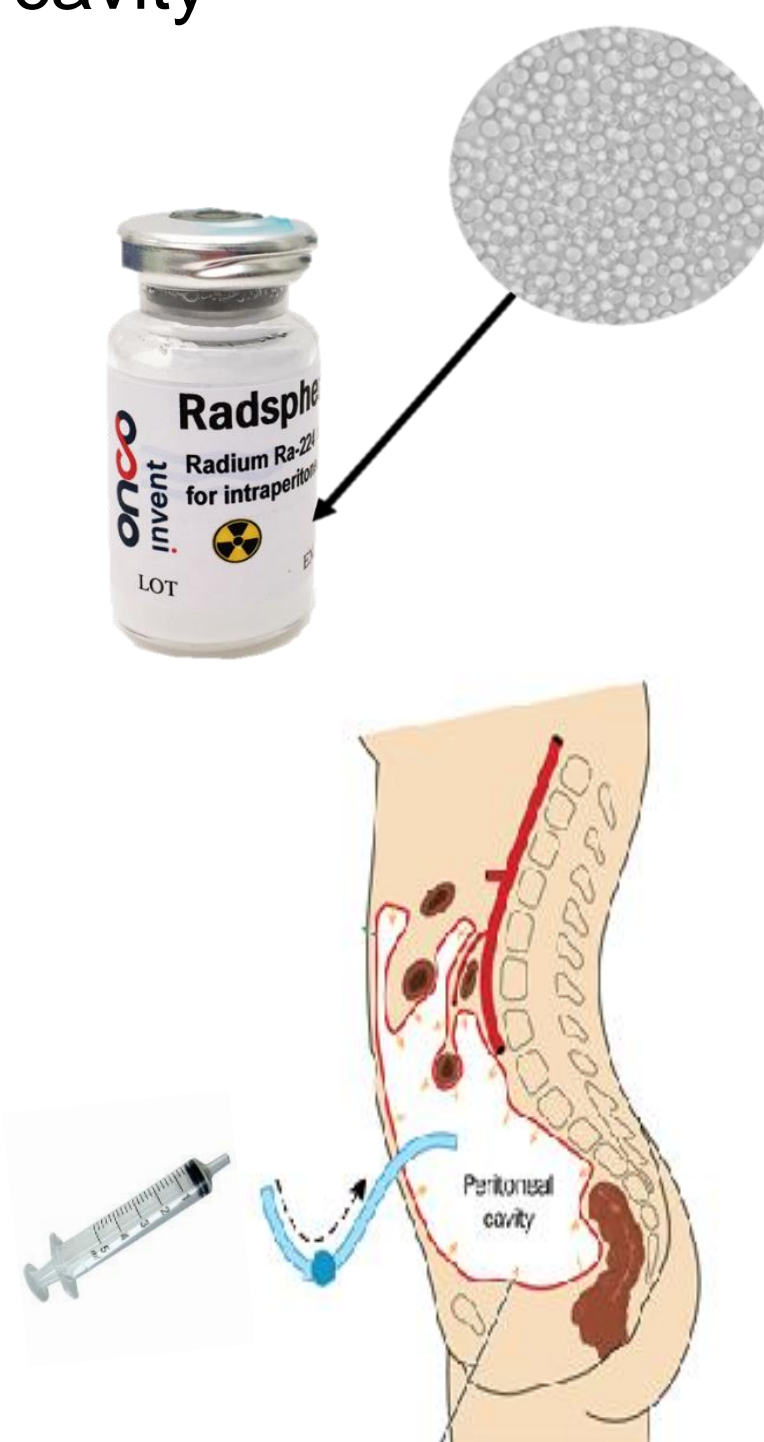


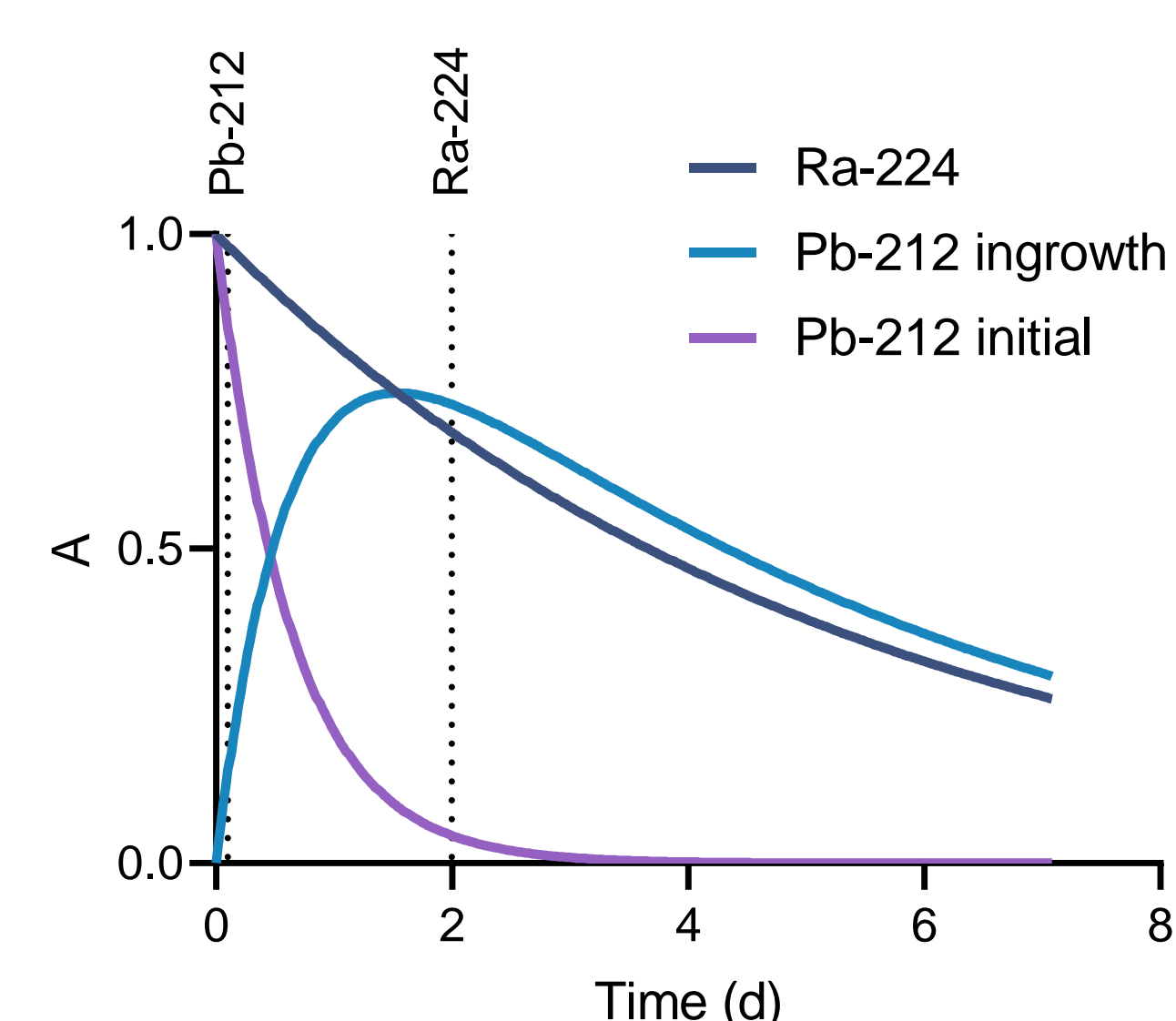
Background and Objectives

- This novel alpha-therapy Radspherin®, consisting of bio-degradable radium-224-labeled calcium carbonate (CaCO₃) microparticles, was developed with the intent to treat micrometastases located in the abdominal cavity
- Designed to be administered intra-peritoneally (IP) following cyto-reductive surgery
- Designed to confine radiation exposure to the peritoneal cavity while treating both the linings of the peritoneal surfaces and liquid volumes
- The distribution of the Ra-224 labeled microparticles was examined using planar gamma imaging, SPECT and CT
- The ex vivo biodistribution of Ra-224 and its progeny Pb-212 was determined



