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CANCER & IMMUNOLOGY



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Brain intratumoral At-211 radiotherapy targeting syndecan-1 leads to durable glioblastoma remission and immune memory in female mice

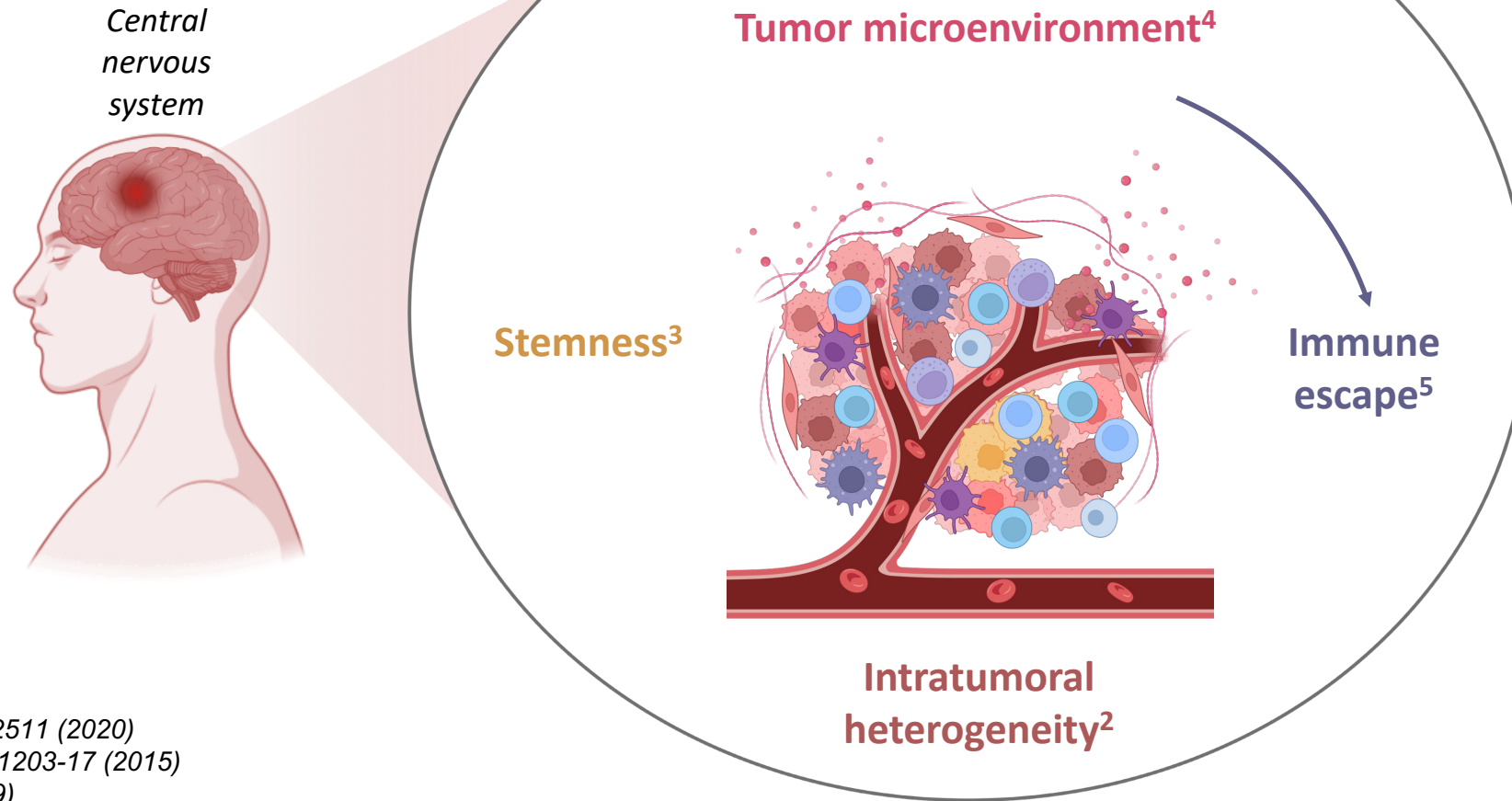
Pr Michel CHÉREL - *CIRCI²NA Nuclear Oncology*

Dr Emmanuel GARCION - *CIRCI²NA GLIAD*

Dr François HINDRÉ - *CIRCI²NA GLIAD*

Glioblastoma : an unmet clinical need

WHO : Grade IV astrocytoma



¹Ali et al. *Cancers (Basel)* 12(9):2511 (2020)

²Lathia et al. *Genes Dev.* 29(12):1203-17 (2015)

³Neftel et al. *Cell* vol. 178,4 (2019)

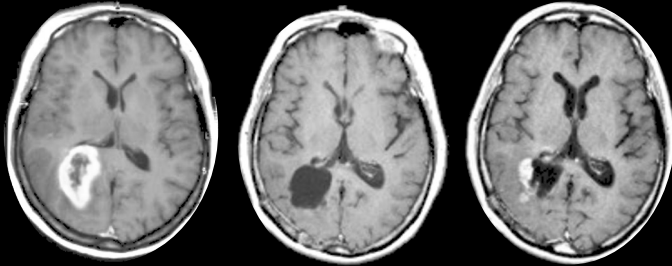
⁴Antunes et al. *eLife* vol. 9 e52176. (2020)

⁵Chédeville and Madureira *Cancers* vol. 13,3 542 (2021)

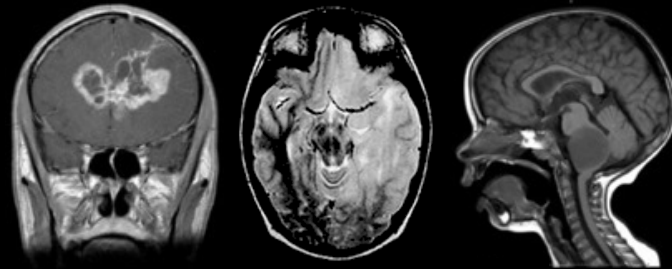
Current therapeutic strategy (since 2005)

Two clinical situations

1. Surgical resection

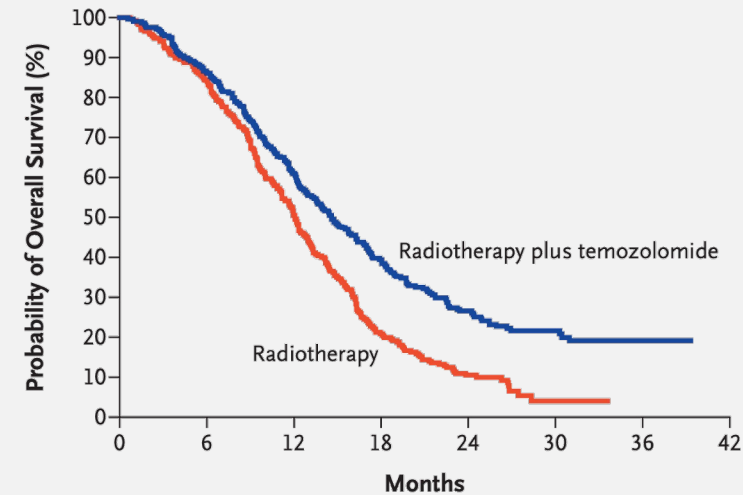


2. Non-resectable tumor



Radiotherapy + chemotherapy (temozolomide)

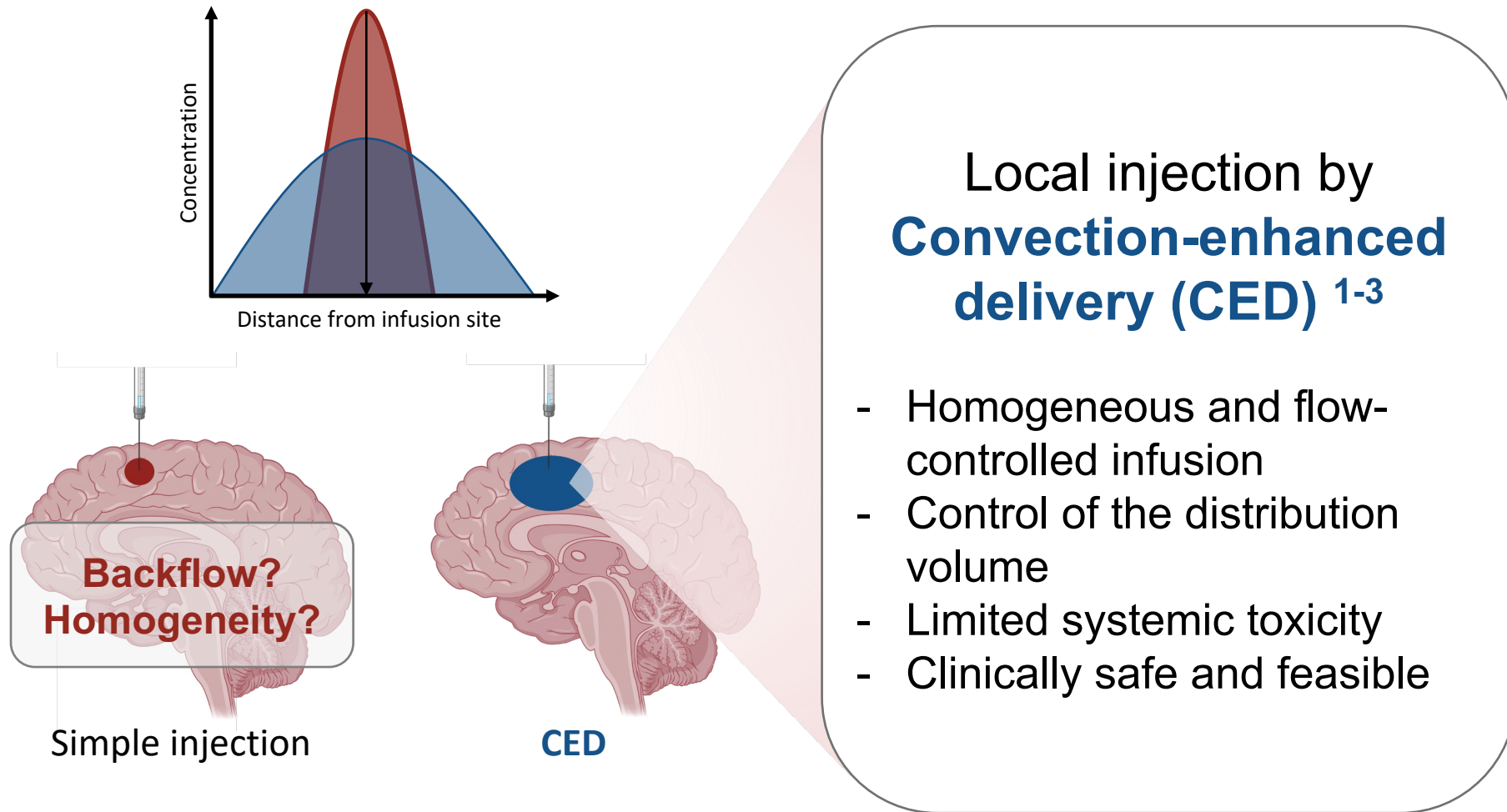
Median survival : 15 months



Stupp et al. (2005) N. Engl. J. Med. 352, 987–996.

Aim: To innovate in terms of targeted radiotherapy for the locoregional treatment of glioblastoma

1. Using locoregional radiotherapy to bypass the blood-brain barrier

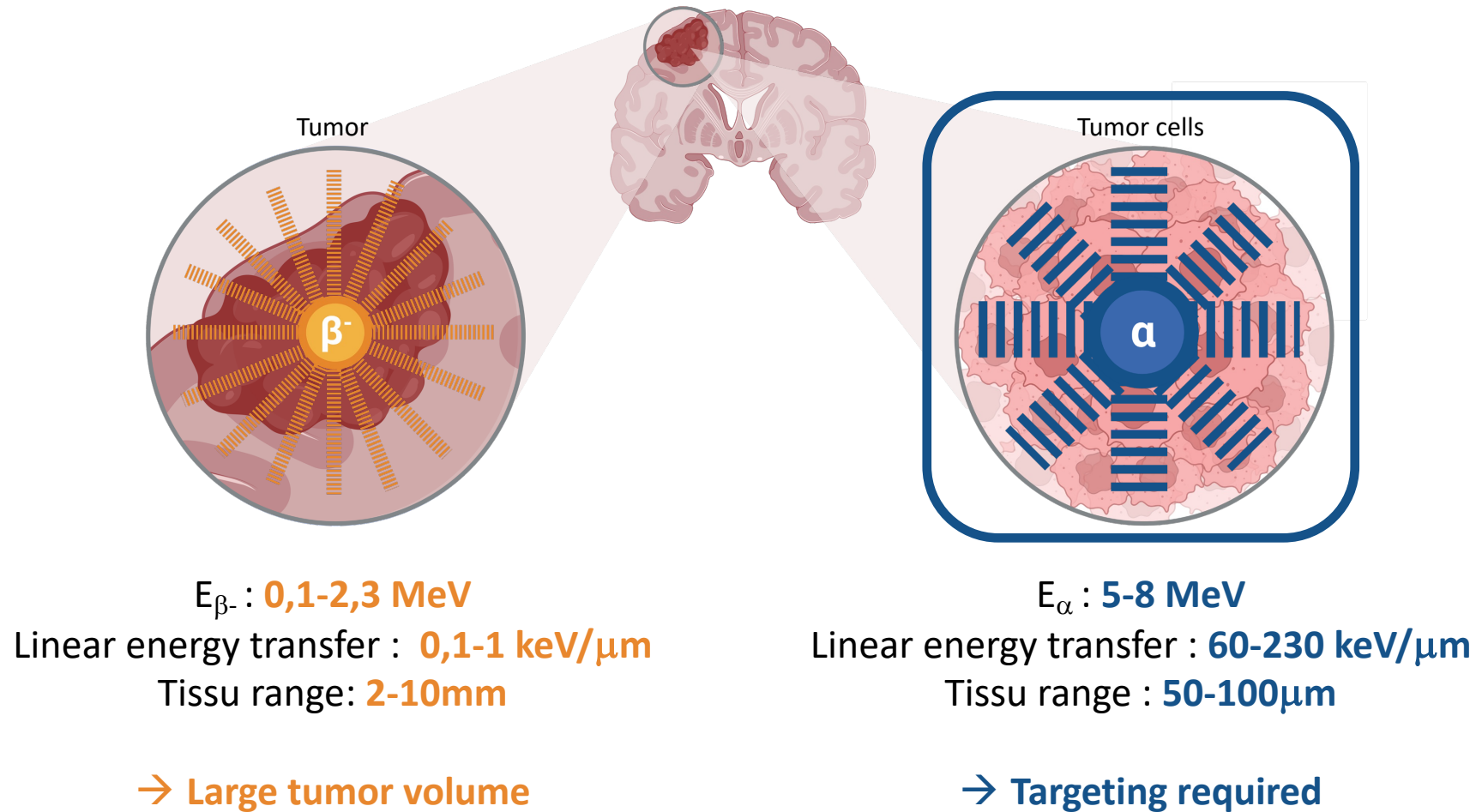


¹Bobo et al. *Proc Natl Acad Sci USA*. Mar 15;91(6):2076-80 (1994)

