

The Future of Immuno-PET in Drug Development

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

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radiopharmaceuticals and radionuclides





Abstract

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

Immuno-PET, the tracking and quantification of mAbs with positron emission tomography (PET) cameras, is an exciting innovation for improving understanding of the 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.

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Introduction: Applications of immuno-PET

Monoclonal antibodies (mAbs) are probably the most rapidly expanding category of medicines. At present the US Food and Drug Administration (FDA) has approved 24 mAbs for therapy; most of them are for systemic treatment of cancer. For example, rituximab, ⁹⁰Y-ibritumomab tiuxetan, ¹³¹I-tositumomab, trastuzumab, cetuximab, panitumumab, and bevacizumab are all FDA approved. The annual sales for these mAbs were estimated at \$20 billion in 2006 [1,2]. The market is growing by about 14% each year [3]. Eight mAbs had sales of more than \$1 billion in 2007 [3]. The average clinical-development phase for FDA-approved mAbs is about 80 months, while for anticancer mAbs it takes on average 90.8 months [3].

More than 200 new mAb candidates are currently under clinical development by biotechnology and pharmaceutical firms worldwide. Most of them are humanized or human mAbs for cancer and immunological diseases. They are full-size immunoglobulin G (IgG) antibodies, rather than antibody fragments or third-generation, nontraditional antibody-like scaffolds [4,5]. The pharmaceutical industry and academic centers are evaluating a large variety of mAbs in preclinical studies at the moment.

Treatment with mAbs is extremely 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 [6]. Costs skyrocket if mAb treatment is used for managing chronic diseases, such as rheumatoid arthritis and cancer, or when combined mAb therapies are necessary. Worse still, the high costs of mAbs go hand in hand with low efficacy: until now there has been no way of identifying patients with the highest chance of success with 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 [7]. How can we improve the situation?

Immuno-PET, the tracking and quantification of mAbs with positron emission tomography (PET), can offer a solution. It is a powerful innovation for improving understanding of the in vivo behavior and efficacy of mAbs. It combines the high sensitivity and resolution of a PET camera with the precision of a mAb [8]. 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 as well as research settings.

In clinical settings, immuno-PET makes it possible to monitor individual patients before administering expensive medicines, which provides an opportunity to individualize mAb therapy. With immuno-PET, oncologists have a fast, efficient, reliable method at hand for matching patients with mAbs with the greatest likelihood of success.

In research, immuno-PET is also rapidly turning into a powerful tool: R & D departments of pharmaceutical companies, for instance, now have a tool at hand for improved selection of novel high-potential mAbs. Immuno-PET

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 assess the potential of new drugs much more effectively.

makes detailed characterization of drugs possible during 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 want the highest probability of cure at minimum morbidity rates
- Physicians who want their patients to have the best possible treatment
- Pharmaceutical companies that aim for rapid and cheap drug development and the application of mAbs in the appropriate patient group
- Insurance companies and health care authorities that demand optimal efficacy of medicines at minimum cost [8]

In this white paper we will provide an overview of the main principles and technical developments of immuno-PET. This will be followed by a discussion of the benefits of immuno-PET in research settings. We will then 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}Zr) achieves a dramatic reduction in complexity for ^{89}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 coincidence 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:

- It should have appropriate decay characteristics for optimal resolution and quantitative accuracy, while the physical half-life of the positron emitter should match with the time needed for a mAb to achieve optimal targeting (typically 2-4 days for intact mAbs).
- Its production should be simple and inexpensive, and it should enable easy, efficient, stable labeling of mAbs.
- The labeling with the positron-emitting radionuclide should not influence the pharmacokinetics and the biodistribution of the mAb.

