THE IN-VIVO GENERATOR ^{128}BA/^{128}CS : A NEW CALCIUM SURROGATE FOR TREATMENT OF OSTEOSARCOMA

CHUV, IRA, NPL & CERN

MEDICIS Board

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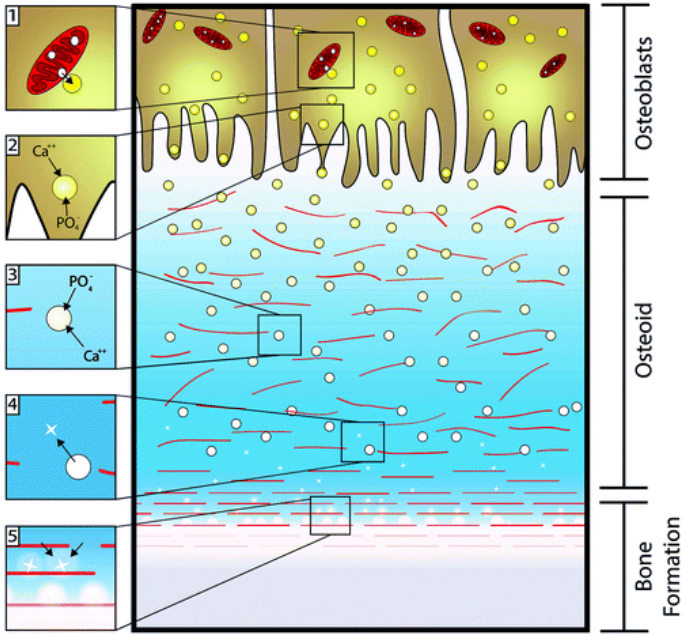
The in vivo generator Ba/Cs-128

- "In vivo generator" → The aim of such approach is to inject a long half-life parent radionuclide, which after accumulation in the target tissue will act as a generator and generate shorter half-life daughter radionuclide
- Theranostics : Auger therapy & PET imaging

Generator system	Half-life	Decay Mode	Emission	Application	Daughter	Half life	Decay mode	Emission	Application
^{128}Ba/^{128}Cs	2.4 d	EC	γ, **Auger e$^-$** (2.5-5.7 keV 79.3%)	Auger therapy	^{128}Cs	3.66 m	EC, β+	γ, Auger e$^-$, **β+** (1315.9 keV 53.2%)	PET

Rational

- $^{128}Ba/^{128}Cs$ enters the bone matrix as a surrogate of Ca^{2+} like ^{223}Ra and ^{89}Sr
- It is metabolized, concentrated in the mithochondria and secreted through the matrix vesicles by the osteoblast



Kyungsup Shin, Timothy Acri, Sean Geary, and Aliasger K. Salem.Tissue Engineering Part A.Oct 2017.1169-1180

Clinical Trials: Targeted Therapy

Clinical Cancer Research

Alpha Particle Radium 223 Dichloride in High-risk Osteosarcoma: A Phase I Dose Escalation Trial

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Abstract

Purpose: The prognosis of metastatic osteosarcoma continues to be poor. We hypothesized that alpha-emitting, bone-targeting radium 223 dichloride ($^{223}RaCl_2$) can be safely administered to patients with osteosarcoma and that early signals of response or resistance can be assessed by quantitative and qualitative correlative imaging studies and biomarkers.

Patients and Methods: A 3+3 phase I, dose-escalation trial of $^{223}RaCl_2$ (50, 75, and 100 kBq/kg) was designed in patients with recurrent/metastatic osteosarcoma aged ≥15 years. Objective measurements included changes in standardized uptake values of positron emission tomography (PET; 18FDG and/or NaF-18) and single-photon emission CT/CT (99mTc-MDP) as well as alkaline phosphatase and bone turnover markers at baseline, midstudy, and the end of the study.

Results: Among 18 patients enrolled (including 15 males) aged 15–71 years, tumor locations included spine ($n = 12$, 67%), pelvis ($n = 10$, 56%), ribs ($n = 9$, 50%), extremity ($n = 7$, 39%), and skull ($n = 2$, 11%). Patients received 1–6 cycles of $^{223}RaCl_2$; cumulative doses were 6.84-57.81 MBq. NaF PET revealed more sites of metastases than did FDG PET. One patient showed a metabolic response on FDG PET and NaF PET. Four patients had mixed responses, and one patient had a response in a brain metastasis. Bronchopulmonary hemorrhage from Grade 3 thrombocytopenia ($N = 1$) was a DLT. The median overall survival time was 25 weeks.

Conclusions: The first evaluation of the safety and efficacy of an alpha particle in high-risk osteosarcoma shows that the recommended phase II dose for $^{223}RaCl_2$ in osteosarcoma is 100 kBq/kg monthly (twice the dose approved for prostate cancer), with minimal hematologic toxicity, setting the stage for combination therapies.

