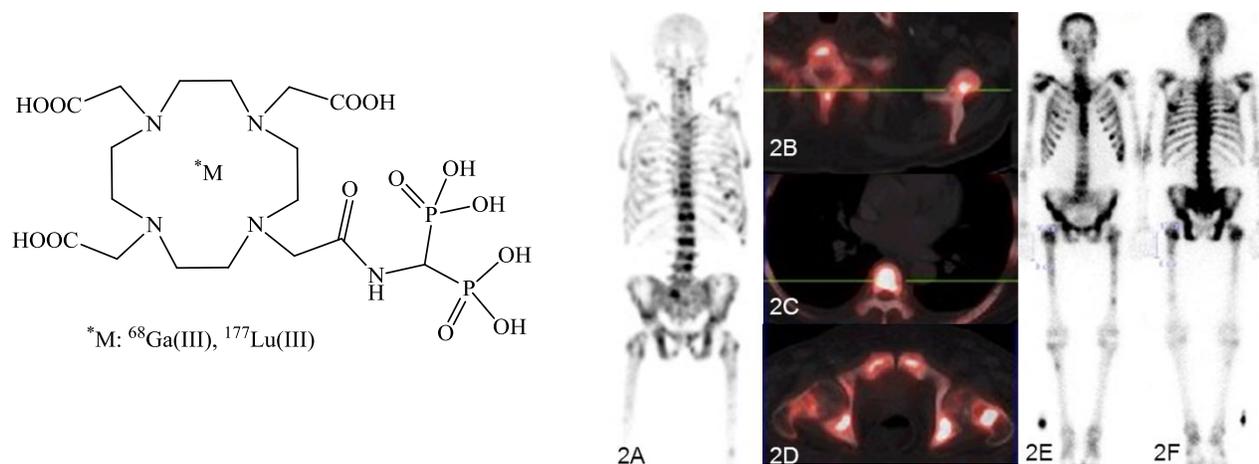


# Macrocyclic Bisphosphonates for PET-Diagnosis and Endoradiotherapy of Bone Metastases

Prostate and breast cancer are high rated in the numbers of cancer cases worldwide. The serious consequence of this disease is the metastatic spread of the cancer into the bones. It is associated with severe bone pain, spinal cord compression, skeletal fractures and a metabolic hypercalcaemie. Finally, the symptoms reduce the patients quality of life dramatically.

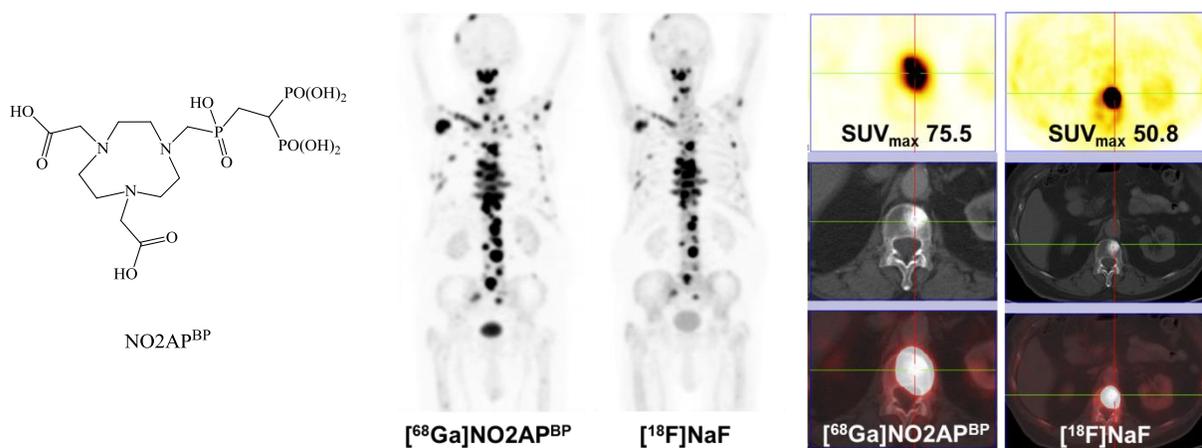
Radiopharmaceuticals play a key role in the assessment and therapy of this disease. Conjugates of macrocyclic chelates and bone affine bisphosphonates are an appropriate means, as so called *theranostics*, to unite diagnosis and therapy in one molecule. In this connection the generator based PET-nuclide  $^{68}\text{Ga}(\text{III})$  and the therapy nuclide  $^{177}\text{Lu}(\text{III})$  showed promising first results with BPAMD in initial patient studies, cf. figure 1.



**Figure 1.** 70-year old male, case of prostate cancer, with rising PSA levels underwent  $^{18}\text{F}$ -Fluoride PET/CT. Coronal MIP image (A) showing intense tracer uptake in multiple bones in axial and appendicular skeleton and axial fused PET/CT (B-D) images showing hypermetabolic metastatic lesions in scapula (B), vertebrae (C) and pelvis (D). Patient was treated with 5358 MBq [ $^{177}\text{Lu}$ ]BPAMD. Post therapy images (Ant-E, Post-F) showing intense localization of tracer in the entire skeleton, in concordance with the pre-therapy  $^{18}\text{F}$ -Fluoride PET/CT study (A).

For both trivalent radiometals, new derivatives were successfully synthesized deduced by further developments of the BPAMD lead structure with enhanced pharmacological properties. These

novel compounds, based on the modern osteoporosis drugs pamidronate and zoledronate, distinguished by an increased bone affinity and a superior target to background ratio. In addition it was also succeeded to develop a derivative of longer blood retention, which finally resulted in an enhanced bioavailability of the tracer. This class of bisphosphonate enables an increased tumor to healthy bone ratio, which might end up in an improved therapeutic success. One of these novel macrocyclic bisphosphonates,  $[^{68}\text{Ga}]\text{NO2AP}^{\text{BP}}$  showed superior results in the animal testing and was therefore chosen for an initial clinical phase 0 and I trials, cf. figure 2.



**Figure 2.** First patient study of  $[^{68}\text{Ga}]\text{NO2AP}^{\text{BP}}$  in a male prostate cancer patient. Left: Whole body scintigraphy of  $[^{68}\text{Ga}]\text{NO2AP}^{\text{BP}}$  vs.  $[^{18}\text{F}]\text{NaF}$ . Right: PET, CT and PET/CT slices of the L4 vertebra of  $[^{68}\text{Ga}]\text{NO2AP}^{\text{BP}}$  vs.  $[^{18}\text{F}]\text{NaF}$ . Acquisitions were obtained after 60 min p.i. developed with 161 MBq  $[^{68}\text{Ga}]\text{NO2AP}^{\text{BP}}$  and 252 MBq  $[^{18}\text{F}]\text{NaF}$  (Prof. R. P. Baum, Zentralklinik Bad Berka, Germany).

Within this study the compound was able to underline its high diagnostic efficiency in combination with  $^{68}\text{Ga}$ -PET. The first series of tests in 12 patients revealed a similar compliance in the detection capability of skeletal metastases as the gold standard  $^{18}\text{F}$ -fluoride. Moreover in selected metastatic foci a higher uptake of the bisphosphonate could be obtained.

The promising results indicate that in future the macrocyclic bisphosphonate concept may play a key role in the management of skeletal metastases in nuclear medicine.