

# The Future of Immuno-PET in Drug Development

Zirconium-89 and Iodine-124 as Key Factors in  
Molecular Imaging

by **CYCLOTRON**  **VU**  
radiopharmaceuticals and radionuclides



## Abstract

Monoclonal antibodies (mAbs) have been approved for therapeutic use in a broad range of medical indications, especially in oncology. Currently, hundreds of new mAbs are under clinical development, directed against validated or novel targets. Although engineered mAb fragments and nontraditional antibody-like scaffolds have been receiving increasing attention, most of such candidates evaluated in clinical trials are full-length mAbs.

Immuno-PET, the tracking and quantification of mAbs using positron emission tomography (PET) cameras, is an exciting innovation to increase the comprehension of *in vivo* behavior and efficacy of mAbs. Immuno-PET has recently reached maturity in terms of technical development and is now entering the phase of broad-scale clinical application.

This white paper will focus on immuno-PET using full-length mAbs and the associated application of the long-lived positron emitters zirconium-89 and iodine-124.

## Table of Contents

<b>Introduction: Immuno-PET applications</b>	<b>3</b>
<b>Immuno-PET: Principles and technical developments</b>	<b>4</b>
<b>Immuno-PET applications in research</b>	<b>6</b>
<b>From bench to bedside</b>	<b>7</b>
<b>Clinical results</b>	<b>9</b>
<b>A research challenge: reducing the radiation dose</b>	<b>11</b>
<b>Outlook</b>	<b>12</b>
<b>Research partners</b>	<b>13</b>
<b>References</b>	<b>15</b>

## Introduction: Immuno-PET applications

Monoclonal antibodies (mAbs) are the most rapidly expanding category of therapeutics. At present, the US Food and Drug Administration (FDA) has approved 30 mAbs for therapy, most of which for systemic treatment of cancer. Thus far, the FDA has approved 12 mAbs: rituximab, <sup>90</sup>Y-ibritumomab tiuxetan, <sup>131</sup>I-tositumomab, trastuzumab, cetuximab, panitumumab, bevacizumab, brentuximab vedotin, alemtuzumab, ipilimumab, ofatumumab and gemtuzumab ozogamicin. Annual sales for these mAbs were estimated at \$30 billion in 2010 [1,2,3]. In fact, despite the economic turndown, the mAb market grew to a massive \$48 billion as of 2010 [4,5]. Each of the top five mAbs had sales worth over \$5 billion in 2010. The average clinical development phase for FDA-approved mAbs is about 80 months [3].

More than 200 new mAb candidates are currently under clinical development by biotechnology and pharmaceutical companies worldwide. Most of these are humanized or human mAbs for treatment of cancer or immunological diseases. They are full-size immunoglobulin G (IgG) antibodies, rather than antibody fragments or third-generation, nontraditional antibody-like scaffolds [6,7]. At present, the pharmaceutical industry and academic centers are evaluating a large variety of mAbs in preclinical studies.

Treatment with mAbs is very expensive. For example, the cost of bevacizumab, also known as Avastin, for the treatment of advanced breast cancer can reach up to \$100,000 per patient per year [8]. Costs skyrocket if mAb treatment is used for managing chronic diseases, such as rheumatoid arthritis; orphan diseases, e.g. Pompe disease; cancer; or when combined mAb therapies are necessary. In view of the high costs for the development of mAbs and their low efficacy, a method should be in place to identify patients with the highest chance of benefiting from antibody-based therapy.

What can we do about this? New therapeutic mAbs already pose a heavy economic burden on national healthcare systems today. Recent national reports show that hospitals will not always treat all patients with the optimal mAb therapy due to excessive costs and limited likelihood of success [9]. How can we improve the situation?

Immuno-PET, the tracking and quantification of mAbs using positron emission tomography (PET), may offer a solution. It is a powerful innovation to improve the understanding of *in vivo* behavior and efficacy of mAbs. It combines the high sensitivity and resolution of a PET camera with the precision of a mAb [10]. Immuno-PET is like performing “comprehensive immunohistochemical staining *in vivo*”: the mAb is labeled with a positron emitter to enable visualization with a PET camera. In the past decade, crucial breakthroughs have been made that allow for broad-scale application of immuno-PET, both in clinical and research settings. Clinically, immuno-PET makes it possible to monitor individual patients before administration of expensive medicine, providing an opportunity to individualize mAb therapy. With immuno-PET, oncologists have a fast, efficient, reliable method at hand for matching patients with mAbs, for the greatest likelihood of success.

The tracking and quantification of monoclonal antibodies (mAbs) with positron emission tomography leads to improved understanding of the *in vivo* behavior and efficacy of mAbs.

By applying molecular imaging methods, pilot or phase 1 studies can much more effectively assess the potential of new drugs.

In research, immuno-PET is also being increasingly recognized as a powerful tool: R&D departments of pharmaceutical companies, for instance, now have an instrument at hand for improved selection of novel high-potential mAbs.

Immuno-PET enables the detailed characterization of drugs even at early stages of development (phase 0, I and II trials). This can help to select the most promising mAbs for large-scale phase III trials.

