

Developing α -radiotherapy for pancreatic cancer

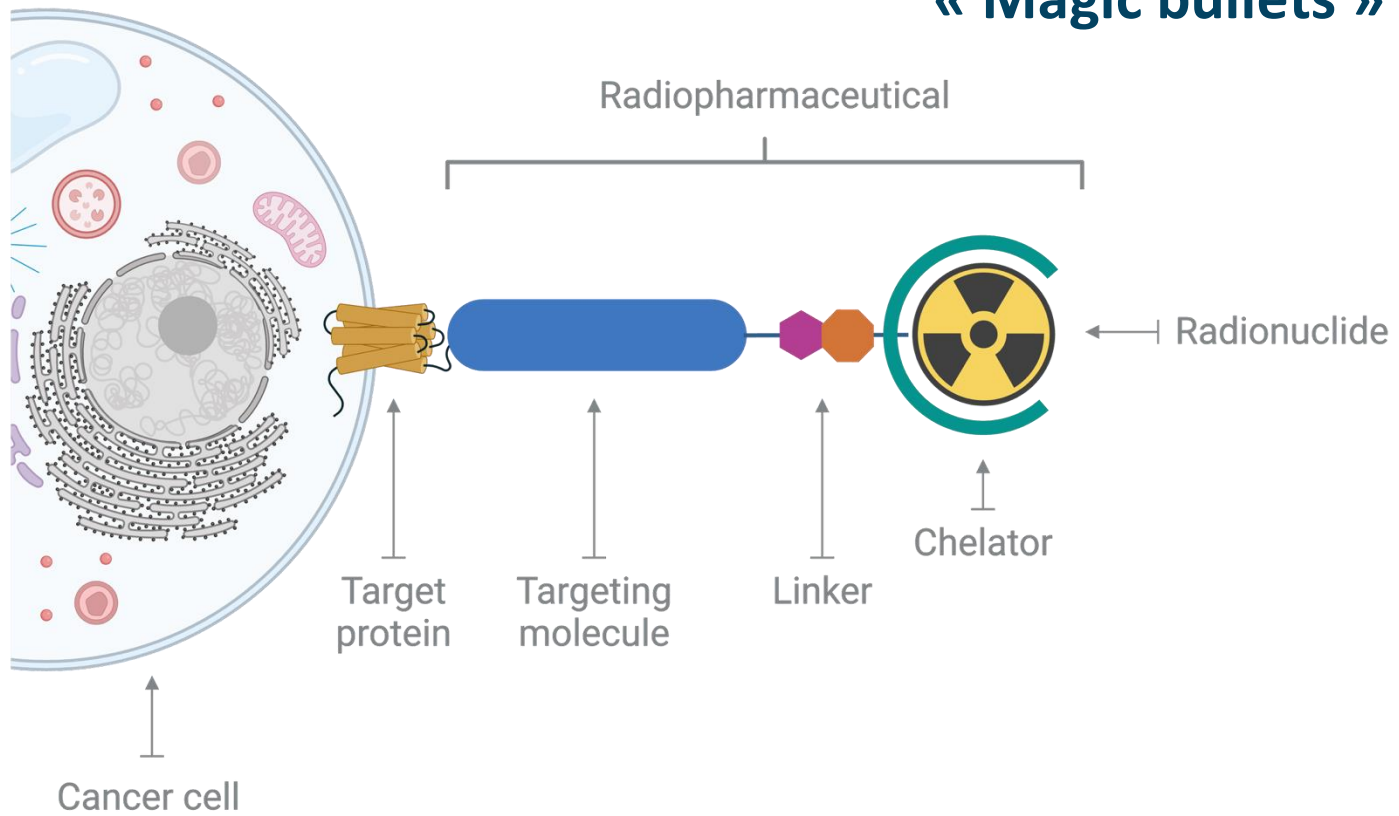
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RITM (Radiopharmaceutiques, Imagerie, Théranostiques et Multimodalité)

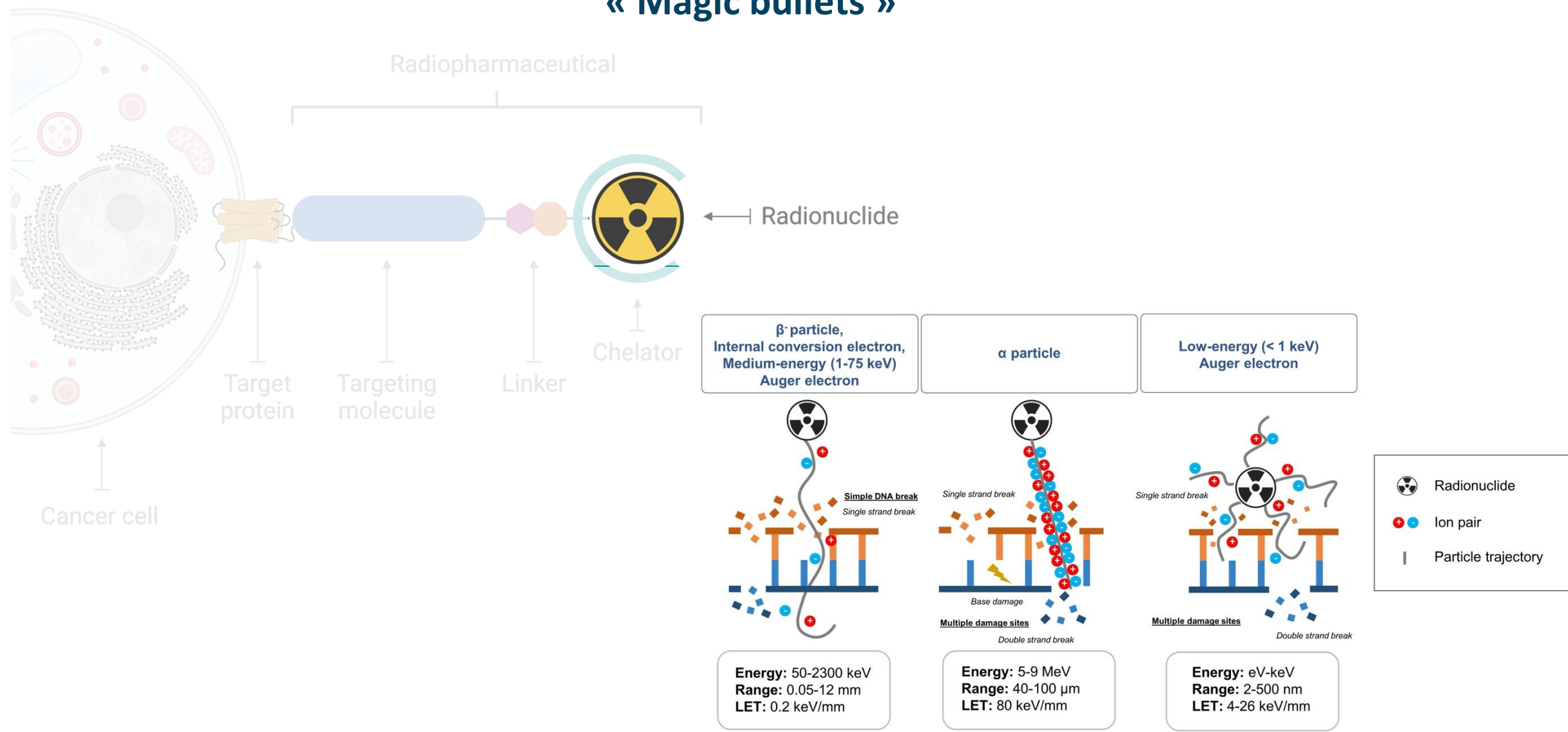
Radiopharmaceutical for therapy

« Magic bullets »