²Nwagwu et al. *Pharmaceutics*. Dec 30;13(1):40 (2020)

³D'Amico et al. *J Neurooncol*. 151(3):415-427 (2021)

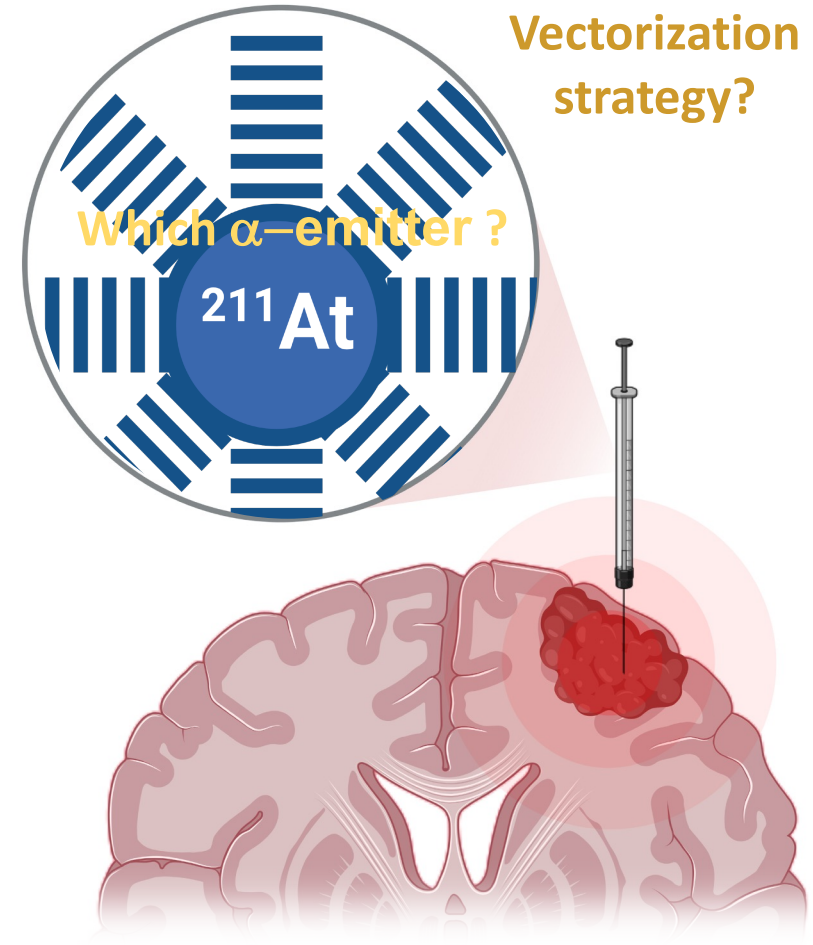
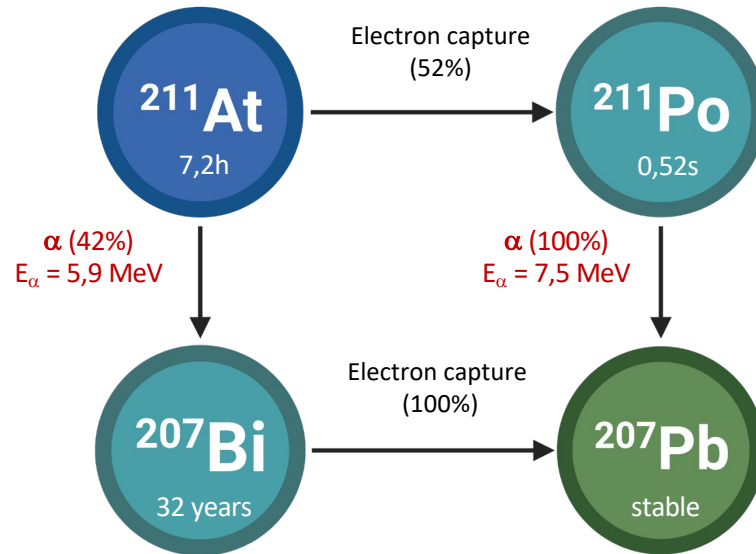
2. α -emitters for vectorized radiotherapy of glioblastoma



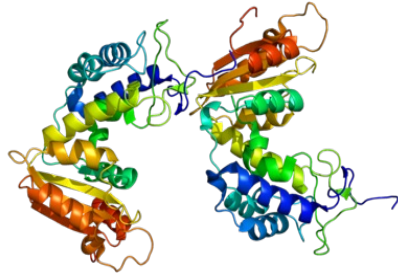
2. α -emitters for vectorized radiotherapy of glioblastoma

Astatine-211 (^{211}At)

Half-life : 7,2h
Tissu range < 100 μm
 E_{α} : 5,9 and 7,5 MeV
LET : 99 keV/ μm



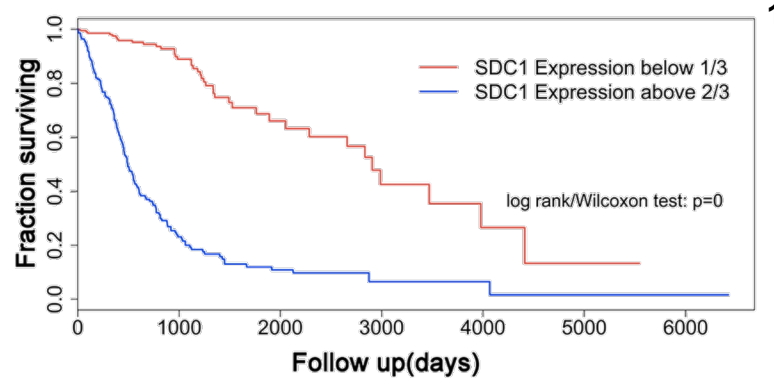
3. Targeted radiotherapy to deliver radiopharmaceuticals



Syndecan-1

Proteoglycan : extracellular matrix integrity

Proliferation¹
Immune escape²
Invasion / Migration³
Angiogenesis⁴



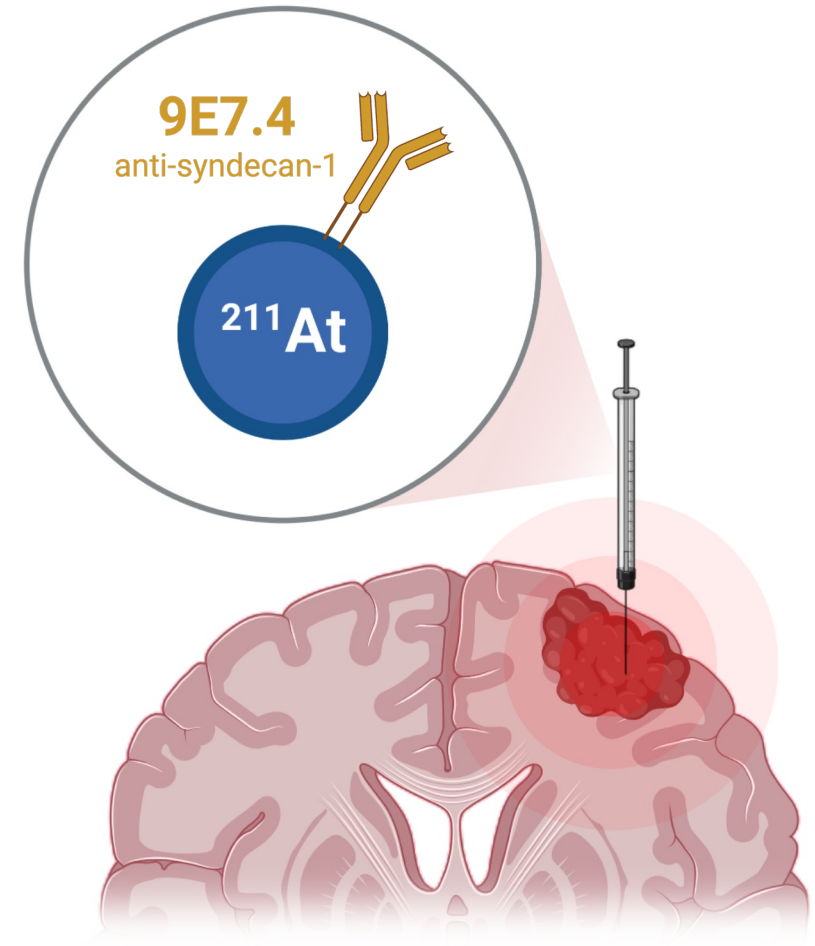
¹Shi et al. (2017) *Oncotarget* 8, 40922–40934

²Zhong et al. (2022) *Front. Genet.* vol. 13 792443

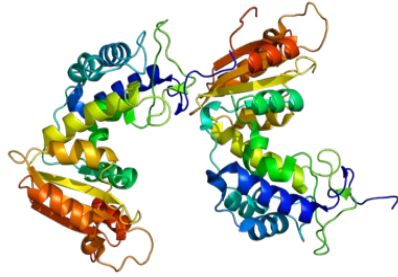
³Chen et al. (2017) *Oncol. Lett.* vol. 14,6

⁴Francescone et al. (2011) *J. Biol. Chem.* vol. 286,17

Monoclonal antibody 9E7.4



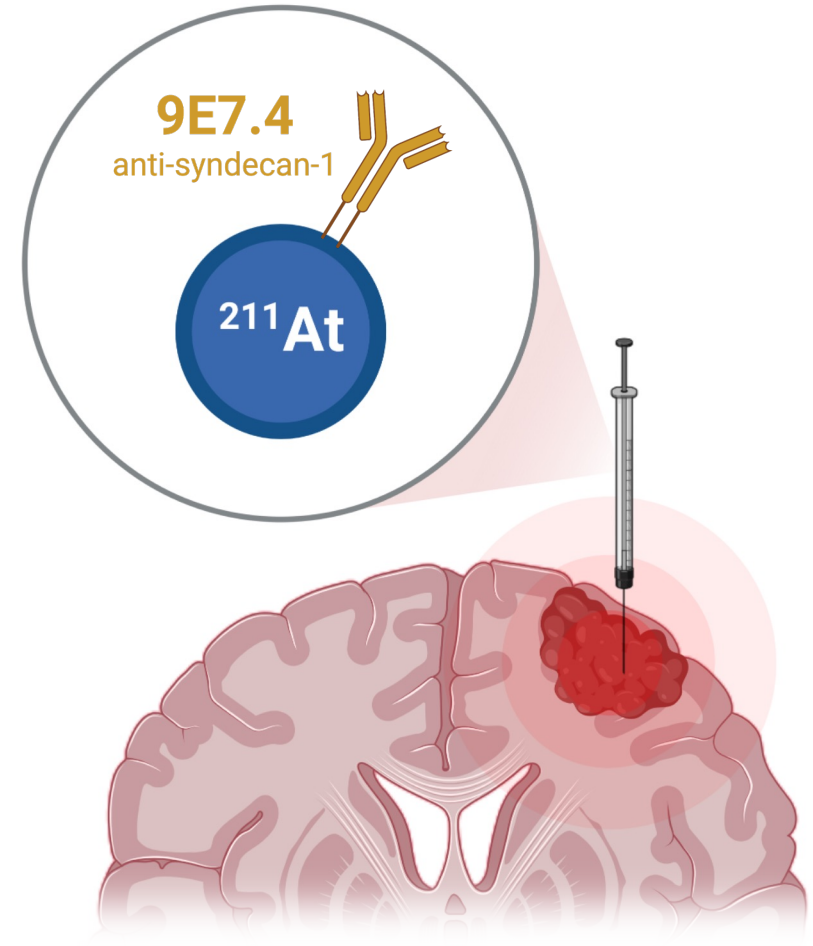
3. Targeted radiotherapy to deliver radiopharmaceuticals



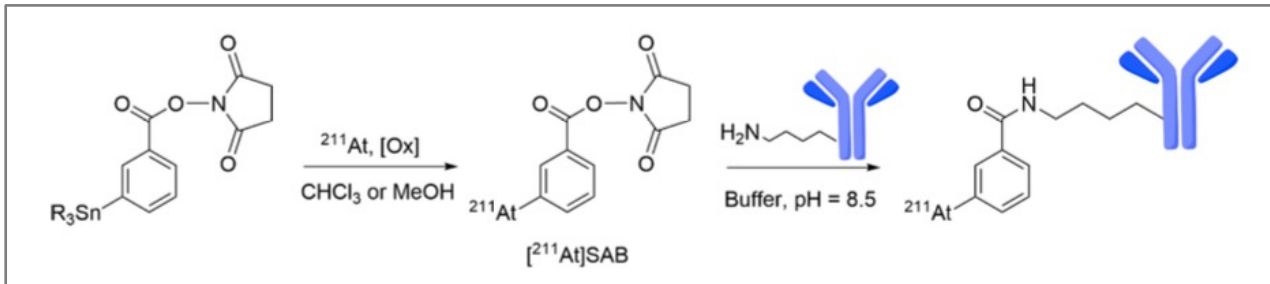
Syndecan-1

Proteoglycan : extracellular matrix integrity

Monoclonal antibody 9E7.4

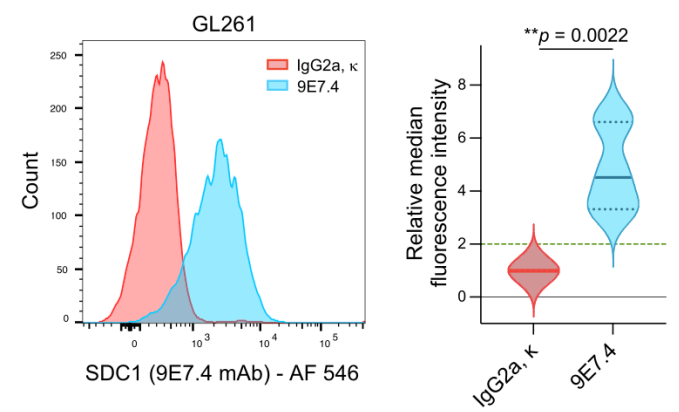


Two-step 9E7.4 radiolabelling using N- succinimidyl-[^{211}At]astatobenzoate (^{211}At]SAB) prosthetic group