Overall, the stakeholders in the use of immuno-PET are:

- Individual patients and patient groups, who hope for the highest probability of cure with minimum morbidity rates.
- Physicians, who want their patients to have the best possible treatment.
- Pharmaceutical companies, which aim for rapid and inexpensive drug development and for application of mAbs in the appropriate patient group.
- Insurance companies and health care authorities, which demand optimal efficacy of medicaments at minimum cost [10].

In this white paper we will provide an overview of the main principles and technical developments around immuno-PET. This will be followed by a discussion of the benefits of immuno-PET in research settings. Finally, we will consider labeling mAbs according to good manufacturing practice (GMP) guidelines. Here, the commercial availability of a new coordinating ligand (chelate) for labeling mAbs with zirconium-89 ( $^{89}\text{Zr}$ ) achieves a dramatic simplification in favor of  $^{89}\text{Zr}$ -immuno-PET. Finally, we will review some impressive recent clinical results.

## Immuno-PET: Principles and technical developments

### Selection of a positron emitter

Immuno-PET is based on detection of a positron-emitting radionuclide that is labeled to a specific mAb. For a positron-emitting nuclide to be suitable for immuno-PET, it has to meet several requirements:

- Having appropriate decay characteristics for optimal resolution and quantitative accuracy, while its physical half-life should match the time needed for a mAb to provide optimal targeting (typically 2-4 days for intact mAbs).
- Simple and low-cost production, while enabling easy, efficient, stable labeling of mAbs.
- Offering labeling properties that do not influence the pharmacokinetics and biodistribution of the mAb.

In our view, two positron emitters are especially well suited for labeling intact mAbs: zirconium-89 ( $^{89}\text{Zr}$ ) and iodine-124 ( $^{124}\text{I}$ ). With their relatively long half-lives, these nuclides are ideal for obtaining maximum information when imaging is carried out several days after injection.

The advantages of  $^{89}\text{Zr}$  are manifold. It can be obtained at high yields with high radionuclidic purity. It has no prompt gamma emission that interferes with the overall image quality and accurate quantification. Recent studies revealed that  $^{89}\text{Zr}$  residualizes outstandingly after internalization of the antibody, a phenomenon also observed with other radiometals, such as yttrium-90, indium-111 and lutetium-177 [11]. In addition, the half-life values of  $^{89}\text{Zr}$  and  $^{124}\text{I}$  show evident advantages for logistics relating to labeling and transportation. A major advantage of  $^{124}\text{I}$  is that the radioiodination of proteins is a common practice within radiochemistry labs. Contrarily, alternative positron emitters like copper-64, yttrium-86 and bromine-76 are less suitable for imaging intact mAbs, especially due to their relatively short half-lives.

Table 1 below shows the main characteristics of positron emitters used in preclinical and clinical studies of immuno-PET.

Immuno-PET can deliver fast, reliable proof of principle. The scientific community and industry alike can now instantly obtain quantifiable results of *in vivo* research.

**Table 1**

Main characteristics of positron emitters used in preclinical and clinical immuno-PET studies

Positron emitter	Common production routes	Half-life (h)	Main $\beta^{+-}$ energies (keV)	(%)	Intrinsic spatial resolution loss (mm)
$^{64}\text{Cu}$	$^{64}\text{Ni}(d,2n)$ $^{64}\text{Ni}(p,n)$	12.7	653	17.4	0.7
$^{86}\text{Y}$	$^{86}\text{Sr}(p,n)$	14.7	1221 1545	11.9 5.6	1.8
$^{76}\text{Br}$	$^{76}\text{Se}(p,n)$	16.2	871 990 3382 3941	6.3 5.2 25.8 6.0	5.3
$^{89}\text{Zr}$	$^{89}\text{Y}(p,n)$	78.4	897	22.7	1.0
$^{124}\text{I}$	$^{124}\text{Te}(p,n)$ $^{124}\text{Te}(d,2n)$ $^{125}\text{Te}(p,2n)$	100.3	1535 2138	11.8 10.9	2.3

## Immuno-PET applications in research

In research settings, quantitative PET imaging of therapeutic mAbs is an invaluable tool at several stages of mAb development and application. For instance, preclinical immuno-PET studies in xenograft-bearing nude mice can help measure the efficiency of tumor targeting with a particular mAb. In toxicology studies of non-human primates, the regulation of target expression can be useful when assessing cross-reactivity with normal tissues, in relation to mAb protein doses.

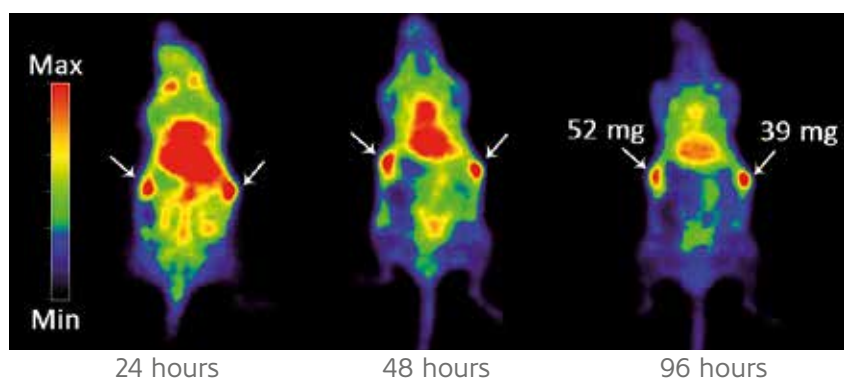
First-in-man clinical trials with new mAbs particularly benefit from immuno-PET. In these studies, it is important to establish the ideal mAb dose required for optimal targeting (e.g. saturation of receptors), the uptake in normal critical organs to anticipate toxicity, as well as inter-patient variations in pharmacokinetics. Imaging mAbs with immuno-PET provides this information efficiently and safely. As a result, fewer patients are treated at suboptimal levels. This approach is particularly favorable when the mAb of interest is directed against a novel target that has not been validated in clinical trials before.

