^{89}Zr-Immuno-PET

Physical Properties, Production, Labeling and Applications of ^{89}Zr

bv CYCLOTRON VU
radiopharmaceuticals and radionuclides

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Introduction

Zirconium-89 (^{89}Zr) is a long-lived positron-emitting radionuclide, finding scientific and medical applications in cancer detection and imaging. ^{89}Zr has a notably longer physical half-life than the most widely used positron-emitter, fluorine-18 (^{89}Zr, $t_{½}$ = 78.4 h; ^{18}F, $t_{½}$ = 110 m). This allows the use of ^{89}Zr in positron emission tomography (PET) applications with monoclonal antibodies (mAbs), which possess long biological half-lives, of up to days.

MAbs are the most rapidly expanding category of therapeutics. The US Food and Drug Administration (FDA) has approved over 30 mAbs for therapy, mostly for the systemic treatment of cancer. Annual sales have reached $30 billion in 2008 [1, 2, 3]; in 2010, this figure has further grown to a massive $48 billion [4, 5].

Immuno-PET - PET-imaging with radiolabeled antibodies or antibody fragments - is an attractive imaging modality at several stages of drug development. With ^{89}Zr as a promising PET-isotope, ^{89}Zr-immuno-PET can offer excellent sensitivity and accurate quantification of mAbs or mAb-fragments, from mouse to man. ^{89}Zr-immuno-PET may be an essential tool for research institutes, university hospitals and pharmaceutical companies interested in initiating or participating in the development of mAbs or mAb-fragments.

As ^{89}Zr-immuno-PET has only been developed and approved for clinical studies fairly recently [6-11], this white paper will provide an overview of the physical properties, production specifications and applications of ^{89}Zr. Furthermore, two methods for labeling of mAbs or mAb-fragments with ^{89}Zr will be described. We will discuss the advantages and disadvantages of both methods, and give a summary of preclinical and clinical study results obtained with ^{89}Zr-immuno-PET thus far.

^{89}Zr-immuno-PET

Immuno-PET - the tracking and quantification of radiolabeled mAbs with PET at high resolution and sensitivity - can be of great value at several stages of mAb development and applications. Immuno-PET can offer answers to two key questions in targeted therapy:

"Where is the target?"
For instance, immuno-PET can offer information on whether a target (e.g. a receptor or ligand) is homogeneously present on a tumor. It can also be used to accomplish efficient patient selection and determination of optimal dosages, so that side effects can be minimized.

"Where is the treatment drug?"
Since the biological behavior of mAbs cannot be exactly predicted by in vitro studies, this is usually a challenging question. Yet, with immuno-PET, newly developed mAb-pharmaceuticals can be tested for their pharmacokinetics and biodistribution. This way, development of new mAb-pharmaceuticals can be substantially enhanced.

These advantages of immuno-PET have enabled valuable improvement in various stages of antibody development and clinical applications in the past decade [6, 9, 12]. In addition to intact, full-sized antibodies, also antibody fragments (e.g. nanobodies, affibodies) and third generation, non-traditional antibody-like scaffolds have been receiving increasing attention. Immuno-PET may also play a crucial role in early drug development of non-traditional antibodies.

Biological and physical properties of ^{89}Zr

^{89}Zr has some ideal characteristics for labeling of intact mAbs and subsequent visualization of mAb distribution using PET. Firstly, its physical half-life of 78.4 h matches the biological half-life of a mAb, as well as the time it needs to perfectly reach optimal target-to-non-target ratios.

Secondly, PET image quality is not disturbed by the decay characteristics of ^{89}Zr. The radionuclide emits a positron (β^+ particle) with 23% efficiency, in addition to a concomitant gamma ray emission of 909 keV. It has been shown that the delayed gamma photons do not interfere with the overall image quality and accurate quantification of the PET image [6, 13]. Table 1 summarizes the decay data of ^{89}Zr.

Furthermore, ^{89}Zr is a residualizing isotope, which means that it is trapped inside the target cell after internalization of the mAb. In comparison, iodine-124 (^{124}I, $t_{1/2}$= 100.3 h), another long-lived PET isotope, is released from the target cell after mAb internalization. It is known that ^{89}Zr residualizes to some extent in organs of mAb catabolism, such as liver, spleen and kidney.