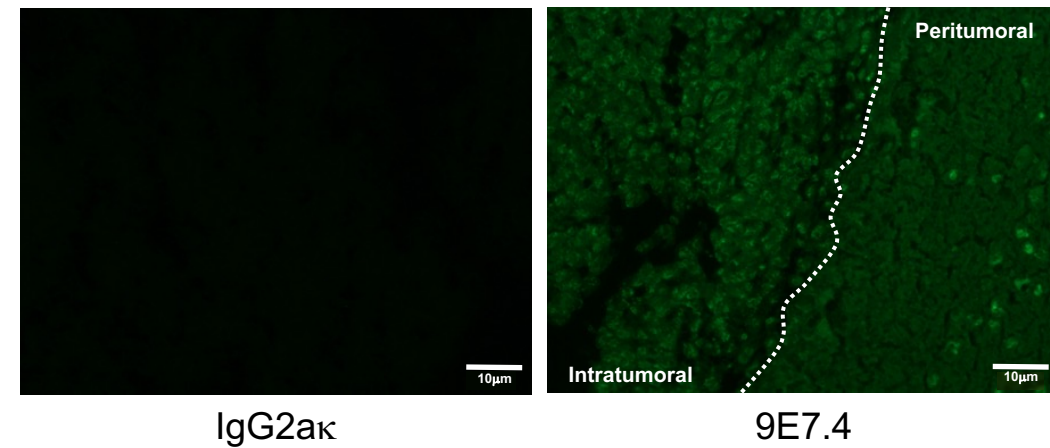


Guérard et al. *Acc. Chem. Res.* 54, 16, 3264–3275 (2021)

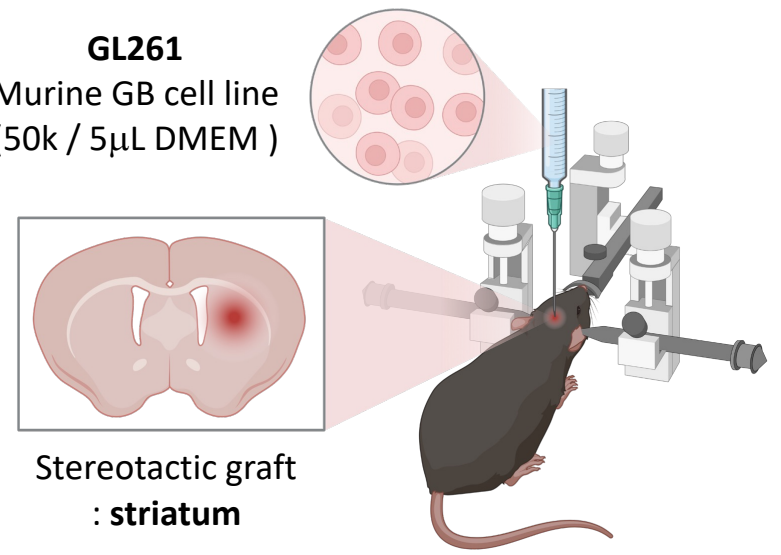
Syndecan-1 is overexpressed in GL261 tumors in the immunocompetent C57BL/6j mouse model



A : Immunofluorescence (n=5)



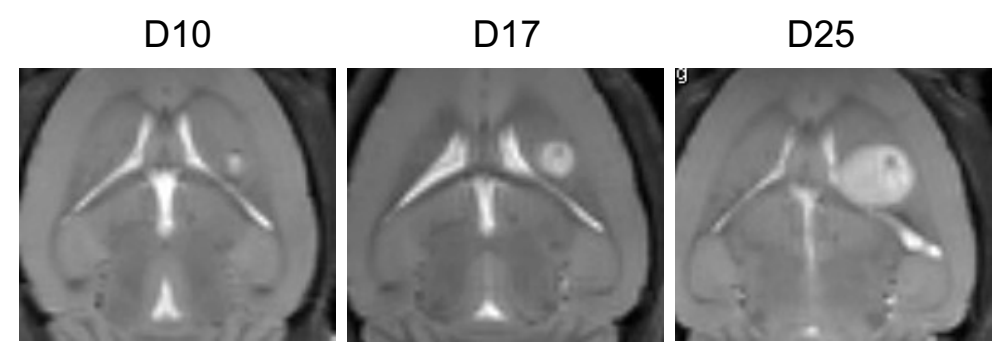
GL261
Murine GB cell line
(50k / 5 μ L DMEM)



Stereotactic graft
: striatum

Immunocompetent
C57BL/6j

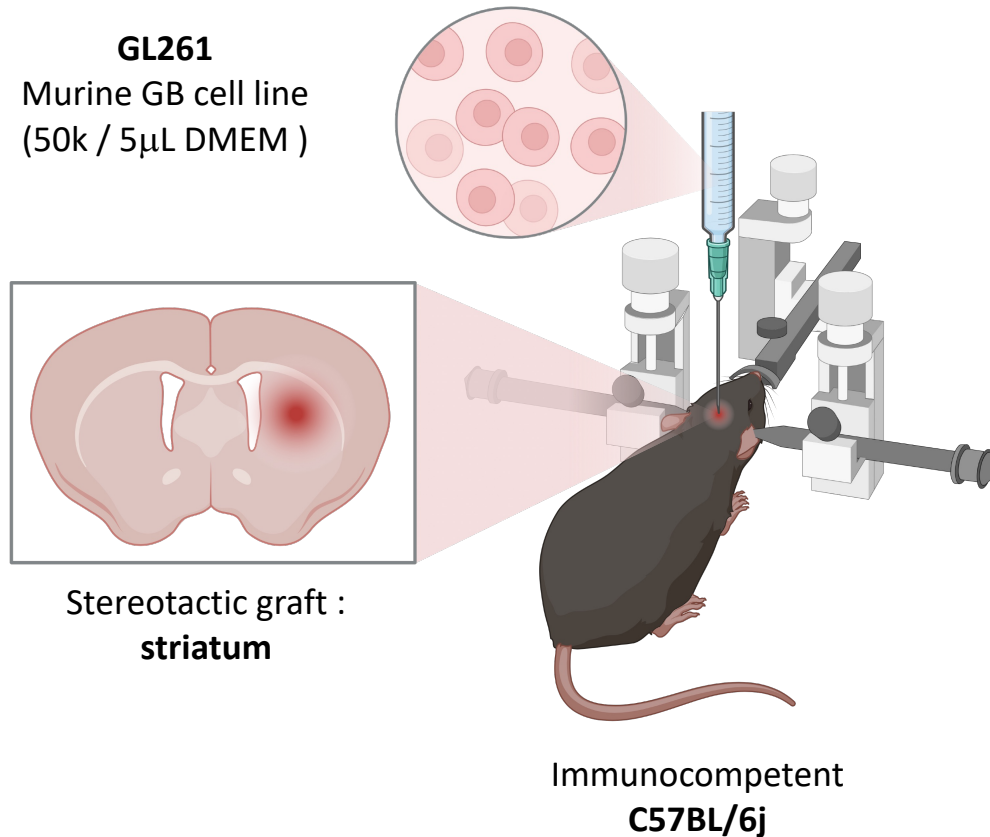
B : MRI follow-up (n=12)



Survival median without treatment: **33 days**

C57BL/6j – GL261 : methodology

D0 : Tumor graft (5 μ L)



D11 : Same coordinates $\rightarrow$ CED (5 μ L)

iodine-125 : 30kBq 9E7.4 : 2.8 μ g



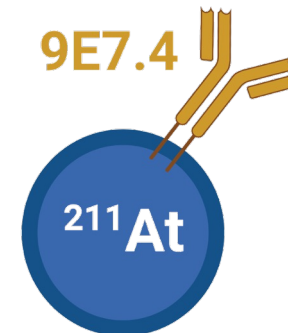
I. Biodistribution

Gamma counting

II. Brain diffusion

Digital autoradiography

astatine-211 : 500-200-100kBq 9E7.4 : 2.8 – 1.12 – 0.56 μ g



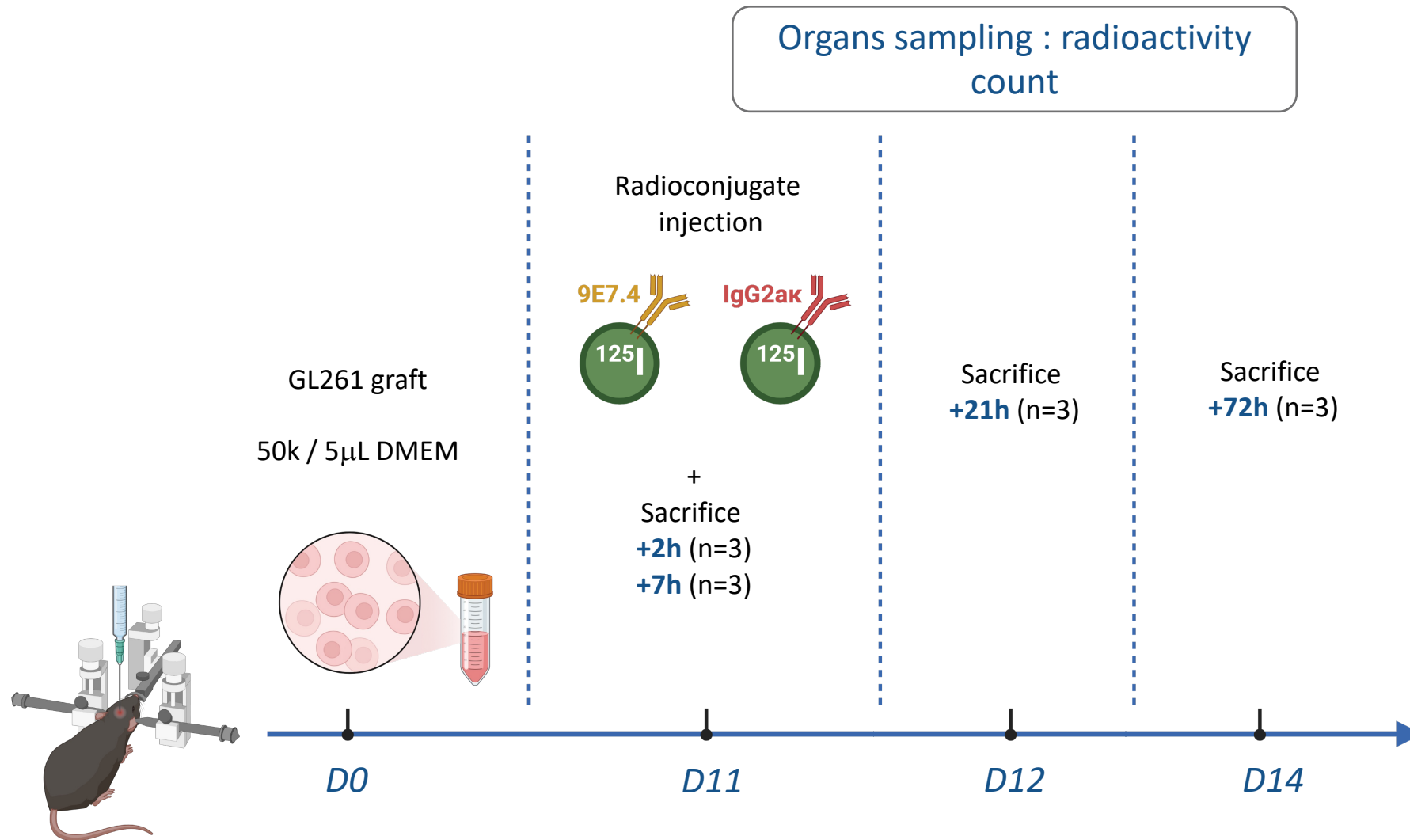
III. Survival / toxicity

MRI, weight, blood samples

**IV. Microenvironment
responses**

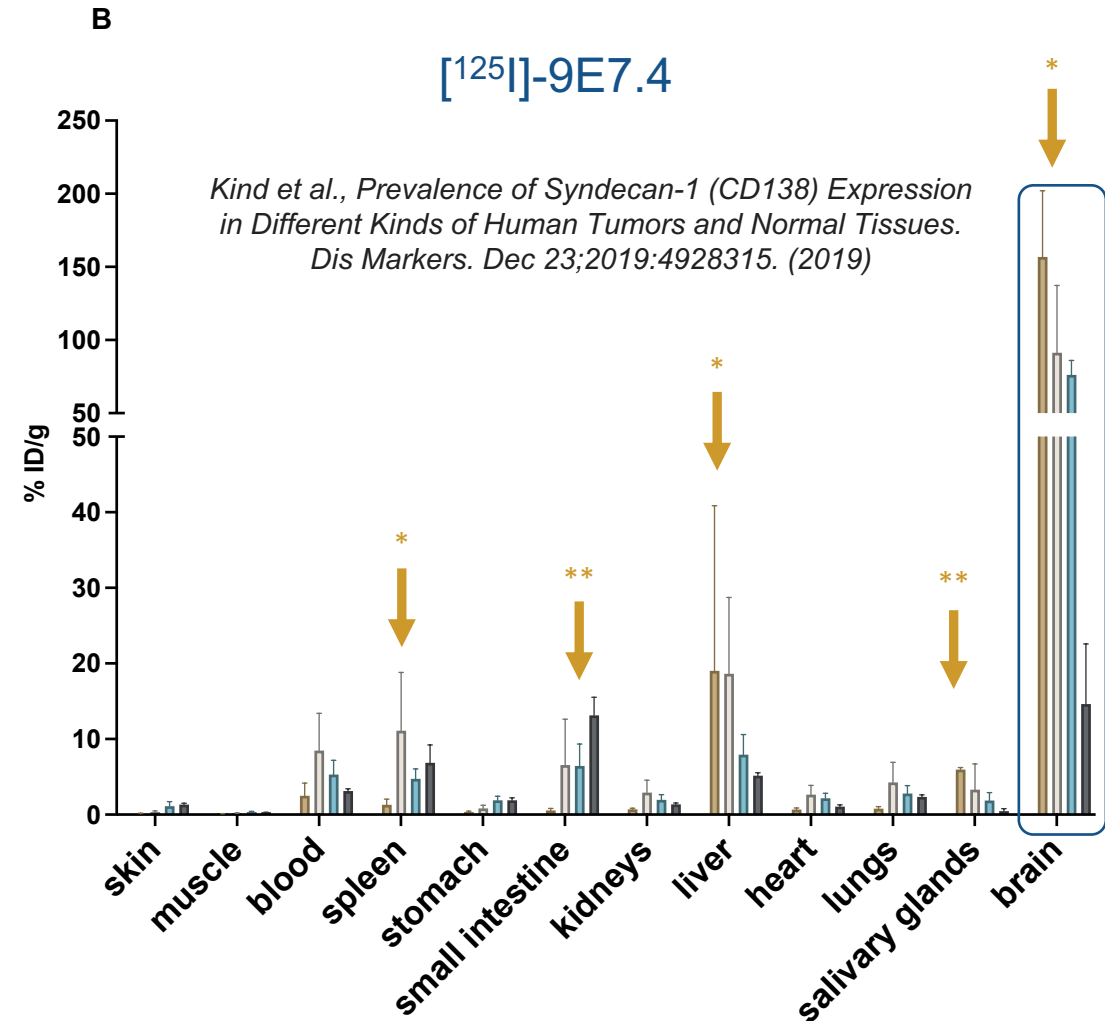
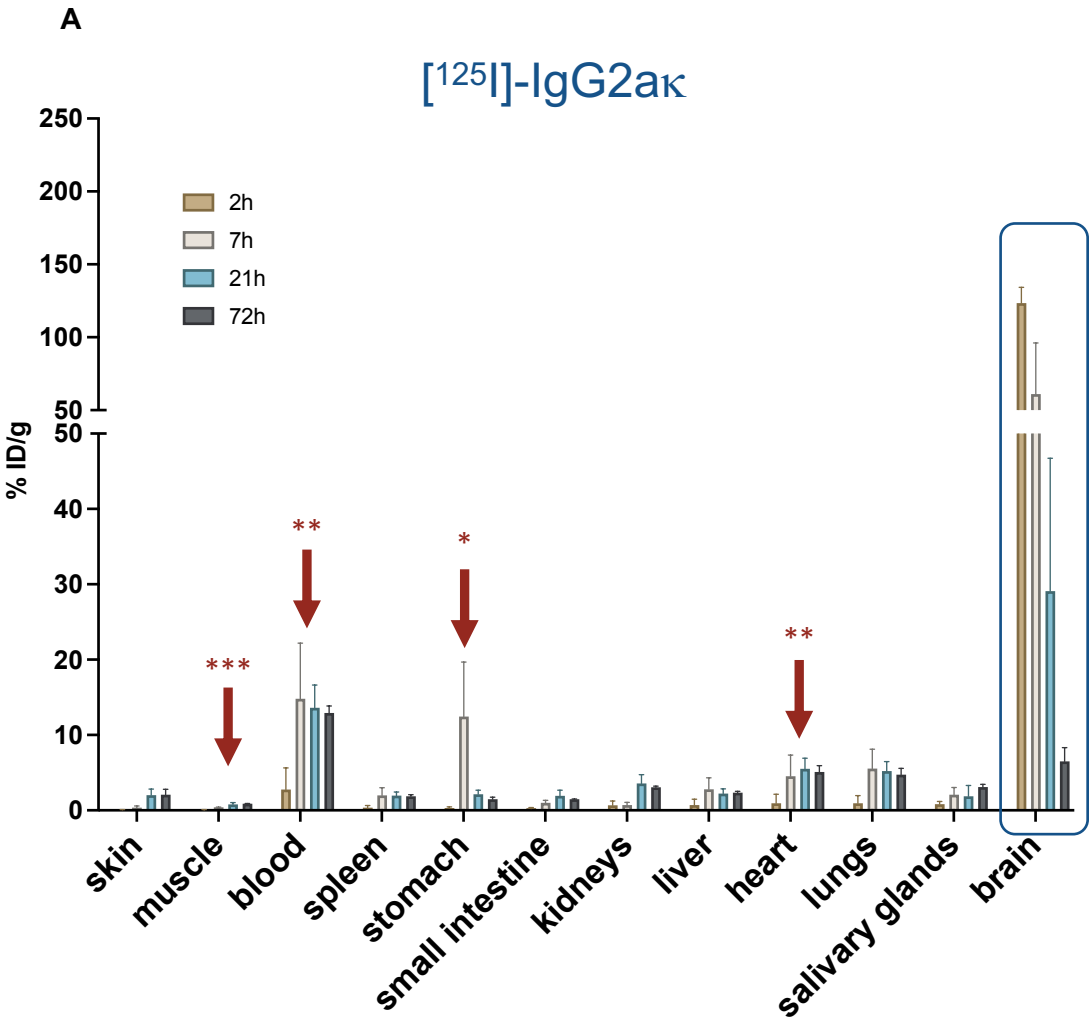
*Immunofluorescence, flow
cytometry*