In our view, two positron emitters are best suited to labeling intact mAbs: zirconium-89 (^{89}Zr) and iodine-124 (^{124}I). Their relatively long half-life makes them ideal for obtaining maximum information when imaging is carried out several days after injection. The advantages of ^{89}Zr are manifold: ^{89}Zr can be obtained at high yields with high radionuclidic purity. ^{89}Zr has no prompt gammas that interfere with the overall image quality and accurate quantification. Recent studies revealed that ^{89}Zr residualizes excellently after internalization of the antibody, a phenomenon also observed with other radiometals, for example, yttrium-90, indium-111, and lutetium-177 [9]. In addition, the half-life of ^{89}Zr and ^{124}I will evidently have advantages for logistics relating to labeling and transportation. A major advantage of ^{124}I is that the radioiodination of proteins is a common practice within radiochemistry labs. Also, alternative positron emitters like copper-64, yttrium-86, and bromium-76 are less suitable for imaging intact mAbs, especially due to their relatively short half-life.

Table 1

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

Positron emitter	Common production routes	Half-life (h)	Main β^{+-} energies (keV)	(%)	Intrinsic spatial resolution loss (mm)
^{64}Cu	$^{64}\text{Ni}(d,2n)$ $^{64}\text{Ni}(p,n)$	12.7	653	17.4	0.7
^{86}Y	$^{86}\text{Sr}(p,n)$	14.7	1221 1545	11.9 5.6	1.8
^{76}Br	$^{76}\text{Se}(p,n)$	16.2	871 990 3382 3941	6.3 5.2 25.8 6.0	5.3
^{89}Zr	$^{89}\text{Y}(p,n)$	78.4	897	22.7	1.0
^{124}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 can deliver fast, reliable proof of principle. The scientific community and industry alike can now obtain quantifiable results of in vivo research instantly.

Applications of immuno-PET 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 to measure the efficiency of tumor targeting with a particular mAb. Another example is toxicology studies in nonhuman primates. Here, 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 trials, it is important to identify the ideal mAb dose required for optimal targeting (e.g., saturation of receptors), the uptake in critical normal organs to anticipate toxicity, and the interpatient variations in pharmacokinetics. Imaging mAbs with immuno-PET provides this information efficiently and safely. As a result, fewer patients will be 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:

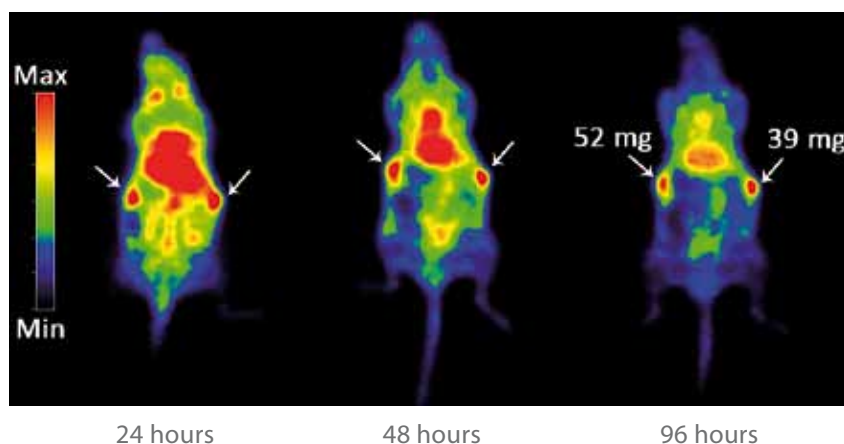
- Assessing target status (“comprehensive immunohistochemistry in vivo”)
- Assessing pharmacokinetics and biodistribution
- Confirming selective targeting and predicting toxicity
- Optimizing mAb dose scheduling
- Identifying indications and patients groups
- Therapy planning and individualization

Immuno-PET can dramatically reduce the number of patients required to carry out clinical studies.

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

Figure 1

High Resolution Research Tomograph (HRRT) PET images (coronal slices) of a GTL-16-xenograft-bearing nude mouse at 24, 48, and 96 hours after injection with the ^{89}Zr -labeled mAb DN30. This mAb targets the extracellular domain of c-Met. The 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 along with some blood pool, which diminished over time, and liver and spleen uptake.