Table 1:
Decay data of ^{89}Zr.

Radiation type	Energy (keV)	Radiation intensity (%)
β^+*	395.5	22.74
Auger-L	1.91	79.00
Auger-K	12.7	19.47
γ-annihillation	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

*= average β^+

Production of ^{89}Zr

^{89}Zr is mostly produced by a nuclear reaction on natural yttrium, the ^{89}Y(p,n)^{89}Zr reaction, using a biomedical cyclotron. The average yield is 38-42 MBq/µAh at an incident energy of 12.5 MeV, resulting in batches of 6-8 GBq of ^{89}Zr within 4 to 6 h. With such batch sizes, a great number of clinical immuno-PET studies can be performed, considering that patients only receive 37 to 74 MBq of ^{89}Zr-labeled mAb. Purification of ^{89}Zr from ^{89}Y, ^{88}Y and other radionuclidic impurities [14] can be achieved via affinity chromatography using a hydroxamate column. ^{89}Zr is eluted from the column using 1 M oxalic acid, resulting in a product with >99.9% radionuclidic purity. In order to omit the potentially toxic oxalic acid from this process, elution of ^{89}Zr from the hydroxamate column using other acids has been extensively tested. The results have shown that, despite its toxic potential, 1 M oxalic acid is the most appropriate trans-chelator, as it can be perfectly removed at subsequent purification steps, during mAb labeling.

Choice of the chelator

Zirconium is a hard Lewis acid, and thus prefers hard Lewis bases as donor groups. Moreover, zirconium favors an 8-coordination. It has been shown that zirconium (IV) can form stable complexes with hydroxamates, which are present in desferrioxamine (DFO, desferal) (Figure 1). To date, DFO is the only chelator known to form stable complexes with ^{89}Zr. Because DFO has been clinically used for the neutralization of iron and aluminum overload for many years, its application as a chelator in clinical immuno-PET studies is easily achievable.

DFO consists of three hydroxamate groups, which allows stable complexation of zirconium as well as iron, gallium and niobium, and results in a 6-coordination. Several different DFO-mAb complexes have been described in the literature, as recently reviewed by Vugts et al. [15]. Next, we will describe the two chelators which are employed in the clinical setting.

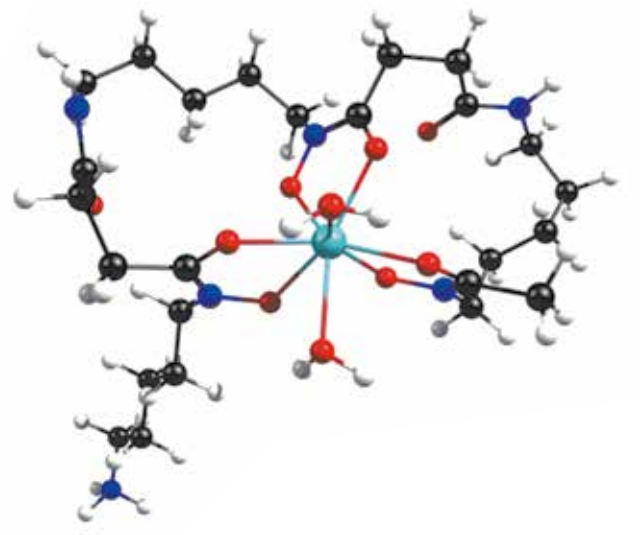

Figure 1.
Density Function Theory (DFT)-optimized structure of 8-coordinate complex [^{89}Zr(HDFO)-cis-$(H_2O)_2$]$^{2+}$ (3-cis).
Reprinted with permission of the Society of Nuclear Medicine from: Holland JP, Divilov V, Bander NH, et al. ^{89}Zr-DFO-J591 for ImmunoPET of Prostate-Specific Membrane Antigen Expression In Vivo. J Nucl Med. 2010; 51(8): 1293-1300. Figure 1b [20].