I. Biodistribution study of the [^{125}I]-9E7.4 conjugate in the C57BL/6j-GL261 model



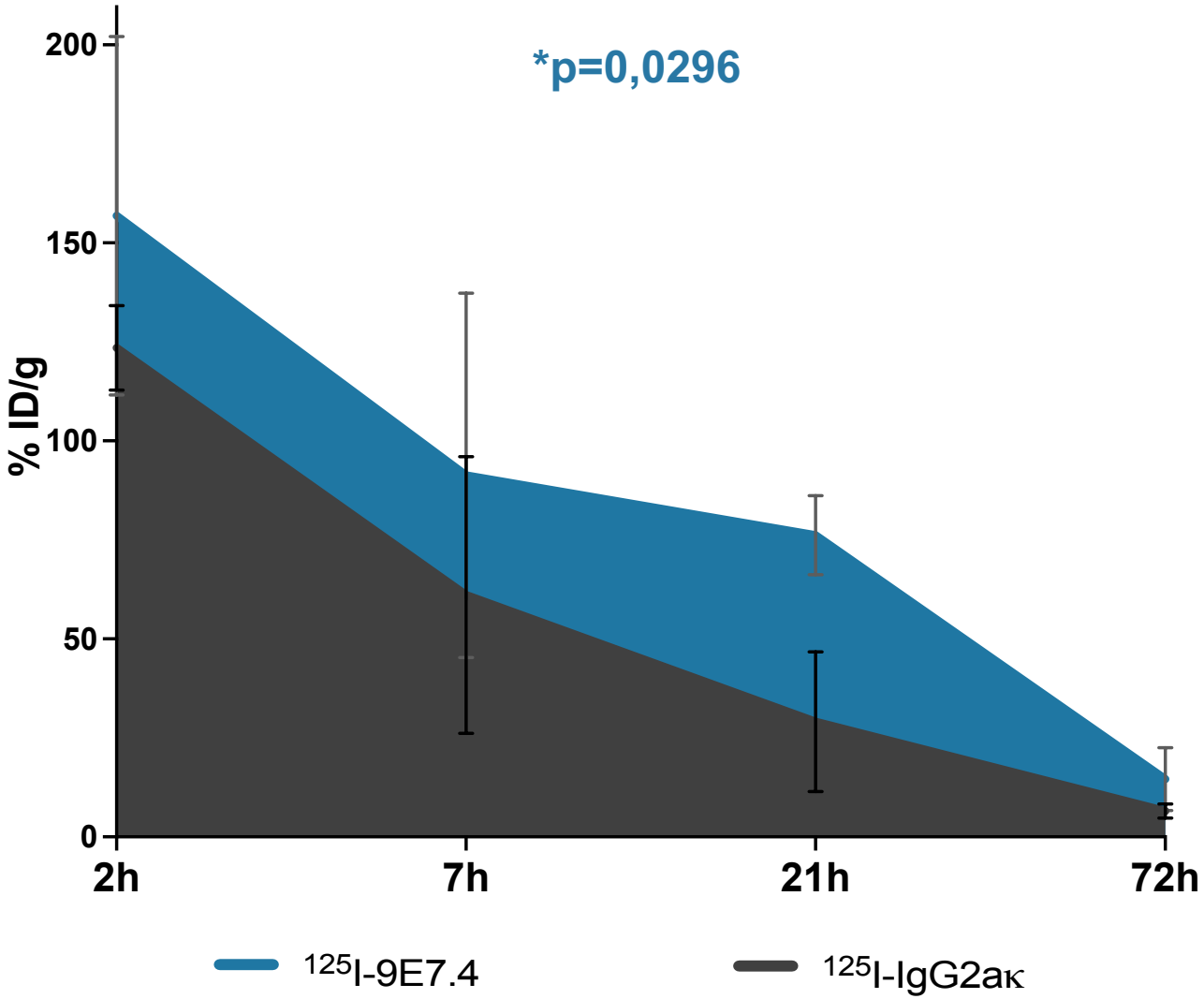
I. The biodistribution study reveals a major brain retention of the $[^{125}\text{I}]$ -9E7.4 conjugate in the C57BL/6j-GL261 model

n=3 for each time point

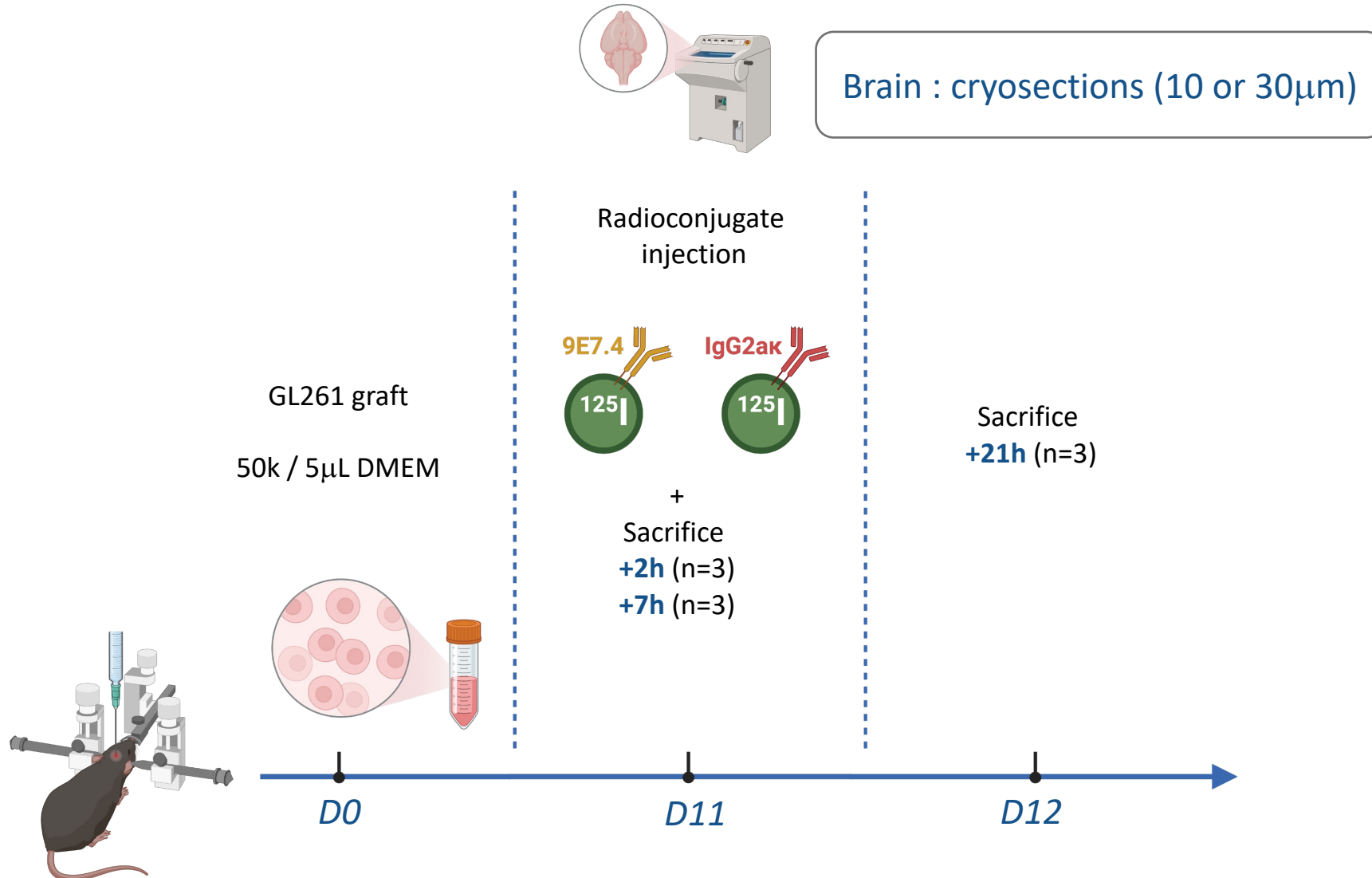


I. The [¹²⁵I]-9E7.4 brain retention is significantly higher than [¹²⁵I]-IgG2aκ over 72h

n=3 for each time point

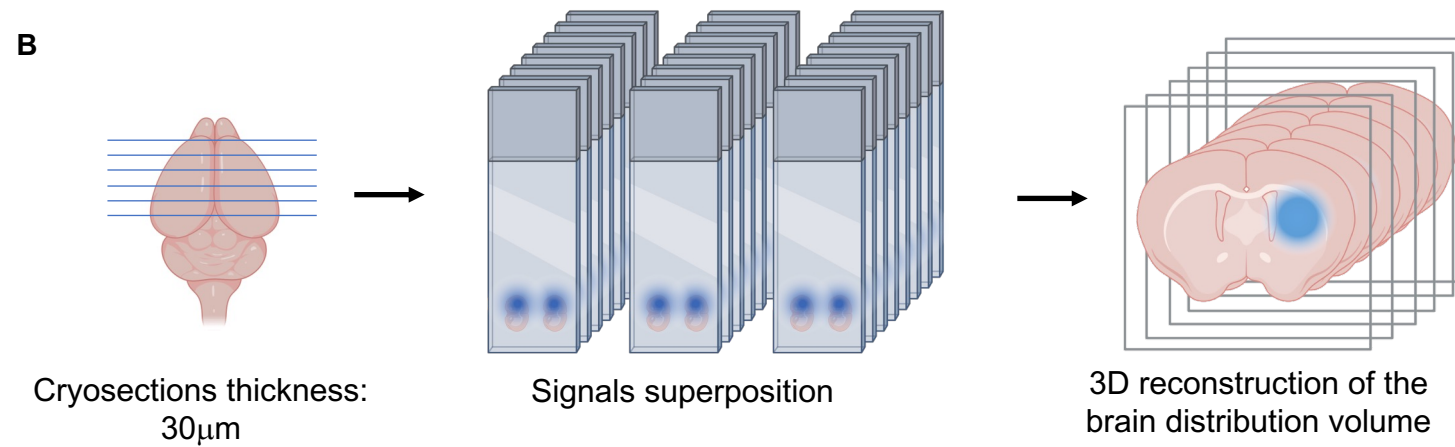
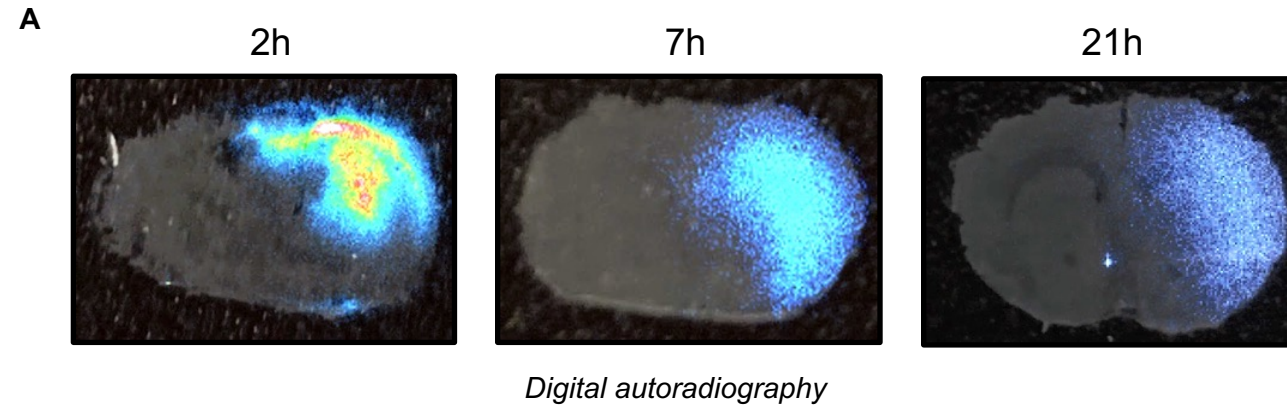


