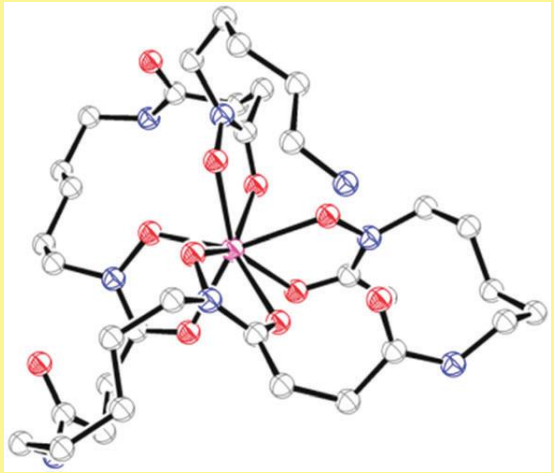
Water molecule in Zr coordination sphere lower the complex stability.

Zr^{4+} ions prefere to be fully Oth structure in sigle coordination sphere.

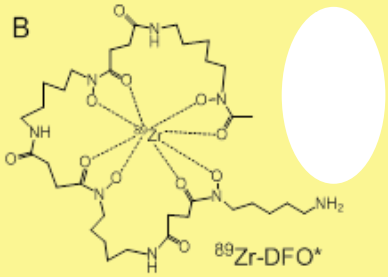
M.Ma et al Dalton Tr.,2015,44,4884

DFO*





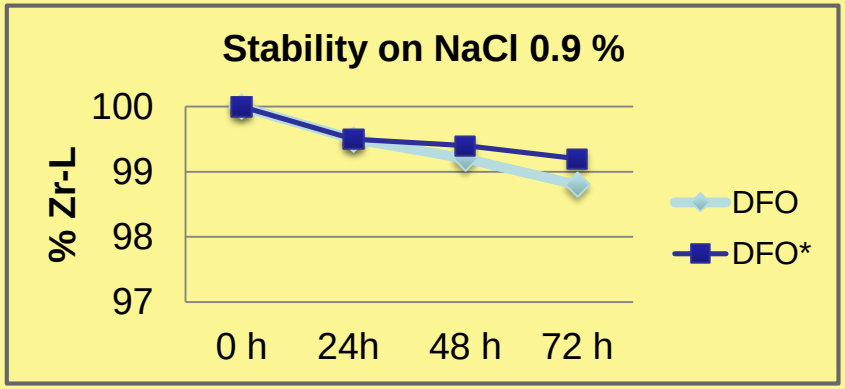
DFT model



DFO* is a chelant wich contain four hydroxamate groups for Octadentate geometry.

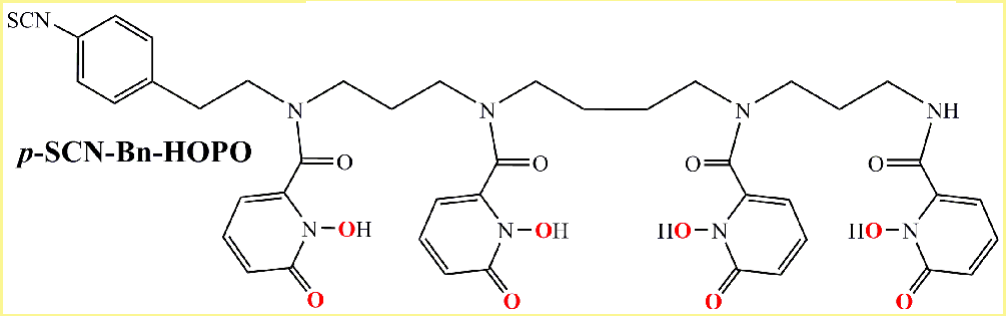
Deprotonation of hydroxy groups result four anion ligand.

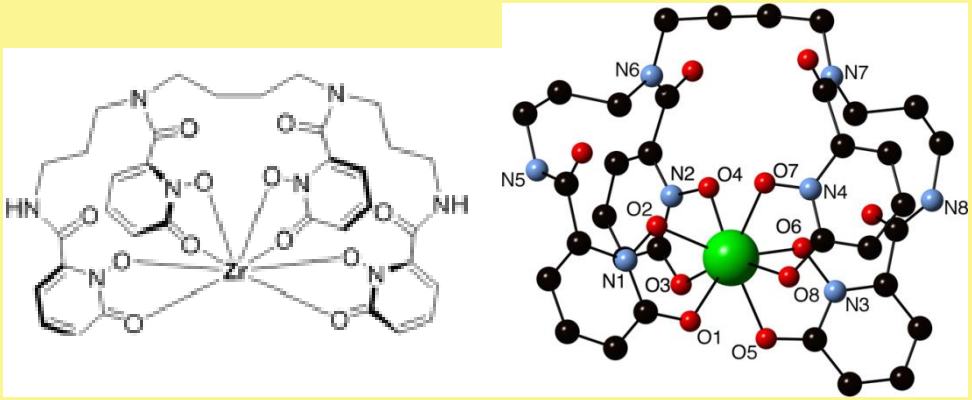
Similar reactivity of DFO.



M. Patra et al Chem.Comm,2014,50,11523-11525

HOPO Ligand





Crystal structure

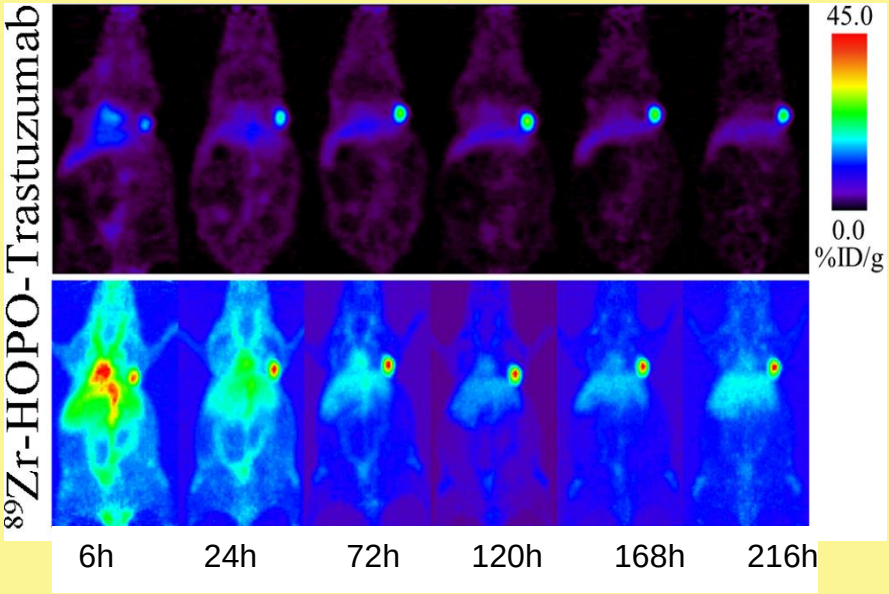
HOPO is a Octadentate chelator with hydroxypyridinone groups ligand for metal binding Zr^{4+} ion.