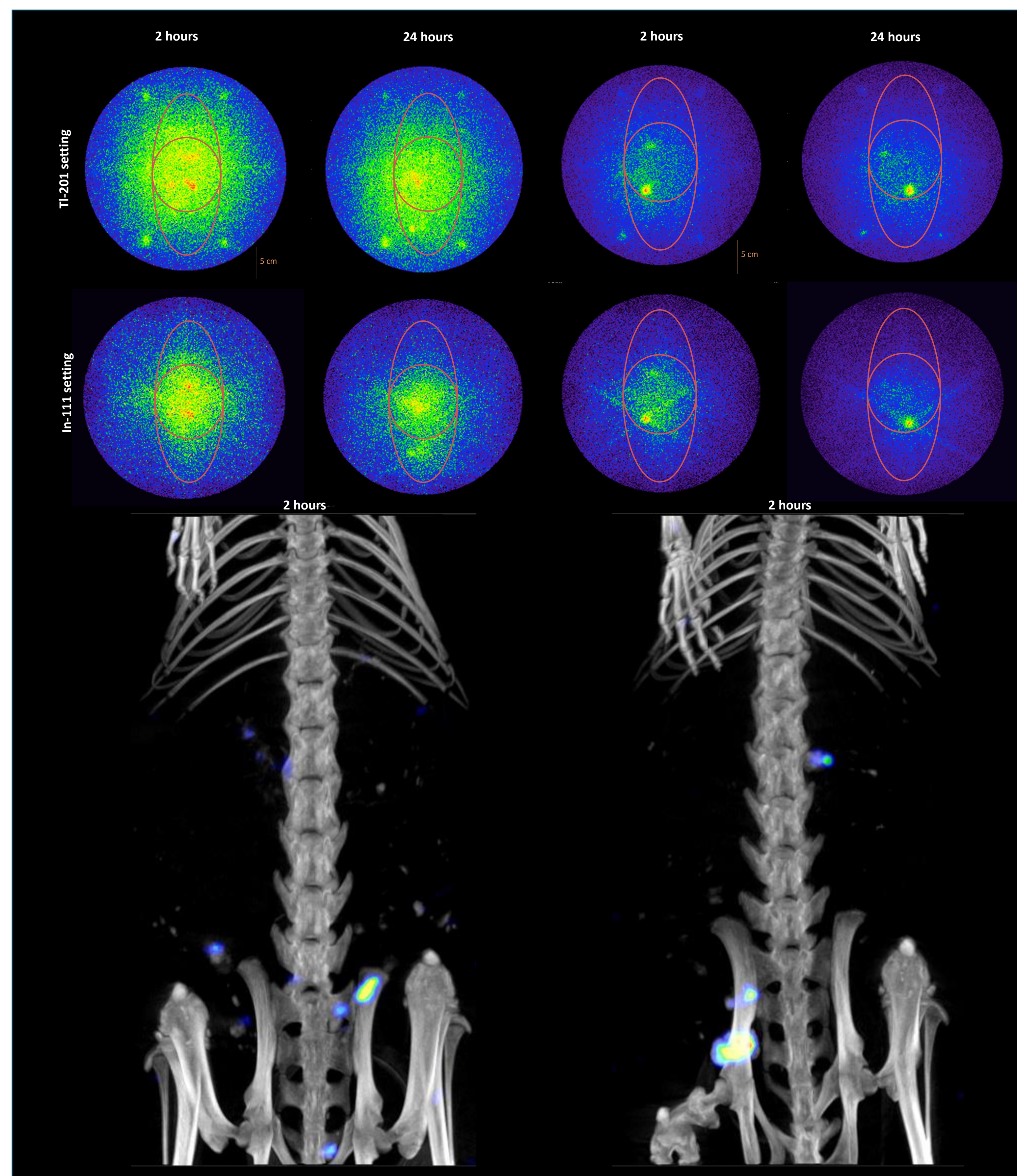
Materials and methods

- Fifteen female Wistar rats were infused IP with Ra-224-labeled microparticles (200-400 kBq, 100 mg CaCO₃, 1 mL + 3 mL Plasmalyte flush) via a multi-hole pigtail catheter
- Four female Wistar rats were infused IP with free Ra-224 (200-400 kBq, RaCl₂) as a reference for uptake of released Ra-224
- The Ra-224 labeled microparticles were imaged using both planar gamma imaging, SPECT and CT to evaluate the distribution over time in the abdominal region
- Longitudinal ex vivo biodistribution was performed after microparticle infusion and organs were harvested for activity measurements