II. Brain diffusion by digital autoradiography of the [^{125}I]-9E7.4 conjugate in the C57BL/6j-GL261 model

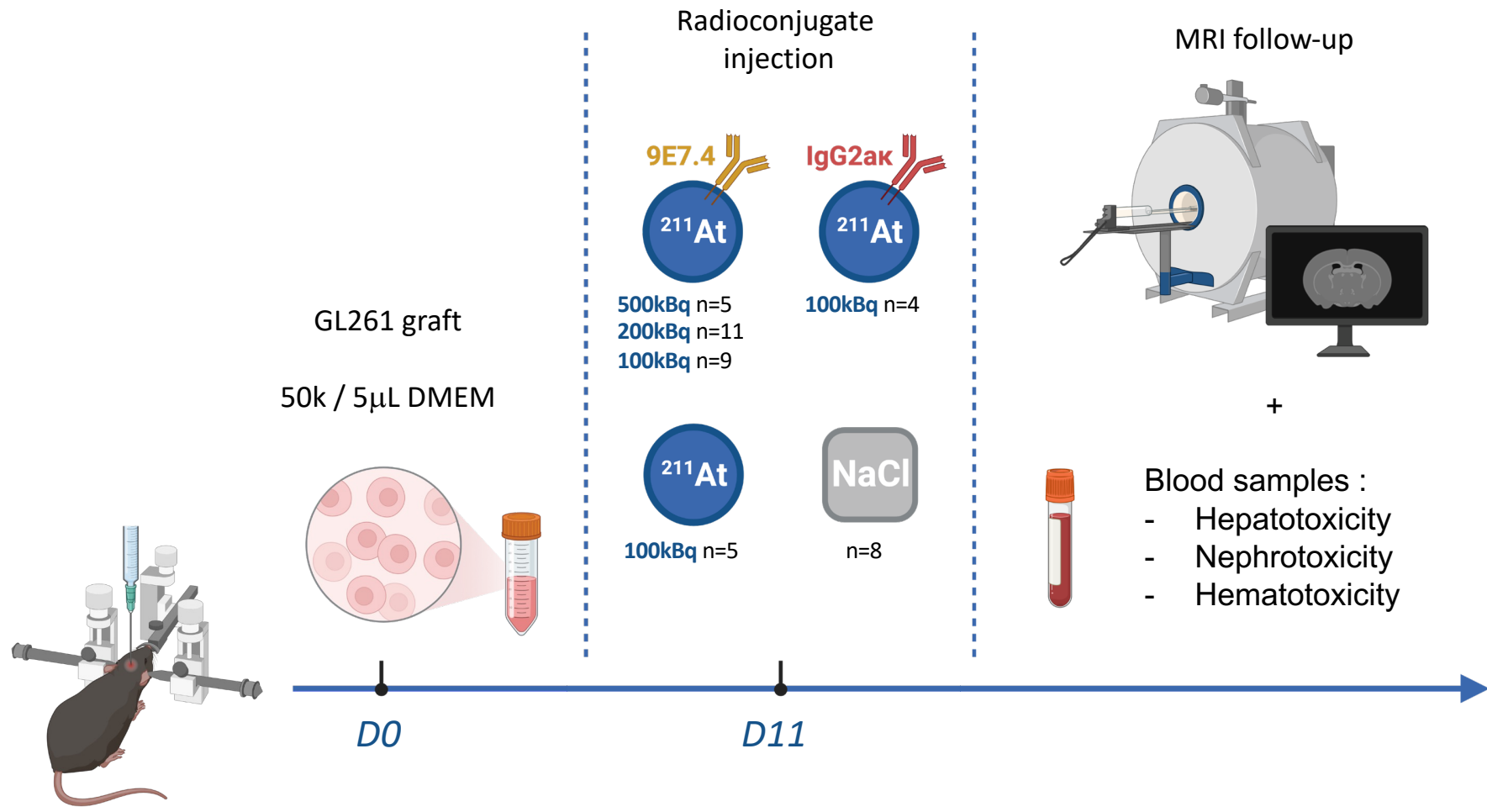


II. The [^{125}I]-9E7.4 conjugate is distributed around the injection site in the C57BL/6j-GL261 model

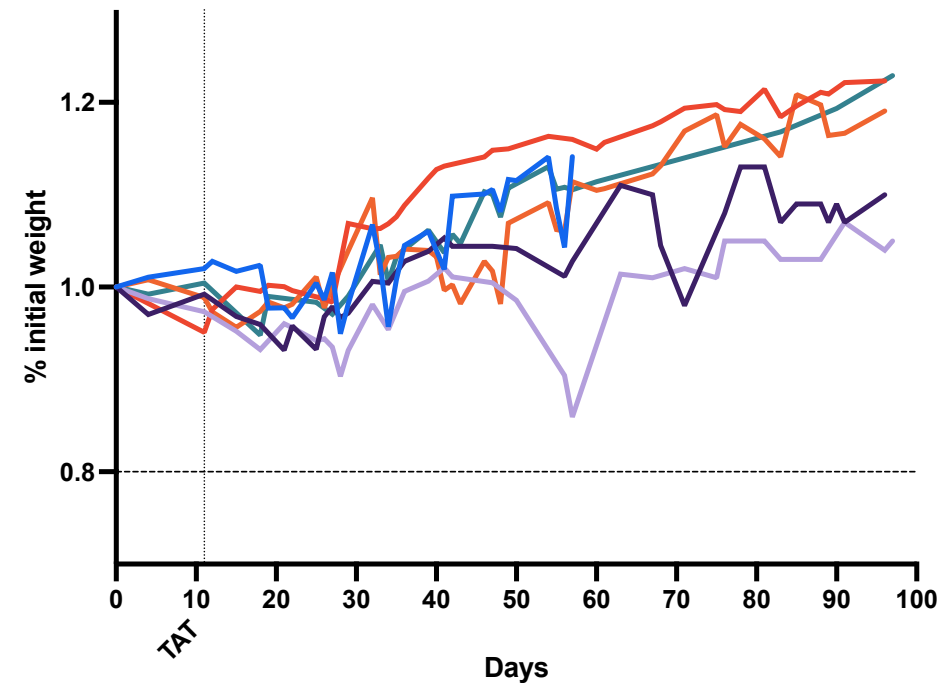
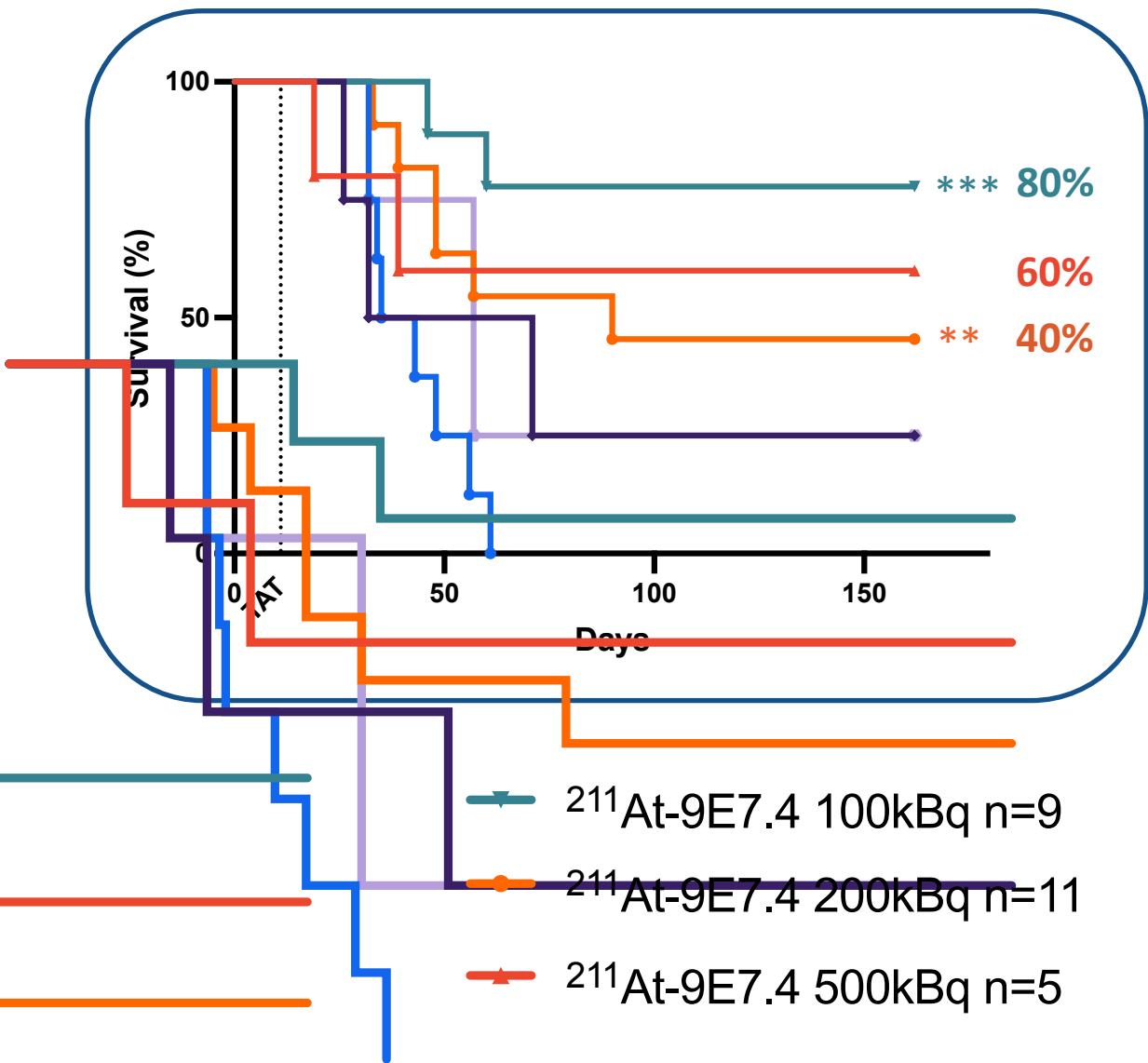
n=3 for each time point



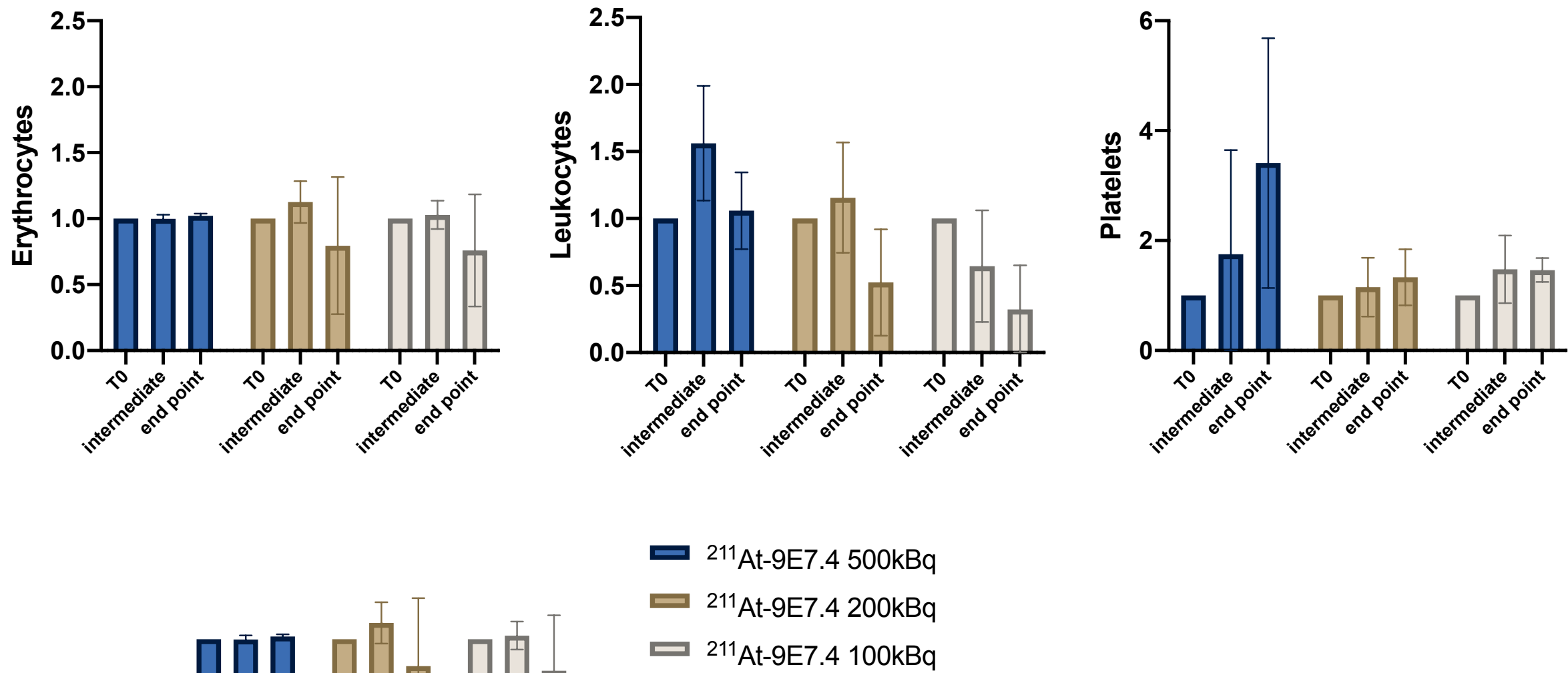
III. Locoregional targeted radiotherapy : Survival study after a single injection of $[^{211}\text{At}]\text{-9E7.4}$