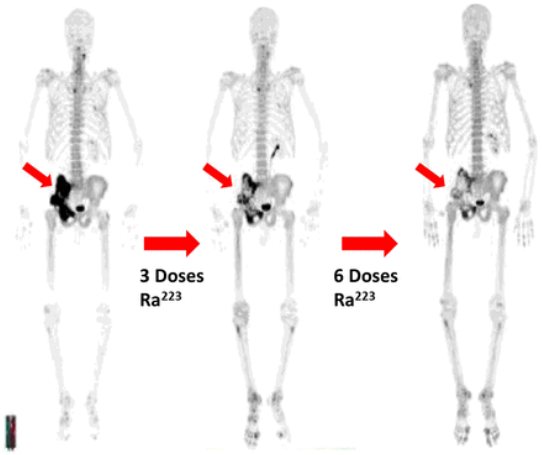
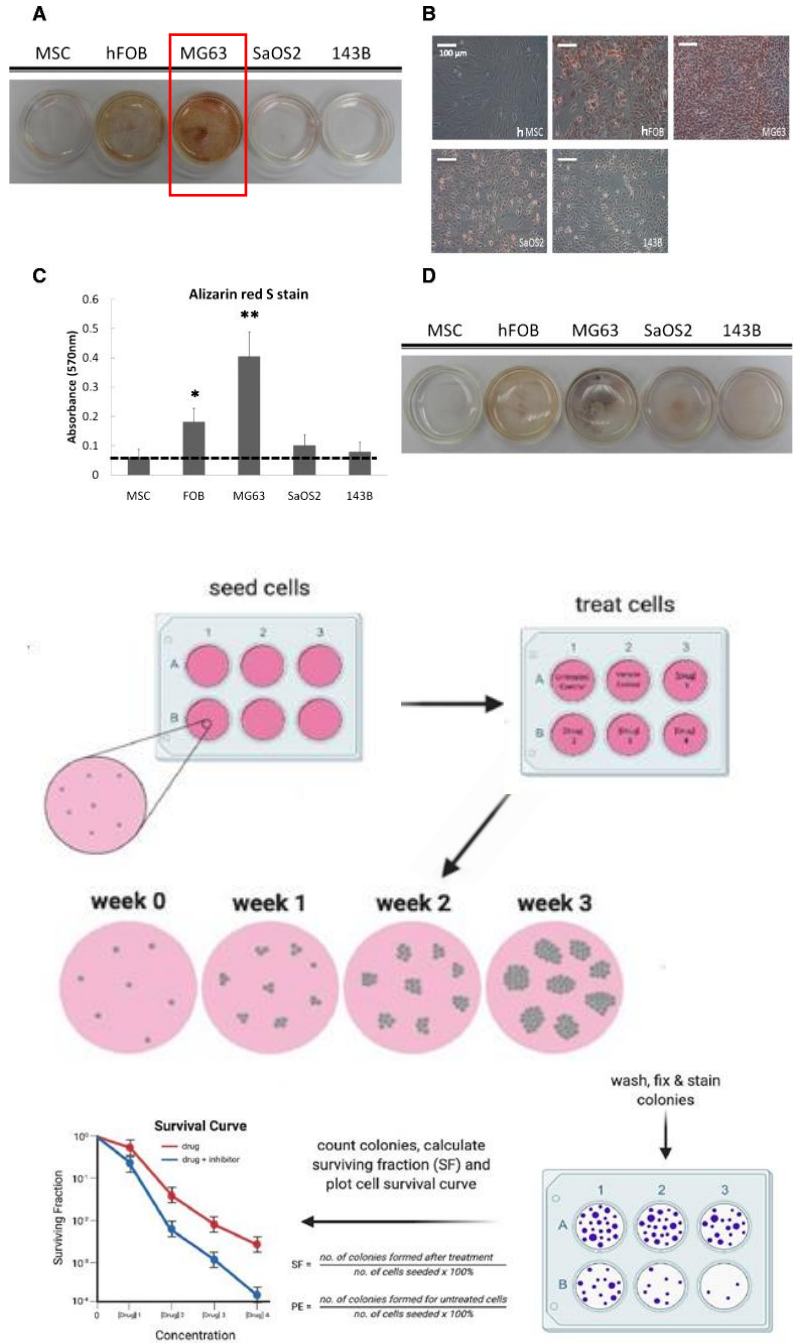


Figure 3. NaF PET–CT in a patient with pelvic osteosarcoma showing decrease in NaF with subsequent doses of $^{223}RaCl_2$.

Experimental overview:

- $^{128}Ba/^{128}Cs$ in vivo generator production and purification
- Cell uptake and internalization study of $^{128}Ba/^{128}Cs$
- Cell survival assay