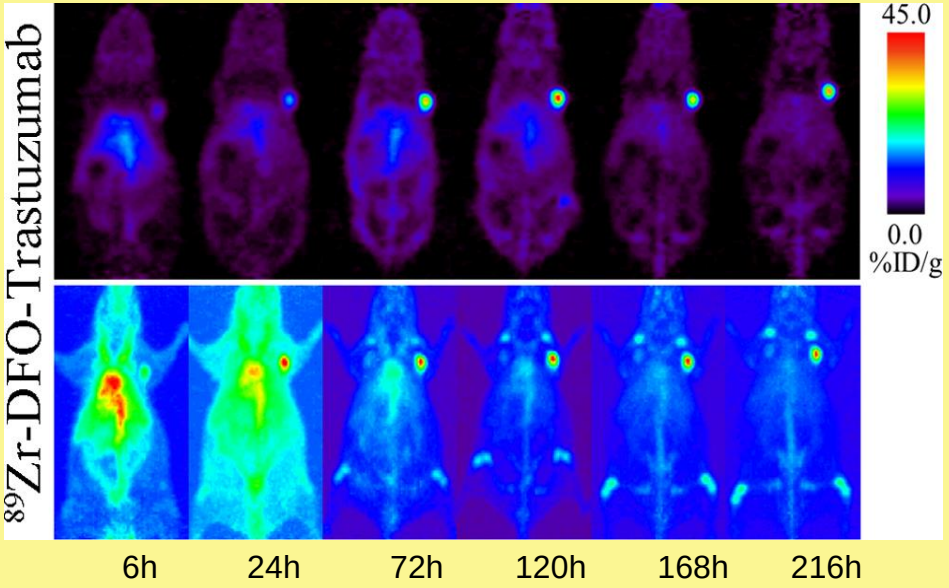
HOPO comes from Actinide sequestration licterature, was studied for Pu^{4+} stable complex.

HOPO present four hydroxypyridone groups with hard oxygen donors, appropriate for Zr^{4+} binding.

M. Deri et al BioConj.Chem,2015,26,2579-2591

HOPO Stability



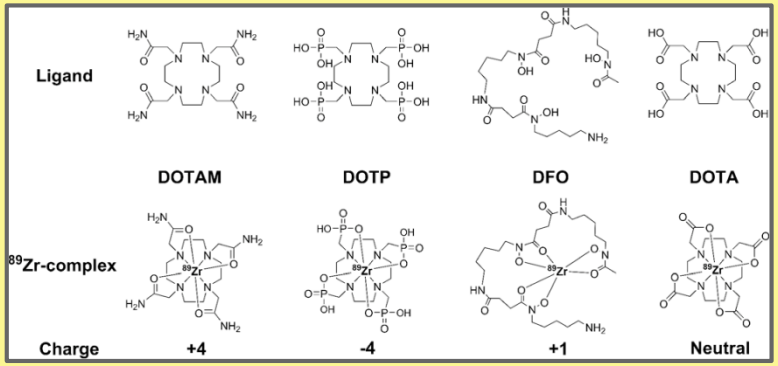


MicroPET images of ^{89}Zr-HOPO-Trastuzumab and ^{89}Zr-DFO-Trastuzumab in female athymic nude mice with BT474 xenografts on right shoulders inj (9.25-9.99 MBq) in 200 µL 0.9 %of sterile saline.

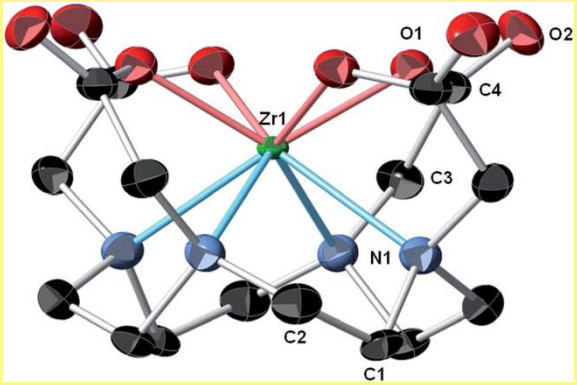
Both compounds show good tumor to background contrast, but ^{89}Zr-DFO-Trastuzumab shows evidence of bone uptake suggestiong in vivo release of $^{89}Zr^{4+}$