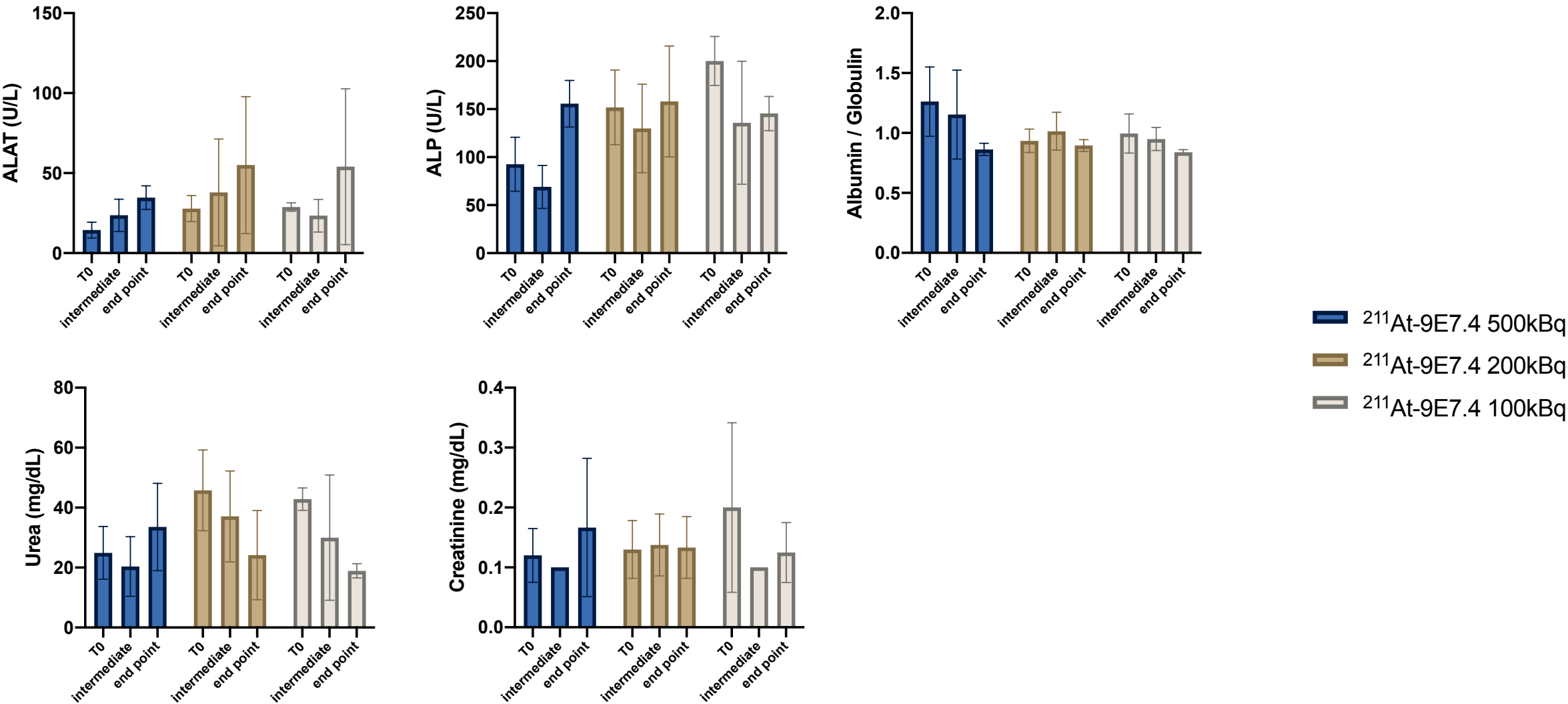
III. The [²¹¹At]-9E7.4 radiotherapy reveals a major survival benefit and generates long-term survivors



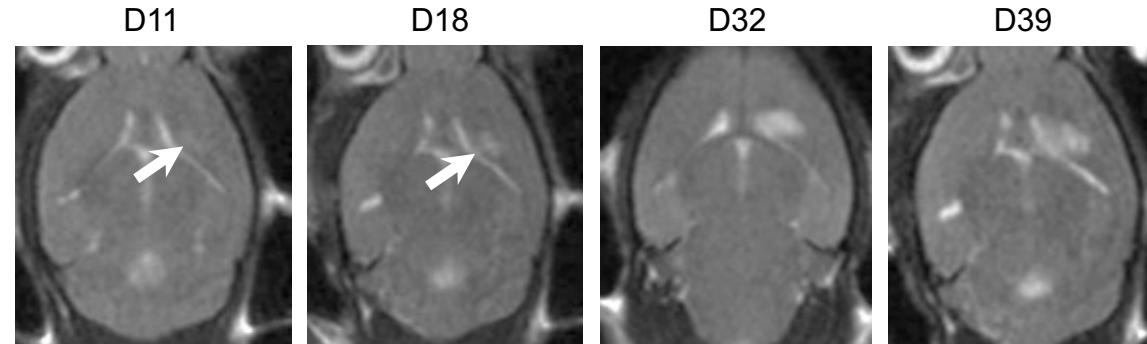
III. The locoregional [²¹¹At]-9E7.4 radiotherapy exhibits no significant hematological toxicity over time



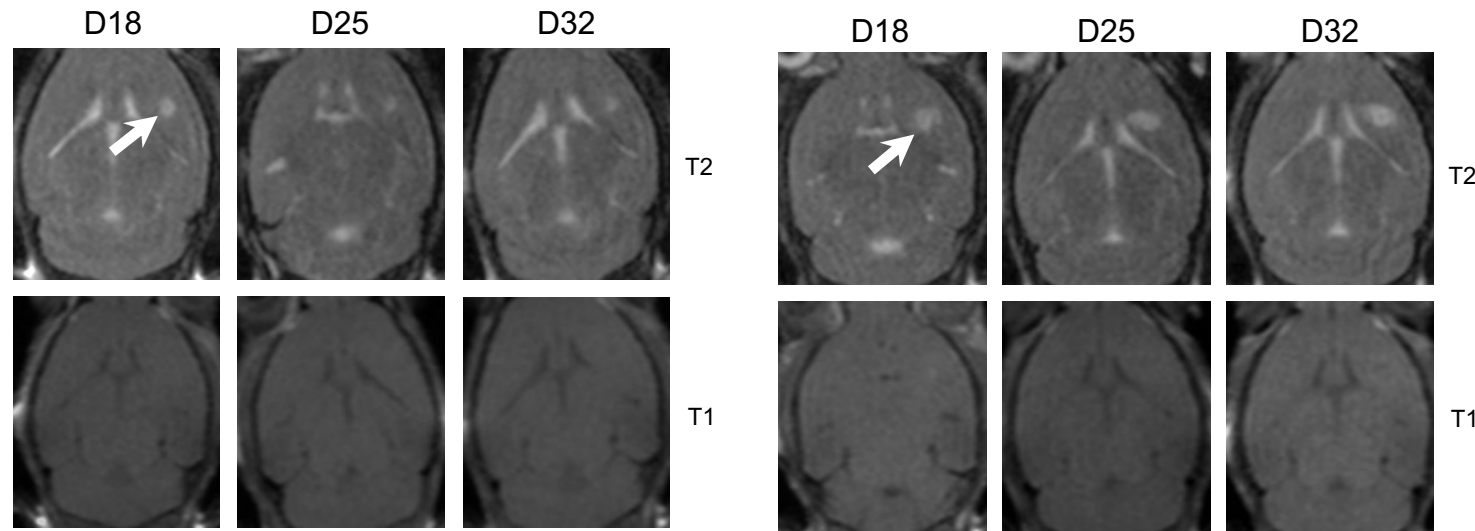
III. The locoregional [²¹¹At]-9E7.4 radiotherapy exhibits no liver, kidney toxicity over time



MRI follow-up : free astatine-211 and radiolabelled IgG2a κ show no significant efficacy on mice survival



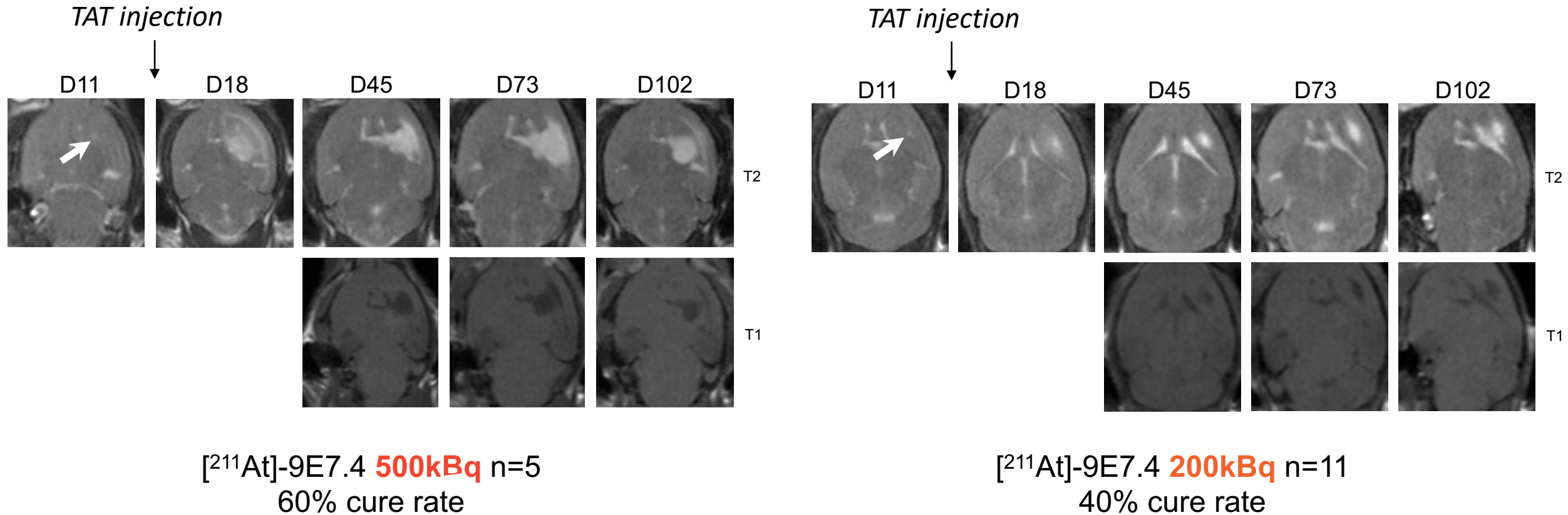
Control groupe n=8



[²¹¹At]-IgG2a κ 100kBq (n=5)

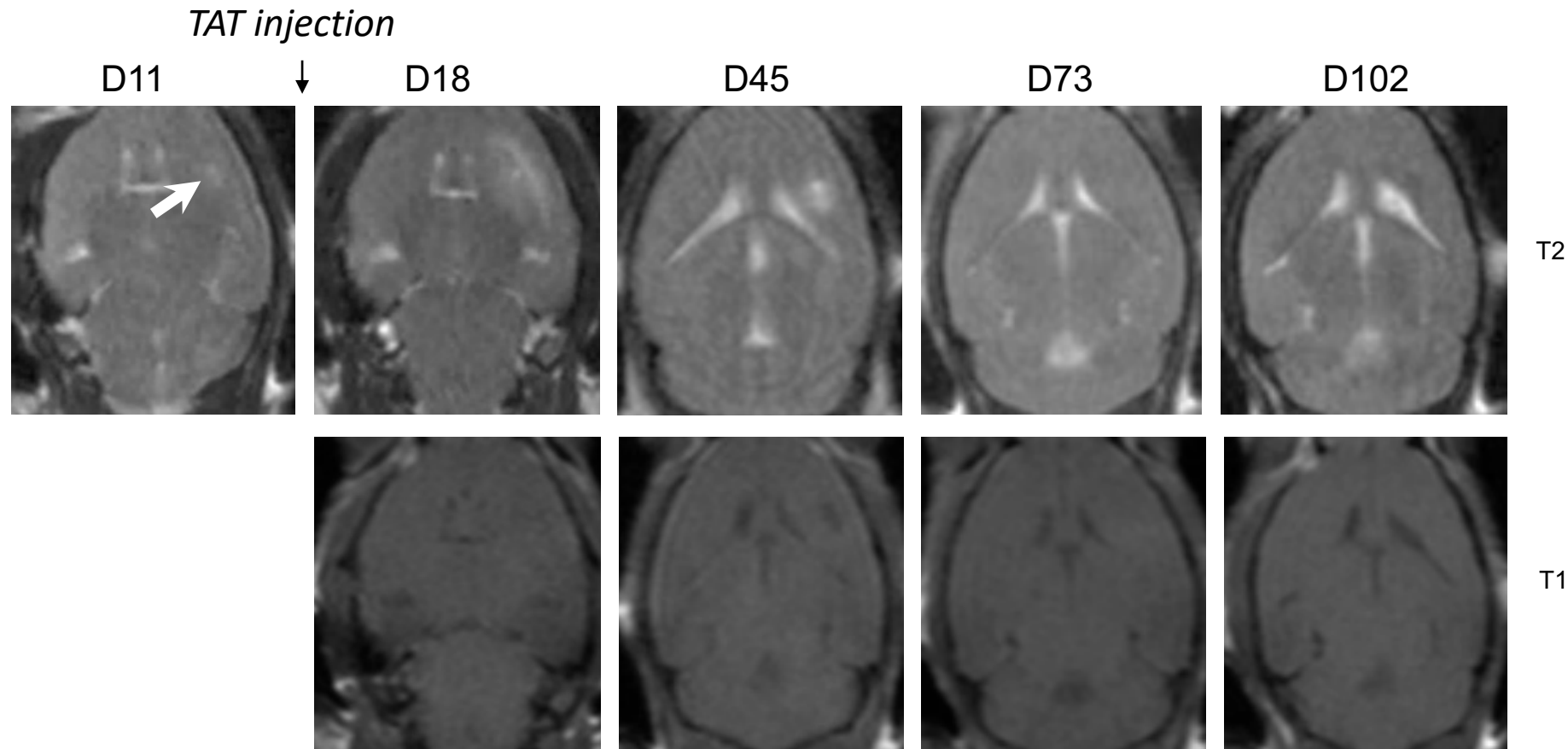
[²¹¹At]-Na 100kBq (n=5)

MRI follow-up : Detection of free water in the injection area with the conjugate $[^{211}\text{At}]\text{-9E7.4}$