Chelator 1: N-suc-DFO-TFP-ester

Until 2010, N-succinyl-desferrioxamine-tetrafluorphenol ester (N-suc-DFO-TFP-ester) was the chelator of choice for the production of stable ^{89}Zr-labeled mAb conjugates [14]. For the preparation of N-suc-DFO-TFP-ester, DFO is first reacted with succinic anhydride, resulting in N-succinyl-DFO (N-suc-DFO). In a second step, DFO is temporarily filled with iron, in order to prevent the reaction of TFP-ester with one of the hydroxamate groups of DFO. Finally, in a third step, the acid groups become activated to Fe-N-suc-DFO-TFP-ester. The resulting ester can be stored at -80°C in acetonitrile for at least one year. The conjugation of Fe-N-suc-DFO-TFP-ester to the lysine residues of a mAb requires a pH of approximately 9.5. In the next step, the iron (Fe) has to be removed from the DFO, which can be achieved with a 100-fold molar excess of ethylenediaminetetraacetic acid (EDTA) at pH 4.2-4.5.

Chelator 2: DFO-Bz-NCS

In 2010, a new DFO-based chelator was introduced: p-isothiocyanatobenzyl-desferrioxamine (DFO-Bz-NCS) [16, 17], patented by Macrocyclics (www.macrocyclics.com). DFO-Bz-NCS is prepared by the reaction of DFO with 1,4-phenylendiisothiocyanate. The isothiocyanate group is frequently used as reactive group in the conjugation to mAbs, for instance with DOTA, which has been safely employed in clinical studies for many years.

Just like N-suc-DFO-TFP-ester, DFO-Bz-NCS is also conjugated to the lysine groups of a mAb. An important difference in the new conjugation procedure is the absence of the iron removal step at low pH. Avoiding the low pH step is a major improvement when dealing with pH-sensitive proteins, as recently shown for ^{89}Zr-nanocolloidal albumin [18].

With both chelators, coupling with ^{89}Zr is achieved by trans-chelation of ^{89}Zr from oxalic acid to DFO at neutral pH (between 6.8-7.2), and almost complete incorporation can be achieved after 30-60 minutes.

Analysis of the conjugation methods

Table 2 shows an overview of the main advantages and disadvantages of the two DFO-chelators for conjugation to mAbs. A convenience of using Fe-N-suc-DFO-TFP-ester is that chelator-to-mAb ratios can be easily determined by size exclusion high performance liquid chromatography (SEC-HPLC) when applying the specific wavelength of Fe (430 nm); the same is not possible with the DFO-Bz-NCS chelator, due to the absence of Fe.

Using DFO-Bz-NCS requires careful consideration of certain issues. The first important aspect is the way how DFO-Bz-NCS is added to the mAb-solution. If added swiftly, without shaking or proper mixing, DFO-Bz-NCS, which is dissolved in DMSO, can cause formation of mAb-aggregates. For this reason, we state [16, 17] that DFO-Bz-NCS should be added stepwise to the mAb-solution.

A second aspect observed when using the DFO-Bz-NCS chelator concerns the stability of the radiolabeled mAb upon storage. Buffers containing Cl^- should be avoided, since they cause detachment of ^{89}Zr from the mAb, due to radiation-induced formation of hypochlorite. In turn, this compound reacts very effectively with the bis-thiourea unit of the new linker, therefore the use of a 0.25 M sodium acetate buffer is strongly recommended.

Availability of the DFO-chelators

Both chelators are commercially available: Macrocyclics trades Df-Bz-NCS, whereas the Fe-N-suc-DFO-TFP-ester was added to the portfolio of ABX (www.ABX.de) in March 2012. On request, each company can produce their DFO chelator at GMP-compliant grade.

Consequently, research groups and pharmaceutical companies can now choose their desired labeling method according to the protein they investigate.

Table 2:
Comparison of the two DFO-chelators for conjugation to mAbs.