Quantitative mAb imaging may also be of value as a guide to the optimal use of FDA-approved mAbs.

In all these settings, immuno-PET offers the following advantages:

- assessment of target status (“comprehensive immunohistochemistry *in vivo*”);
- assessment of pharmacokinetics and biodistribution;
- confirmation of selective targeting and prediction of toxicity;
- optimization of mAb dose scheduling;
- identification of indications and patient groups;
- therapy planning and individualization.

These advantages are clearly visible from early preclinical trials with immuno-PET in tumor-bearing mice (see Figure 1). The  $^{89}\text{Zr}$ -labeled mAb demonstrated very good *in vivo* stability and selective tumor targeting.



**Figure 1**

PET images (coronal slices) of a GTL-16-xenograft-bearing nude mouse at 24, 48 and 96 hours after injection with  $^{89}\text{Zr}$ -labeled mAb DN30. This mAb targets the extracellular domain of c-Met. Tumors (arrows) could be clearly visualized as early as 24 hours p.i. and good delineation of the tumors persisted throughout the final imaging session. Tumor localization was obvious, in addition to some blood pools, which diminished over time, and liver and spleen uptake.

To translate immuno-PET from preclinical research to a phase I clinical trial, it is necessary to create a pharmaceutical quality formulation. This formulation has to be manufactured according to current good manufacturing practice (cGMP) guidelines. How can this be achieved?

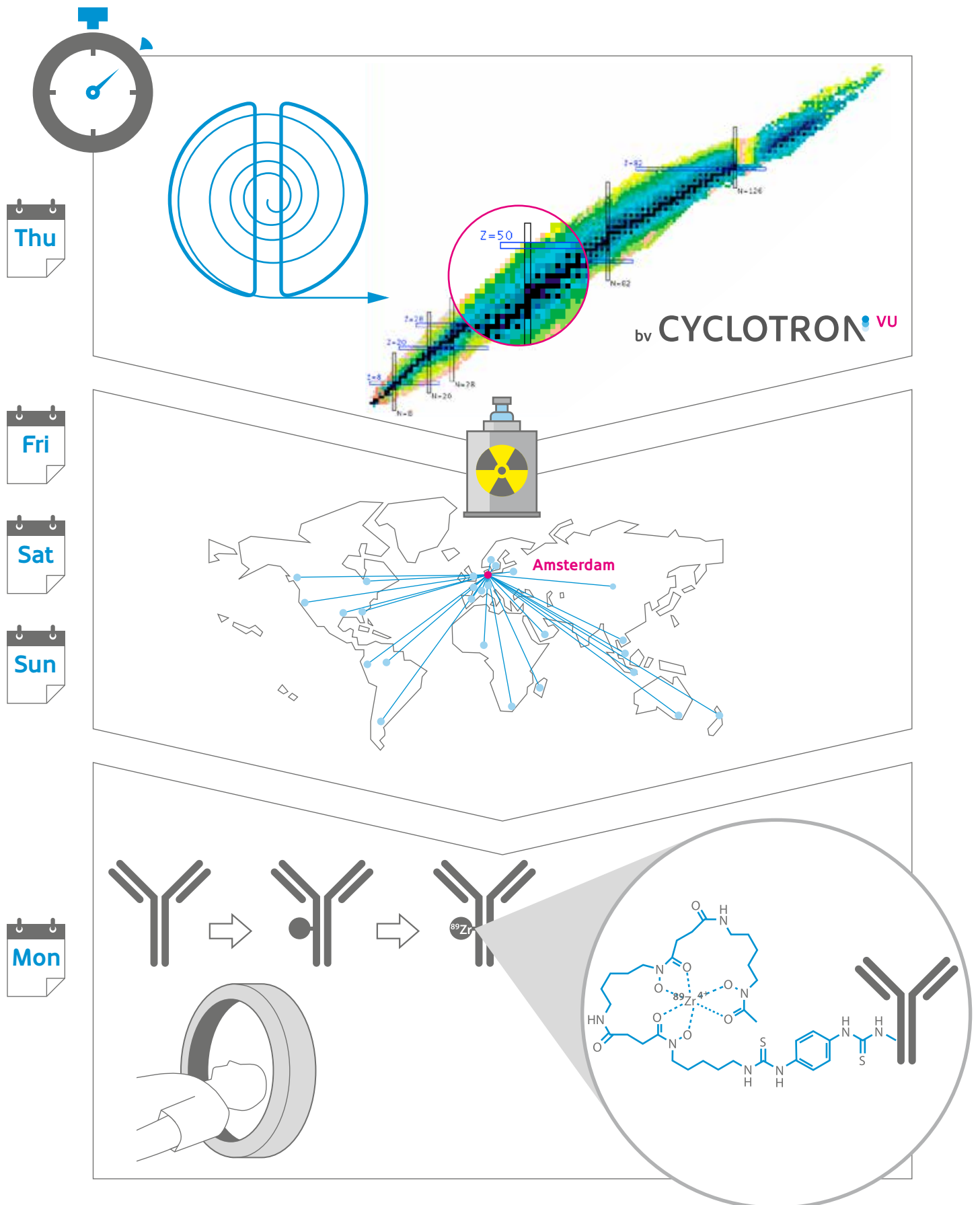
In most cases, the radionuclides used for radiolabeling have to be classified as active pharmaceutical ingredients (APIs). This is especially so when the final preparation is released for use without further purification. Also the coordinating ligands (chelates), which are used for binding the radionuclides to the mAb, have to be classified as APIs.

