



# PSMA: A windfall for PET/CT imaging

**Retrospective clinical data suggests PET/CT imaging using  $^{68}\text{Ga}$ -labelled PSMA-11 will radically transform diagnostics, staging and surgical planning of prostate cancer. A prospective multicenter trial is currently under way, offering a compelling example of translational medicine.**

By Hildegard Kaulen, PhD

Affecting almost 420,000 people in Europe alone, prostate cancer is one of the most common carcinomas among men. Currently, diagnosis requires a biopsy, which also provides data used for staging. With only one in seven prostate carcinomas requiring aggressive treatment, it would be very helpful to have a non-invasive diagnostic method that provides information on the status and the spread of the lesions. Many prostate carcinomas remain symptom-free and therefore do not have to be addressed at all. A test that helps to differentiate and combines diagnosis and therapy on a theranostic basis is urgently needed.

The prostate-specific membrane antigen (PSMA) is a protein that ticks a number of boxes, thus making it an excellent target candidate. It is very specific, occurring from a hundred up to a thousand times more frequently on prostate cancer cells than on the cells of normal organs. PSMA is capable of binding small-molecule ligands that are quickly cleared from the blood with low background activity. Not only that, but PSMA is internalized by the prostate cancer cell after binding of the ligand resulting in an effective trapping. Therefore, if coupled either with a diagnostic or a therapeutic radionuclide, a PSMA ligand is an ideal tracer for diagnostic PET/CT imaging, and treatments such as endoradiotherapy.  $^{68}\text{Ga}$ -labelled

“With this academically funded study we also want to give something back to the healthcare system and society. We have high expectations.”

**Professor Dr. Klaus Kopka**  
Head of Radiopharmaceutical Chemistry  
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PSMA-11<sup>1</sup> and <sup>177</sup>Lu-labelled PSMA-617 are a perfect theranostic duo.

<sup>68</sup>Ga-labelled PSMA-11 was developed by Professor Michael Eisenhut and Dr. Matthias Eder at the German Cancer Research Center (DKFZ) in Heidelberg, Germany. Professor Uwe Haberkorn, who directs the nuclear medicine clinic in Heidelberg, first deployed the novel tracer in compassionate use four years ago. In the meantime, several hundred such instances worldwide have shown that <sup>68</sup>Ga-labelled PSMA-11 detects recurrent prostate cancer at a high level of sensitivity in PET/CT scans.<sup>2, 3, 4</sup> Detection of lymph node metastases is below the threshold of other usual imaging methods. However, there is still a lack of prospective clinical data on <sup>68</sup>Ga PSMA-11 imaging. Pros-

tate-specific tracers in the field of nuclear medicine may have the potential to fill in this gap.

These data are now to be captured in an exclusively academically funded multicenter clinical trial under the umbrella of the German Consortium for Translational Cancer Research (DKTK), or in short, the German Cancer Consortium. This makes the clinical trial a great milestone in translational medicine. Responsible for planning and organization are Professor Frederik Giesel at Heidelberg University Hospital and Professor Klaus Kopka at the DKFZ. Giesel is vice chair of the Nuclear Medicine department and the clinical trial director. Kopka is a chemist who heads the Division of Radiopharmaceutical Chemistry at the DKFZ. He is responsible for the coordi-

nation of the prospective study. The two are an excellent tandem crew for this unique bridging of basic research and clinical practice.

#### **On the way to being included in clinical guidelines**

Why is this prospective phase I and II clinical trial so important? “The PET/CT imaging data gathered for prostate carcinoma with <sup>68</sup>Ga-labelled PSMA-11 so far are retrospective data, where the PSMA-PET/CT imaging was compared with the choline-PET/CT imaging that is usually used for the diagnosis of prostate carcinoma,” explains Giesel. “While these results are groundbreaking to the extent they have shown that <sup>68</sup>Ga-labelled PSMA-11 is more sensitive than the choline tracer for diagnosing recurrent prostate cancer,<sup>2, 3, 4</sup> only pro-

## Combining all the parameters in a single convenient scan

For some time, Professor Frederik Giesel has been working with FlowMotion™ continuous bed motion PET technology. Using this acquisition mode, the patient is moved through the gantry while the PET data are gathered continuously and without sequential overlapping.