Synthesis step	Fe-N-suc-DFO-TFP-ester	Remarks	DFO-Bz-NCS	Remarks
Conjugation mAb	30' at pH 9.5-9.7	Typically: two-fold molar excess of DFO-TFP-ester results in 1-1.5 DFO-groups coupled per mAb	30' at pH 9.0	Adding of DFO-Bz-NCS should be done stepwise to avoid aggregation or precipitation of mAb. Typically: three-fold molar excess of DFO-Bz-NCS results in 0.3-0.9 DFO-groups coupled per mAb
Quality control: conjugation efficiency	Size exclusion HPLC at 280 nm and 430 nm		No HPLC analysis possible	Determination via MS is possible, or by titration with known amount of cold zirconium oxalate [ref 19]
Removal of Fe	30' at pH 4.2-4.5		n.a.	
Purification via PD-10 column	Eluent 0.9% NaCl		Eluent 0.25 M NaOAc pH 5.5	In this step, 0.9% NaCl may be used as eluent
^{89}Zr labeling of modified mAb	30-60' in HEPES buffer at pH 7		30-60' in HEPES buffer at pH 7	
Purification via PD-10 column	Eluent 0.9% NaCl with 5 mg/ml gentisic acid, pH 5.5	Different anti-oxidizing agents have been tested; gentisic acid was found as most favorable	Eluent 0.25 M NaOAc, with 5 mg/ml gentisic acid, pH 5.5	Use of Cl^--ions should be avoided

Abbreviations: DFO = desferrioxamine, desferal; HPLC = High Performance Liquid Chromatography; n.a. = not applicable; NaOAc = sodium acetate; QC = quality control.

Quality control

In order to fulfill clinical requirements, it is important that ^{89}Zr-labeled mAbs are produced under current good manufacturing practice (cGMP) [21]. When a ^{89}Zr-labeled mAb has been prepared, it is important to execute the following tests:

1) Appearance: a clear and colorless solution should be observed.

2) Chelator-to-mAb ratio: though varying according to the applied DFO-chelator, no more than two to three DFO-groups per mAb molecule should be attached, in average, to preserve immunoreactivity and pharmacokinetics of the radiolabeled mAb.

3) Radiochemical purity: ideally, this should be > 95%. Aggregate or dimer formation caused by modification and radiolabeling, as well as free ^{89}Zr and ^{89}Zr-DFO, should be < 5%. HPLC can be employed to evaluate both criteria, while instant thin layer chromatography (ITLC) can only be used to determine the percentage of free ^{89}Zr and ^{89}Zr-DFO.

4) Immunoreactivity: this can be examined with a binding assay (according to Lindmo et al. [22]) or an ELISA assay [23]. Immunoreactivity should not be affected during modification and subsequent labeling.

5) Apyrogenicity: concentration of endotoxins in the product should be minimized. An assay can be performed, for instance using an endosafe PTS reader.

6) Sterility: the final product should be filtered through a 0.22 µm filter. The integrity of the used filter should be tested with a bubble point test. Due to time constraints, it is unfeasible to perform sterility tests for each product. However, during validation experiments, it is important to obtain sterility information. Moreover, a media fill test can be executed on a regular basis.

As can be seen from the list above, all quality controls are regular tests for a dedicated radiolabeling facility. Thus, implementing these quality controls for ^{89}Zr-immuno-PET in laboratories and quality systems should be fairly straightforward.

