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Decay induced de-chelation of positron-emitting electron-capture daughters and its use in preclinical PET.

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Abstract

The purpose of this study was to assess the value of ^{140}Nd/^{140}Pr and ^{134}Ce/^{134}La as *in vivo* PET generators through kinetic evaluation of the pairs with somatostatin analogues in the neuroendocrine tumor-based somatostatin receptor 2 (sst_2) system. By employing a known sst_2 internalizing vector, DOTATATE, and a known non-internalizing vector, DOTALM3, we attempted to determine *in vivo* diffusion kinetics of a freed positron-emitting daughter $^{140}Pr^{3+}$ in tumor-bearing mice.

Methods: ^{140}Nd and ^{134}Ce were produced by proton-induced spallation of a tantalum target at ISOLDE, electromagnetically separated, and implanted in a thin zinc layer on gold foils. After dissolving the zinc, the products were chemically separated, reacted with sst_2 targeting vectors DOTATATE or DOTALM3, and the ^{140}Nd labeled vectors were i.v. injected into dual-flank H727 xenograft bearing mice (n = 8 for each tracer). PET scans were taken at 1, 3, and 16 hours post injection. Following the last image, the animals were euthanized, and then imaged intact at 30 min post-mortem. The differences between the 16 h PET scan and the post-mortem scan were used to study the diffusion behavior of $^{140}Pr^{3+}$ following the parent ^{140}Nd EC decay. Three additional mice were scanned under the same protocol after injection of $^{140}Nd^{3+}$ in HEPES-buffered isotonic saline to investigate the free ion distributions in the tumor model.

Results: In total 950 MBq of ^{140}Nd and 140 MBq of ^{134}Ce were collected at ISOLDE and shipped to Hevesy Lab. ^{140}Nd reactions with DOTATATE and DOTALM3 were efficient at 5 MBq/nmol (n = 2 each). ^{134}Ce labeling was inefficient, and could only be achieved with receptor-saturating levels of the vectors, thereby precluding their use *in vivo*. The *in vivo* scans showed only a small difference in the tumor PET signal between pre- and post-mortem scans, with a slight increase in tumor signal post-mortem when DOTALM3 was used. Non-targeted organs, however, showed interesting source and sink behaviors illuminating some properties of the renal and hepatic interaction with neodymium and praseodymium.

Conclusion: Based upon the results of this study we conclude that ^{140}Nd imaging in preclinical models might be possible without designing an electron-capture-dislocation resistant chelate. In such cases, the imaging protocol established here is a useful test to determine how ^{140}Nd PET is altered by diffusion. Further, with careful experimental design it may be possible to exploit the diffusion effects to observe biological phenomena such as vector internalization.