M. Deri et al BioConj.Chem,2015,26,2579-2591

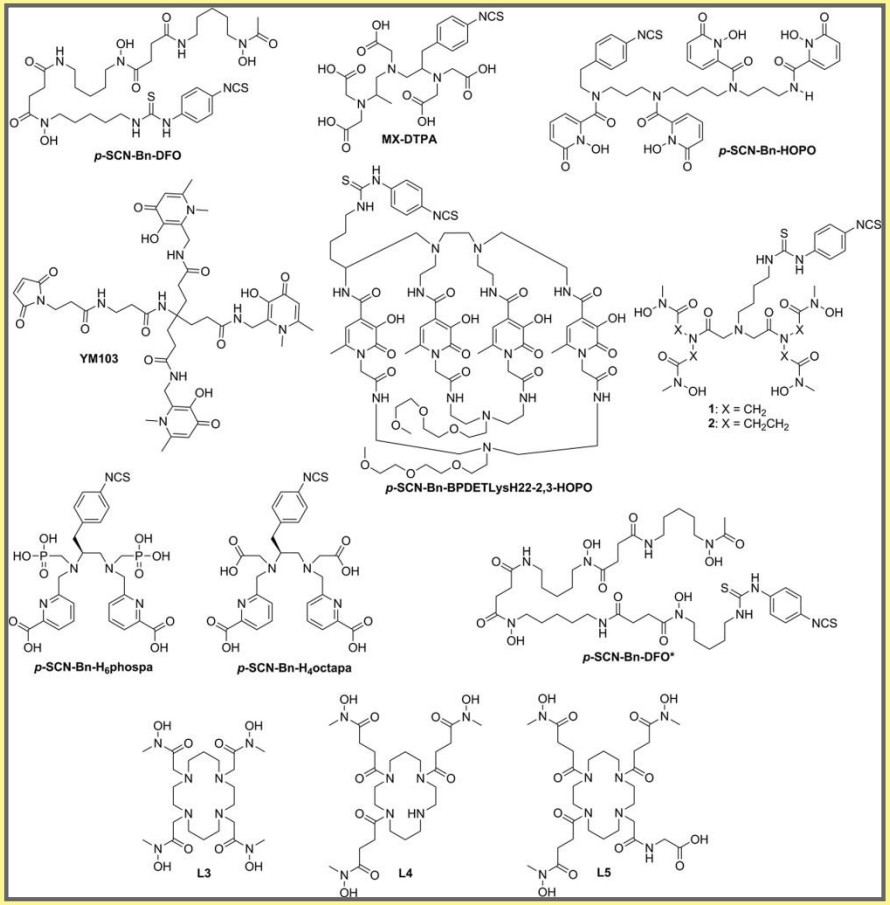
Next generation ligands



Back to the future



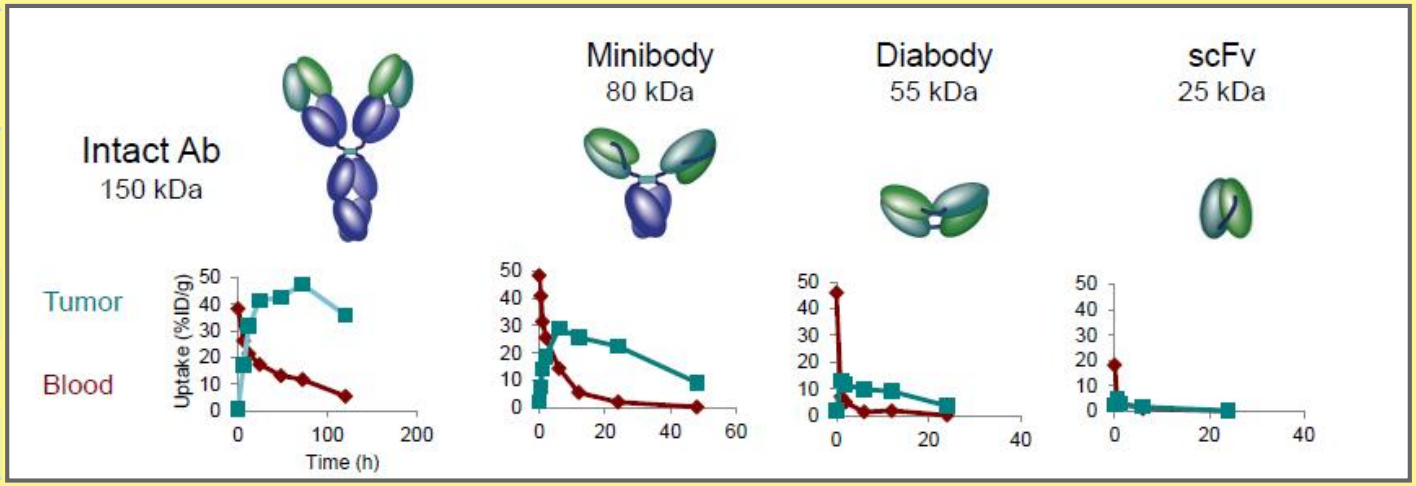
Crystal structure
ZrDOTA



*M. Pandya et al Chem. Sci.,**2017**DOI:10.1039/c6sc04128k*
*J.Rousseau et al Bioorg.&Med.Chem. Let.,**2017**,27,708-712*

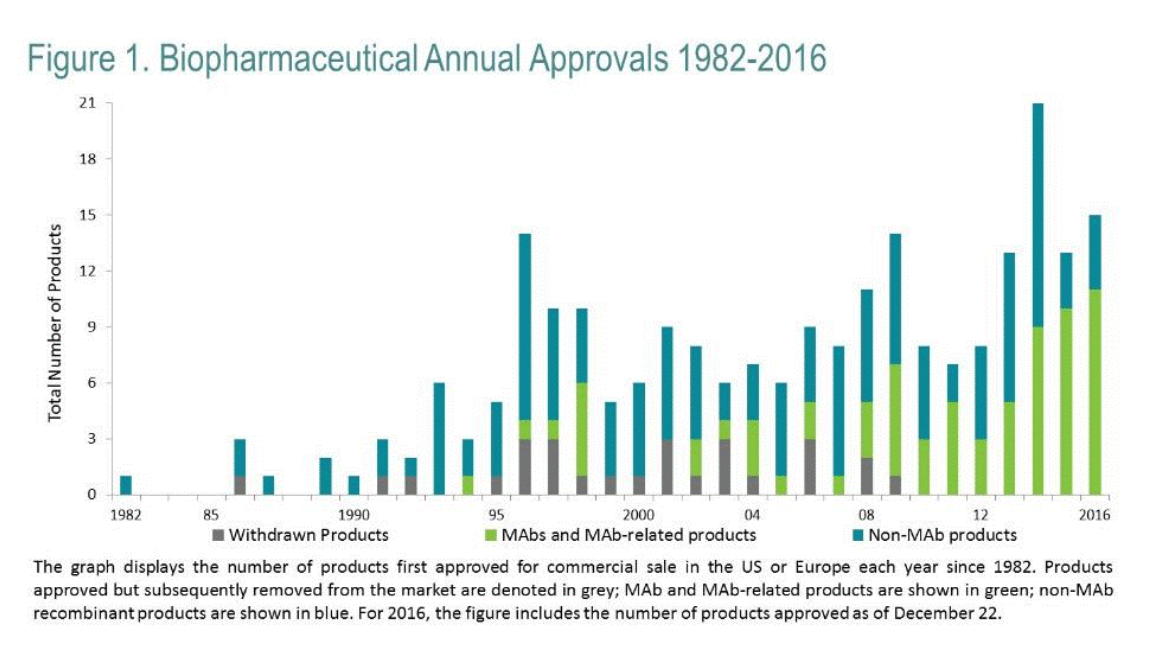
Why we need ^{89}Zr ?