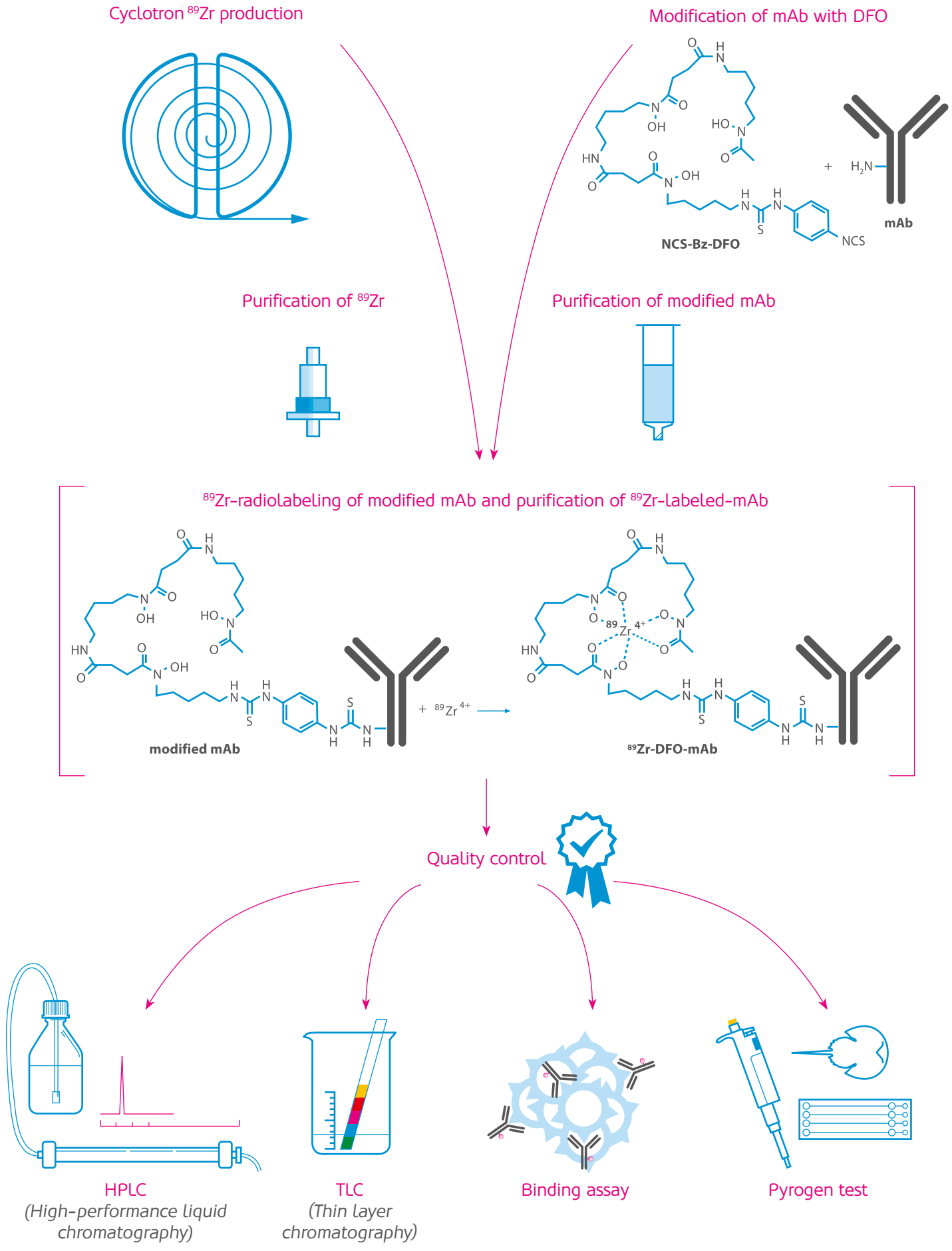

Figure 2: Preparation of clinical grade ^{89}Zr-DFO mAbs.

Settings for clinical PET/CT scanners

The minimum standard for the acquisition and interpretation of PET and PET/CT scans with [^{18}F]-FDG was well described by Boellaard et al. (2010) [24]. The published guideline allows physicians and physicists to perform, interpret and document quantitative [^{18}F]-FDG PET/CT examinations.

Until recently, however, clear reconstruction algorithms for newly developed PET-compounds, using PET-radionuclides other than ^{18}F, were missing. In a multicenter study of Makris et al. [25], three types of clinical PET/CT scanners were cross-calibrated using a known ^{89}Zr compound. Table 3 gives recommendations for these three different clinical PET/CT-scanner types, as well as information for users on quantifying obtained ^{89}Zr-immuno-PET images.

Table 3:
Recommended reconstruction algorithms and settings for ^{89}Zr-labeled studies in PET/CT scanners*.