While a large number of radiochemistry centers in the world have licenses and experience working with iodine isotopes, this is not the case with  $^{89}\text{Zr}$ . Until recently, radiolabeling with  $^{89}\text{Zr}$  was a complicated procedure requiring multiple steps, and it proved challenging to maintain cGMP compliant. The multistep procedure was developed between 2001 and 2003 by researchers at the VU University Medical Center (VUmc), Amsterdam. They used a succinylated derivative of desferrioxamine B (N-sucDf) as a bifunctional chelate [12]. Desferrioxamine B was an attractive option, having been used safely in clinical practice for many years.

In May 2012, ABX, a company that produces and develops chemicals for nuclear medicine, added the N-sucDf chelate to their portfolio. In the mean time, researchers at the VU University Medical Center developed, together with Macrocyclics, Dallas, USA, a more suitable way of binding  $^{89}\text{Zr}$  to mAbs, which overcomes the main flaw of existing labeling procedures. It is a simple two-step process, fast and easy to carry out. The two ingredients,  $^{89}\text{Zr}$  and the appropriate chelate, are available to order as stock products and can be delivered worldwide within a few days (see Figure 2 and our white paper " $^{89}\text{Zr}$ -immuno-PET").

As mentioned previously, it is important to note that  $^{89}\text{Zr}$  is trapped inside the cell after internalization of the mAb.  $^{89}\text{Zr}$  also residualizes to some extent in organs affected by mAb catabolism, such as liver, kidney and spleen [11]. As for the new chelate, it is still based on desferrioxamine B, but in a modified form. The novel chelate is *p*-isothiocyanatobenzyl-desferrioxamine B (Df-Bz-NCS) [13]. This chelate is key for easily labeling mAbs, as it allows for efficient and rapid preparation of the final  $^{89}\text{Zr}$ -labeled molecule. After radiolabeling, quality analyses must be performed. These include routine tests to assess the chelate-substitution ratio, radiochemical purity, mAb integrity and immunoreactivity, and apyrogenicity.

A different routine is required for labeling with  $^{124}\text{I}$ . Unlike  $^{89}\text{Zr}$ , which needs to be coupled via a chelate to the lysine residues of the mAb,  $^{124}\text{I}$  can be directly bound via tyrosine residues. Procedures have been established for efficient coupling of  $^{124}\text{I}$  [14]. This makes the handling of  $^{124}\text{I}$  much easier in a high-grade, cGMP-compliant setting. For both these nuclides, all clinical reagents and procedures are in place to introduce broad-scale application of immuno-PET with  $^{89}\text{Zr}$ - and  $^{124}\text{I}$ -labeled intact mAbs. In our view,  $^{89}\text{Zr}$  shall be the best candidate for about 80% of the immuno-PET applications.  $^{89}\text{Zr}$  is particularly suitable for PET imaging of internalizing mAbs, while  $^{124}\text{I}$  is the radionuclide of choice in combination with noninternalizing mAbs.



**Figure 2**

Due to the half-life of radioactive materials, a short turnaround period between production and clinical application is vital. The logistics of immuno-PET is depicted above. Step 1: we produce  $^{89}\text{Zr}$  in a cGMP-compliant way in batches of up to 20 GBq, and  $^{124}\text{I}$  in batches of up to 3 GBq. Step 2: our partners distribute our products. Step 3: labeling the antibody requires two ingredients -  $^{89}\text{Zr}$  and the appropriate chelate. Both can be easily ordered as stock products.



## <sup>89</sup>Zr-labeled mAbs

In recent years, highly successful clinical trials have been carried out using immuno-PET.

The first-in-human <sup>89</sup>Zr-immuno-PET trial was conducted between 2003 and 2005, at the VUmc in Amsterdam, with <sup>89</sup>Zr-labeled-cmAb U36 [15,16]. The objective of this study was to verify whether the imaging probe was safe and capable of clearly delineating CD44v6-positive tumors. The study aimed to determine the diagnostic value of immuno-PET with <sup>89</sup>Zr-mAb U36 in patients with head and neck squamous cell carcinoma (HNSCC) who were at high risk of having neck lymph node metastases. Twenty HNSCC patients scheduled to undergo resection of the primary tumor and unior bilateral neck dissection underwent computed tomography (CT) or magnetic resonance imaging (MRI), or both, and <sup>89</sup>Zr-cmAb U36 immuno-PET prior to surgery.