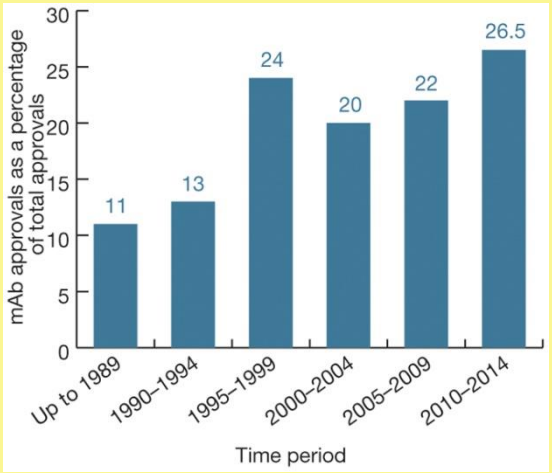
isotope	T ½ (h)
^{68}Ga	1.1
^{18}F	1.8
^{64}Cu	12.7
^{89}Zr	78.4
^{124}I	100.3



- Ideal for labelling compounds with long blood circulation times.
- Low positron emission energy provides better spatial resolution compared to other non standards isotopes (^{124}I, ^{68}Ga)
- Pub med 180 papers on ^{89}Zr and in the last 5 years 124 articles majority of them related to Antibody labelling on immunoPET field.

Biopharmaceutical





Exponential approval in last 5 years.

Not only for Oncology.

Lot of focus on neurodegenerative pathology.

ImmunoPET potential help on drug approval studies.

^{89}Zr on pre-clinic

	Targeting Moiety	Target	Type of cancer	Conjugation Method
Antibodies	Cetuximab	EGFR	Multiple	*N*-suc-DFO
	Bevacizumab	VEGF	Head and neck squamous cell carcinoma; ovarian; breast	*N*-suc-DFO
	Trastuzumab	HER2	Breast; ovarian	*N*-suc-DFO
	J591	PSMA	Prostate	*N*-suc-DFO
	cmAb U36	CD44v6	Head and neck squamous cell carcinoma	*N*-suc-DFO
	5A10	fPSA	Prostate	*N*-suc-DFO
	cG250	MN/CA IX	Renal cell carcinoma	*N*-suc-DFO
	R1507	IGF-1R	Triple-negative breast	*N*-suc-DFO
	Fresolimumab	TGF-b	Multiple	*N*-suc-DFO
	DN30	Met	Gastric; head and neck squamous cell carcinoma	*N*-suc-DFO
	7E11	PSMA	Prostate	*N*-suc-DFO
	hRS7	EGP-1	Prostate	*N*-suc-DFO
	Panitumumab	HER1	Colorectal	DFO-Bz-NCS
	TRC105	CD105	Breast	DFO-Bz-NCS
	Anti-B220	B cells	Unspecified	DFO-Bz-NCS
	E48 and 323/A3	Unspecified surface antigens	Head and neck squamous cell carcinoma; ovarian	SATA/SMCC thioether
Antibody fragments	(aHGF)-Nanobodies	HGF	Glioma	DFO-Bz-NCS
	Ranibizumab (Fab)	VEGF-A isoforms	Ovarian	*N*-suc-DFO
	cG250-F(ab9)2	CAIX	Head and neck squamous cell carcinoma	*N*-suc-DFO
Peptides	c(RGDfK) with and w/o PEG	Integrin $\alpha v\beta 3$	Breast	DFO-Bz-NCS
Nanomaterials	Albumin	n/a	Prostate	*N*-suc-DFO
	Resin microspheres and SIR-Spheres	n/a	Liver	n/a
	Nanocolloidal albumin	n/a	Head and neck squamous cell carcinoma	DFO-Bz-NCS
	Dextran nanoparticles	Macrophages	Colon	DFO-Bz-NCS
	Single wall carbon nanotubes	VE-cad based on attached antibody E4G10	Colon adenocarcinoma	*N*-suc-DFO

16 Antibodies alreay labelled.

Multiple district adressed.

Interessing nanoparticle application.

Only DFO chelanting used.

M.Deri et al Nucl.Med&Biol.,2013,40,3-14

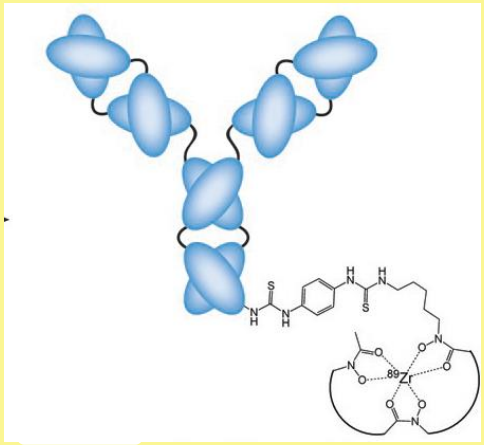
^{89}Zr on clinic

TABLE 1 | Summary of clinical studies on ^{89}Zr-immuno-PET in oncology.

Author	Year	Target	mAb	Tumor type	N
Börjesson	2006	CD44v6	cmAb U36	Head and neck cancer	20
	2009				
Dijkers	2010	HER2	trastuzumab	Breast cancer	14
Rizvi	2012	CD20	ibritumomab-tiuxetan	B-cell lymphoma	7
Gaykema	2013	VEGF-A	bevacizumab	Breast cancer	23
van Zanten	2013	VEGF-A	bevacizumab	Glioma	3
van Asselt	2014	VEGF-A	bevacizumab	Neuroendocrine tumors	14
Bahce	2014	VEGF-A	bevacizumab	Non-small cell lung cancer	7
Pandit-Taskar	2014	PSMA	Hu-J591	Prostate cancer	50
	2015				
Den Hollander	2015	TGF-β	fresolimumab	Glioma	12
Gaykema	2015	HER2	trastuzumab	Breast cancer	10
		VEGF-A	bevacizumab		6
Gebhart	2015	HER2	trastuzumab	Breast cancer	56
Lamberts	2015	MSLN	MMOT0530A	Pancreatic cancer	11
				Ovarian cancer	4
Menke-van der Houven van Oordt	2015	EGFR	cetuximab	Colorectal cancer	10
Muylle	2015	CD20	rituximab	B-cell lymphoma	5
Oosting	2015	VEGF-A	bevacizumab	Renal cell carcinoma	22