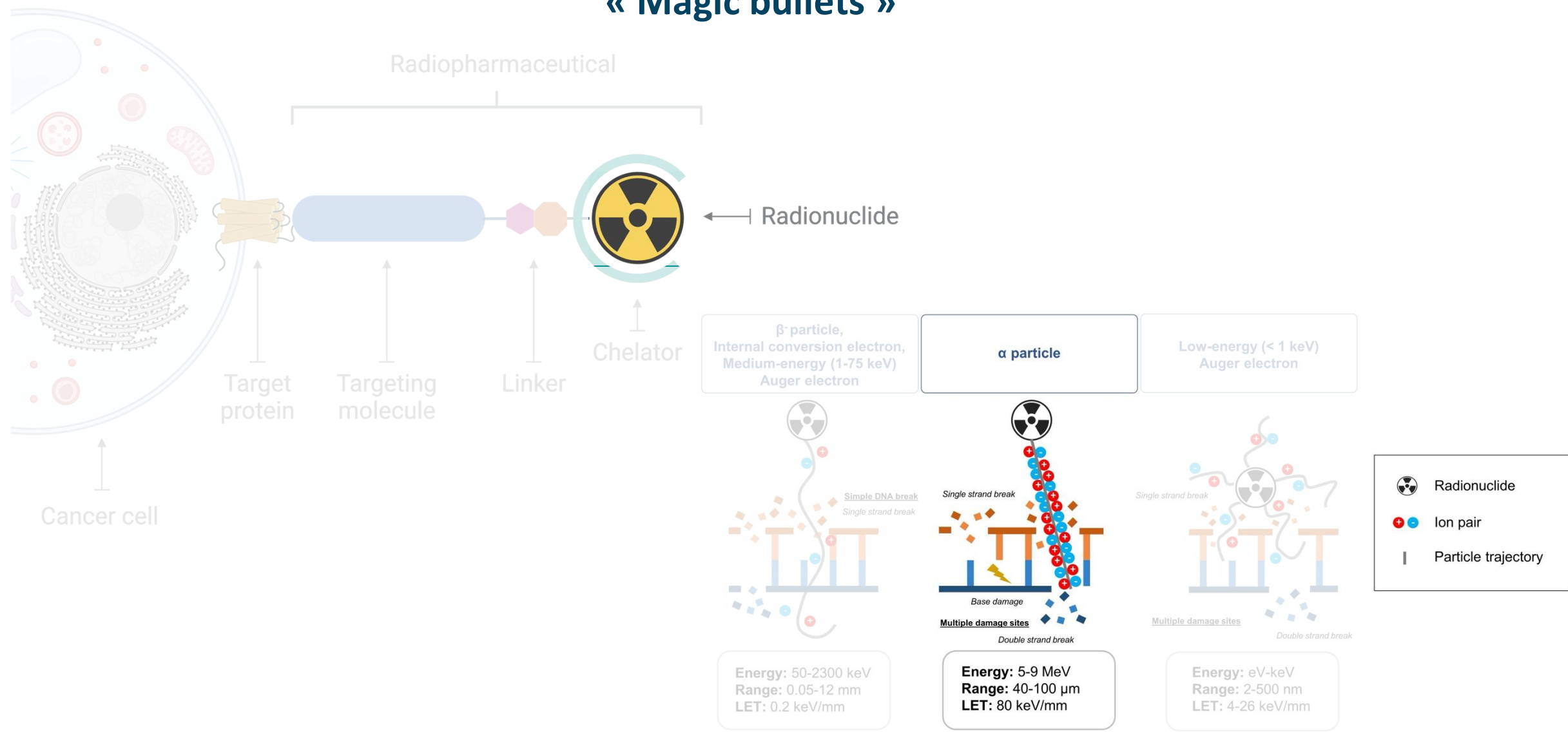
Radiopharmaceutical for therapy

« Magic bullets »



Radiopharmaceutical for therapy

« Magic bullets »



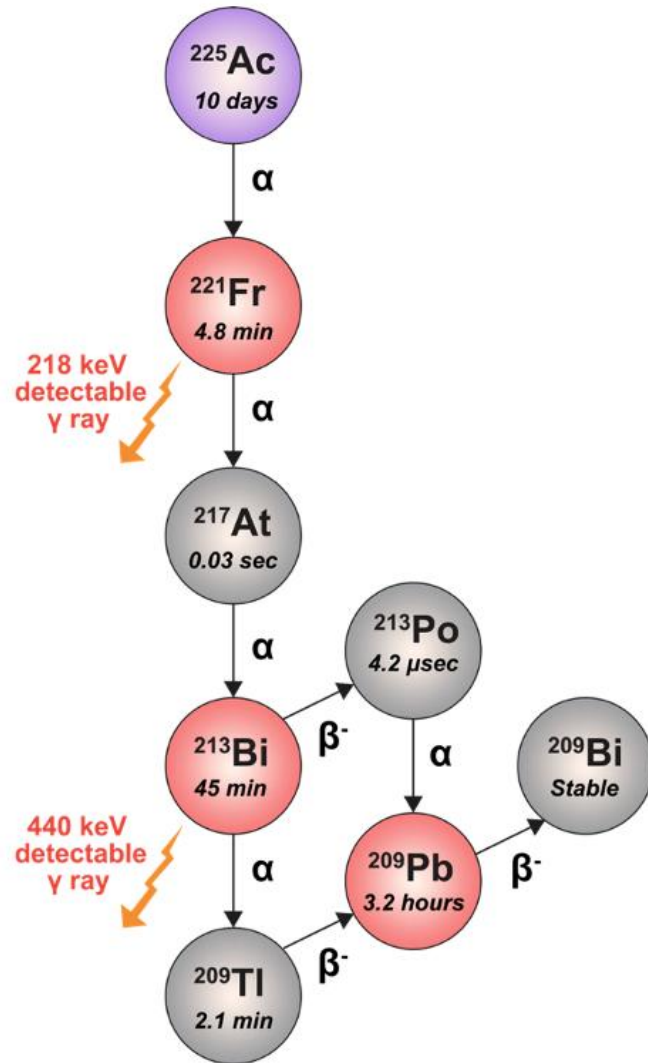
Alpha nuclear chocolate box

Periodic Table: Medical radioactive isotopes																		He																	
Li		Be																																	
Na		Mg																																	
K		Ca		Sc		Ti		V		Cr		Mn		Fe		Co		Ni		Cu		Zn		Ga		Ge		As		Se		Br		Kr	
Rb		Sr		Y		Zr		Nb		Mo		Tc		Ru		Rh		Pd		Ag		Cd		In		Sn		Sb		Te		I		Xe	
Cs		Ba		La		Hf		Ta		W		Re		Os		Ir		Pt		Au		Hg		Tl		Pb		Bi		Po		At		Rn	
Fr		Ra		Ac																															
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Alpha nuclear chocolate box

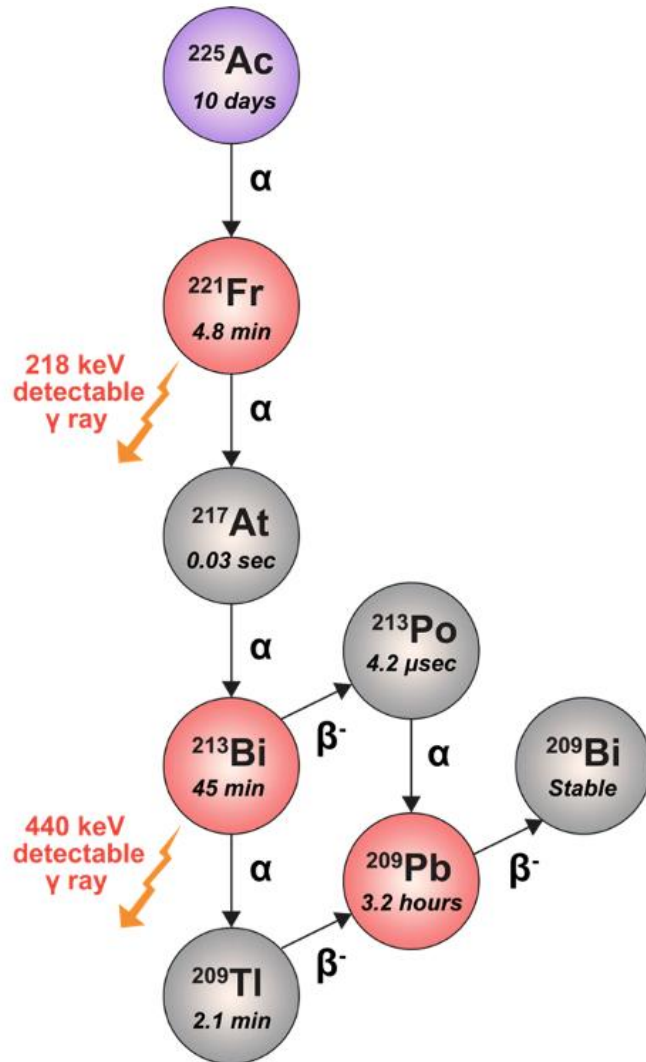
Periodic Table: Medical radioactive isotopes																		He						
Li		Be																B		C	N	O	F	Ne
																				11 14	13	15	18	19
Na		Mg																Al		Si	P	S	Cl	Ar
																					32 33	35	34m 36 38 39	
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr							
38 42 43	45	43 44 46 47	44 46		48 51	52 52m 54	52 55 59	55 57 58 60	63	60 61 62 64 67	63 65 69m	66 67 68	68	72 73 74	75	75 76 77 82	85 77 79 79m 81m							
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe							
81 82 84 86	85 87m 89 90	86 88 90	89	90 95	99	94m 95 99m	103	103m 105	103	109m 111		110m 111 113m 114m 115m	117m		123m	122 123 124 125 128 131 132	125 127 127m 133							
Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn							
129 134 137	133m 137m	134 135		178		186 188		191m 192	191 193m 195 195m	195m 198 199	197 197m 203	199 201	203 212	204 205 206 207 212 213		211								
*Fr	*Ra	*Ac																						
	223 226	225																						
			Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu								
			139 141	140 143		149	153		153	149 152 155 161	157	166	165 169	167	169	172 177								
			*Th	*Pa	*U	*Np	*Pu	*A	*C	*BK	*Cf	*Es	*Fm	*Md	*No	*Lr								
			226 227																					