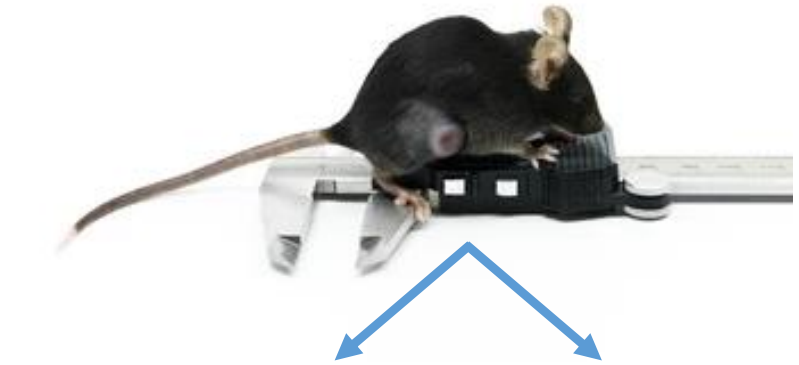
To be compared with ^{223}Ra

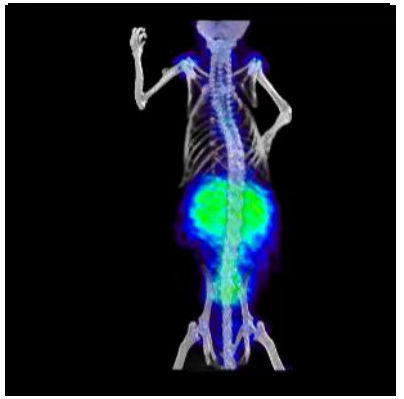


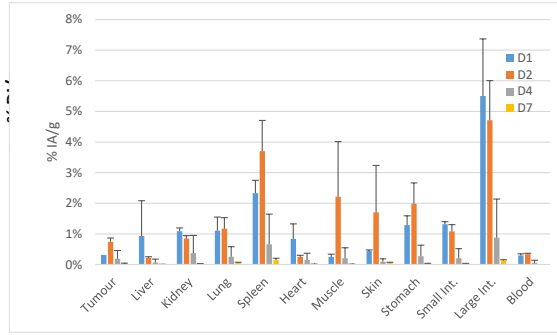
Chiang YH and al. Raman spectroscopy for grading of live osteosarcoma cells. Stem Cell Res Ther. 2015 Apr 18;6(1):81.

Experimental overview:

- Biodistribution and dosimetry study in mice bearing xenograft tumours
- Small animal PET imaging







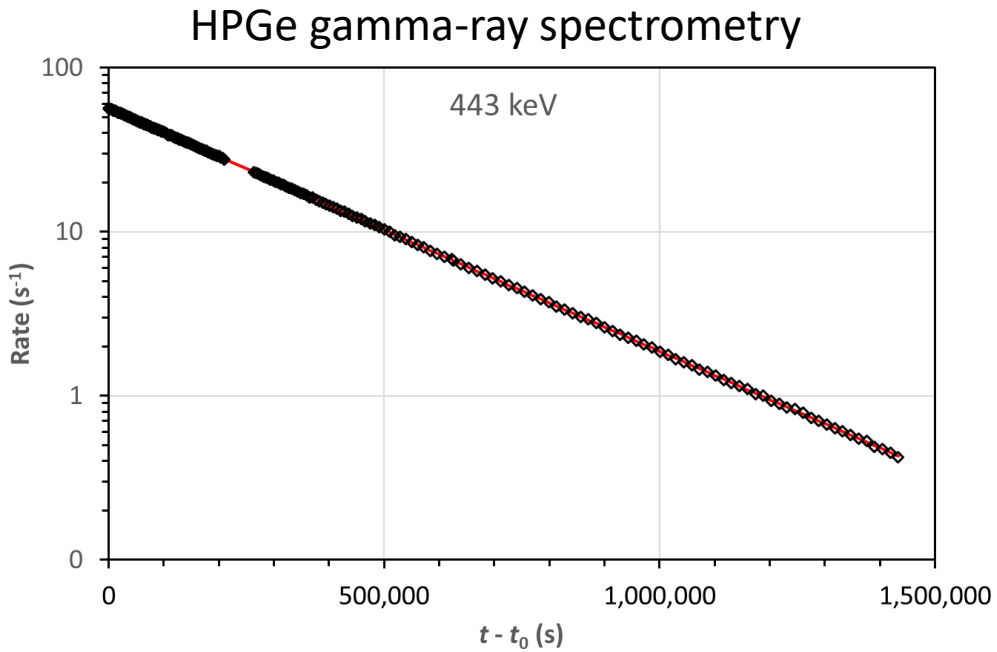
Internal dosimetry evaluation study

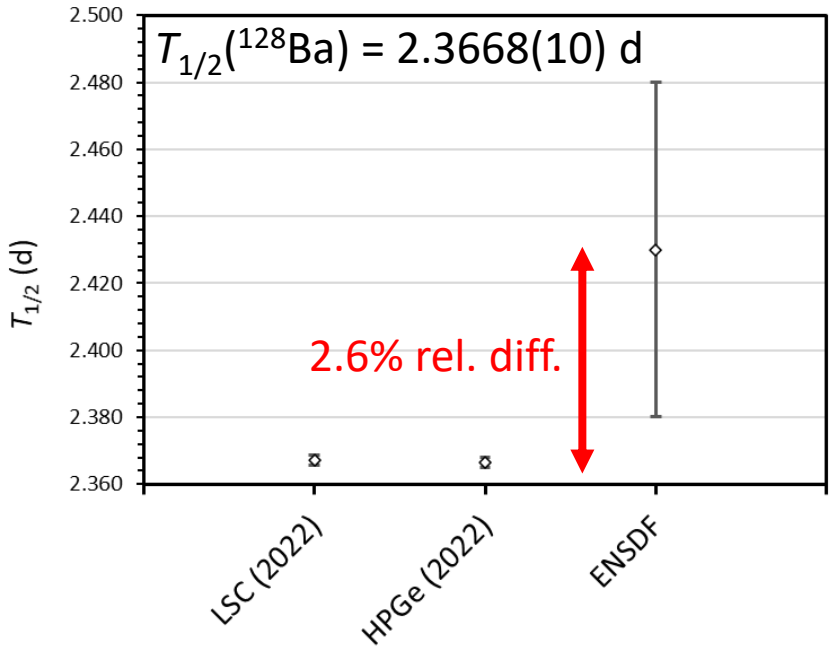
Production & Purification

- Produced and purified at the CERN-MEDICIS Facility
- Tantalum targets were irradiated by the CERN PS Booster proton beam at 1.4 GeV
- After irradiation, the targets is placed on the MEDICIS isotope separator and the Ba ions were implanted on “salt foils” or zinc coated gold foils
- The zinc foils were dissolved in concentrated HCl and loaded in TK-100 resin
- $^{128}Ba/^{128}Cs$ was then eluted with HCl
- At least 75% activity yield was obtained