Y.Jauw et al Front.Pharm.,2016,7,1-15

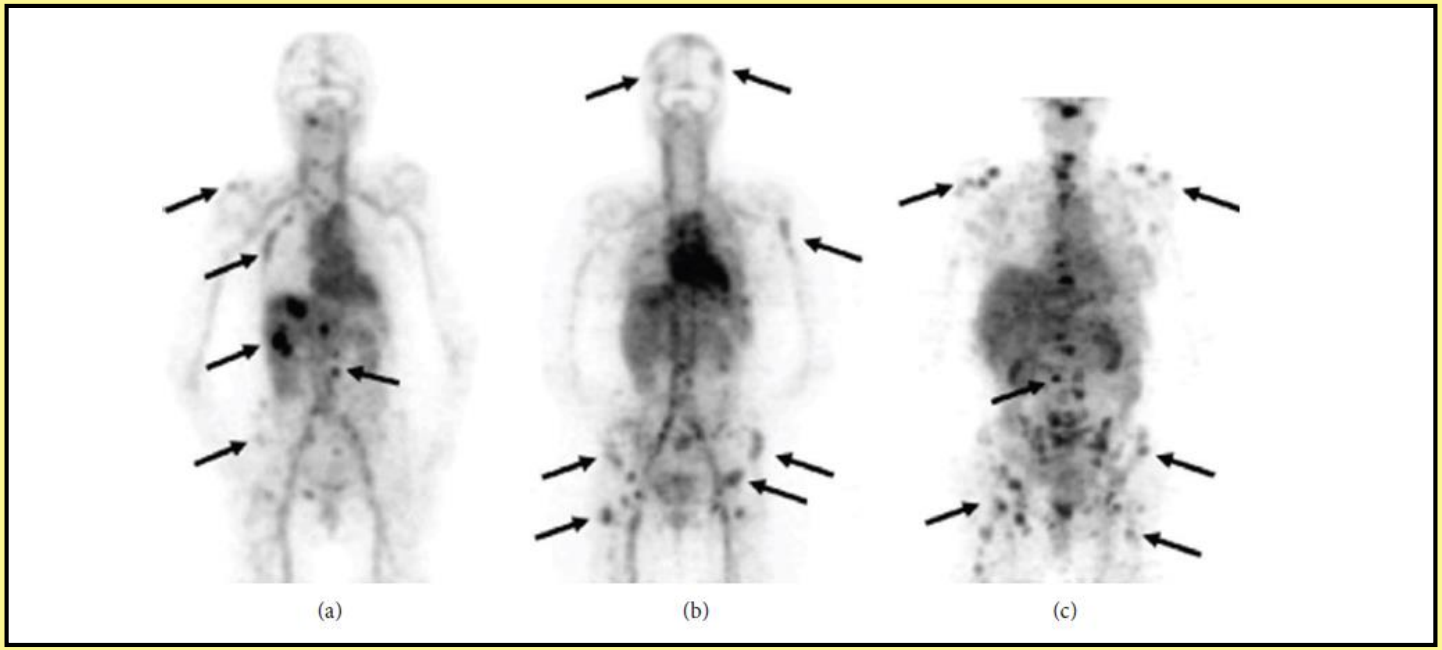
^{89}ZrTrastuzumab



In 25 % of invasive breast carcinomas, there is an overexpression of HER2 receptor. Trastuzumab is the inhibitor tumor cell proliferation agent used in pharmacological treatment of breast cancer for the HER2+ overexpressing metastatic breast cancer.

Biological t½ over 28d and washout 20w.

^{89}ZrTrastuzumab



^{89}Zr-Trastuzumab uptake 5 days after inj. (a) a patient with liver and bone metastases (b)and (c) two patients with multiple bone metastases. A numbers of leasions havent's see before immunoPET.

This images indicate the potential use of 89Zr-Trastuzumab to improve the diagnosis of patientes with HER2-positve breat cancer expecially when lesions are inaccessible for biopsy.

E.Dijkers et al Clin.Pharm. &Ther.,2010,87,586-592

^{89}Zr-nanoparticles

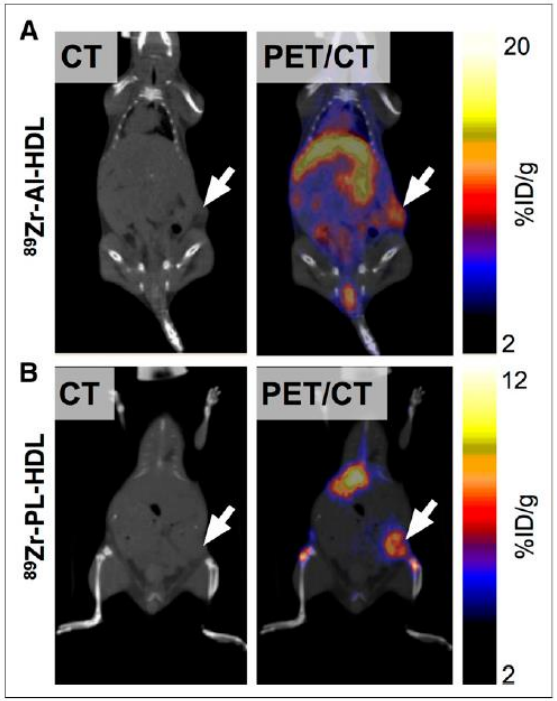
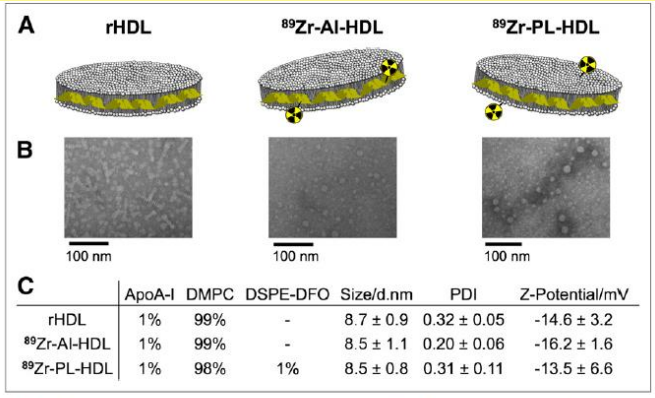


FIGURE 4. Accumulation of ^{89}Zr-HDL nanotracers in tumor tissues can be visualized by in vivo PET imaging. CT (left) and PET/CT fusion (right) images of ^{89}Zr-AI-HDL (A) and ^{89}Zr-PL-HDL (B) obtained at 24 h after injection in mice bearing orthotopic 4T1 tumors (indicated by arrows).