Actinium-225

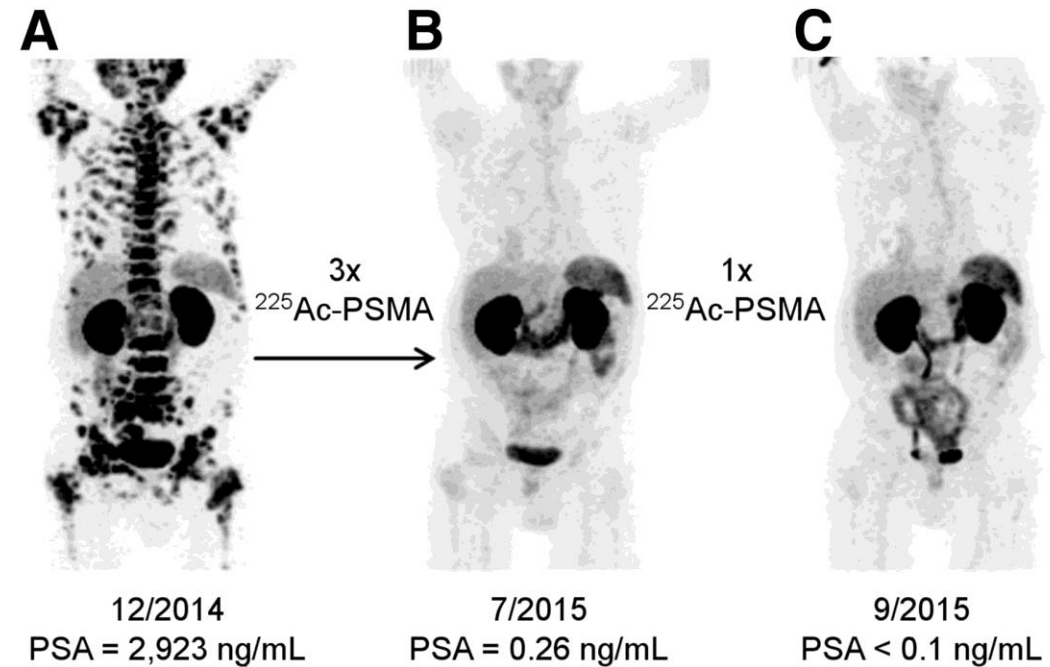


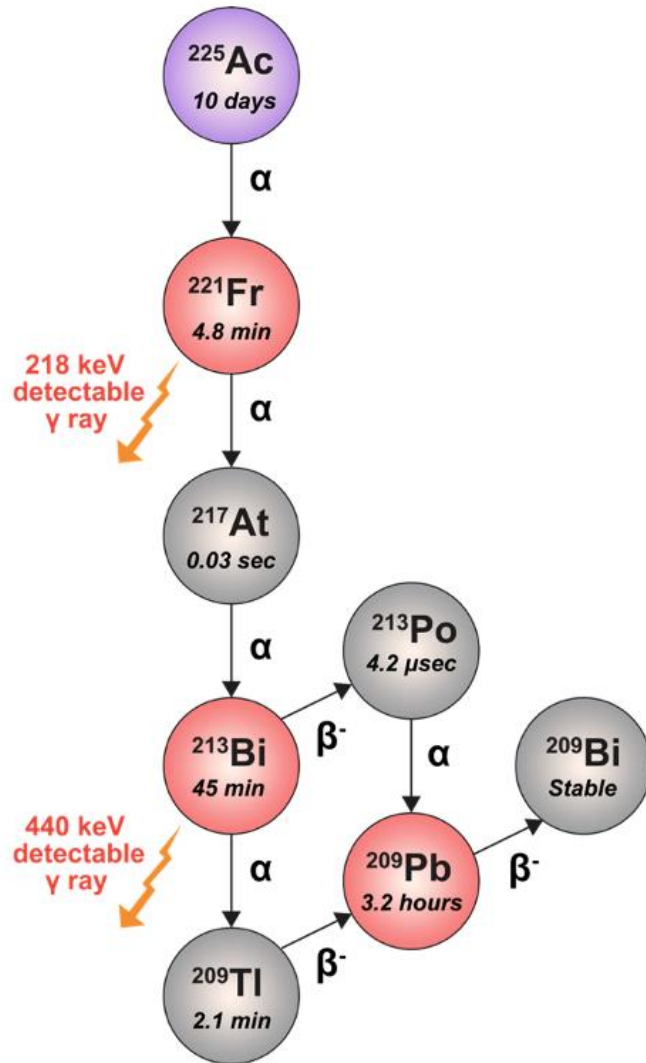
Poty et al., J. Nucl Med., 2018, Jun.

Poty et al., J. Nucl Med., 2018, Jul.

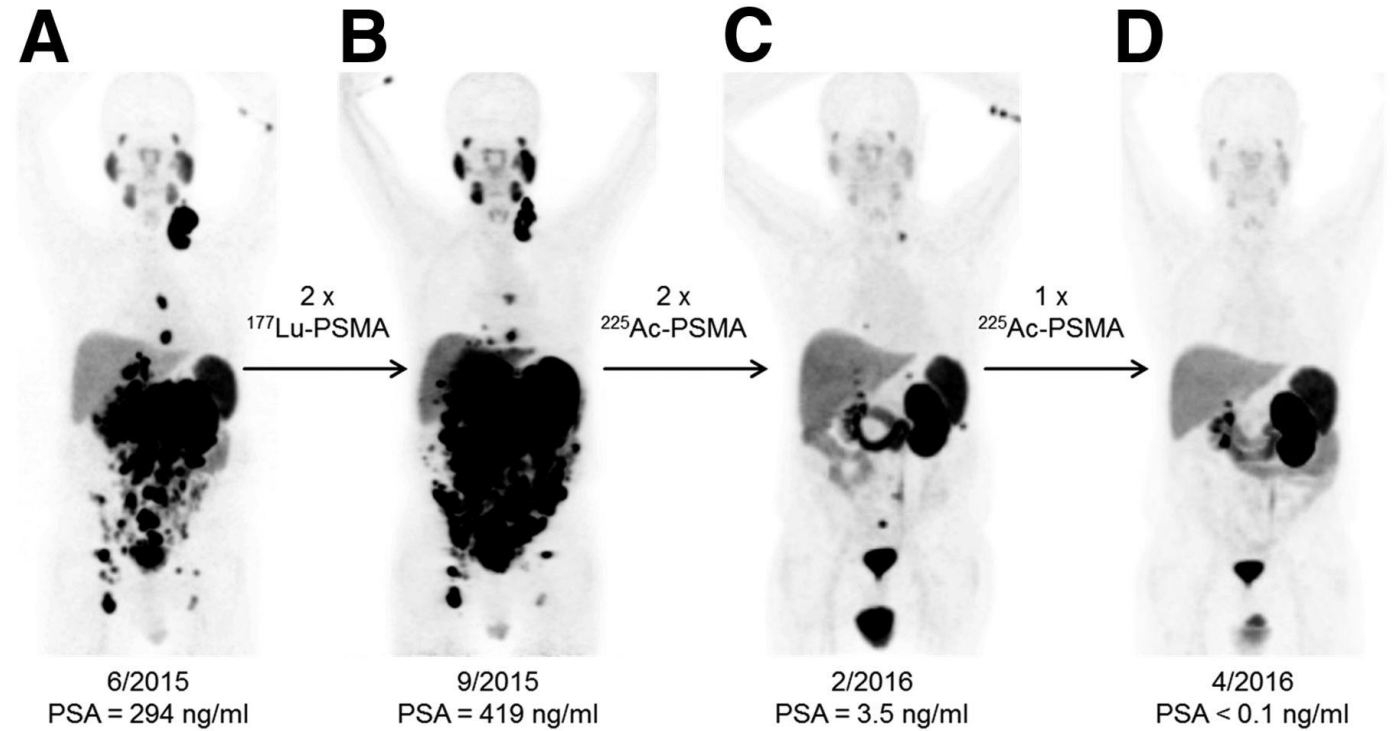


Validated in the clinic



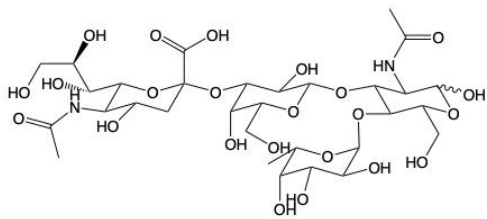


Validated in the clinic



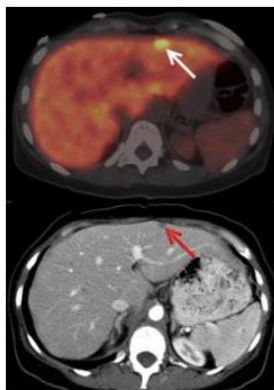
Targeted alpha therapy for pancreatic cancer