Metrology & Calibration

- At NPL and IRA
- Radiochemical purity assay by HPGe
  - No long-lived gamma-emitting contaminants detected
- Half-life
  - ENSDF half-life = 2.43(5) d
  - Primary TCIR (transportable reference ionization chamber):
    2.3566(5) d
  - HPGe gamma-ray spectrometry (273 keV & 443 keV) = 2.3665(15) d
- Calibration factors using activity from TCIR for dose calibrator, gamma counter and microPET were created

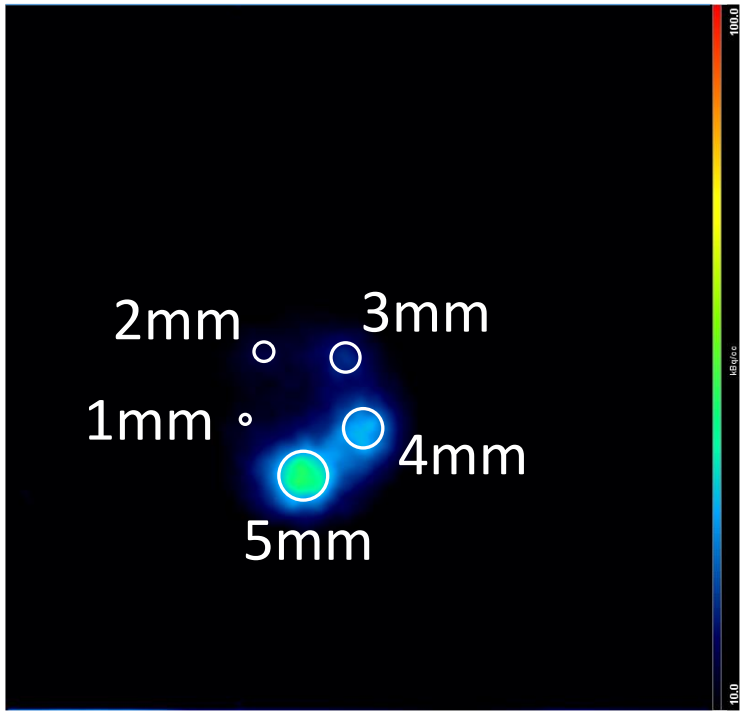


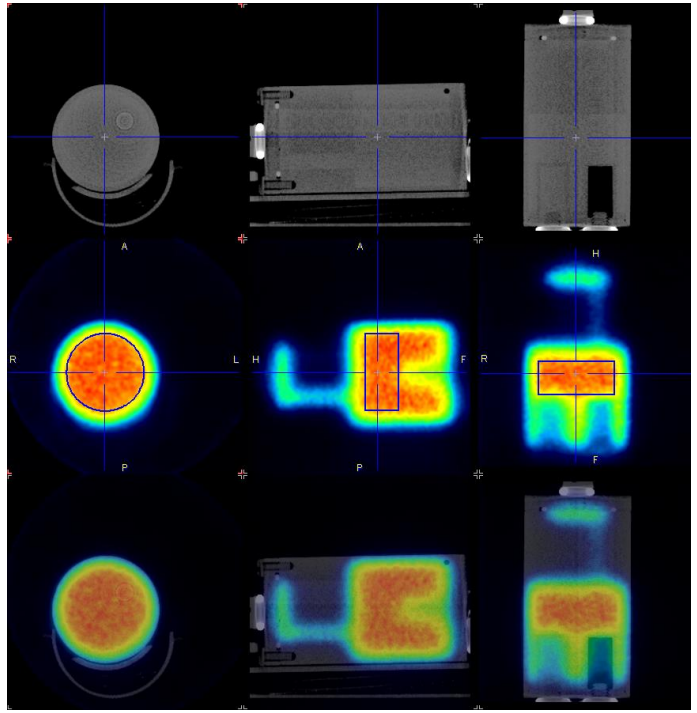


In Vitro uptake of $^{128}Ba/^{128}Cs$ by MG63 osteosarcoma

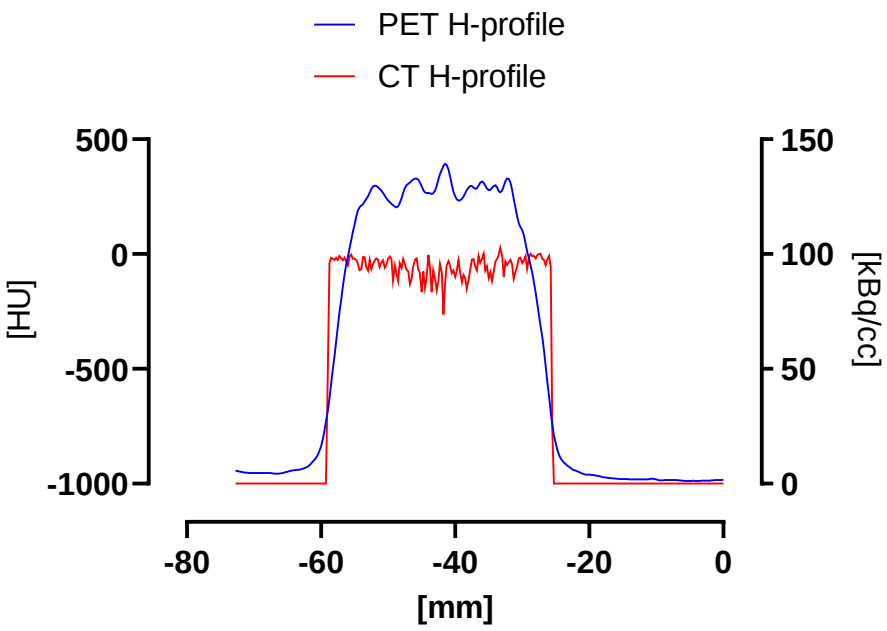
- Induced MG63 calcification with osteogenic medium (MEM media with 10 nM dexamethasone, 10 mM β-glycerophosphonate, and 50 mg/mL ascorbic acid)