From bench to bedside

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, will 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}Zr . Until recently, radiolabeling with ^{89}Zr was a complicated procedure requiring multiple steps, and it proved challenging to remain 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 [10]. Desferrioxamine B was an attractive option because it has been used safely in clinical practice for many years.

Recently, however, we have developed a much better way of binding ^{89}Zr to mAbs that overcomes the main flaw of existing labeling procedures. It is a simple two-step process that is fast and easy to carry out. The two ingredients, ^{89}Zr and the appropriate chelate, are available to order as stock products and can be delivered worldwide within a few days (see figure 3).

As mentioned previously, it is important to note that ^{89}Zr is trapped inside the cell after internalization of the mAb. ^{89}Zr also residualizes to some extent in organs affected by mAb catabolism, such as the liver, kidney, and spleen [9].

As for the new chelate, it is still based on desferrioxamine B, but in a modified form. The modification was developed at VUmc together with Macrocyclics, Dallas, USA. The novel chelate is BFC p-isothiocyanatobenzyl-desferrioxamine B (Df-Bz-NCS) [11]. This chelate is key to labeling mAbs easily, as it allows for efficient and rapid preparation of ^{89}Zr -labeled mAbs.

After radiolabeling, quality analyses have to be performed. These include routine tests to assess the chelate-substitution ratio, radiochemical purity, mAb integrity and immunoreactivity, and apyrogenicity.

Unlike ^{89}Zr , which needs to be coupled via a chelate to the lysine residues of a mAb, ^{124}I can be coupled directly via tyrosine residues. Procedures have been established for efficient coupling of ^{124}I [12]. This makes the handling of ^{124}I much easier in a high-grade cGMP-compliant setting.

For both ^{89}Zr and ^{124}I , all clinical reagents and procedures are in place to introduce broad-scale application of immuno-PET with ^{89}Zr - and ^{124}I -labeled intact mAbs.

In our view, ^{89}Zr will be the best candidate for about 80% of the immuno-PET applications. ^{89}Zr is particularly suitable for PET imaging of internalizing mAbs, while ^{124}I is the radionuclide of choice in combination with noninternalizing mAbs.

The technology for labeling antibodies with ^{89}Zr and ^{124}I has been made very accessible. A simple two-step procedure makes it ideal for preclinical and clinical settings.

Clinical results

In recent years highly successful clinical trials have been conducted using immuno-PET.

The first-in-human ^{89}Zr -immuno-PET trial was conducted between 2003 and 2005 at the VUmc in Amsterdam with ^{89}Zr -labeled-cmAb U36 [13,14]. The objective of this study was to see 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 ^{89}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 uni- or bilateral neck dissection underwent computed tomography (CT) or magnetic resonance imaging (MRI), or both, and ^{89}Zr -cmAb U36 immuno-PET prior to surgery.

Compared to the CT and MRI scans, the immuno-PET results were remarkably accurate. The ^{89}Zr -cmAb U36 immuno-PET scans detected all primary tumors (n=17) as well as 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 ^{89}Zr , other Dutch sites began clinical trials using ^{89}Zr as well. At academic hospitals in Groningen, Nijmegen, and Maastricht, several trial programs were started. Shortly thereafter, sites in Brussels and London also initiated their first clinical trials with ^{89}Zr -immuno-PET.