*This area is stable over time for the **500kBq** and **200kBq** doses*

MRI follow-up : The free water area is resolved over time for the 100kBq dose



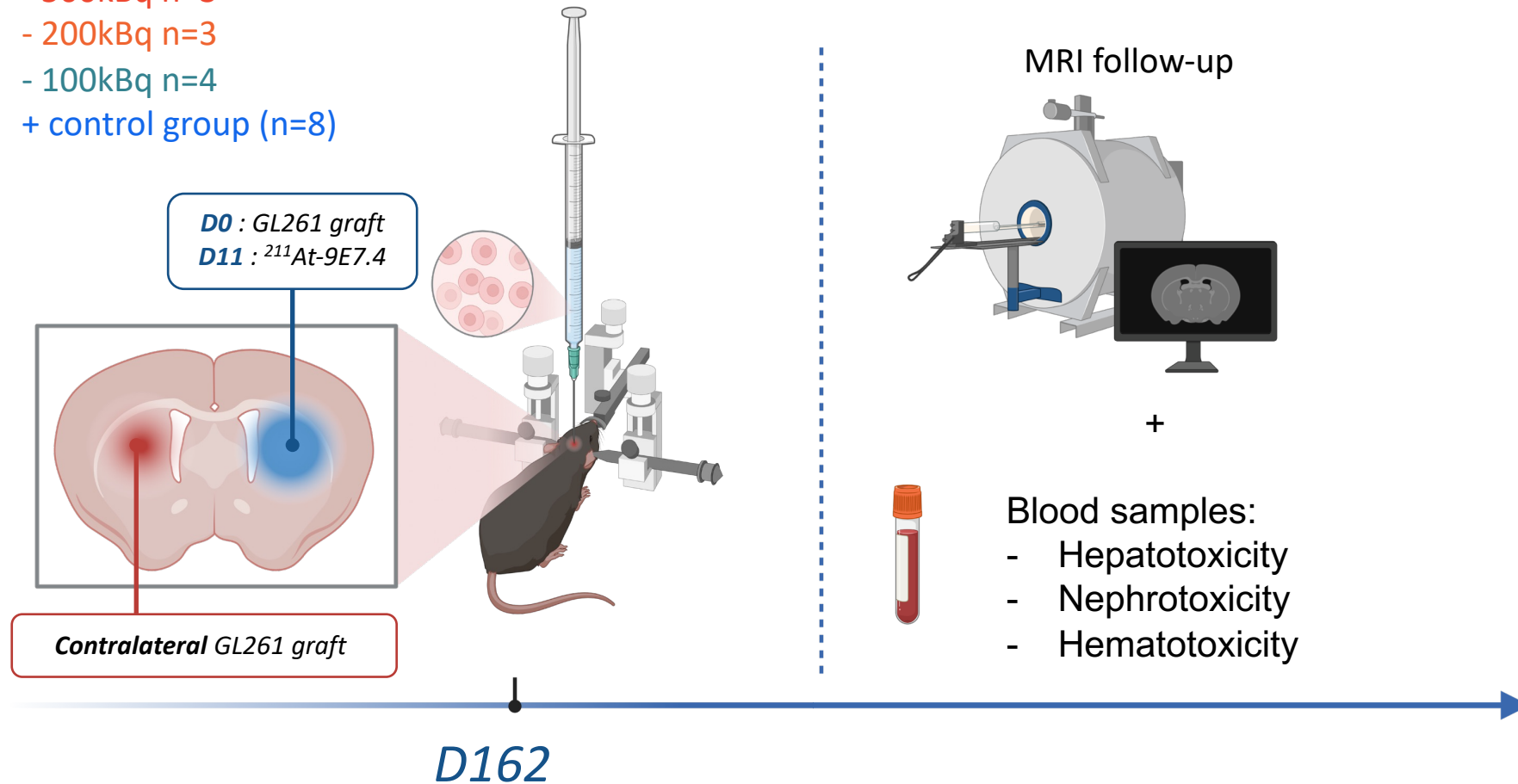
[²¹¹At]-9E7.4 100kBq n=9
80% cure rate

IV. Long-term memory response?

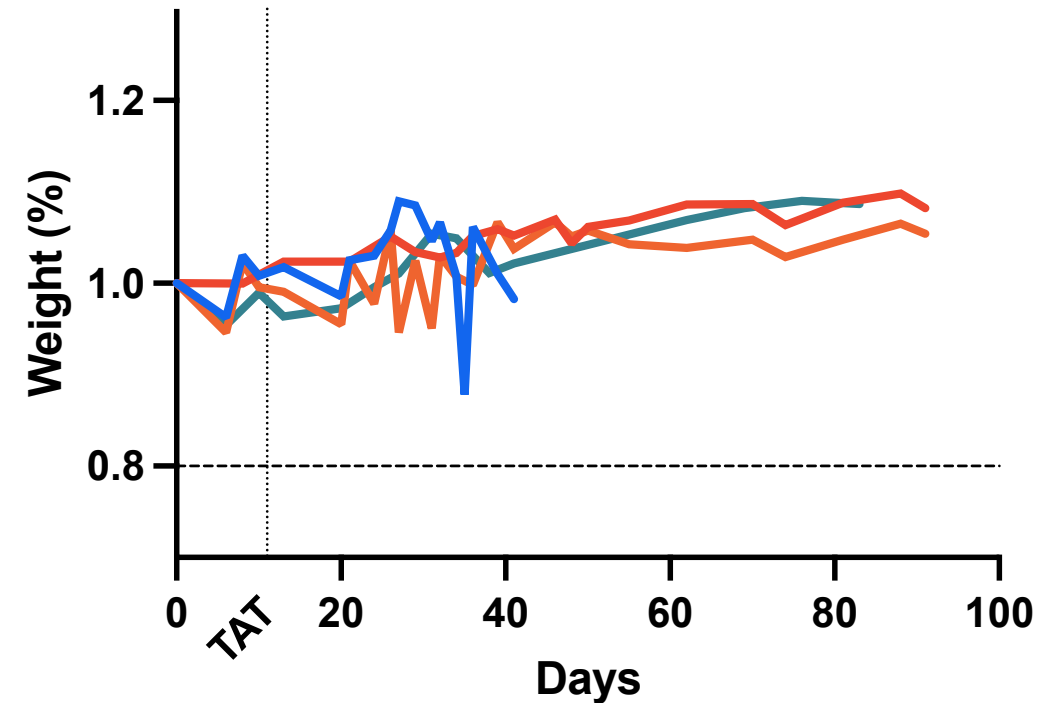
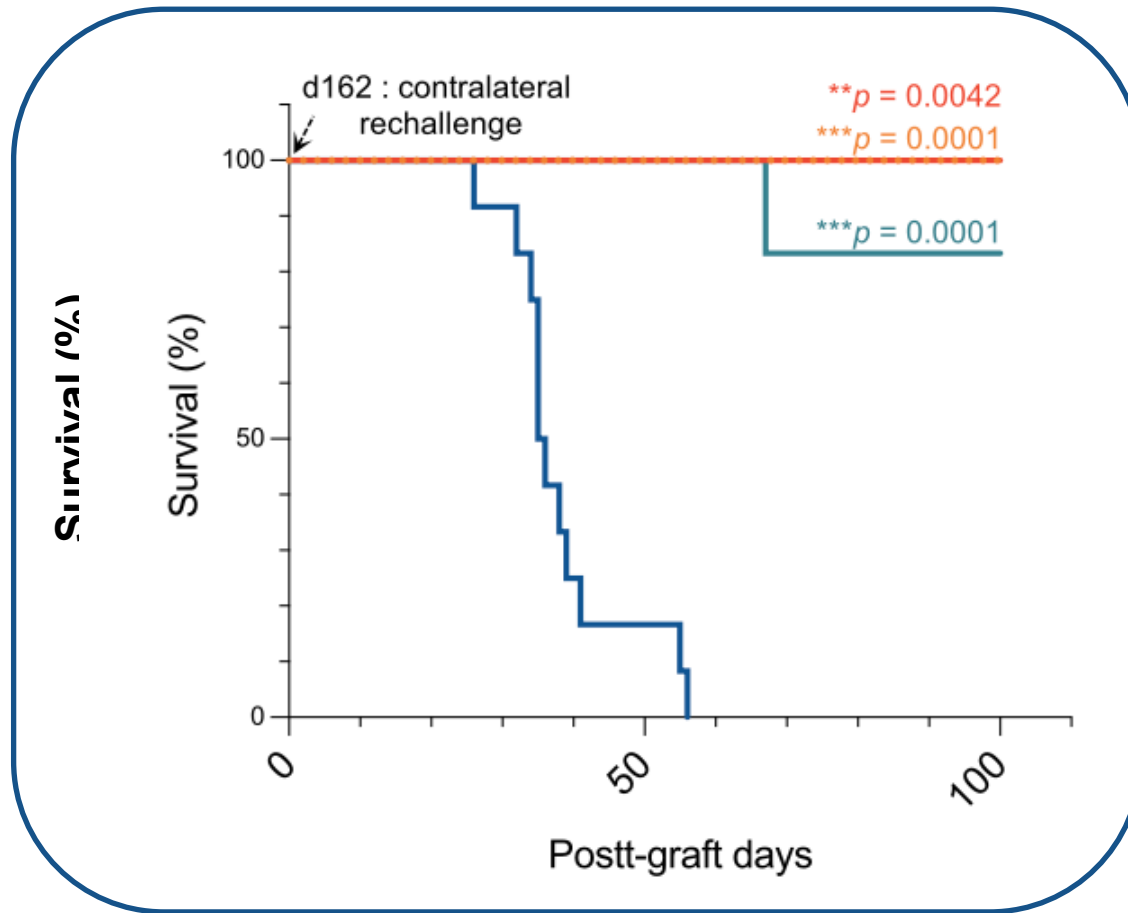
Survivors rechallenge with a new contralateral graft in the striatum

Long-term survivors:

- 500kBq n=3
- 200kBq n=3
- 100kBq n=4
- + control group (n=8)

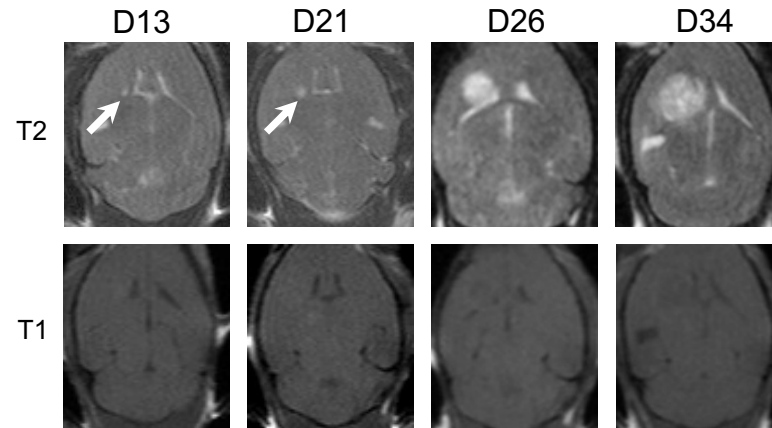


100% of the rechallenged long-term survivors do not develop a new contralateral tumor

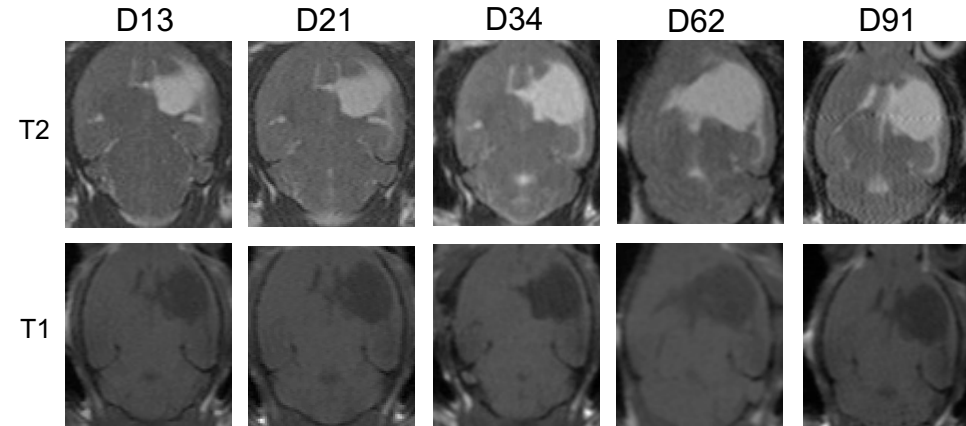


100% of the rechallenged long-term survivors do not develop a new contralateral tumor

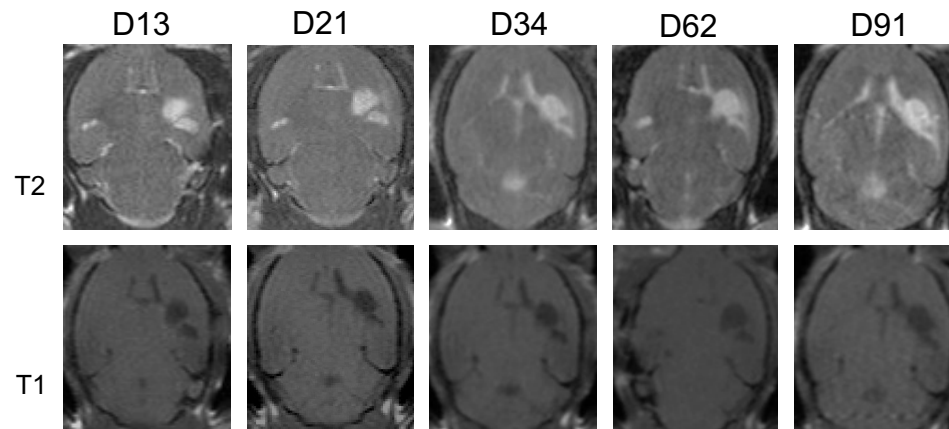
Control group n=8



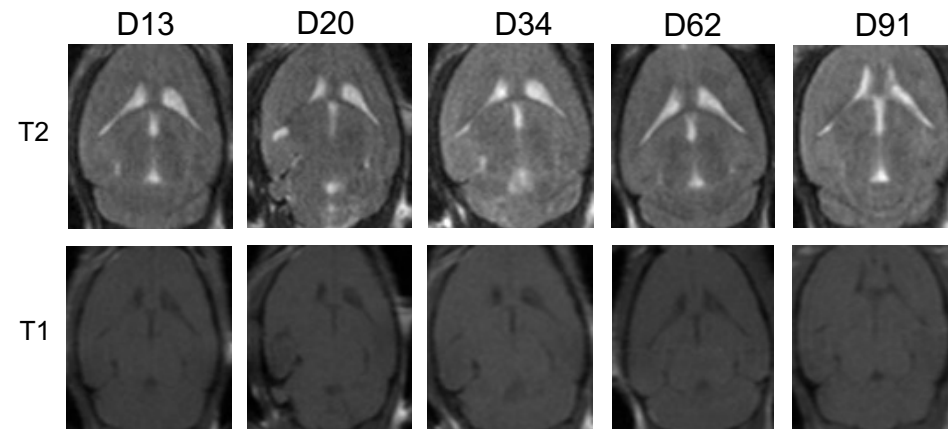
Long-term survivors: [^{211}At]-9E7.4 **500kBq** n=3



Long-term survivors: [^{211}At]-9E7.4 **200kBq** n=3

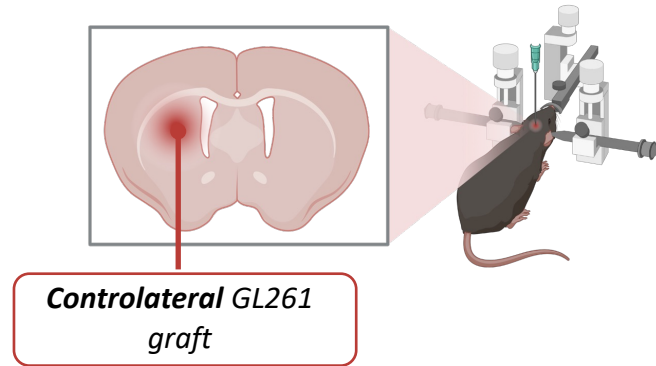


Long-term survivors: [^{211}At]-9E7.4 **100kBq** n=4

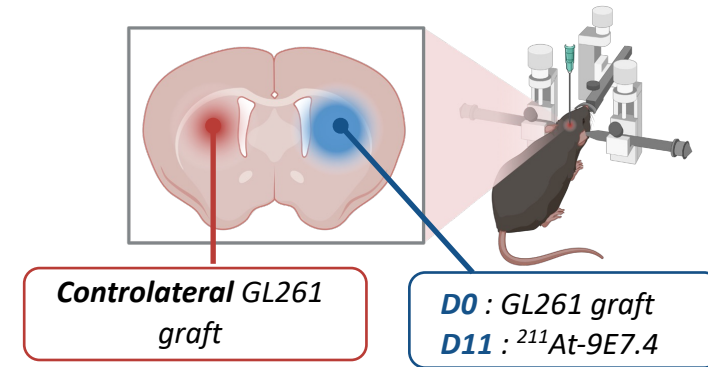


100% of the rechallenged long-term survivors do not develop a new contralateral tumor