Compared to CT and MRI scans, immuno-PET results were remarkably accurate. The <sup>89</sup>Zr-cmAb U36 immuno-PET scans detected all primary tumors (n=17), in addition to 18 lymph node metastases, out of 25 positive neck nodes. The missed lymph nodes were relatively small in size, and they contained only a small proportion of tumor tissue.

After this first clinical trial with <sup>89</sup>Zr, other Dutch sites also began clinical trials using <sup>89</sup>Zr. Several trial programs were started at academic hospitals in Groningen, Nijmegen and Maastricht. Shortly thereafter, sites in Brussels and London also initiated their first clinical trials with <sup>89</sup>Zr-immuno-PET.

One of the first examples of clinical immuno-PET trials is currently being conducted at the Jules Bordet Institute in Brussels, Belgium. Researchers performed immuno-PET imaging with <sup>89</sup>Zr-labeled rituximab in patients with CD20+ B-cell lymphoma. Excellent images were obtained (see Figure 3). One of the objectives of this research is to compare the diagnostic accuracy of <sup>89</sup>Zr-rituximab-PET/CT with standard [<sup>18</sup>F]FDG-PET/CT. A preliminary evaluation in 14 patients with follicular lymphoma showed significant uptake of [<sup>89</sup>Zr]rituximab in all FDG-positive lesions. In some patients, <sup>89</sup>Zr-rituximab-PET/CT revealed additional CD20+ lesions that were strictly negative on [<sup>18</sup>F]FDG-PET/CT (unpublished data). Those lesions corresponded to particularly small (≤ 1 cm) lymph nodes and mesenteric nodules on CT images.

It was established that <sup>89</sup>Zr-rituximab-PET/CT is an outstanding diagnostic tool for precise quantification of CD20 antigen expression. This is of particular interest for dosimetry as a prelude to radioimmunotherapy with <sup>90</sup>Y-rituximab.

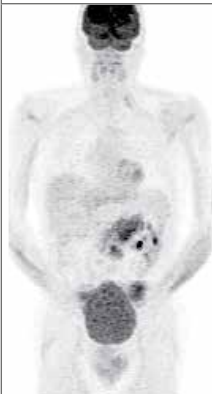
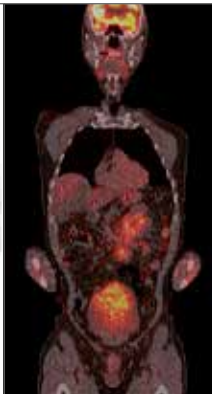

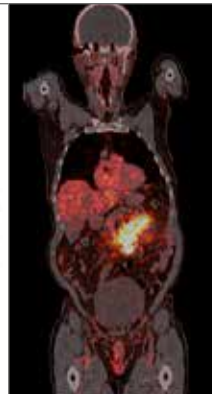

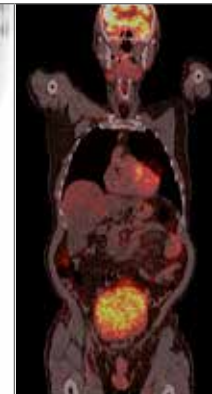
The European results also led to the first clinical trials for <sup>89</sup>Zr-immuno-PET in the United States. The trials currently carried out in clinical research centers in Frederick (MD), New York (NY) and Sacramento (CA) are part of programs being conducted at the National Cancer Institute, Memorial Sloan-Kettering Cancer Center and the University of California (see Figure 4).

Furthermore, pharmaceutical companies such as Genentech, considered the forerunner of the biotechnology industry, have recently started to incorporate <sup>89</sup>Zr-immuno-PET into their antibody develop-

The technology for labeling antibodies with <sup>89</sup>Zr and <sup>124</sup>I has become very accessible. A simple two-step procedure makes it ideal for preclinical and clinical settings.

ment research programs [17]. In this type of research, immuno-PET technology can be especially beneficial when the mAb of interest is directed against a novel target that has not previously been validated in clinical trials. This includes, for instance, mAbs directed against new tumor cell and tumor stroma targets, such as c-Met, vascular endothelial growth factor receptors (VEGFRs), insulin-like growth factor receptors and death receptors.

The overall effect of these applications is that the number of papers published about preclinical and clinical results with  $^{89}\text{Zr}$ -immuno-PET is steadily growing [10].

$^{18}\text{F}$ FDG-PET/CT before treatment with $^{90}\text{Y}$ -rituximab		Immuno-PET/CT 6 days p.i. of $^{89}\text{Zr}$ -rituximab		$^{18}\text{F}$ FDG-PET/CT 6 months after treatment with $^{90}\text{Y}$ -rituximab (0,4 mCi/kg) showing a complete remission	
					
MIP	Coronal Slice	MIP	Coronal Slice	MIP	Coronal Slice

**Figure 3**

Immuno-PET imaging with  $^{89}\text{Zr}$ -rituximab in a patient with CD20+ B-cell lymphoma. Immuno-PET with  $^{89}\text{Zr}$ -rituximab shows a remarkably higher tumor-to-background ratio compared to  $^{18}\text{F}$ FDG-PET/CT.