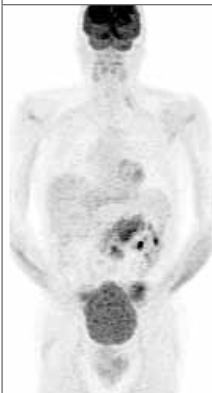
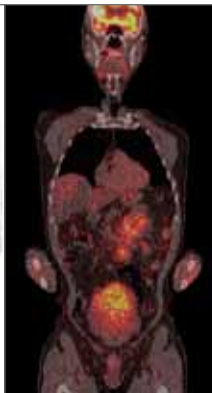

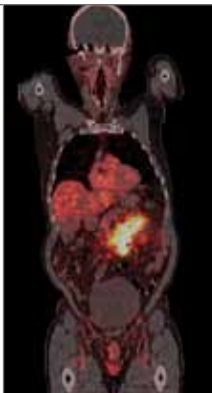

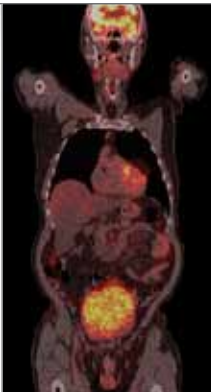
One of the most recent examples of clinical immuno-PET trials is currently being conducted at the Jules Bordet Institute in Brussels. Researchers performed immuno-PET imaging with ^{89}Zr -labeled rituximab in patients with CD20+ B-cell lymphoma. Excellent images were obtained (see figure 2). One of the main objectives of this research is to compare the diagnostic accuracy

of ^{89}Zr -rituximab-PET/CT with standard ^{18}F FDG-PET/CT. All FDG-positive lesions showed significant uptake of ^{89}Zr -rituximab. In 2 out of 6 patients, ^{89}Zr -rituximab-PET/CT revealed 8 supplementary CD20+ lesions that were strictly negative in images taken with ^{18}F FDG-PET/CT (unpublished data). The lesions corresponded to particularly small ($\leq 1\text{cm}$) lymph nodes and mesenteric nodules in CT images.

It was established that ^{89}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 ^{90}Y -rituximab.

Figure 2

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

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

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

The European results also led to the first clinical trials for ^{89}Zr -immuno-PET in the United States. The trials currently carried out in clinical research centers in Frederick, New York, and Sacramento are part of programs that are 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 to be the founding father of the biotechnology industry, have recently started to incorporate ^{89}Zr -immuno-PET into their antibody development research program [15]. In this type of research, immuno-PET technology can be especially beneficial when the mAb of interest is directed against a novel tumor target that has not previously been validated in clinical trials. This includes, for example, 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 result of these applications is that the number of papers published on preclinical and clinical results from ^{89}Zr -immuno-PET is growing steadily [8].

^{124}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 [16, 17]. So far, diagnostic results have been suboptimal, partly because of the poor quality of the murine mAbs used, which lacked the precision of today's mAbs [18]. Now, however, interest in ^{124}I -labeled MABs has returned.

This is to a certain degree due to the improved methods of production for ^{124}I and its coupling to mAbs. Two clinical applications have attracted much attention recently. Jayson et al. [19] used various doses of ^{124}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}I -immuno-PET imaging, it was demonstrated that antibody distribution and clearance were markedly heterogeneous between and within patients. Even between and within individual tumors, distribution and clearance can vary substantially. These differences may represent the variation in available targets for the mAb.

This is highly valuable knowledge, and it may have implications for future anti-VEGF therapies. Similar studies have begun using ^{89}Zr -bevacizumab as the imaging probe [20, 21].

In another clinical setting, ^{124}I -immuno-PET was used for in vivo profiling of renal cancer. Divgi et al. [22] used ^{124}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 because it can then guide future treatment decisions, although opinions on this point vary [23]. With immuno-PET, it was possible to accurately identify 15 out of 16 clear-cell carcinomas and all 9 nonclear-cell renal masses.

This study illustrates how molecular imaging with specific probes can contribute to personalized medicine.

The overall results of the clinical trials with ^{89}Zr -immuno-PET and ^{124}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 of 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}Zr - and ^{124}I -immuno-PET.

With immuno-PET, individual patients or patient groups can now be identified. Even the differences in antibody half-time in individual patients can now be made visible.

Mechanisms of antibodies are now much easier to understand. This can lead to highly effective drug optimization strategies.