Type of PET-CT scanner	Reconstruction algorithm	Iteration subsets	Matrix size	Slice thick-ness (mm)	Smoothing (mm)
Biograph mCT ToF	PSF-ToF**	21_3	256 x 256	3.0	8.0
Philips TF Gemini	Blob-OSEM-ToF***	33_3	144 x 144	4.0	5.0
GE Discovery-690	OSEM-ToF	18_3	128 x 128	3.3	6.4

*All scans were performed with 5 min per bed position
**Point Spread Function-Time of Flight.
***Blob-Ordered Subsets Expectation Maximization-Time of Flight (WB CTAC NAC).

Results: preclinical and clinical applications

To date, more than 20 preclinical studies have been published using ^{89}Zr (Table 4), in addition to more than 25 clinical ^{89}Zr-immuno-PET studies. The first clinical study with ^{89}Zr-immuno-PET was reported by Börjesson et al. [7] in 2006. In this feasibility study, 20 head and neck cancer patients received ^{89}Zr-N-suc-DFO-U36. This study showed that primary tumors, as well as lymph node metastasis, can be detected using ^{89}Zr-immuno-PET, and that ^{89}Zr-N-suc-DFO-U36 can be safely applied to patients.

After this first-in-human-study, other clinical trials using ^{89}Zr-immuno-PET were initiated. An overview of the present clinical trials can be seen in Table 5.

As an example, we consider the imaging hub of Roche with medical oncology and nuclear medicine departments of three Dutch University Medical Centers. Thanks to this collaboration, the various phases of translational research can be completed in a more effective and efficient manner. One of the studies within this hub is an open-label, two-arm study that will assess the pharmacokinetics, pharmacodynamics, safety and efficacy of an anti-CD44 antibody in patients with metastatic and/or locally advanced CD44-expressing malignant solid tumors. In part A, cohorts of patients receive anti-CD44 antibody intravenously at escalating doses, while in Part B, patients receive ^{89}Zr-labeled anti-CD44 antibody, followed by 'cold' antibody.

A second study within this hub is a phase II molecular imaging trial of RO5323441, a mAb directed against the placental growth factor (PlGF), in patients with recurrent Glioblastoma Multiforma (GBM) treated with bevacizumab, a mAb directed against vascular endothelial growth factor (VEGF). Both VEGF and PlGF are involved in tumor growth, enabling the development of tumor vasculature. Treatment consists of bevacizumab administration every two weeks. Patients receive ^{89}Zr-labeled anti-PlGF antibody on days -3 and 11 after the first bevacizumab cycle. A brain PET-scan is performed two hours post-injection of the radiolabeled mAb. In addition, a whole body PET-scan is performed on days 1 and 15. Within this study, the investigators mainly aim to quantify the amount of anti-PlGF antibody in the GBM lesions; as a second objective, accumulation in normal, non-tumor organs is assessed, as well as the possibility that bevacizumab influences anti-PlGF antibody penetration in tumor lesions.

Table 4:
Overview of published* preclinical ^{89}Zr-immuno-PET studies.
* From PubMed search in August 2012.

#	Drug	Target	References
1	^{89}Zr-ranibizumab	VEGF A	26
2	^{89}Zr-R1507	IGF-1R	27
3	^{89}Zr-J591	PSMA	28
4	^{89}Zr-cG250	CA IX	29
5	^{89}Zr-cmAb U36	CD44v6	13
6	^{89}Zr-bevacizumab	VEGF	30
7	^{89}Zr-DN30	c-Met	31
8	^{89}Zr-fresolimumab	TGF-β	32
9	^{89}Zr-FK-3PEG	$\alpha_v\beta_3$ integrin	33
10	^{89}Zr-FK	$\alpha_v\beta_3$ integrin	33
11	^{89}Zr-[FK](2)-3PEG	$\alpha_v\beta_3$ integrin	33
12	^{89}Zr-[FK]	$\alpha_v\beta_3$ integrin	33
13	^{89}Zr- trastuzumab	HER2	34
14	^{89}Zr-cetuximab	EGFR	35
15	^{89}Zr-TRC105	CD105	36
16	^{89}Zr-hRS1	EGP-1, TROP2	37
17	^{89}Zr-7E11	PSMA or NAALADase	38
18	^{89}Zr-7D12	EGFR	39
19	^{89}Zr-cG250-F(ab')$_2$	CA IX	40
20	^{89}Zr-panitumumab	EGFR	41
21	^{89}Zr-nanocolloidal albumin	sentinel node	17
22	^{89}Zr-anti-B220	anti-B-cell	42