C

	ApoA-I	DMPC	DSPE-DFO	Size/d.nm	PDI	Z-Potential/mV
rHDL	1%	99%	-	8.7 ± 0.9	0.32 ± 0.05	-14.6 ± 3.2
^{89}Zr-AI-HDL	1%	99%	-	8.5 ± 1.1	0.20 ± 0.06	-16.2 ± 1.6
^{89}Zr-PL-HDL	1%	98%	1%	8.5 ± 0.8	0.31 ± 0.11	-13.5 ± 6.6

FIGURE 1. Structure and composition of rHDL and ^{89}Zr-HDL nanotracers. (A) Schematic of rHDL (left), ^{89}Zr-AI-HDL (middle), and ^{89}Zr-PL-HDL (right). (B) Transmission electron microscopy images of rHDL (left), Zr-AI-HDL (middle), and Zr-PL-HDL (right). (C) Composition (in mol %), size, polydispersity index (PDI), and surface charge of rHDL, ^{89}Zr-A
presented as mean ± SD ($n \geq 3$).

High-density lipoprotein (H
been exploited for MR mol

plaque, and its specificity for macrophages has been established (*16*). Furthermore, in 2 recent studies, we have demonstrated its ability to deliver an antiinflammatory drug to macrophages in atherosclerotic plaques with great specificity (*17,18*). To enable HDL use for quantitative PET imaging of TAMs, we here present the design and synthesis of 2 different ^{89}Zr-modified reconstituted HDL (rHDL) nanotracers and their in vivo evaluation in an orthotopic mouse model of breast cancer. Specifically, we labeled either its protein component (apolipoprotein A-I [apoA-I]) or its phospholipid load and examined the agent's TAM targeting using in vivo PET imaging and ex vivo analyses, including immunohistochemistry. Additionally, we prepared 2 fluorescent analogs of our radiolabeled ^{89}Zr-rHDL nanotracers to allow us to gain insight into their cellular targets by flow cytometry.

C.Medina et al JNM.,2015,56,1272-1277

Development and Characterization of Clinical-Grade ^{89}Zr-Trastuzumab for HER2/*neu* ImmunoPET Imaging

CONCLUSION

The present study showed that clinical-grade ^{89}Zr-trastuzumab can be manufactured with high stability and maintenance of antigen binding. The first immunoPET radiopharmaceutical displayed excellent tumor accumulation, with high T/NT ratios and a biodistribution similar to that of ^{111}In-trastuzumab (which was previously used successfully in a clinical study of metastatic breast cancer patients) at a significantly higher spatial resolution and with better T/NT ratios. These data validate this radiopharmaceutical for further clinical testing.

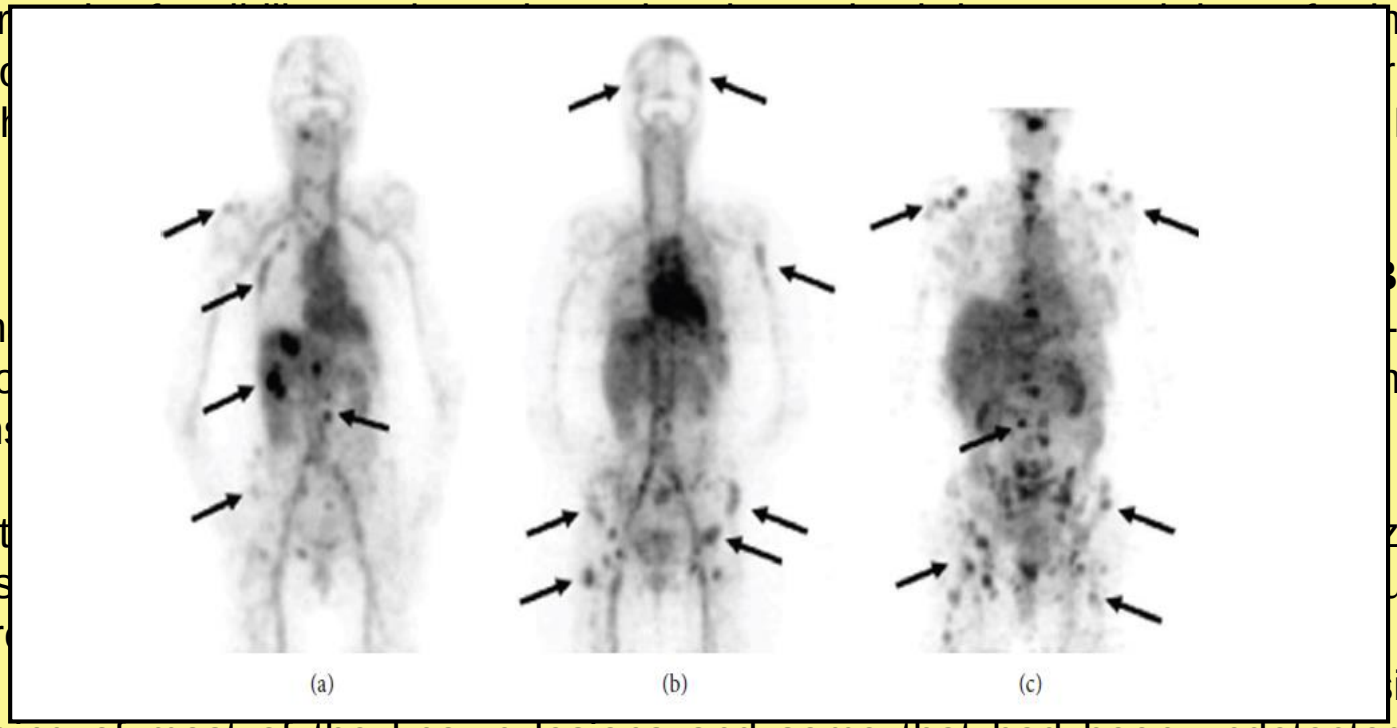
Biodistribution of 89Zr-trastuzumab and PET Imaging of HER2-Positive Lesions in Patients With Metastatic Breast Cancer

EC Dijkers et al. Clinical Pharmacology & Therapeutics 2010. Volume 87 Number 5, 586593.