“PET with FlowMotion greatly reduces our data acquisition time,” says Giesel. “Thanks to our very good reputation for prostate carcinoma diagnosis, we receive a lot of referrals. We need a rapid workflow to be able to do all the scans. FlowMotion technology enables us to make the protocol more efficient by allowing us to spend more time examining regions where we suspect tumor lesions and giving us higher spatial resolution in these areas,” explains Giesel. “It also enables us to design the scan around the anatomy of the patient while maintaining the same image quality.” He explains that the image quality settings used to be determined by the bed position. Now different scan parameters can be easily combined in a single scan. The continuous scanning motion is also more pleasant for patients.

For Giesel, adequate diagnosis includes quantification of the tracer via the SUV value besides the descriptive analysis. “Because we can now spend longer image acquisition times on those parts of the body, where the lesions are localized, we get more counts and more precise allocation of counts. This improves our statistics and by extension quantification. That’s very important for our diagnostics,” says Giesel.

He also has great expectations of SPECT. He believes the advantage of this modality is that the same radionuclide is used for diagnosis (including dosimetry) and treatment. Not only that, but there are more gamma cameras than PET/CTs in emerging nations. This, plus the fact that SPECT gives very good spatial resolution, makes this type of imaging especially important in these countries. “That’s why it’s also very interesting to have the PSMA ligand with a radionuclide for the gamma camera,” explains Giesel. “Apart from this, SPECT can also be quantified, another major plus-point.” In Giesel’s view, the varying availability of radionuclides means that there will always be a place for both imaging procedures, SPECT and PET.

spective trials count when it comes to inclusion in clinical guidelines and having the costs covered. So retrospective studies aren’t really much use,” continues Giesel. They are not accepted as a basis for guidelines because they are not homogenized (harmonized) and are only based on individual cases of compassionate use. But the potential of the new diagnostic tracer is already underscored by the fact that due to the extraordinarily good results for PSMA-PET/CT imaging in retrospective studies, the method has already been included, even without prospective data, in the proposed amendments for the next revision of the German clinical guidelines.

Which centers are behind the prospective clinical trial? “Seven of the eight DKTK centers will be involved, along with four other sites,” says Kopka, “including one in Austria, and one in Switzerland.” He explains the trial will be funded primarily by the German Cancer Consortium, and that it is already seen as a type of role model for translational clinical studies in nuclear medicine. “Our trial is a flagship project. In Germany, we’re right at the forefront in terms of translation in cancer research.”

### **Trial will be launched in 2017**

What precisely are they planning? “The clinical trial will include 150 high-risk patients with prostate cancer before radical prostatectomy,” says Giesel. “It will begin in quarter 2 of 2017. Patients with a high PSA value and a positive biopsy, and have not yet received therapy, are included. <sup>68</sup>Ga-labelled PSMA-11 PET/CT imaging will then be done prior to prostatectomy to check the extent to which the tracer correctly reflects the staging and the spread of the lesions determined in surgery,” Giesel continues. To assure the comparability of data, the biopsy and the pathological examination of the tissue samples will be standardized. “The <sup>68</sup>Ga-labelled PSMA-11 PET/CT scan will be quantified by cross-calibrating with a phantom,” explains Kopka.

**Professor Dr. Klaus Kopka**

Klaus Kopka studied chemistry at the University of Münster (WWU Münster) in Germany. After stations in Münster and at ETH Zurich in Switzerland, he successfully completed his habilitation on radiopharmaceutical chemistry at the University of Münster. From 2001, Kopka headed the radiochemistry/radiopharmacy subdepartment of the department of nuclear medicine at the University Hospital Münster, and in 2012, was appointed adjunct professor at the same university. In 2013, he moved to Heidelberg, as full professor W3 (the highest-level professorship in Germany) and took over as head of the Radiopharmaceutical Chemistry Division at the DKFZ.