Abbreviations: CA IX = carbonic anhydrase IX; CD44v6 = splice variant 6 of CD44; EGFR = epidermal growth factor receptor; EGP-1 = TROP2 = epithelial/carcinoma glycoprotein; HER2 = human epidermal growth factor receptor 2; IGF-1R = insulin-like growth factor 1 receptor; NAALADase = N-acetyl α-linked acidic dipeptidase; PSMA = prostate-specific membrane antigen; TGF-β = transforming growth factor β; VEGF A = vascular endothelial growth factor A.

Table 5:
Currently known* clinical ^{89}Zr-immuno-PET studies.
*= Adapted from clinicaltrials.gov and personal communications.

	Drug	Target/ Effect of	Cancer/ Disease	No patient	Dose	Institute [ref]	Country
1	^{89}Zr-cmAb-U36	CD44v6	HNSCC	20	74 MBq/ 10 mg	VUmc [6,7]	NL
2	^{89}Zr-huJ591	PSMA	Prostate	50	unknown	MSKCC	USA
3	^{89}Zr-RO5323441	PlGF	Glioblastoma	7	x MBq/ 5 mg	UMCG	NL
4	^{89}Zr-bevacizumab	VEGF/ HSP90	Breast	11	unk	UMCG	NL
5	^{89}Zr-trastuzumab	HER2	Breast	11	unknown	UMCG [9,12]	NL
6	^{89}Zr-trastuzumab	HER2/ HSP90	Breast	11	unknown	UMCG	NL
7	^{89}Zr-bevacizumab	VEGF	Neuroendocrine	14	37 MBq/ 5 mg	UMCG	NL
8	^{89}Zr-GC1008	TGF-β	Glioblastoma	12	37 MBq/ 5 mg	UMCG	NL
8b	^{89}Zr-GC1008	TGF-β	Glioblastoma	12-20	37 MBq/ 5 mg	UMCG	NL
9	^{89}Zr-bevacizumab	VEGF	Renal Cell CA	14	37 MBq/ 5 mg	UMCG	NL
10	^{89}Zr-bevacizumab	VEGF	Renal Cell CA	26	unknown	UMCG	NL
11	^{89}Zr-bevacizumab	VEGF	Breast	23	37 MBq/ 5 mg	UMCG	NL
12	^{89}Zr-bevacizumab	VEGF	Von Hippel-Lindau	30	unknown	UMCG	NL
13	^{89}Zr-RO5429083	CD44	CD44-positive	25-30	37 MBq/ 1 mg	Roche	NL
14	^{89}Zr-trastuzumab	HER2/ T-DM1	Breast	60	unknown	Bordet	B/NL
15	^{89}Zr-trastuzumab	HER2	Breast	20	unknown	Bordet	B
16	^{89}Zr-cetuximab	EGFR	Stage IV CA	12	unknown	Maastricht	NL
17	^{89}Zr-rituximab	CD20	Non hodgkin	34	74 MBq/ 5 mg	Bordet	B
18	^{89}Zr-rituximab	CD20	Rheumatology	15	18 MBq/ 10 mg	VUmc	NL
19	^{89}Zr-cetuximab	EGFR	NSCLC		74 MBq/ 5 mg	VUmc	NL
20	^{89}Zr-bevacizumab	VEGF	Glioblastoma (Ped)	5	18-37 MBq/ 2-5 mg	VUmc	NL
21	^{89}Zr-cetuximab	EGFR	HNSCC	268	unknown	VUmc	NL/GB/ S/F/E
22	^{89}Zr-rituximab	CD20	MS	8	18 MBq/ 10 mg	VUmc	NL
23	^{89}Zr-ofatumumab	CD20	Lymphoma	15	74 MBq/ 10 mg	VUmc	NL
24	^{89}Zr-rituximab	CD20	Lymphoma	30	74 MBq/ 10 mg	VUmc	NL
25	^{89}Zr-cetuximab	EGFR	Colorectal	38	37 MBq/ 10 mg	VUmc	NL
26	^{89}Zr-bevacizumab	VEGF/FAZA	NSCLC	15-20	37 MBq/ 5 mg	VUmc	NL
27	^{89}Zr-nanocoll	sentinel node	HNSCC	5-10	5 MBq	VUmc	NL

