SUPPLEMENTARY INFORMATION

General: All chemicals and solvents were of analytic or high-performance liquid chromatography (HPLC) grade from Sigma-Aldrich, except as noted otherwise. Enriched water ($[^{18}O]H_2O$, >98%) was purchased from Advanced Biochemical Compounds (ABX, Radeberg, Germany).

NPs preparation: All experimental procedures were carried out under nitrogen atmosphere unless noted otherwise. Al_2O_3 NPs were prepared by precipitation under basic conditions starting from 10 mL of 0.4M aqueous solutions of aluminum chloride using ^{18}O-enriched water or natural isotope abundance ultrapure type 1 water. $NH_{3(g)}$ (Sigma Aldrich, anhydrous, >99.9%) was bubbled into the aluminum salt solution held at room temperature until the precipitate was formed. The resulting precipitate was centrifuged at 8000g for 5 min, washed four times with 2 mL of ultrapure water or ^{18}O-enriched water for natural isotopic-abundant and ^{18}O-enriched NPs, respectively, heated at 700ºC for 2 hours under continuous argon flow, cooled to room temperature and characterized.

NPs characterization: Size distribution and crystal phase were determined for all samples. TEM was performed using a JEOL JEM-1230 microscope operated at 120 kV. With that purpose, Al_2O_3 NPs dispersions in hexane were dropped on a 3-mm copper grid covered with a continuous layer of carbon film and were then dried in a vacuum Plate Degasser overnight. DLS measurements were performed using a Malvern Zetasizer Nano ZS system. The X-ray diffraction patterns of the NPs were recorded using a Philips PW1710 with PW1729 generator, equipped with a vertical PW1050/25 goniometer (Bragg-Brentano geometry).

Activation of the NPs: For the generation of the radioactive isotopes, NPs (~90 mg) were introduced in an aluminum capsule, which was introduced in the solid target holder (Costis, IBA) and irradiated with 16 MeV protons in a cyclone IBA 18/9 cyclotron, with a beam current of 5 µA. An integrated current of 0.5 µAh was used for those experiments devoted to NPs characterization, while an integrated current of 3.2 µAh was used for *in vivo* experiments.

Radiologic characterization of the NPs: For those experiments devoted to NP characterization, the aluminum disc was collected in a shielded container immediately after beam irradiation. A small fraction was allowed to decay and another fraction (4-5

mg) was introduced into a specially designed polymethyl methacrylate phantom and inserted in the center of the FOV of an eXploreVista-CT small animal PET-CT system (GE Healthcare). Dynamic images (energy window: 410-700 KeV, frames: 5x1, 5x3, 5x4, 5x5 5x10, 12x20 min, total acquisition time 365 min) were acquired, followed by a CT scan (X-Ray energy: 40 KV, intensity: 140 µA) for attenuation correction. Images were reconstructed using filtered back projection (FBP) with a ramp filter (cut-off frequency = 0.5 mm^{-1}). VOIs were drawn on the sample cavity and time–activity curves were obtained as Bq/cm^3. The relative amount of activity present as ^{18}F and ^{13}N was estimated by fitting bi-exponential equations using Origin Pro 8 Software.

***In vivo* studies:** For those experiments devoted to *in vivo* studies, the aluminum disc was collected in a shielded container and allowed to decay 60 minutes for complete ^{13}N elimination. The animals were maintained and handled in accordance with the Guidelines for Accommodation and Care of Animals (European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes) and internal guidelines. All studies involving animals were approved by the Animal Ethics Committee of CIC biomaGUNE. PET scans were performed using an eXploreVista-CT small animal PET-CT system (GE Healthcare). Prior to the scans, animals (male Sprague-Dawley rats weighting 175-225 g, 7-8 weeks, Harlan, Udine, Italy, n = 3) were anesthetized with 1.5% (v/v) isoflurane and were placed in the scanner. Radioactive NPs were suspended in 0.005M NaCl aqueous solution, sonicated for 2 min and centrifuged at 200g for 4 min. 300 µL of the supernatant (3.7 ± 1.0 MBq) were withdrawn with a syringe and administered via a tail vein. A dynamic PET acquisition (energy window: 400-700 KeV) was started immediately and performed in dynamic mode (frames: 5x1 min, 5x2min, 3x5min, 3x10min 4x14min, total screening time = 7 hours 45 min). For each frame, four beds were defined to acquire whole body images and a CT scan (X-Ray energy: 40 KV, intensity: 140 µA) was performed for attenuation correction at the end of the study. Images were reconstructed (random and scatter corrected) using OSEM2D iterative algorithm (Number of Iterations = 2), generating a 175x175x220 dimension image, with a 1.5 mm axial full width at half maximum spatial resolution in the centre of the field of view. A small sample of the irradiated NPs contained in a sealed plastic vial was imaged simultaneously to define the decay curve and results were applied to data correction. After image acquisition, the animals were euthanized without recovering from anesthesia.