**Professor Dr. Frederik Giesel**

Frederik Giesel studied medicine at the Universities of Mainz and Heidelberg in Germany. After graduating from medical school, Dr. Giesel went to the National Institutes of Health (NIH) in Bethesda, Maryland (USA) during his residency. He also holds an executive MBA-program at the Frankfurt School of Finance in Germany. Since 2015, Dr. Giesel has served as a professor of radiology and vice chair for nuclear medicine at the University Hospital Heidelberg, and was recently a visiting professor at Stanford University in the United States and Yonsei University in South Korea. Today, Dr. Giesel leads the phase I/III multi-center study of a new PET tracer, which has been recently introduced into the clinical environment for prostate cancer patients (PSMA).

As stated previously, PSMA is not just an excellent candidate for imaging; together with a therapeutic radionuclide it can also be used for therapy.

Did they consider the possibility of combining diagnosis and therapy from the outset? "It developed as things progressed," says Kopka. "Imaging allows you to get to the tumor and decide whether endoradiotherapy makes sense. Given the biodistribution of  $^{68}\text{Ga}$ -labelled PSMA-11, it was immediately clear that we should develop a therapeutic option. We then did precisely that with  $^{177}\text{Lu}$ -labelled PSMA-617." This therapeutic variant has already been licensed out to ABX advanced biochemical compounds GmbH.

#### $^{18}\text{F}$ instead of $^{68}\text{Ga}$

Kopka and his team are also pursuing a diagnostic option with fluorine-18,  $^{18}\text{F}$ -labelled PSMA-1007. "There are various reasons for this," explains the

chemist. "Like gallium-68, the cyclotron-produced positron-emitter fluorine-18 can be also used all over the world. However, in some countries, such as in Japan, they don't use gallium-68 at all. Fluorine-18 also has a longer half-life than gallium-68: around 110 minutes versus only 68 minutes. Despite this, there will still be a place for gallium-68, because not every center has a cyclotron, and centers without a cyclotron will continue to work with generator-produced  $^{68}\text{Ga}$ -labelled PSMA-11," says Kopka. Initial results show that  $^{18}\text{F}$ -labelled PSMA-1007 and  $^{68}\text{Ga}$ -labelled PSMA-11 are similar in terms of structure, biodistribution and uptake by prostate cancer cells. Just last year we introduced PSMA-1007 also successfully into the clinic also with very impressive tracer-characteristics (see Giesel et al., EJNMMI 2016<sup>5,6</sup>).

What role will these therapies play in the future? Kopka believes it is time

for nuclear medicine to leave behind the reputation of being only responsible for niche treatments. Therefore, the concept of theranostics should be developed further in oncology. This would also justify the personnel-intensive collaboration with radiochemistry and radiopharmacy. Giesel shares this view. While he concedes that nuclear medicine is a small discipline, he believes this will change once it gets involved in diagnosing and treating common cancers. "With almost 80,000 new cases a year in Germany, prostate carcinoma are highly relevant," says Giesel. "The retrospective data have shown that after a  $^{68}\text{Ga}$ -labelled PSMA-11 PET/CT imaging fifty percent of patients receive a different therapy in radio-oncology.<sup>7</sup> That's a very important finding." The radiologist and nuclear medicine specialist participated in a meeting in Seoul, under the umbrella of the IAEA, which included discussion on how nuclear medicine could best



develop in emerging countries. Giesel says the consensus was that this would only be possible by way of theranostics and prospective clinical trials. This is why <sup>68</sup>Ga-labelled PSMA-11 is so important, because it could potentially help give PET/CT imaging high status in terms of diagnosing and therapeutic management.

Kopka also points to the other common cancers, for example melanoma, breast, colon, pancreas, or bronchial carcinoma, that can be addressed with theranostics. He explains there is plenty of work in progress, also in his division. But first the prospective clinical trial on prostate carcinoma has to be driven forward. “With this academically funded study we also want to give something back to the healthcare system and society. We have high expectations.” ■

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