Control group



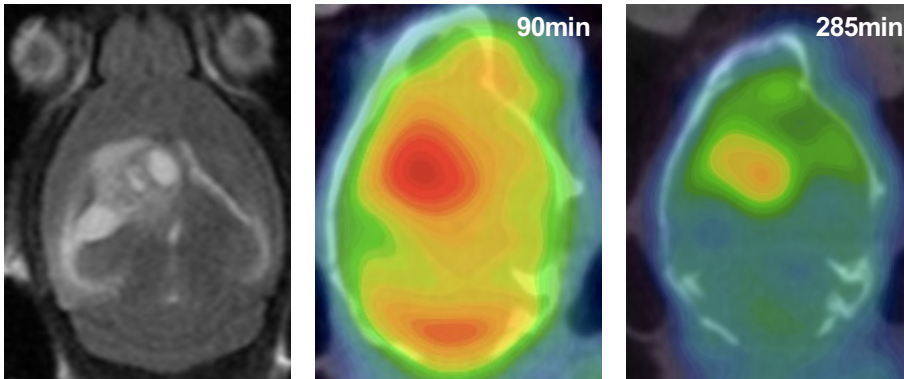
Long-term survivors : [^{211}At]-9E7.4 200kBq



MRI (T2)

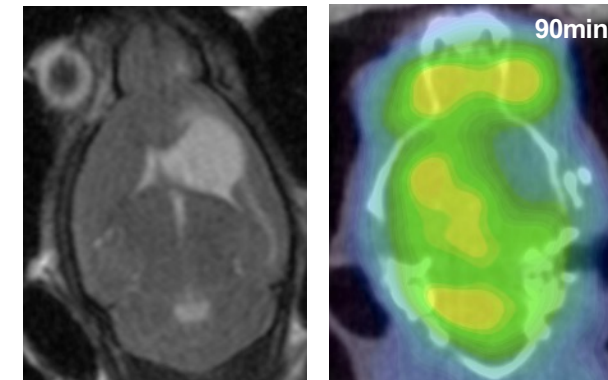
Positron emission tomography [^{18}F]-Fluorodeoxyglucose

D34 after tumor graft

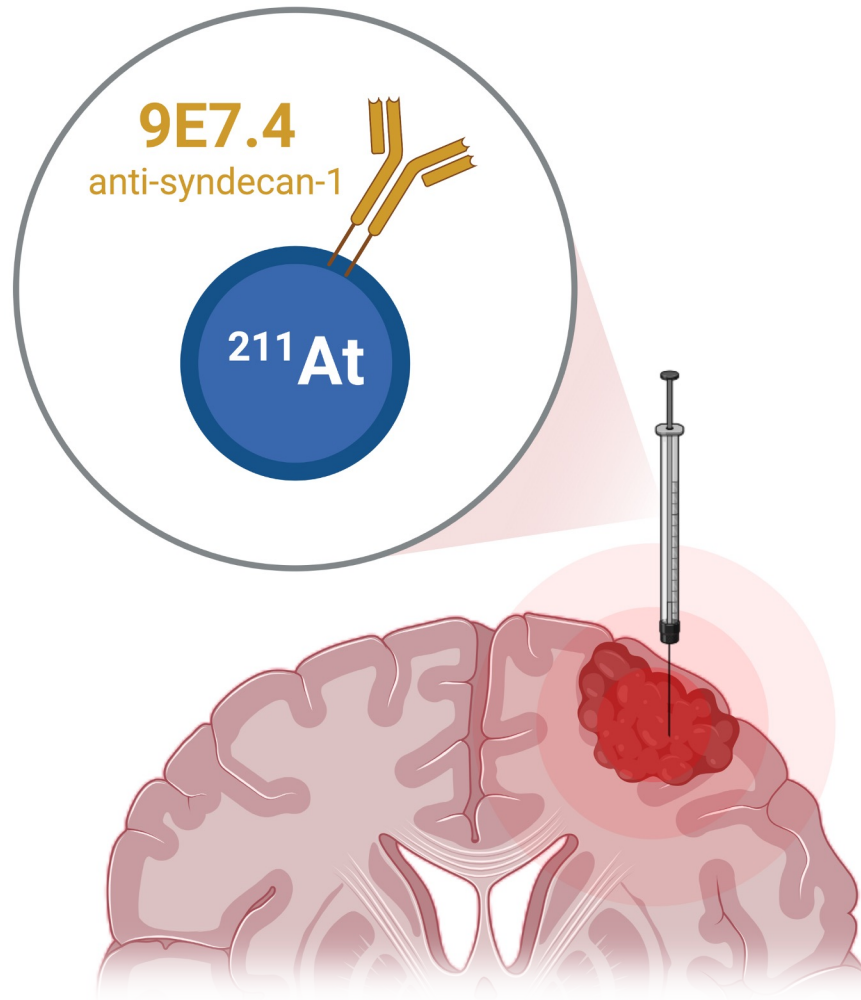


[^{18}F]-FDG PET

D34 after tumor graft

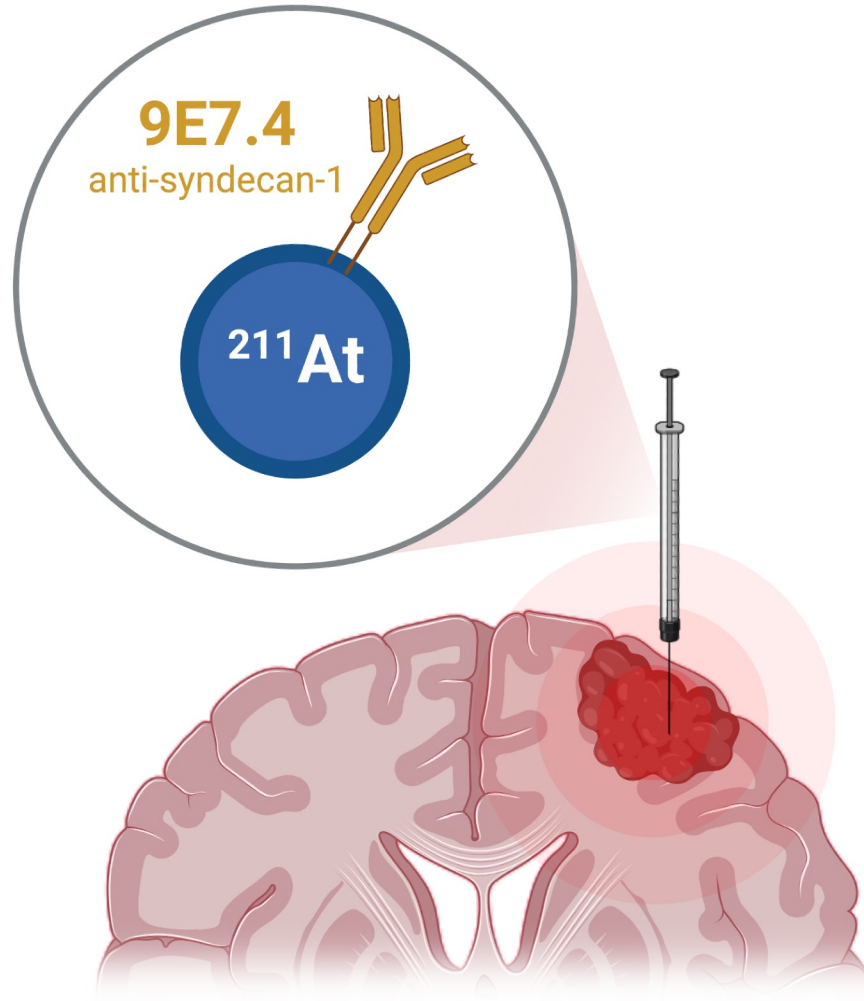


Conclusions



- The syndecan-1 targeting by 9E7.4 provides a **prolonged brain retention of radioactivity over time** which is demonstrated to be decisive regarding survival
- **Controlled brain distribution** (limited area around the injection site)
- **Survival benefit + 80% cure rate** with the locoregional [^{211}At]-9E7.4 radiotherapy (100kBq)
- **Long-term immunization:** investigation on immune populations involved

Perspectives



Ongoing: 3D reconstruction

- Diffusion volumes of $[^{125}\text{I}]\text{-9E7.4}$ versus $[^{125}\text{I}]\text{-IgG2a}\kappa$

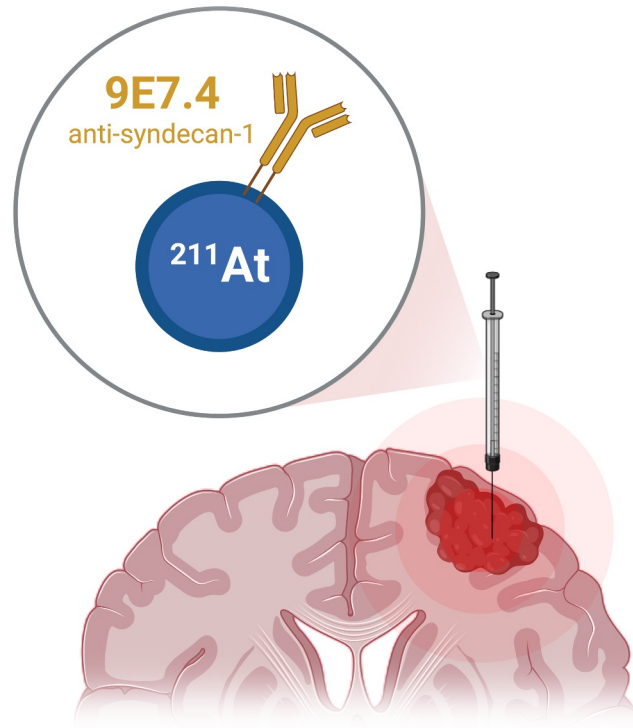
What is the impact of syndecan-1 targeting with 9E7.4 on the diffusion volume?

Dosimetric évaluation

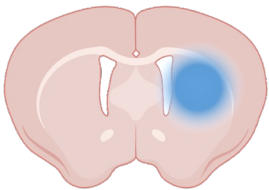
Perspectives

Mechanisms implied in tumor eradication

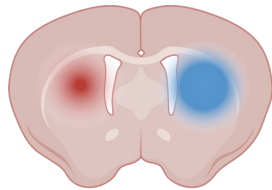
- **Immunofluorescence** (brain, spleen, lymph nodes) : detection of T cells subsets, dendritic cells
- **Flow cytometry**: detection of memory T cells from blood samples



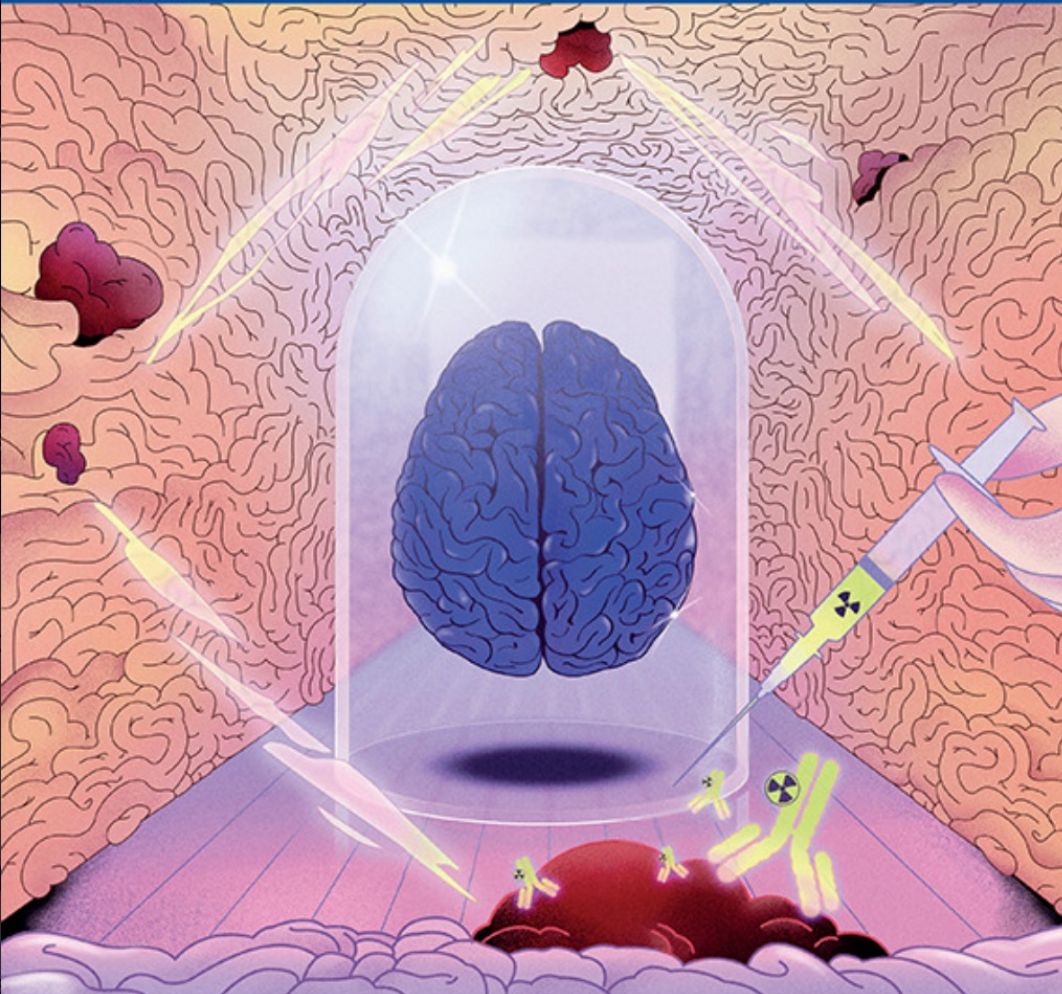
Long-term survivors



D7
After treatment



J4-7-10
After a new graft



Editorial

Post-COVID-19 condition, brain fog, and fatigue—what do we know now?

Articles

Intratumoural astatine-211 radiotherapy targeting syndecan-1 leads to GBM remission and immune memory

Review

Boosting antitumour efficacy of nanoparticles by modulating tumour mechanical microenvironment



Brain intratumoural astatine-211 radiotherapy targeting syndecan-1 leads to durable glioblastoma remission and immune memory in female mice

Loris Roncali,^{a,b} Séverine Marionneau-Lambot,^{b,c,d} Charlotte Roy,^{a,e} Romain Eychenne,^{b,f} Sébastien Gouard,^{b,d} Sylvie Avril,^a Nicolas Chouin,^{b,g} Jérémie Riou,^h Mathilde Allard,^b Audrey Rousseau,^{a,h} François Guérard,^b François Hindré,^{a,e} Michel Chérel,^{b,d,i,k,*} and Emmanuel Garcion^{a,e,j,k,**}

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Nuclear Oncology Team (Nantes, France)

Michel Chérel Séverine Marionneau-Lambot
François Guérard Sébastien Gouard
Romain Eychenne Nicolas Chouin
Mathilde Allard



GLIAD Team (Angers, France)

Emmanuel Garcion Charlotte Roy
François Hindré Sylvie Avril
Loris Roncali