Targeted alpha therapy for pancreatic cancer



Fully-human anti-CA19.9 Phase I clinical trials at MSKCC

- [⁸⁹Zr]Zr-DFO-HuMab-5B1
- [¹⁷⁷Lu]Lu-CHX-A"-DTPA-HuMab-5B1



Courtesy of Dr. Christian Lohrmann

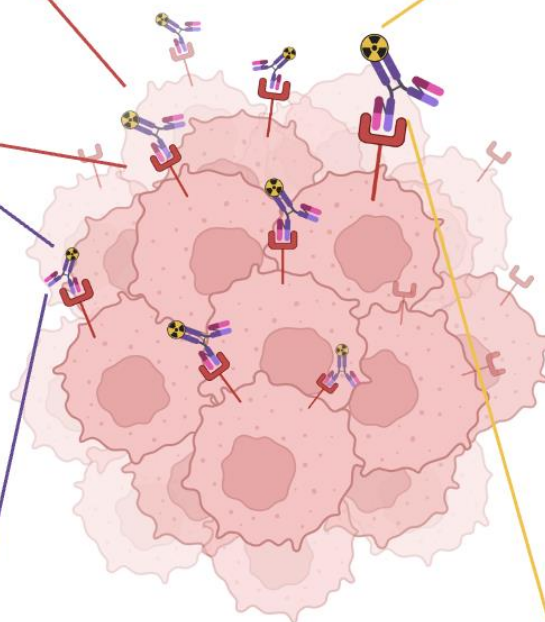


Diagram illustrating the decay chain of ^{225}Ac (Actinium-225) to stable ^{209}Bi (Bismuth-209):

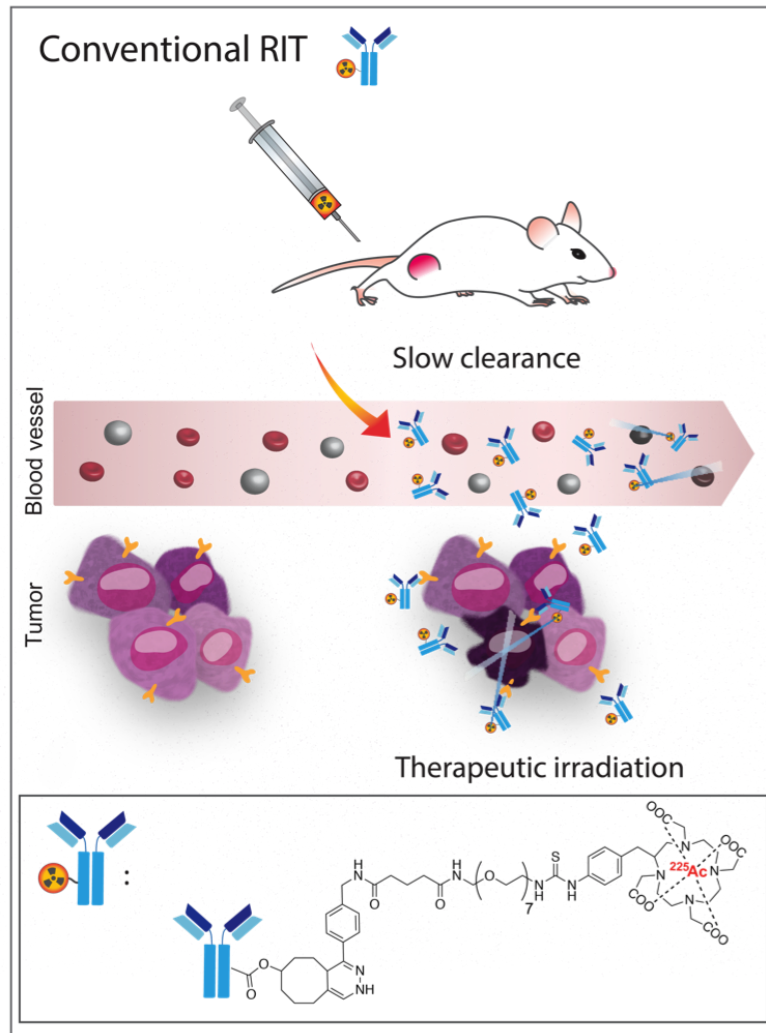
- ^{225}Ac (10 days) decays via α to ^{221}Fr (Francium-221, 4.8 min).
- ^{221}Fr decays via α to ^{217}At (Astatine-217, 0.03 sec).
- ^{217}At decays via α to ^{213}Bi (Bismuth-213, 45 min).
- ^{213}Bi has two decay paths:
 - β^- decay to ^{213}Po (Polonium-213, 4.2 μsec).
 - α decay to ^{209}Tl (Thallium-209, 2.1 min).
- ^{213}Po decays via α to ^{209}Pb (Lead-209, 3.2 hours).
- ^{209}Tl decays via β^- to ^{209}Pb .
- ^{209}Pb decays via β^- to stable ^{209}Bi .

Key features of the chain:

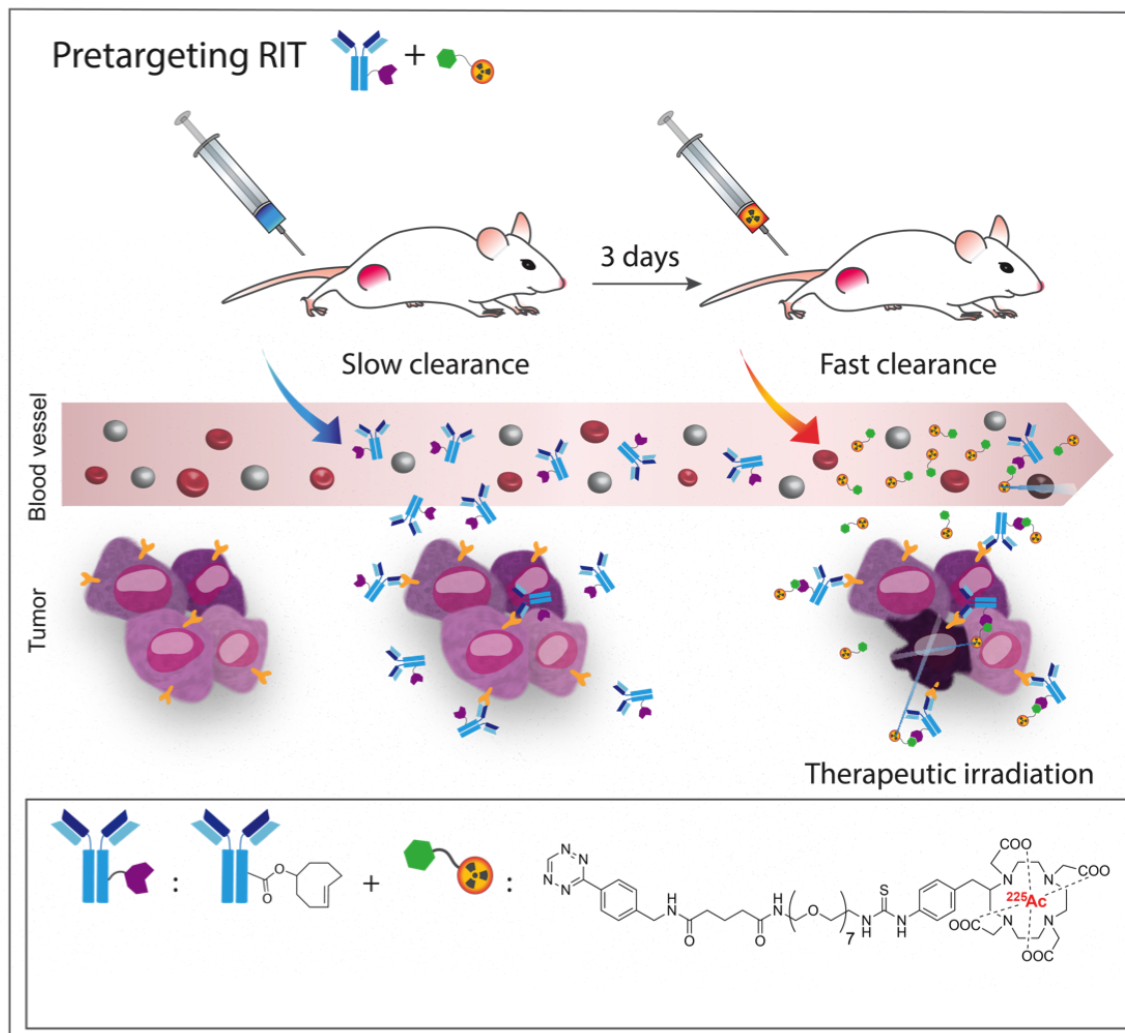
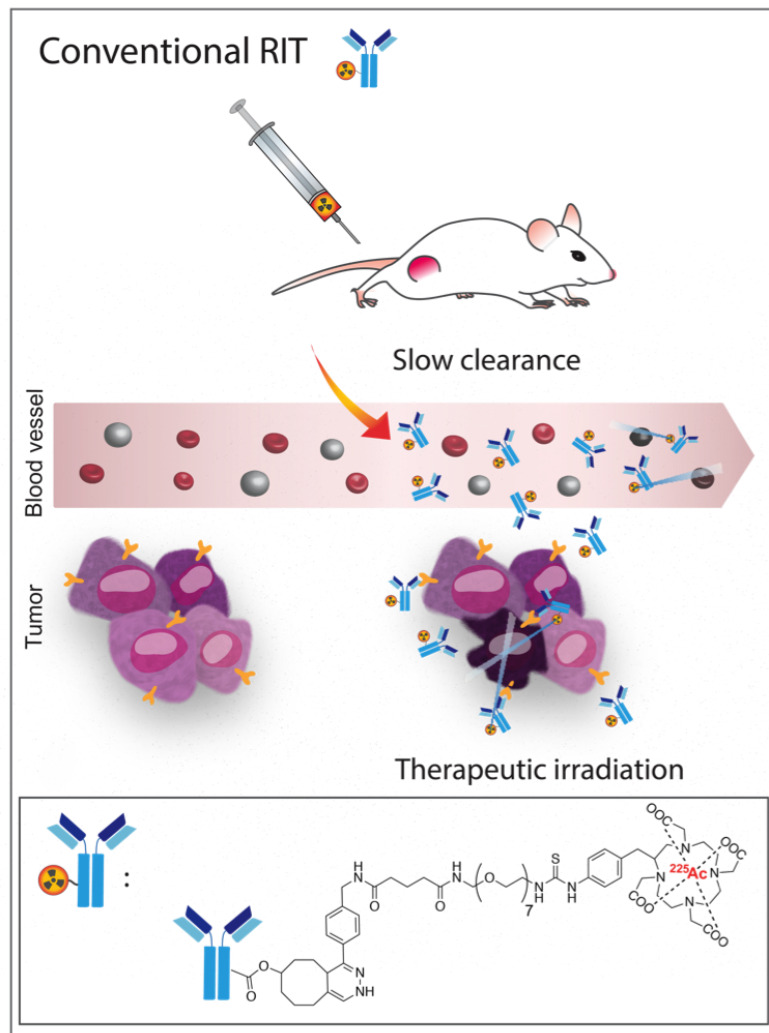
- ^{221}Fr emits a 218 keV detectable γ ray.
- ^{213}Bi emits a 440 keV detectable γ ray.