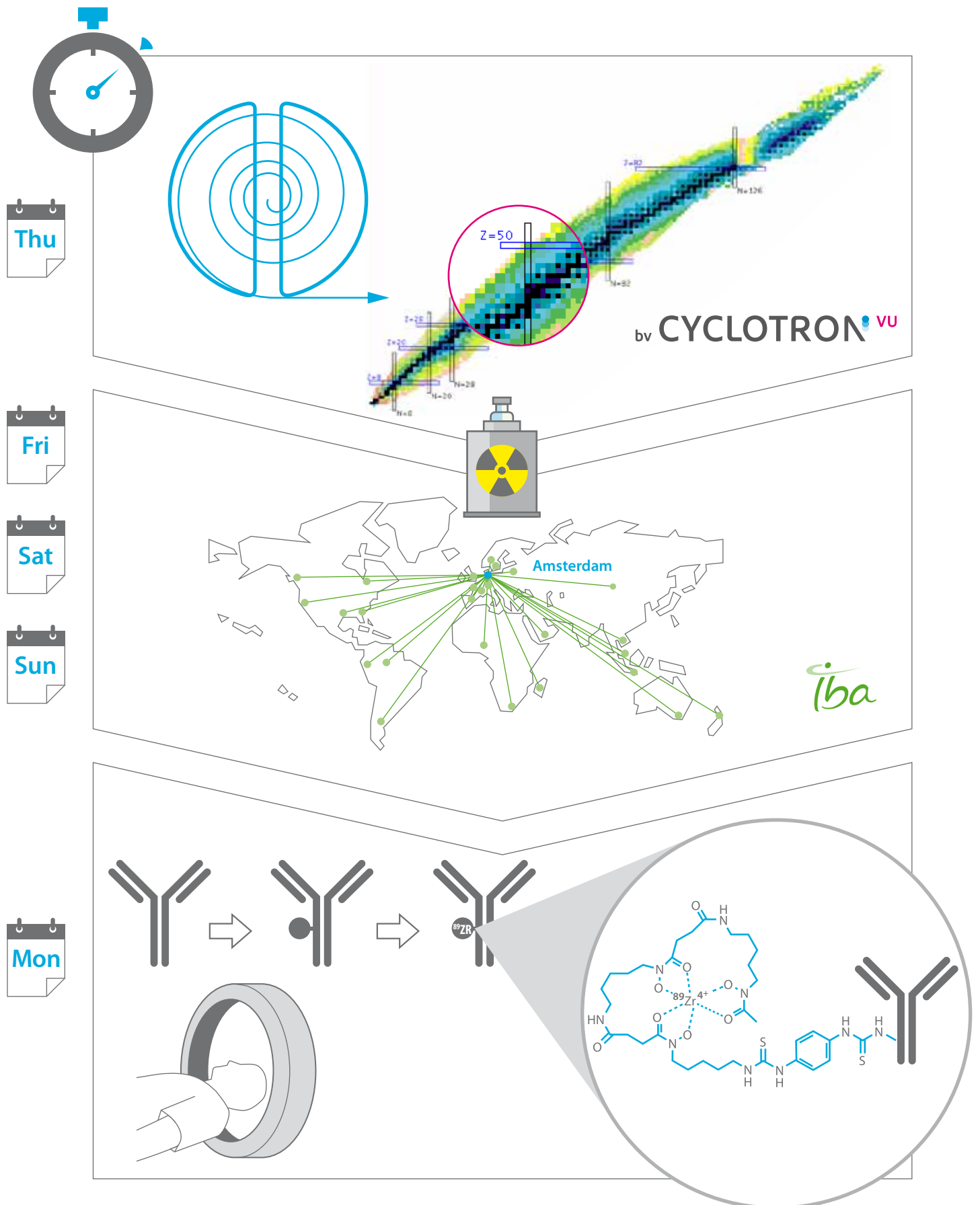


Figure 3

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}Zr in a cGMP-compliant way in batches of up to 20 GBq, and ^{124}I in batches of up to 3 GBq. Step 2: Our partner IBA distributes our products. Step 3: Labeling the antibody requires two ingredients, ^{89}Zr and the appropriate chelate. Both can be ordered easily as stock products.