### $^{124}\text{I}$ -Labeled mAbs

$^{124}\text{I}$ -labeled mAbs were already used for clinical immuno-PET about 15 years ago, but the number of patients included in these studies was small [18,19]. At that time, diagnostic results were suboptimal, partly because of poor quality of the murine mAbs used, which lacked the precision of today's mAbs [20]. Now, however, interest in  $^{124}\text{I}$ -labeled mAbs has returned.

This is, to a certain degree, due to the improved methods of  $^{124}\text{I}$  production and its coupling to mAbs. Recently, two clinical applications have particularly attracted much attention. Jayson et al. [21] used various doses of  $^{124}\text{I}$ -HuMV833, a mAb binding to VEGF121 and VEGF165, to perform PET-imaging studies in 12 patients with various progressive solid tumors. The results were very promising: by using  $^{124}\text{I}$ -immuno-PET imaging, it was demonstrated that antibody distribution and clearance were markedly heterogeneous between and within patients, varying substantially even between and within individual tumors. These differences may represent the variation in available targets for the mAb.

This is highly valuable knowledge, and may have implications for future anti-VEGF therapies. Similar studies have begun using  $^{89}\text{Zr}$ -bevacizumab as imaging probe [22,23].

In another clinical setting,  $^{124}\text{I}$ -immuno-PET was used for *in vivo* profiling of renal cancer. Divgi et al. [24] used  $^{124}\text{I}$ -cmAb G250 to predict the presence of clear-cell renal carcinomas in 25 patients scheduled for surgical tumor resection. G250 is directed against carbonic anhydrase-IX and overexpressed in clear-cell renal carcinoma. It might be worthwhile to know which renal cancer patients have this aggressive tumor type, an information that can be used to guide future treatment decisions, although opinions on this point vary [25]. With immuno-PET, it was possible to accurately identify 15 out of 16 clear-cell carcinomas, as well as all nine non-clear-cell renal masses. In addition,  $^{124}\text{I}$ -immuno-PET with G250 is currently in a phase III clinical trial in the United States, aiming to assess the potential of the G250 antibody as adjuvant therapy, i.e., a therapy given after surgical removal of the tumor, in patients with non-metastatic RCC.

These studies illustrate how molecular imaging with specific probes can contribute to personalized medicine.

The overall results of clinical trials with  $^{89}\text{Zr}$ -immuno-PET and  $^{124}\text{I}$ -immuno-PET show that both methods have already been successful in clinical settings. Immuno-PET provides a new, clinically safe precision tool for enhancing knowledge on the efficacy of mAb therapy. In turn, this may lead to more efficient mAb development and to more patient-tailored therapy. These crucial achievements have prepared the way for broad-scale clinical application of  $^{89}\text{Zr}$ - and  $^{124}\text{I}$ -immuno-PET.

## A research challenge: reducing the radiation dose

At present, one of the most challenging research questions in the field of immuno-PET is how to reduce the radiation dose of an immuno-PET imaging procedure. The mean radiation dose for patients receiving 74 MBq  $^{89}\text{Zr}$  is about 40 mSv [17], which is high and limits repeated applications of  $^{89}\text{Zr}$ -immuno-PET.

However, solutions have already been found: higher-sensitivity PET scanners are currently being developed and entering the market. These scanners require less radioactivity to be injected, without any loss of resolution. Better scanning softwares will further improve sensitivity and resolution, which directly translates into lower doses of injected radioactivity. Indeed, recent PET/CT studies using 37 MBq of  $^{89}\text{Zr}$ -trastuzumab produced images of excellent quality at an effective dose of about 20 mSv [26].

Both  $^{89}\text{Zr}$  and  $^{124}\text{I}$  are produced commercially on a weekly basis. Worldwide distribution channels make high-grade material available within two days.

Immuno-PET makes it possible to identify individual patients or patient groups. Even the differences in antibody half-time in individual patients can be made visible this way. Mechanisms of antibodies are now much easier to understand. This can lead to highly effective drug optimization strategies.

Immuno-PET supports academic research institutes to more easily initiate potential industry and investor partnerships, as new research results are quantified with greater accuracy.

Immuno-PET is an important step forward on the path towards personalized medicine.

## Outlook

Molecular imaging with the innovative PET tracers  $^{89}\text{Zr}$  and  $^{124}\text{I}$  can considerably accelerate drug development and facilitate improved patient selection. The ability to understand the added value of new antibodies during early stages of preclinical or clinical trials amounts to nothing less than a paradigm shift. The pharmaceutical industry realizes that molecular imaging may help transform its research and development operations and find more efficient ways to be innovative. Academic biomedical research institutions are also able to initiate potential partnerships with investors more easily if the results of new research can be quantified with greater accuracy.

Overall, this may support researchers in both academia and industry to more effectively translate their ideas and research into improved drug therapies. A review of recent literature on clinical trials shows that immuno-PET with  $^{89}\text{Zr}$  and  $^{124}\text{I}$  may be an effective instrument for improving knowledge on the efficacy of mAb therapy. This comprehension will ultimately contribute to the development of more efficient mAbs, as well as therapies more tailored towards patient needs.