  - →~ 5% $^{128}Ba/^{128}Cs$ incorporation by MG63 but no difference between untreated cells, cells treated for 24h, 72h and 96h
  - →21 days of induction still results in weak uptake (4.4 % compared to 6.3 % for untreated cells)
- LNCaP, PC3
- Subcellular localization of the $^{128}Ba/^{128}Cs$ (membrane, cytoplasm, mitochondria, nucleus)

First phantom study of ^{128}Ba/^{128}Cs PET imaging



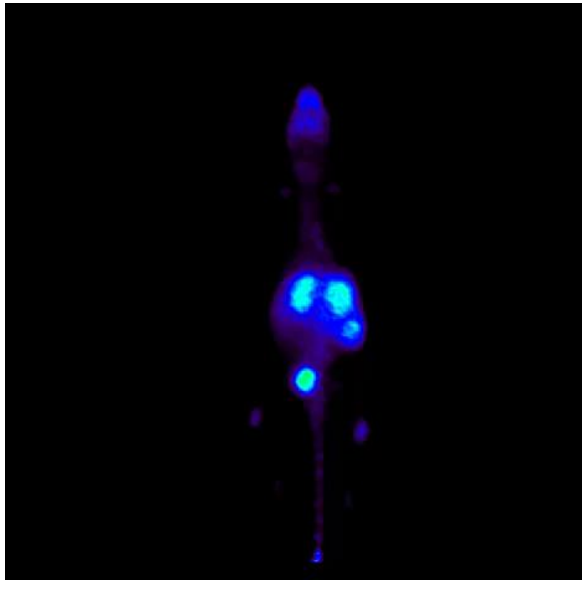


Micro-PET IQ Phantom
(according to NEMA NU 4-2008)

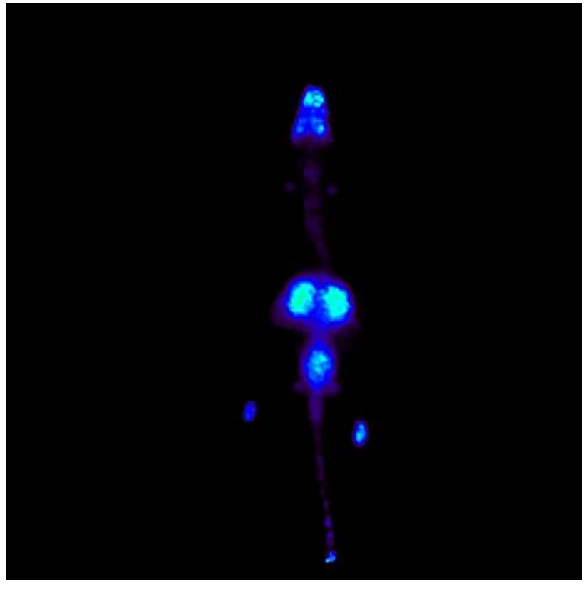


4 MBq in 21 ml → 190 kBq/ml
In VOI → 134 kBq/ml
MLEM 12 iteration

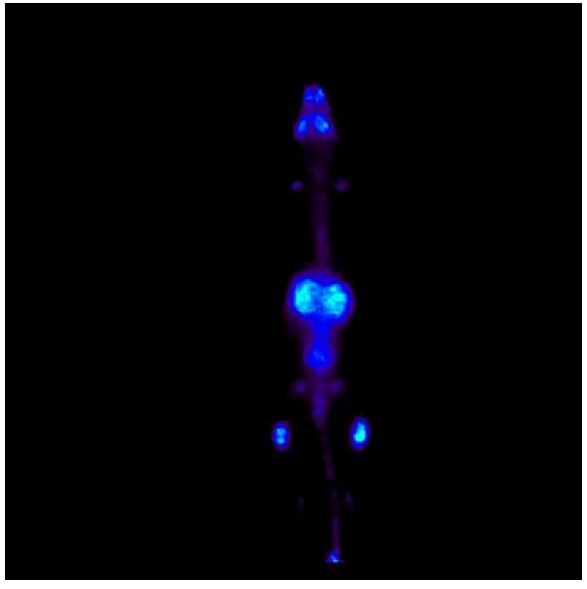
Whole body PET imaging of $^{128}Ba/^{128}Cs$ in naïve mice