Poty et al., J. Nucl Med., 2018, Jun.
Poty et al., J. Nucl Med., 2018, Jul.

Optimisation of pharmacokinetic profiles

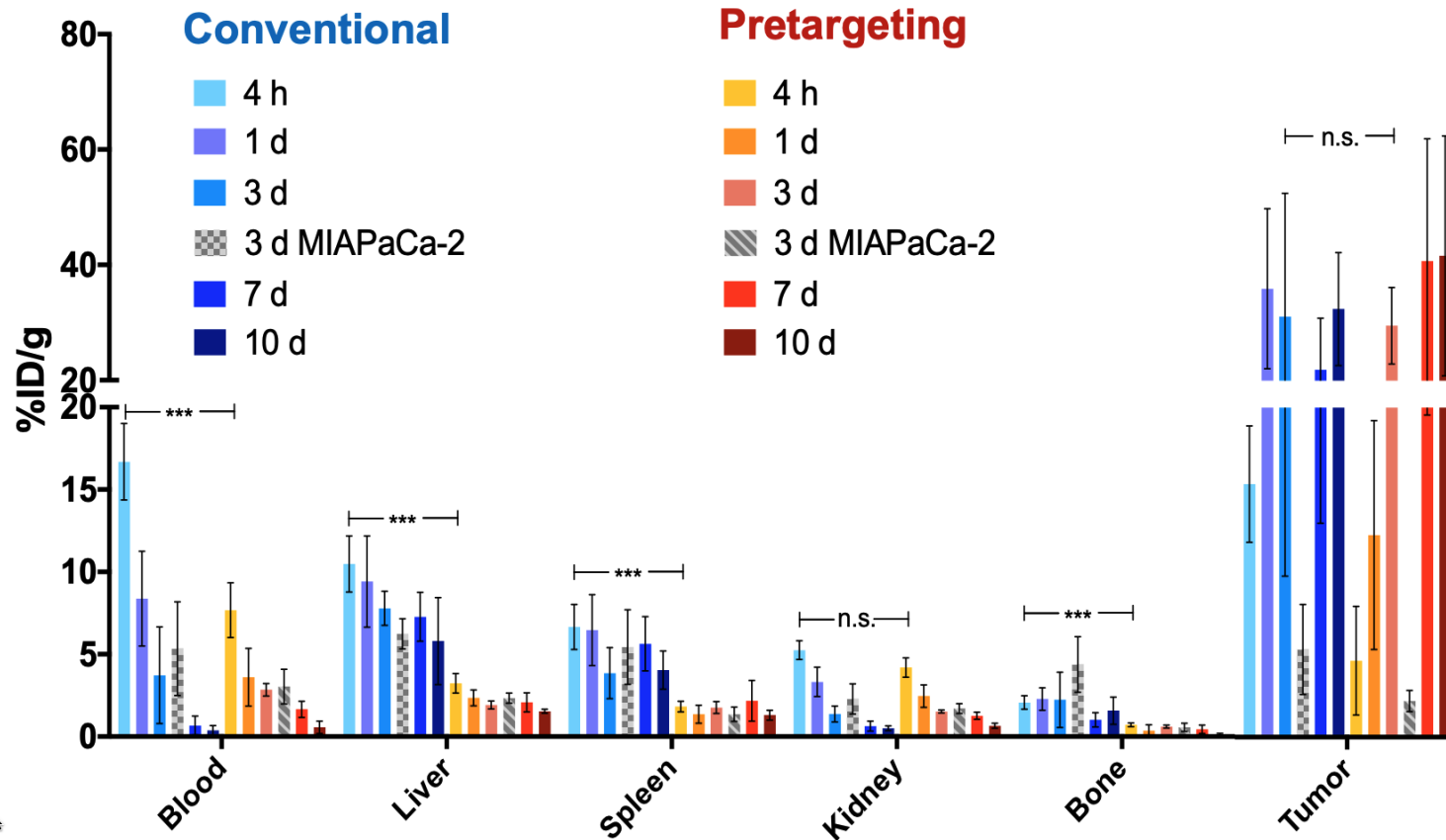
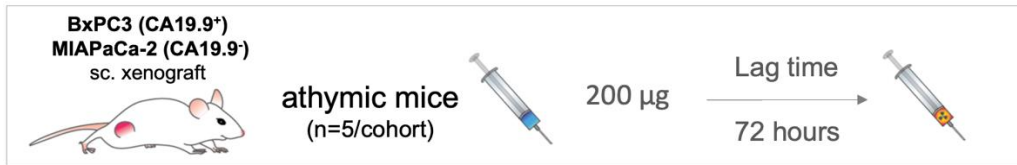


Mitigating hematotoxicity using pretargeting

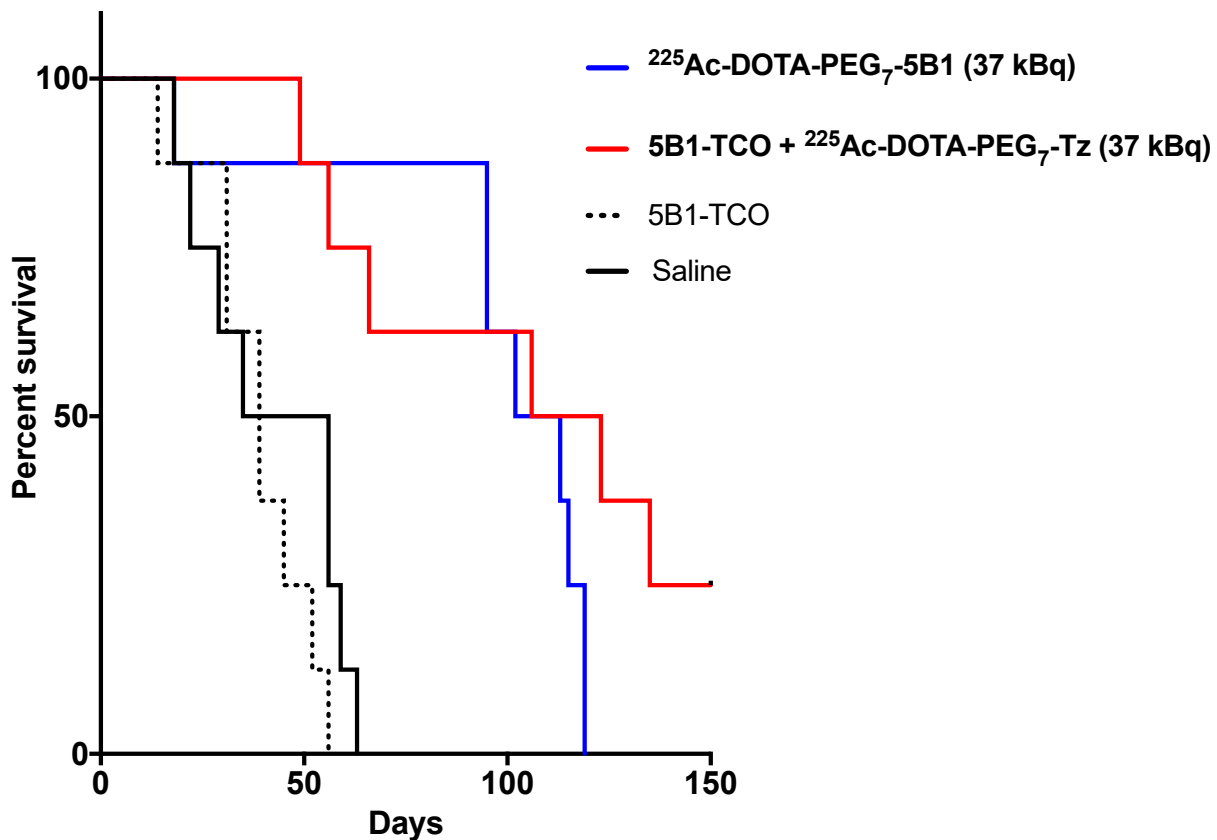
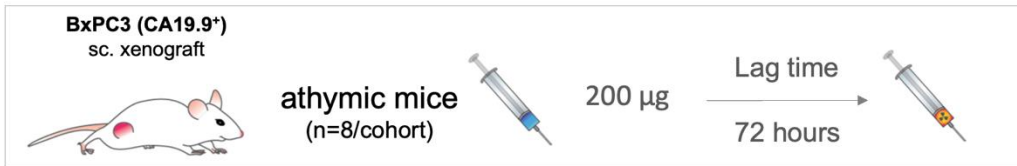