A research challenge: Reducing the radiation dose

One of the most challenging research questions at present 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}Zr is about 40 mSv [15], which is high and will limit repeated applications of ^{89}Zr -immuno-PET.

However, solutions have already been found. Higher-sensitivity PET scanners are currently being developed and are entering the market. These scanners require less radioactivity to be injected without any loss of resolution. Better scanning software 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}Zr -trastuzumab produced images of excellent quality at an effective dose of about 20 mSv [24].

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

Outlook

Molecular imaging with the innovative PET tracers ^{89}Zr and ^{124}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 to 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 help researchers in both academia and industry to translate their ideas and research into improved drug therapies more effectively. A review of recent literature on the first clinical trials shows that ^{89}Zr - and ^{124}I -immuno-PET may be an effective instrument for improving knowledge of the efficacy of mAb therapy, for developing more efficient mAbs, and tailoring therapy more towards patient needs.

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

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

Research partners

About BV Cyclotron VU

BV Cyclotron VU is a private company located at the campus of 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]-NaF, ^{124}I , ^{89}Zr , and other [^{18}F]-labeled compounds for the PET community, and ^{123}I and [$^{81}\text{Rb}/^{81\text{m}}\text{Kr}$]-generators for the SPECT community.

They are the only commercial production site of ^{89}Zr in the world. Academic sites such as the Memorial Sloan Kettering in New York and Paul Scherrer Institute in Zurich produce ^{89}Zr on request for research purposes only [25].

BV Cyclotron VU's mission is to make a wide range of PET compounds available. Their goal is to make products of the highest pharmaceutical quality and to be a highly reliable supplier of those products. To achieve this goal, BV Cyclotron VU continuously invest in the best equipment available on the market.

Their partners Covidien and IBA distribute their products. The department of Nuclear Medicine and PET Research of the VU University Medical Center is their partner in research and development of new PET tracers.

Website: www.cyclotron.nl

VU University Medical Center



About VUmc

The core activities of 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 important both for the hospital itself, and for society in general. Its main focal areas are oncology, neurology, immunology, vital function, 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 ensures the smooth and efficient running of the medical center.