We perfor ministration of the monc ron emission tomograph ER2)-positive lesions.

Fourteen **q** of 89 Zr-trastuzum -naive and 10 mg for tho t at least two PET scans

The result zumab uptake by tumors uzumab-naive patients r trastuzumab treatment ions allowed PET imaging of most of the known lesions and some that had been undetected earlier. The relative uptake values (RUVs) (mean ± SEM) were 12.8 ± 5.8, 4.1 ± 1.6, and 3.5 ± 4.2 in liver, bone, and brain lesions, respectively, and 5.9 ± 2.4, 2.8 ± 0.7, 4.0 ± 0.7, and 0.20 ± 0.1 in normal liver, spleen, kidneys, and brain tissue, respectively.



PET scanning after administration of 89 Zr-trastuzumab at appropriate doses allows visualization and quantification of uptake in HER2-positive lesions in patients with metastatic breast cancer.

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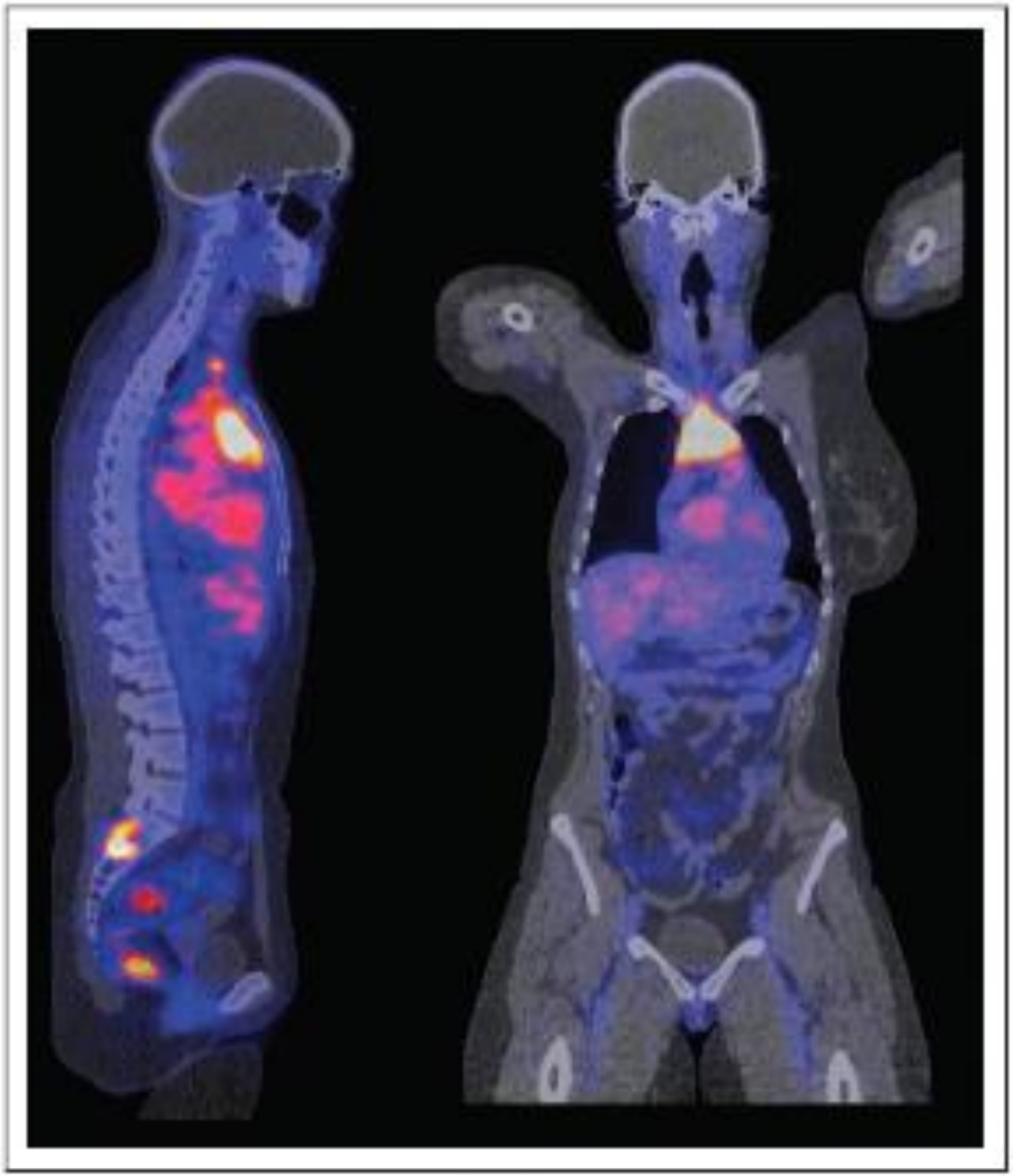

Fig 1.

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Clinical Cancer Research

Personalized Medicine and Imaging

^{89}Zr-trastuzumab and ^{89}Zr-bevacizumab PET to Evaluate the Effect of the HSP90 Inhibitor NVP-AUY922 in Metastatic Breast Cancer Patients

Sietske B.M. Gaykema[1], Carolien P. Schröder[1], Joanna Vitfell-Rasmussen[5], Sue Chua[5], Thijs H. Oude Munnink[1], Adrienne H. Brouwers[2], Alfons H.H. Bongaerts[3], Mikhail Akimov[6,7], Cristina Fernandez-Ibarra[6,7], Marjolijn N. Lub-de Hooge[2,4], Elisabeth G.E. de Vries[1], Charles Swanton[5], and Udai Banerji[5]

Clin Cancer Res; 20(15) August 1, 2014

Purpose: HSP90 chaperones have key client proteins that are involved in all hallmarks of breast cancer growth and progression. The primary aim of this clinical trial was to evaluate the feasibility of using ^{89}Zr-trastuzumab PET (for HER2-positive breast cancer) or ^{89}Zr-bevacizumab PET [for estrogen receptor (ER)–positive breast cancer] to determine *in vivo* degradation of client proteins caused by the novel HSP90 inhibitor NVP-AUY922.