Optimisation of pharmacokinetic profiles

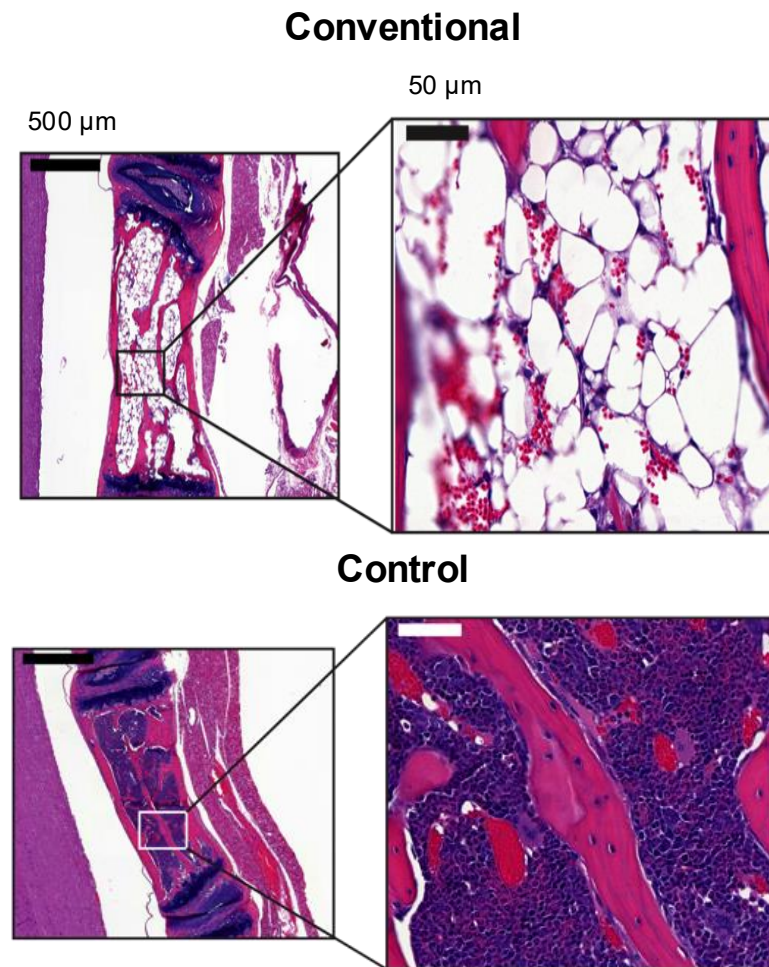
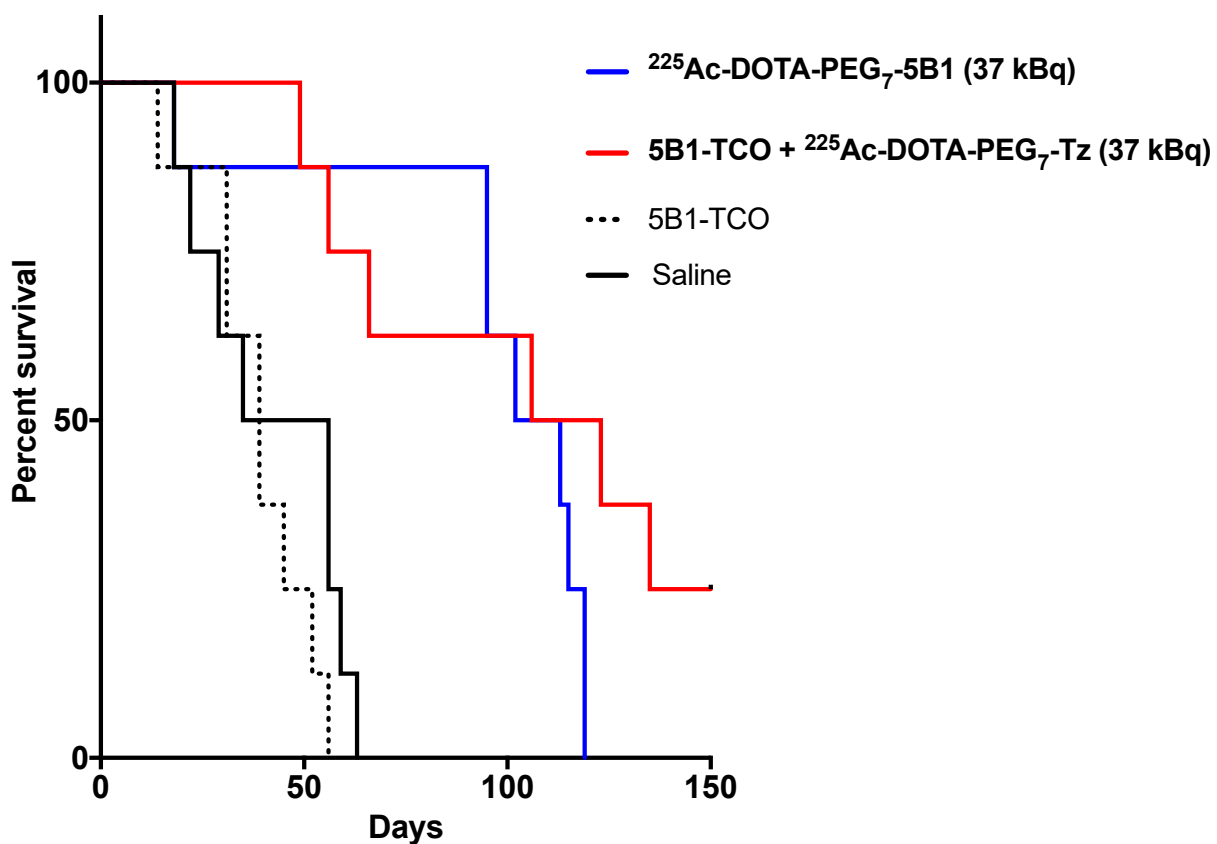
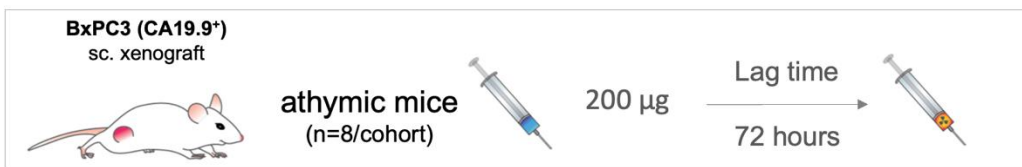
Mitigating hematotoxicity using pretargeting