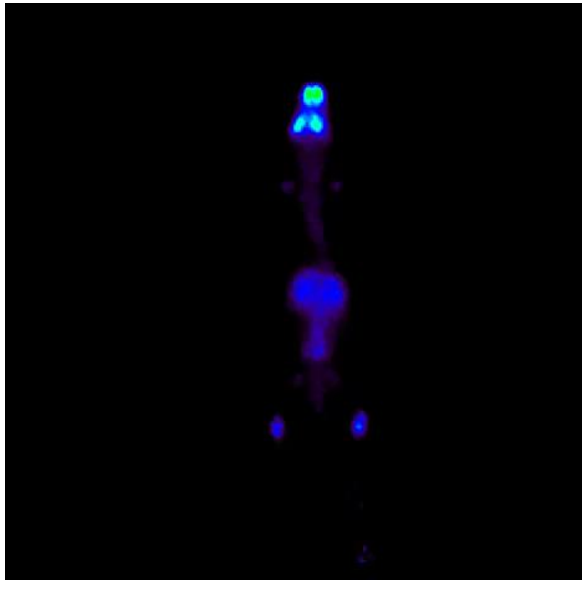
2 hours



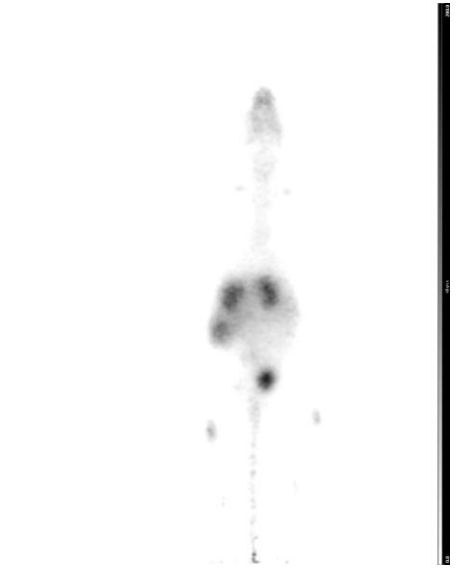
22 hours

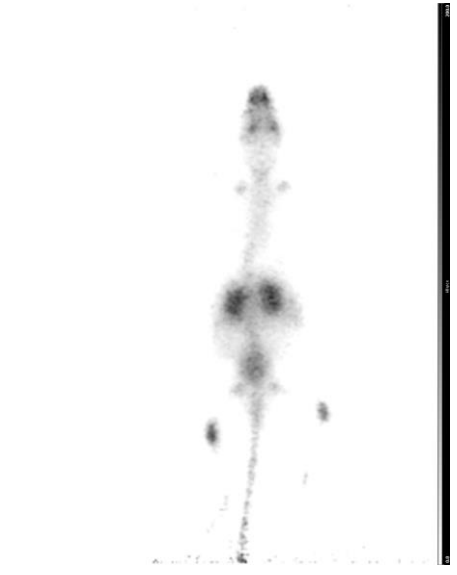


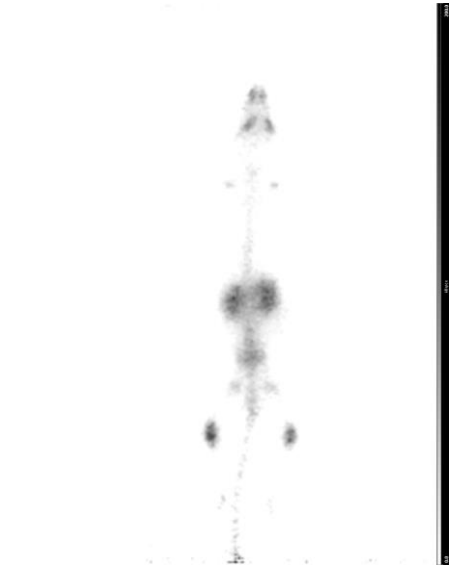
4 Days

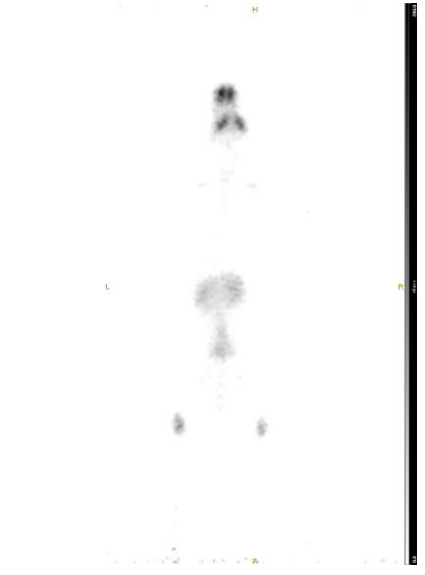


7 Days

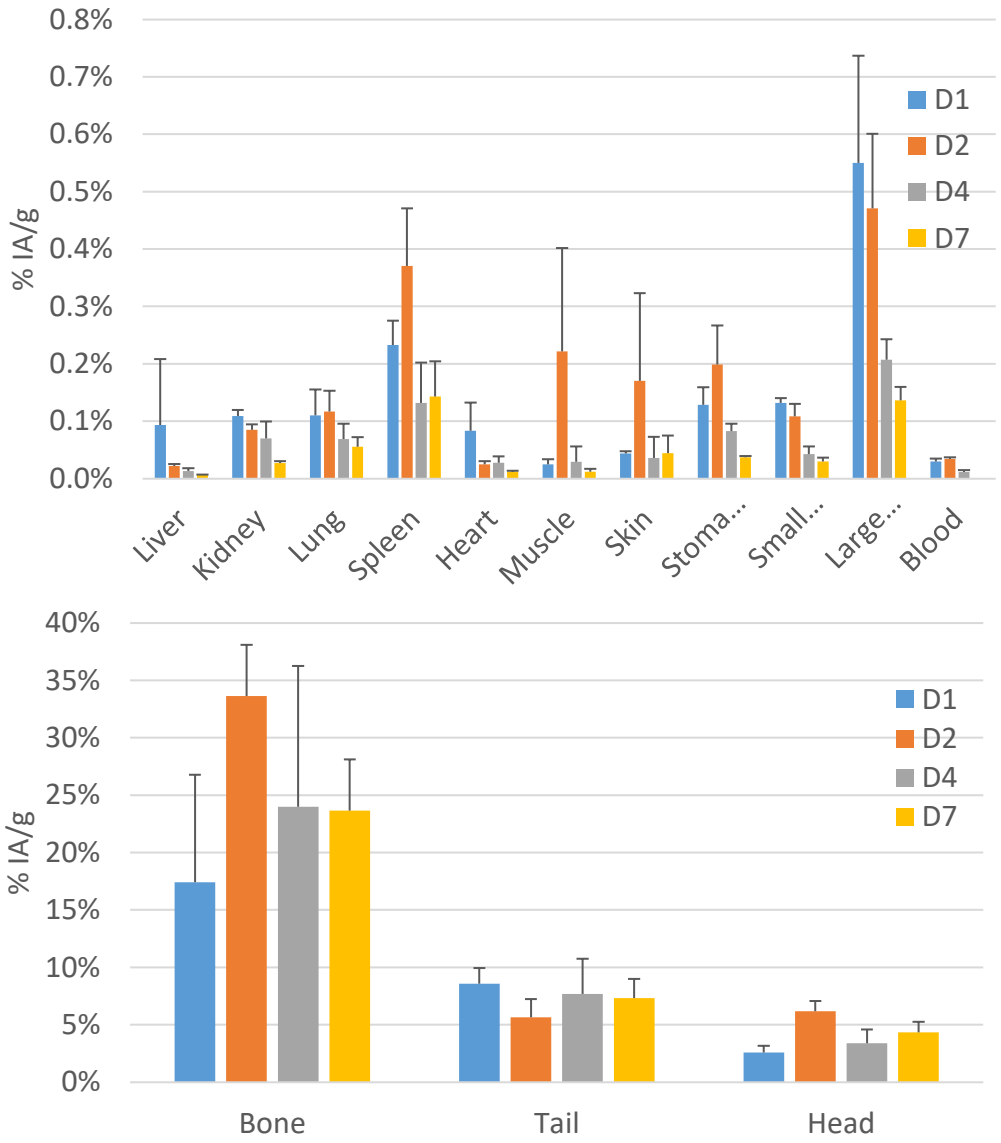








Biodistribution of ^{128}Ba/^{128}Cs in naïve mice & Dosimetry



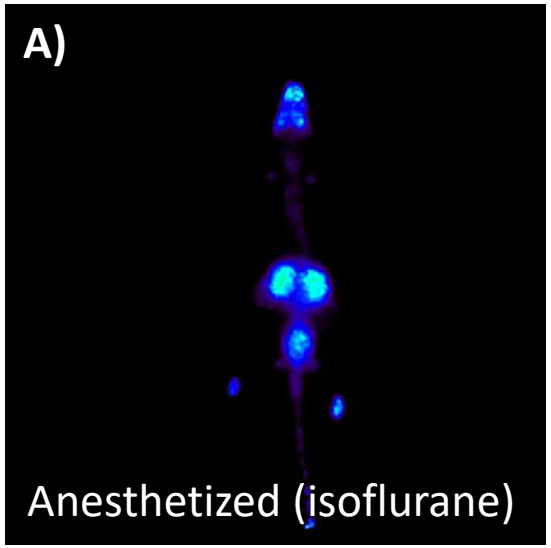
Organs	TIAC (h)	**Ba-128** Total [mGy/MBq]]	**Cs-128** Total [mGy/MBq]
Brain		5.06E+00	6.05E+02
Large Int	5.01E-01	7.98E+00	1.89E+02
Small Intestine	1.90E-01	3.57E+00	1.31E+02
Stomach Wall	4.24E-02	7.59E+00	2.65E+02
Heart	1.14E-01	8.21E+00	9.21E+02
Kidneys	5.20E-02	4.41E+00	2.36E+02
Liver	4.42E-02	4.29E+00	3.90E+02
Lungs	2.70E-02	1.02E+01	1.12E+03
Skeleton	2.00E+01	**7.14E+01**	**2.78E+03**
Spleen	3.46E-02	4.68E+00	1.96E+02
Total Body		5.69E+00	5.46E+02