Experimental Design: Of note, 70 mg/m^2 NVP-AUY922 was administered intravenously in a weekly schedule to patients with advanced HER2 or ER-positive breast cancer. Biomarker analysis consisted of serial PET imaging with 2[18F]fluoro-2-deoxy-D-glucose (FDG), ^{89}Zr-trastuzumab, or ^{89}Zr-bevacizumab. Response evaluation was performed according to RECIST1.0. FDG, ^{89}Zr-trastuzumab, and ^{89}Zr-bevacizumab distributions were scored visually and quantitatively by calculating the maximum standardized uptake values (SUV_{max}). In blood samples, serial HSP70 levels, extracellular form of HER2 (HER2-ECD), and pharmacokinetic and pharmacodynamic parameters were measured.

Results: Sixteen patients (ten HER2-positive and six ER-positive tumors) were included. One partial response was observed; seven patients showed stable disease. SUV_{max} change in individual tumor lesions on baseline versus 3 weeks ^{89}Zr-trastuzumab PET was heterogeneous and related to size change on CT after 8 weeks treatment ($r^2 = 0.69$; $P = 0.006$). Tumor response on ^{89}Zr-bevacizumab PET and FDG-PET was not correlated with CT response.

Conclusions: NVP-AUY922 showed proof-of-concept clinical response in HER2-amplified metastatic breast cancer. Early change on ^{89}Zr-trastuzumab PET was positively associated with change in size of individual lesions assessed by CT. *Clin Cancer Res; 20(15); 3945–54. ©2014 AACR.*

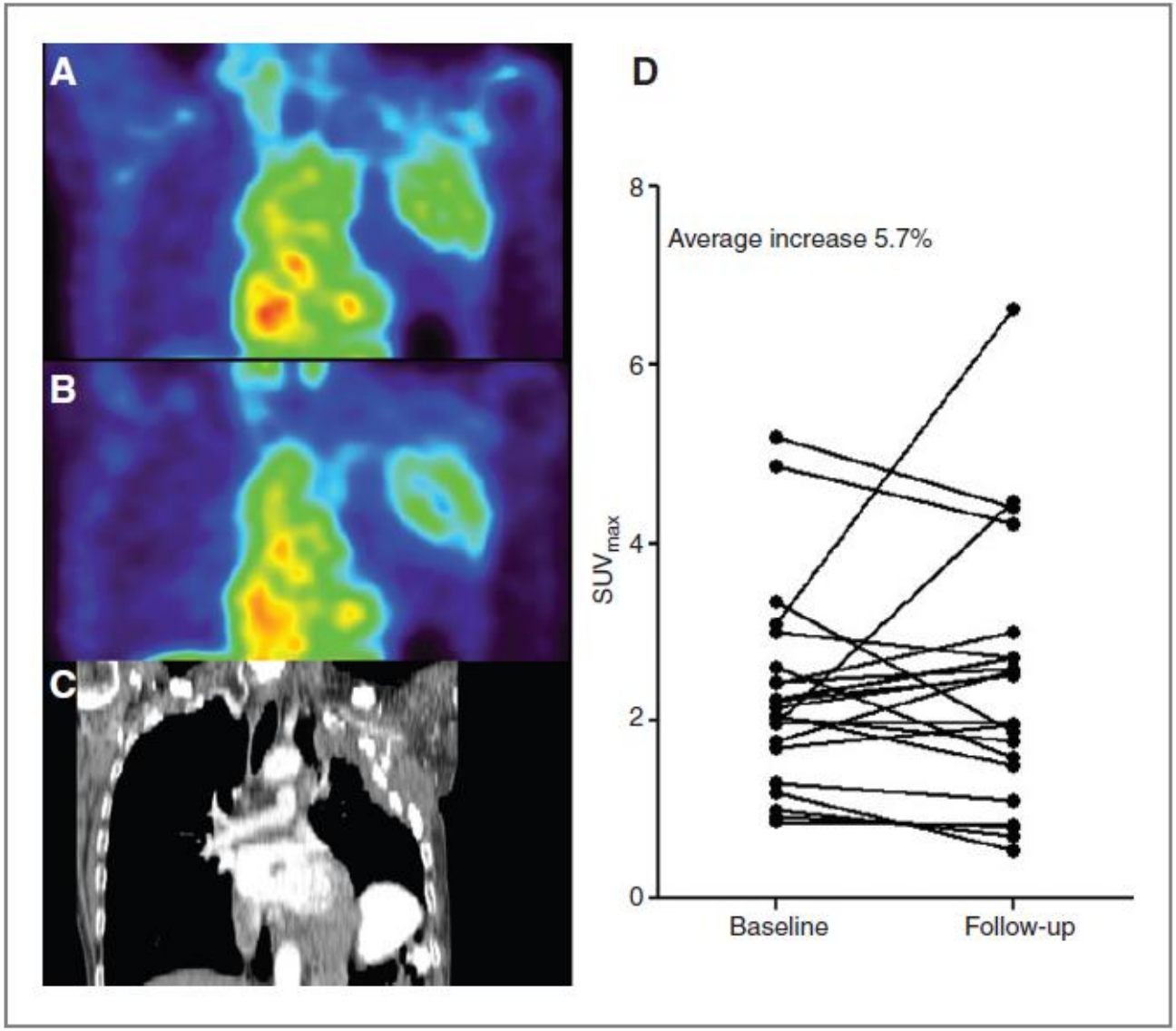

Figure 4. Representative coronal ^{89}Zr-bevacizumab PET images of a patient scanned before (A) and after (B) 3 weeks of treatment. The patient had a large tumor mass in the chest wall. ^{89}Zr-bevacizumab PET could be performed in 6 of 10 patients of which 5 underwent repeated scan procedures. The CT scan pretreatment is shown in C. D, a heterogeneous response in individual tumor lesions ($n = 23$) between baseline and follow-up, with an average increase of SUV_{max} of 5.7%.

Conclusion

- ^{89}Zr Nuclear proprieties ($t_{1/2}$=78.4h, $E\beta^{+}$= 395.5 kev) are switable for immunoPET.
- How to produce ^{89}Zr from Medical Cyclotron.
- The actual recovery and formulation solution, with the evaluation of the different media used.
- Overview of ^{89}Zr ligands and challenge for the future
- ^{89}Zrtracers application state of art and possible future applicaton.