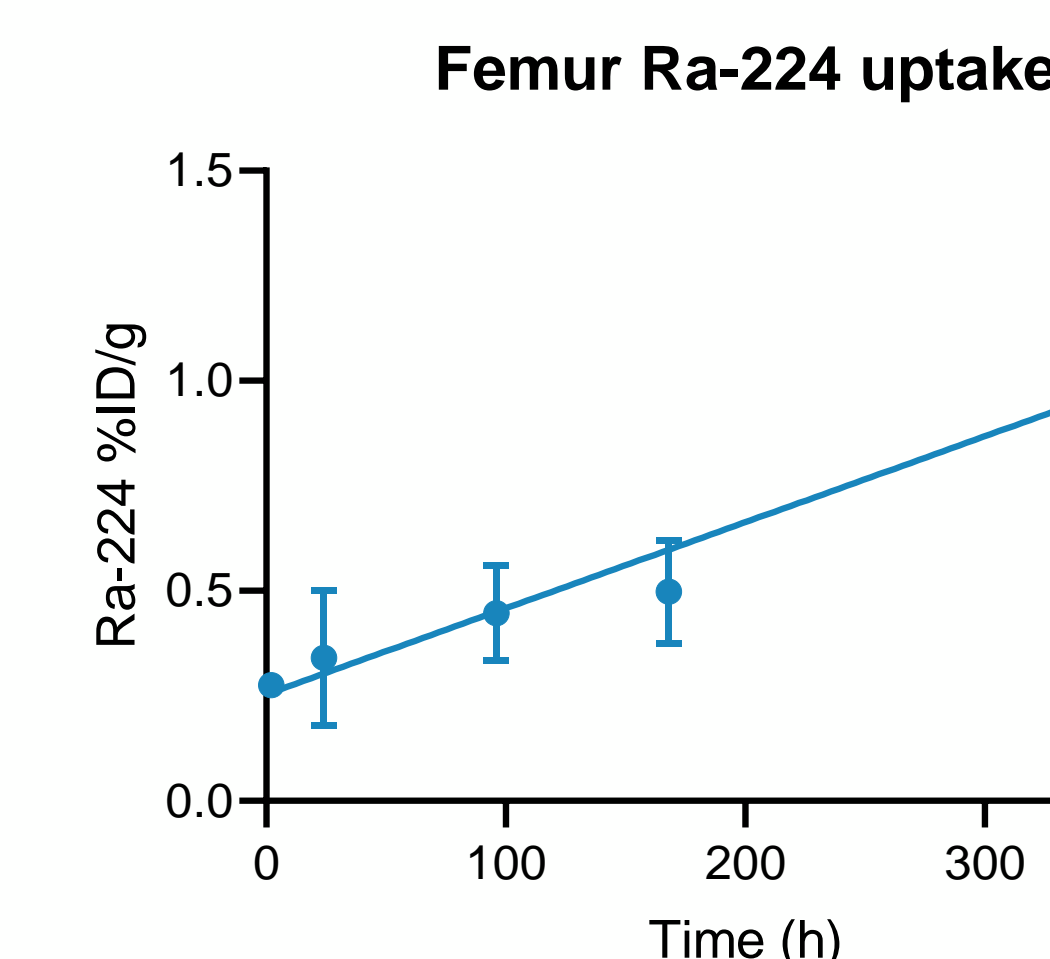
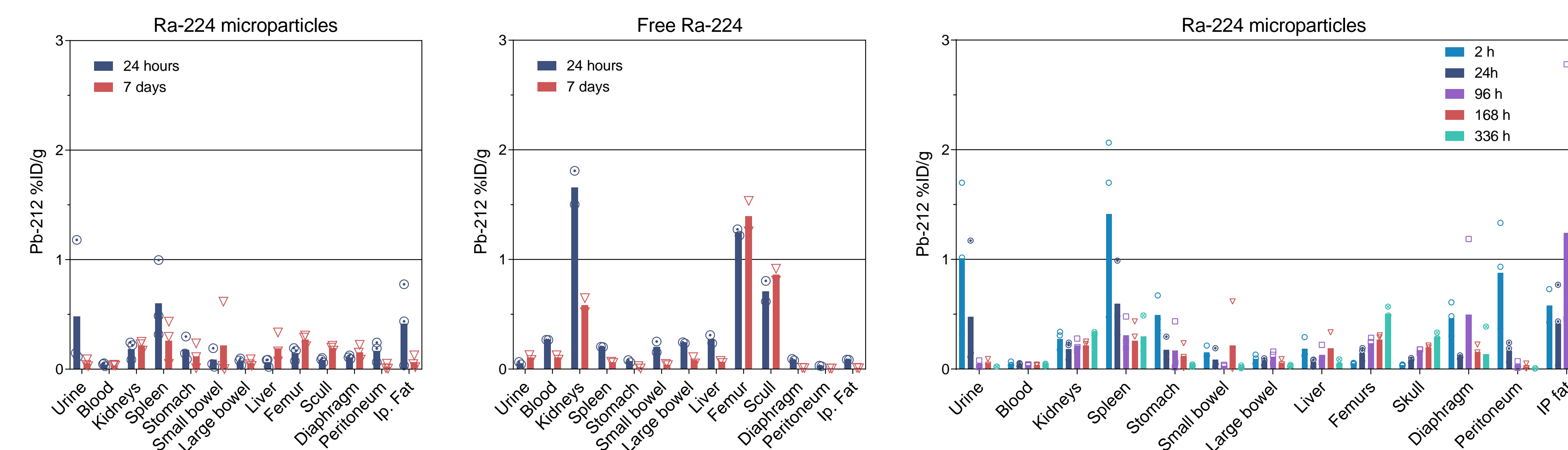
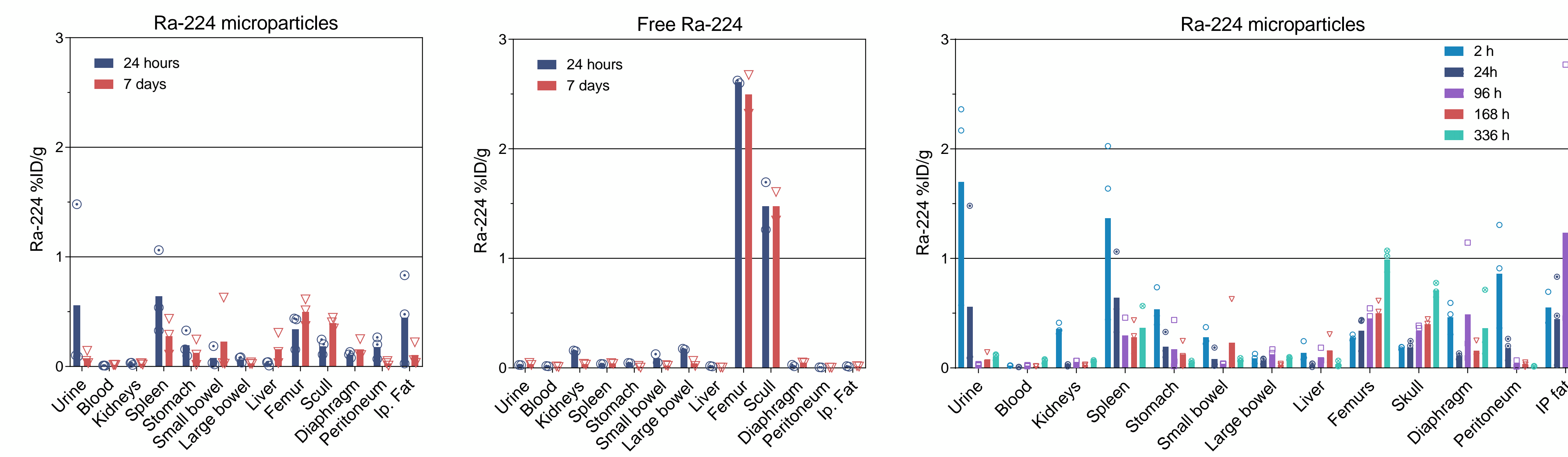