Website: www.vumc.nl



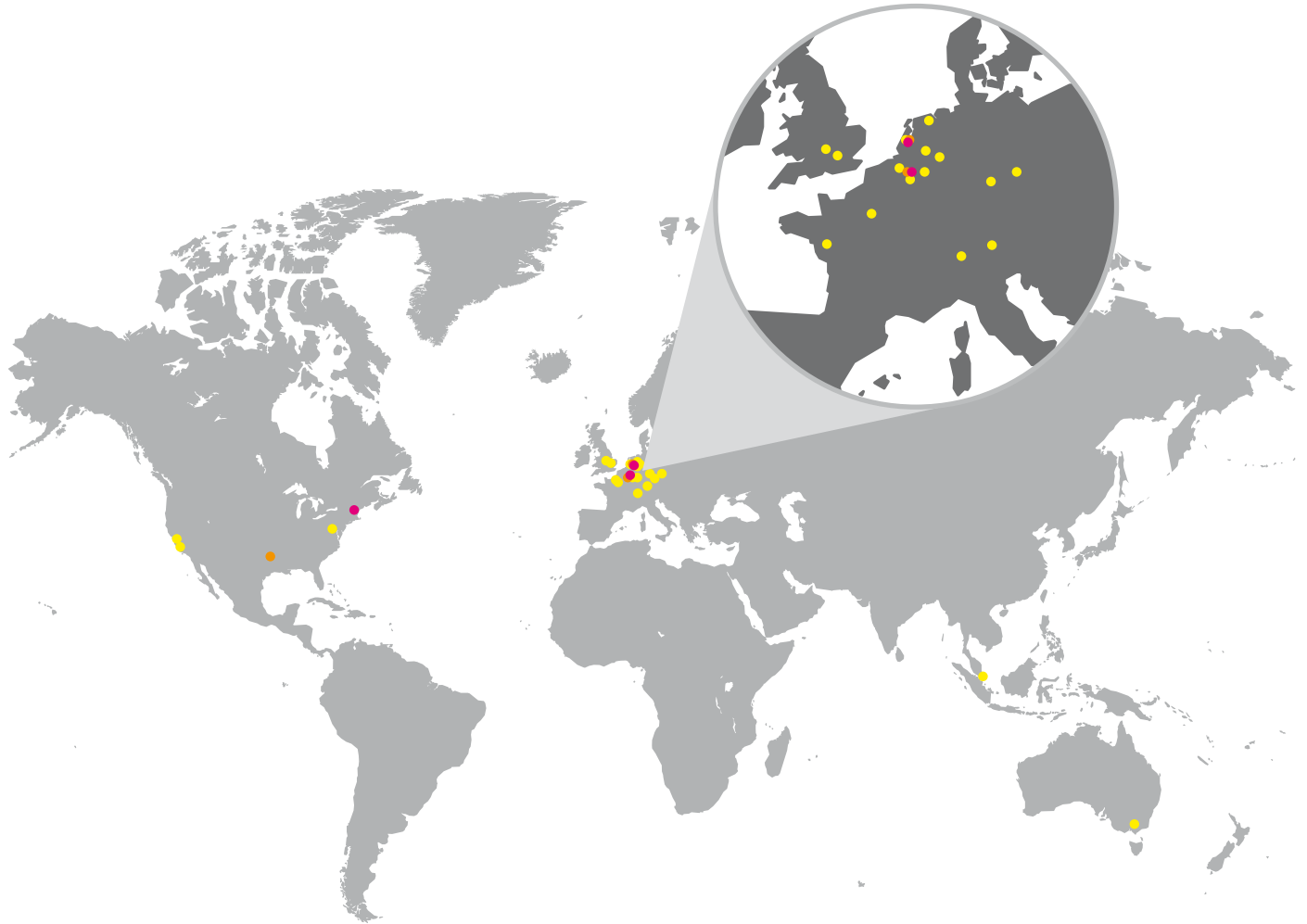
About IBA

IBA develops and markets leading-edge technologies, pharmaceuticals, and tailor-made solutions for healthcare with a focus on cancer diagnosis and therapy. Leveraging on its scientific expertise, IBA is also active in the field of industrial sterilization and ionization. Listed on the pan-European stock exchange EURONEXT, IBA is included in the BelMid Index. (IBA: Reuters IBAB.BR and Bloomberg IBAB.BB).

Website: www.iba-worldwide.com

Figure 4

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



- **Partners in research**

VU University Medical Center, Amsterdam, The Netherlands
 IBA, Louvain-La Neuve, Belgium
 Macrocyclics, Dallas, USA
 VU Imaging Center, Amsterdam, The Netherlands (will be established in 2014)

- **Partners in logistics**

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

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

in the Netherlands:

Amsterdam*
 Nijmegen
 Groningen*
 Maastricht*

in Belgium:

Brussels
 Liege

in France:

Paris
 Nantes

in Germany:

Jena
 Dresden
 Essen
 Munich

in Switzerland:

Zurich

in the United Kingdom:

London
 Oxford

overseas:

San Francisco, CA, USA
 Sacramento, CA, USA
 Frederick, MD, USA
 Singapore
 Heidelberg, Victoria, AUS

*Institutes where clinical trials are running with ^{89}Zr - or ^{124}I -immuno-PET

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