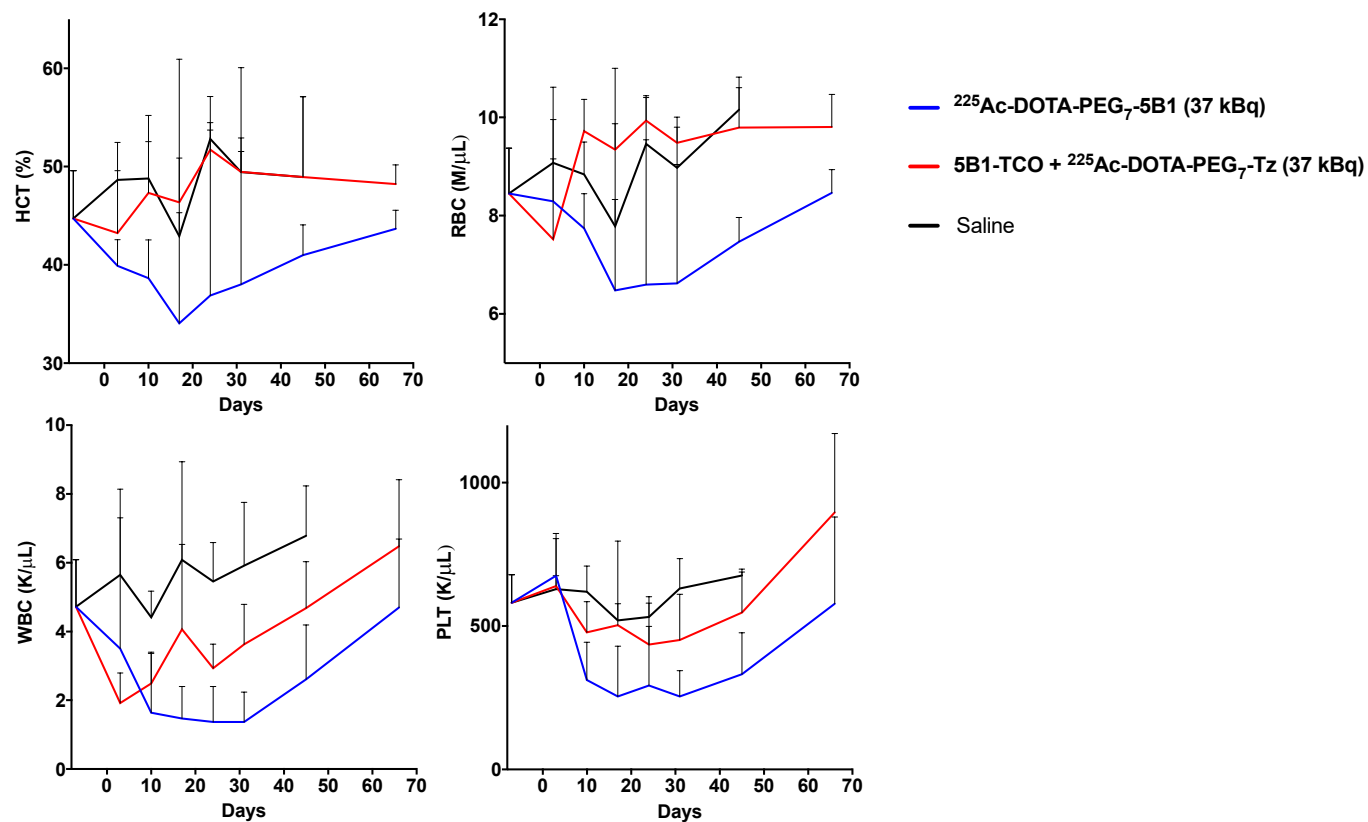
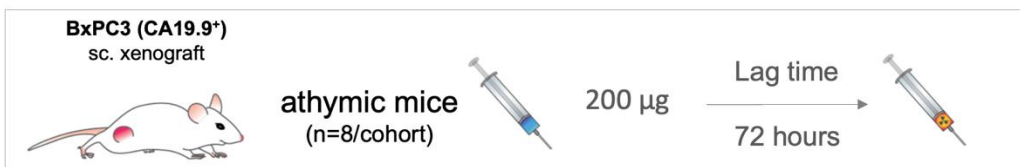
Mitigating hematotoxicity using pretargeting



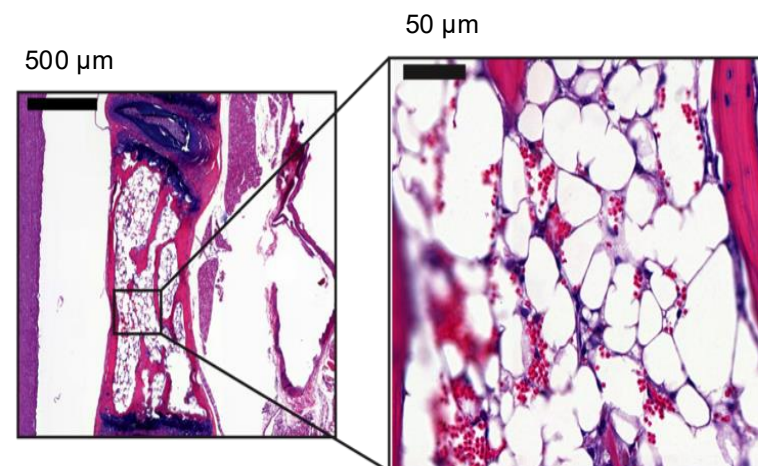
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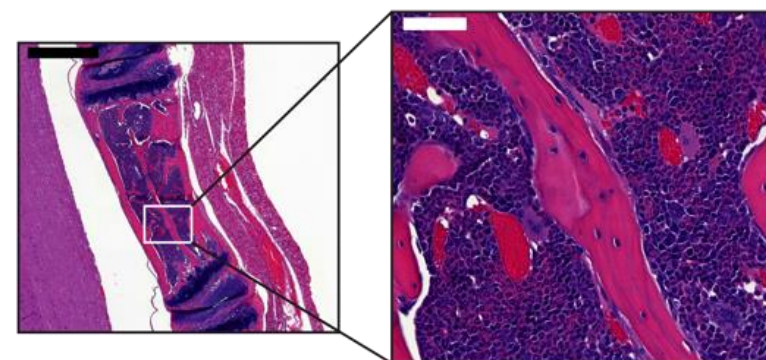
Mitigating hematotoxicity using pretargeting



Conventional



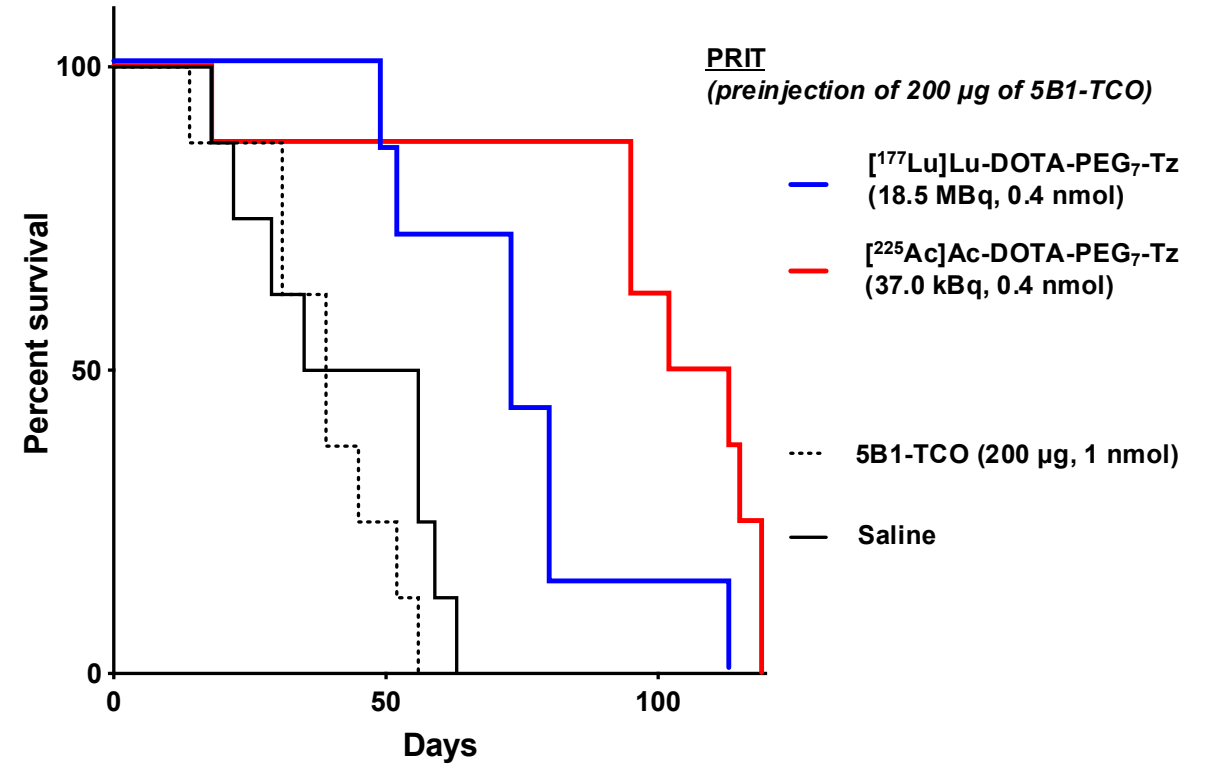
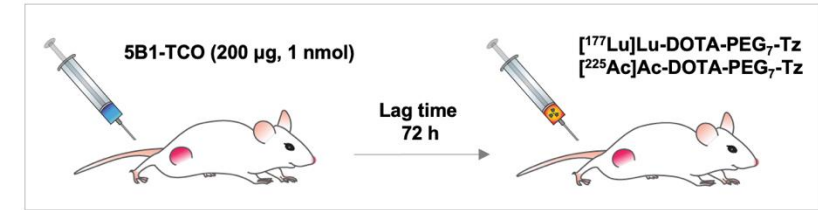
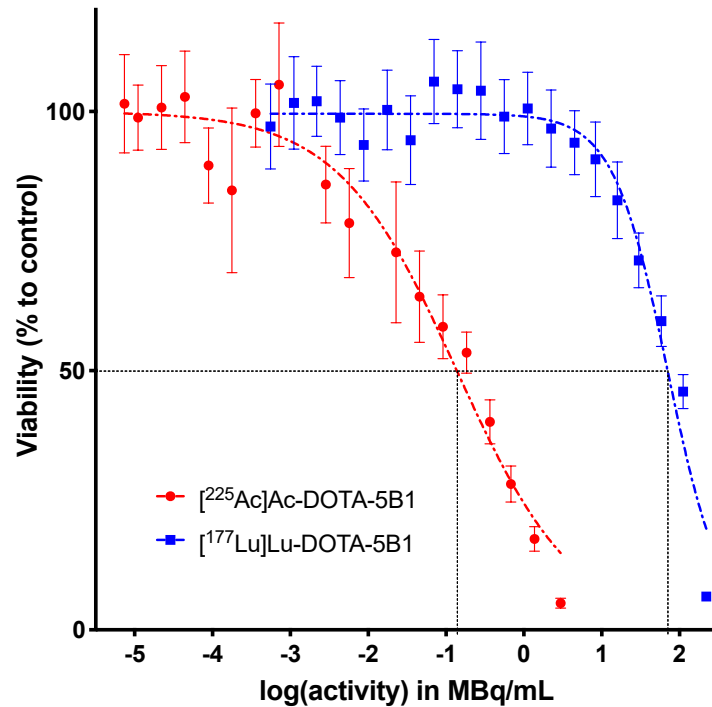
Control