The graph illustrates the method of measurement of both Ra-224 and Pb-212. Only the Pb-212 daughter has usable gamma emission. Therefore initial measurement of organs yield the Pb-212 activity present in the organs at the time of euthanasia. Remeasurement 48 hours post mortem, allowed the initial Pb-212 to decay and the ingrowing Pb-212 to reach equilibrium with Ra-224. The second measurement therefore represents Ra-224.

Results



Planar gamma imaging was successful in visualizing the IP distribution of microparticles, with the hotspots identified as aggregates both in SPECT and under visual inspection ex vivo. Bottom left shows a representative image with little aggregation in the SPECT. The planar gamma images of the same animal showed fairly uniform exposure top left. Bottom right shows high levels of aggregation seen in only one rat. In the planar gamma image top right, this shows as a very high contrast between hotspots and background. All three modalities, planar gamma imaging, SPECT and CT were able to visualize the microparticle distribution.



- Both CT and SPECT images show distribution of the infused microparticles to the entire peritoneum albeit with local areas of high microparticle concentration
- Modest but evident systemic leakage of Ra-224 from the microparticles in the peritoneal cavity was observed
- Based on the bone uptake of Ra-224, the retention of Ra-224 in the peritoneal cavity was found to be > 87% at 24 hours and > 77% at 168 hours
- Redistribution of the progeny Pb-212 was observed as modest uptake in the kidneys

Conclusion

- High peritoneal retention of both Ra-224 and its progeny Pb-212 after IP injection of Ra-224 labeled CaCO₃ microparticles, was found in rats with assumed high translational value to the clinical setting
- SPECT and planar imaging demonstrated that distribution of the Ra-224 labeled microparticles occur to the entire peritoneal lumen in the animals. SPECT and CT revealed some clusters of the labeled microparticles
- Due to the short range of the therapeutically active alpha-particles, the clusters are not expected to have an impact on safety of the product