We strongly believe that the overall positive clinical results of recent years will develop into broad-scale preclinical and clinical application of  $^{89}\text{Zr}$ - and  $^{124}\text{I}$ -immuno-PET. This is a major breakthrough as it is a crucial step forward on the path towards personalized medicine.

# Research partners

## About BV Cyclotron VU

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 [ $^{18}\text{F}$ ]FDG, [ $^{18}\text{F}$ ]FCH, [ $^{18}\text{F}$ ]Florbetaben (NeuraCeq<sup>TM</sup>),  $^{124}\text{I}$ ,  $^{89}\text{Zr}$  and other  $^{18}\text{F}$ -labeled compounds for the PET community, as well as  $^{123}\text{I}$  and  $^{81}\text{Rb}/^{81\text{m}}\text{Kr}$  generators for the SPECT community.

In Amsterdam, BV Cyclotron VU runs one of the first commercial production sites of  $^{89}\text{Zr}$  in the world. Academic sites such as the Memorial Sloan Kettering in New York, University of Wisconsin, Madison, and Paul Scherrer Institute in Zurich, Switzerland, produce  $^{89}\text{Zr}$  on request and for research purposes only [27].

BV Cyclotron VU's mission is to make a wide range of PET compounds available. The 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 distributed by our worldwide distributor partners see our website: [www.cyclotron.nl/distributors](http://www.cyclotron.nl/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.

[www.cyclotron.nl](http://www.cyclotron.nl)



## About VUmc

The core activities of the VU University Medical Center (VUmc) are patient care, education and scientific research. The scientific research carried out at VUmc is closely linked to issues that are relevant both for the hospital itself and for society in general. Its main focal areas are oncology, neurology, immunology, vital functions and extramural research. The research output at VUmc translates to approximately 2,000 publications and reports per year, of which around 100 are doctoral theses. The aim of the research is to expand knowledge (fundamental research) and to apply this knowledge to health services (strategic and applied research). A staff of around 7,000 professionals and trainees ensure the smooth and efficient running of the medical center.

[www.vumc.nl](http://www.vumc.nl)





● **Partners in research**

VU University Medical Center, Amsterdam, The Netherlands  
 Macrocyclics, Dallas, USA  
 VU Imaging Center, Amsterdam, The Netherlands (will be established in 2016)

● **Partners in logistics**

IBA, Louvain-La Neuve, Belgium  
 Covidien, Petten, The Netherlands  
 Von Gahlen, Zevenaar, The Netherlands  
 PerkinElmer, USA

● **Zirconium-89 and iodine-124 client sites**

EUROPE

Austria:  
 Wien  
 Belgium:  
 Antwerpen  
 Brussels\*  
 Leuven  
 Liège  
 France:  
 Cedex  
 Nantes  
 Paris  
 Vitry-Sur-Seine  
 Germany:  
 Dresden  
 Essen  
 Halle  
 Jena  
 Mainz  
 Munich  
 Tübingen  
 Netherlands:  
 Amsterdam\*  
 Delft  
 Eindhoven  
 Groningen\*

Nijmegen\*  
 Maastricht\*  
 Spain:  
 Madrid,  
 San Sebastian  
 Pamplona  
 Switzerland:  
 Zurich  
 United Kingdom:  
 London  
 Manchester  
 Oxford

WORLDWIDE

Beijing, China  
 Singapore  
 Heidelberg, Victoria, AUS  
 Melbourne, AUS

USA & CANADA

Austin, TX, USA  
 Boston, MA, USA  
 Cambridge, MA, USA  
 Davis, CA, USA  
 Frederick, MD, USA  
 New Haven, CT, USA  
 New York, NY, USA\*  
 Sacramento, CA, USA  
 San Francisco, CA, USA  
 Hamilton, ON, Canada  
 Vancouver, BC, Canada

\*Institutes where clinical trials are running with <sup>89</sup>Zr- or <sup>124</sup>I-immuno-PET

**Figure 4**

BV Cyclotron VU cooperates with some of the most important immuno-PET research centers in Europe and the USA. With three cyclotrons and several GMP hot labs, we are one of the best-equipped centers for the production of radiopharmaceuticals in the world. With PerkinElmer as a logistics partner, GMP-compliant grade <sup>89</sup>Zr and <sup>124</sup>I can be delivered anywhere in the world within a few days.