Abbreviations: B = Belgium; CA = carcinoma; EGFR = epidermal growth factor receptor; F = France; FAZA = 1-α-D-(5-Fluoro-5-deoxyarabinofuranosyl)-2-nitroimidazole; GB = Great Britain; HER2 = human epidermal growth factor receptor 2; HNSCC = head and neck squamous cell carcinoma; HSP90 = heat shock protein-90; MS = multiple sclerosis; MSKCC = Memorial Sloan-Kettering Cancer Center; NL = The Netherlands; NSCLC = non-small cell lung cancer; Ped = pediatrics; PlGF = Placental growth factor; PSMA = prostate-specific membrane antigen; S = Sweden; T-DM1 = trastuzumab emtansine; TGF-β = transforming growth factor β; UMCG = University Medical Center Groningen; USA = United States of America; VEGF = vascular endothelial growth factor; VUmc = VU University Medical Center.

Outlook

Molecular imaging with the PET tracer ^{89}Zr may considerably accelerate drug development. Major players within the pharmaceutical industry now realize that immuno-PET offers excellent sensitivity and accurate quantification in PET-studies using ^{89}Zr-labeled mAbs or mAb-fragments, allowing quick translation from mouse to man [43]. Several pharmaceutical companies have already shown their interest in ^{89}Zr-immuno-PET, with the first clinical trials currently ongoing (e.g. Roche hub). What is more, academic biomedical research institutions are encouraged to initiate ^{89}Zr-immuno-PET studies.

^{89}Zr has been produced at clinical grade since 2008, and can be obtained on a weekly basis. Besides the worldwide delivery of ^{89}Zr, also the two DFO chelators are now commercially available. With these ingredients in place, it is now possible for research groups and pharmaceutical companies to easily set up ^{89}Zr-immuno-PET in their facilities. In addition, a 3-day training on ^{89}Zr-immuno-PET can be attended at BV Cyclotron VU, which gives trainees the tools to start their own ^{89}Zr-immuno-PET studies within a few months (for more details, see: 2cyc.eu/training).

Thus, the physical properties of ^{89}Zr, its worldwide availability, the improved situation of commercially available chelators, the ease of use in standard laboratory settings, and the impressive results from preclinical and clinical applications make ^{89}Zr in immuno-PET an important new technology for research institutes, university hospitals and pharmaceutical companies.

Company profile

BV Cyclotron VU is a private company located in the campus of the VU University Medical Center in Amsterdam, the Netherlands. Since 1987, BV Cyclotron VU has been producing SPECT and PET radiopharmaceuticals and PET radiochemicals for medical diagnostics and research. BV Cyclotron VU produces [^{18}F]FDG, [^{18}F]FCH, [^{18}F]Florbetaben (NeuraCeq™), ^{124}I, ^{89}Zr and other ^{18}F-labeled compounds for the PET community, as well as ^{123}I and ^{81}Rb/^{81m}Kr generators for the SPECT community.

In Amsterdam, BV Cyclotron VU runs one of the first commercial production sites of ^{89}Zr in the world. Academic establishments such as the Memorial Sloan-Kettering Cancer Center (NY, USA), University of Wisconsin (Madison, WI, USA) and Paul Scherrer Institute (Zurich, Switzerland) produce ^{89}Zr on request and for research purposes only.

BV Cyclotron VU's mission is to make a wide range of PET compounds available. Our goal is to make products of the highest pharmaceutical quality, and to be a highly reliable supplier of those products. To achieve this, BV Cyclotron VU continuously invests in the best equipment available on the market. The products are delivered by our worldwide distribution partners (see: 2cyc.eu/distributors). The department of Nuclear Medicine and PET Research of the VU University Medical Center is our partner in research and development of new PET tracers.

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www.cyclotron.nl

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