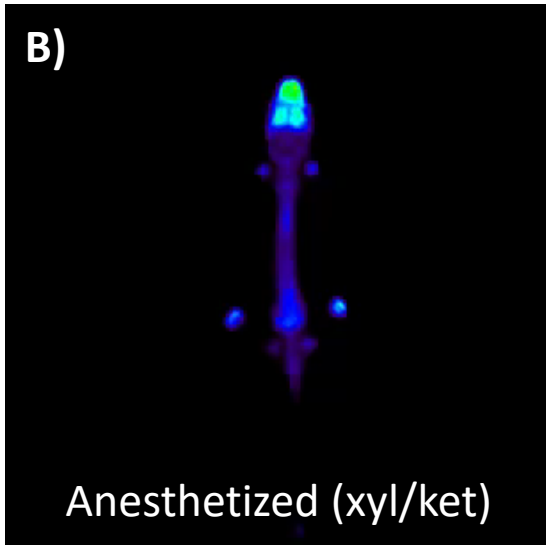
Table 1: Dosimetry of ^{128}Ba/^{128}Cs in mice. The most contribution is due to the ^{128}Cs and principally in the bones.

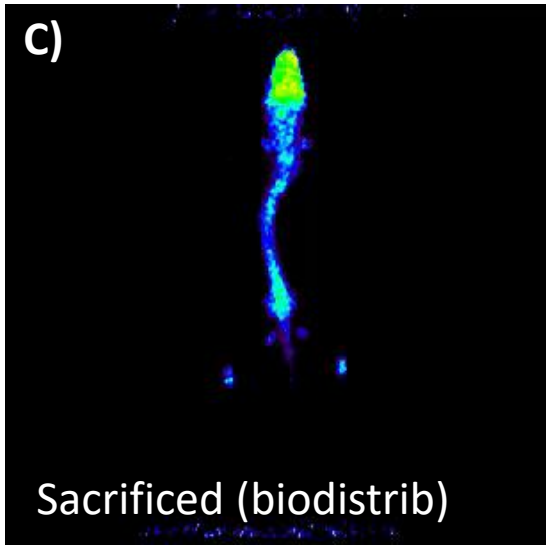
Impact of mouse preparation for Preclinical PET images & biodistributions of ^{129}Cs

PET images 24 hours post injection of $^{128}Ba/^{128}Cs$

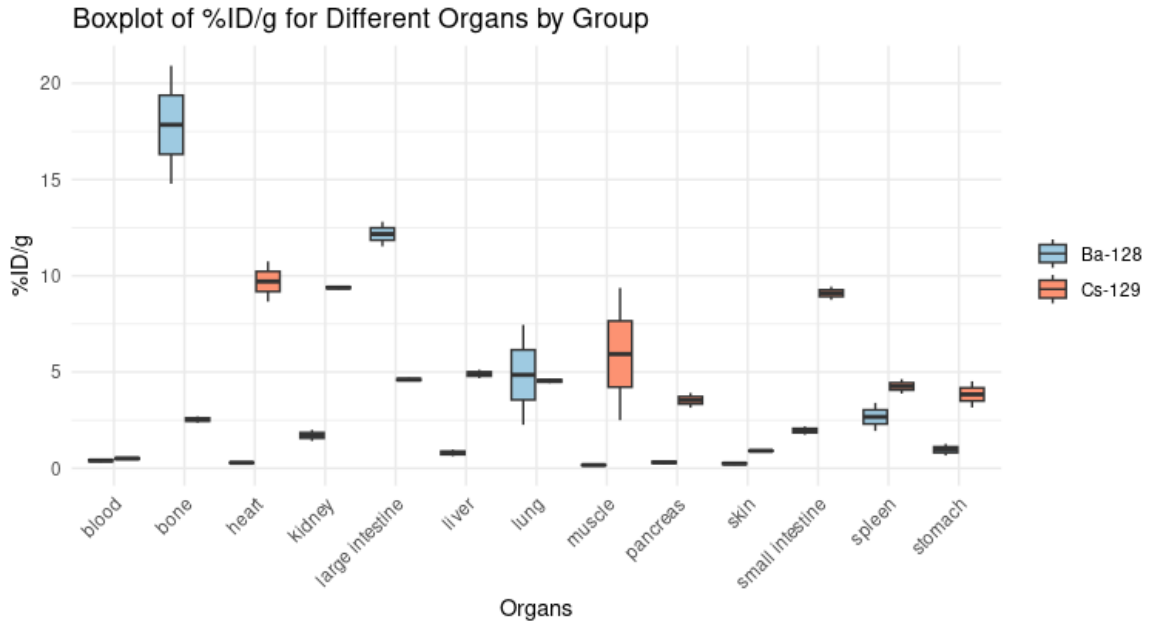
$^{128}Ba/^{128}Cs$ strongly accumulates in the bones of mice, but also in the kidney according to the physiological status of the animal (Figure1). It is important to understand this undesirable kidney accumulation as it will severely impact the dosimetry of $^{128}Ba/^{128}Cs$ in patient







Biodistribution of $^{128}Ba/^{128}Cs$ and ^{129}Cs. $^{128}Ba/^{128}Cs$ showed a strong uptake by the bone while ^{129}Cs accumulated in kidneys



Outlook

- Continue our effort to find a suitable in vitro model (Auger microdosimetry)
- Consolidate PET imaging and biodistribution for reliable dosimetry
- Intensification of the project, strengthening collaboration between GRT & MedNuc + others (CERN, Messina, NPL, …) to get founding (SNFS, OncoSuisse, …)

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- *NPL:*
  - *S. Collins*
- CERN
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