- 1 Maggon K. Monoclonal antibody “gold rush”. *Curr Med Chem.* 2007;14:1978.
- 2 Lawrence S. Billion dollar babies-biotech drugs as blockbusters. *Nat Biotechnol.* 2007;25:380.
- 3 Reichert JM. Monoclonal antibodies as innovative therapeutics. *Curr Pharm Biotechnol.* 2008;9:423.
- 4 Reichert JM. Antibody-based therapeutics to watch in 2011. *MAbs.* 2011; 3: 76-99.
- 5 Maggon K. Top Ten Monoclonal Antibodies. *KnoL* 2012.
- 6 Nelson AL, Reichert JM. Development trends for therapeutic antibody fragments. *Nat Biotechnol.* 2009;27:331.
- 7 Reichert JM. Monoclonal antibody. *MAbs.* 2009;1:189.
- 8 Kolata G, Pollack A. The evidence gap--Costly cancer drug offers hope, but also a dilemma. *New York Times.* July 6, 2008.
- 9 Neyt M, Albrecht J, Cocquyt V. An economic evaluation of Herceptin in adjuvant setting: The breast Cancer International Research Group 006 trial. *Ann Oncol.* 2006;17:381.
- 10 van Dongen GAMS, Vosjan MJWD. Immuno-positron emission tomography: Shedding light on clinical antibody therapy. *Cancer Biother Radiopharm.* 2010;25;375.
- 11 Perk LR, Visser GWM, Vosjan MJWD, et al. (89)Zr as a PET surrogate radioisotope for scouting biodistribution of the therapeutic radiometals (90)Y and (177)Lu in tumor-bearing nude mice after coupling to the internalizing antibody cetuximab. *J Nucl Med.* 2005;46:1898.
- 12 Verel I, Visser GWM, Boellaard R, et al. <sup>89</sup>Zr immuno-PET: Comprehensive procedures for the production of <sup>89</sup>Zr-labeled monoclonal antibodies. *J Nucl Med.* 2003;44:1271.
- 13 Perk LR, Vosjan MJWD, Visser GWM, et al. p-Isothiocyanatobenzyl- desferrioxamine: A new bifunctional chelate for facile radiolabeling of monoclonal antibodies with zirconium-89 for immuno-PET imaging. *Eur J Nucl Med Mol Imaging.* 2010;37:250.
- 14 Tijink BM, Perk LR, Budde M, et al. (124)I-L19-SIP for immuno-PET imaging of tumour vasculature and guidance of (131)I-L19-SIP radioimmunotherapy. *Eur J Nucl Med Mol Imaging.* 2009;36:1235.
- 15 Börjesson PKE, Jauw YWS, Boellaard R, et al. Performance of immunopositron emission tomography with zirconium-89-labeled chimeric monoclonal antibody U36 in the detection of lymph node metastases in head and neck cancer patients. *Clin Cancer Res.* 2006;12:2133.
- 16 Börjesson PKE, Jauw YWS, De Bree R, et al. Radiation dosimetry of zirconium-89-labeled chimeric monoclonal antibody U36 as used for immuno-PET in head and neck cancer patients. *J Nucl Med.* 2009;50:1828.
- 17 Tinianow JN, Gill HS, Ogasawara A, et al. Site-specifically <sup>89</sup>Zr-labeled monoclonal antibodies for immunoPET. *Nucl Med Biol.* 2010;37:289.

- 18 Wilson CB, Snook DE, Dhokia B, et al. Quantitative measurement of monoclonal antibody distribution and blood flow using positron emission tomography and  $^{124}\text{I}$  in patients with breast cancer. *Int J Cancer*. 1991;47:344
- 19 Larson SM, Pentlow KS, Volkow ND, et al. PET scanning of iodine-124-3F9 as an approach to tumor dosimetry during treatment planning for radioimmunotherapy in a child with neuroblastoma. *J Nucl Med*. 1992;33:2020.
- 20 Zukier LS, DeNardo GL. Trials and tribulations: oncological antibody imaging comes to the fore. *Semin Nucl Med*. 1997;27:10.
- 21 Jayson GC, Zweit J, Jackson A, et al. Molecular imaging and biological evaluation of huMV833 anti-VEGF antibody: implications for trial design of antiangiogenic antibodies. *J Natl Cancer Inst*. 2002;94:1484.
- 22 Nagengast WB, De Vries EG, Hospers GA, et al. In vivo VEGF imaging with radio-labeled bevacizumab in a human ovarian tumor xenograft. *J Nucl Med*. 2007;48:1313.
- 23 Nagengast WB, De Korte A, Oude Munnink TH, et al.  $^{89}\text{Zr}$ -bevacizumab PET of early anti-angiogenic tumor response to treatment with HSP90 inhibitor NVP-AUY922. *J Nucl Med*. 2010;51:761.
- 24 Divgi CR, Pandit-Taskar N, Jungbluth AA, et al. Preoperative characterization of clear-cell renal carcinoma using iodine-124-labeled antibody chimeric G250 ( $^{124}\text{I}$ -cG250) and PET in patients with renal masses: a phase I trial. *Lancet Oncol*. 2007;8:304.
- 25 Powles T, Ell PJ. Does PET imaging have a role in renal cancers after all? *Lancet Oncol*. 2007;8:279.
- 26 Dijkers EC, Oude Munnink TH, Kosterink JG, et al. Biodistribution of  $^{89}\text{Zr}$ -trastuzumab and PET imaging of HER2-positive lesions in patients with metastatic breast cancer. *Clin Pharmacol Ther*. 2010;87:586.
- 27 Holland JP, Sheh Y, Lewis JS. Standardized methods for the production of high specific-activity zirconium-89. *Nucl Med Biol*. 2009;36:729.

For more information see: [2cyc.eu/zr89a](http://2cyc.eu/zr89a)

## Imprint

### Text

Lars R. Perk, PhD, Sybe I. Rispens, PhD

### Editing and Production

Knowledgeatwork ([www.knowledgeatwork.eu](http://www.knowledgeatwork.eu))

### Infographics and Layout

WERNERWERKE GbR