Alpha versus beta

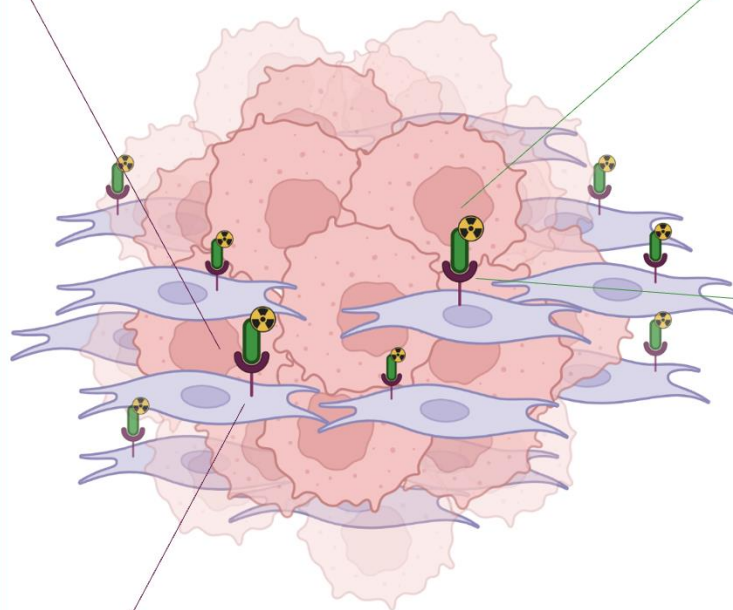
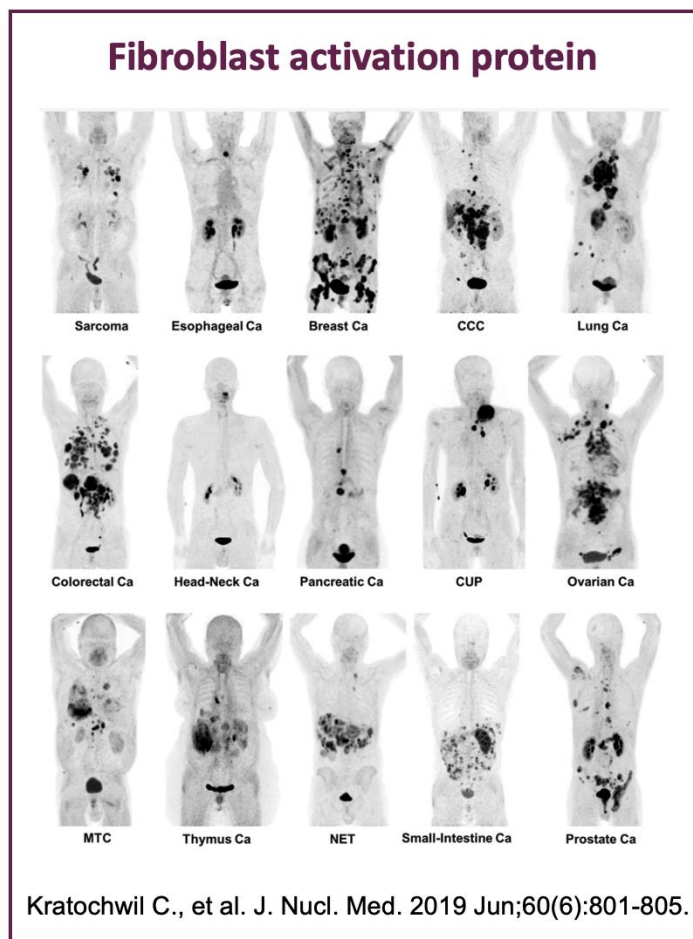
Alpha versus beta

MTT assay on BxPC3 cells (20'000)
after 48 hours of treatment



Beyond pancreatic cancer neoplasm

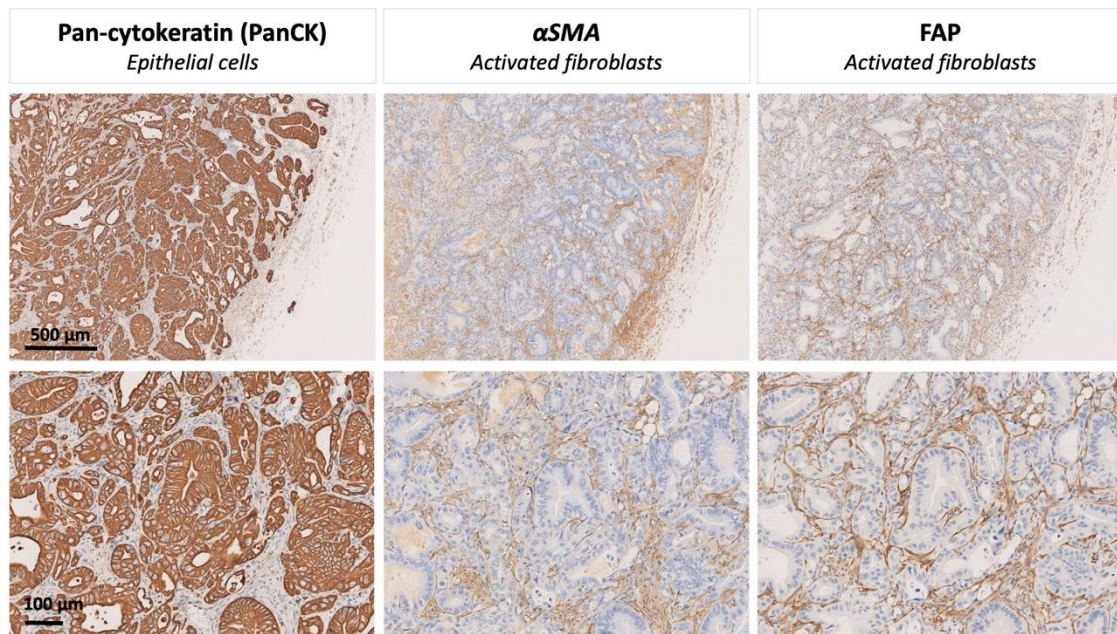
Targeting cancer associated fibroblasts



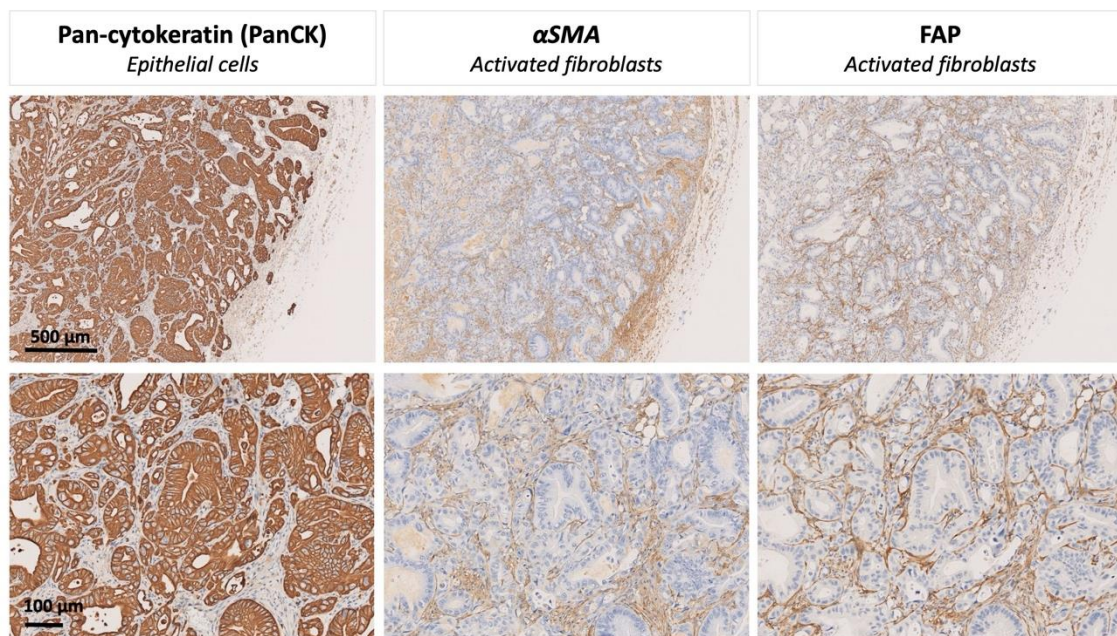
Single domain antibody
(sdAb/nanobody)

PRECIRIX

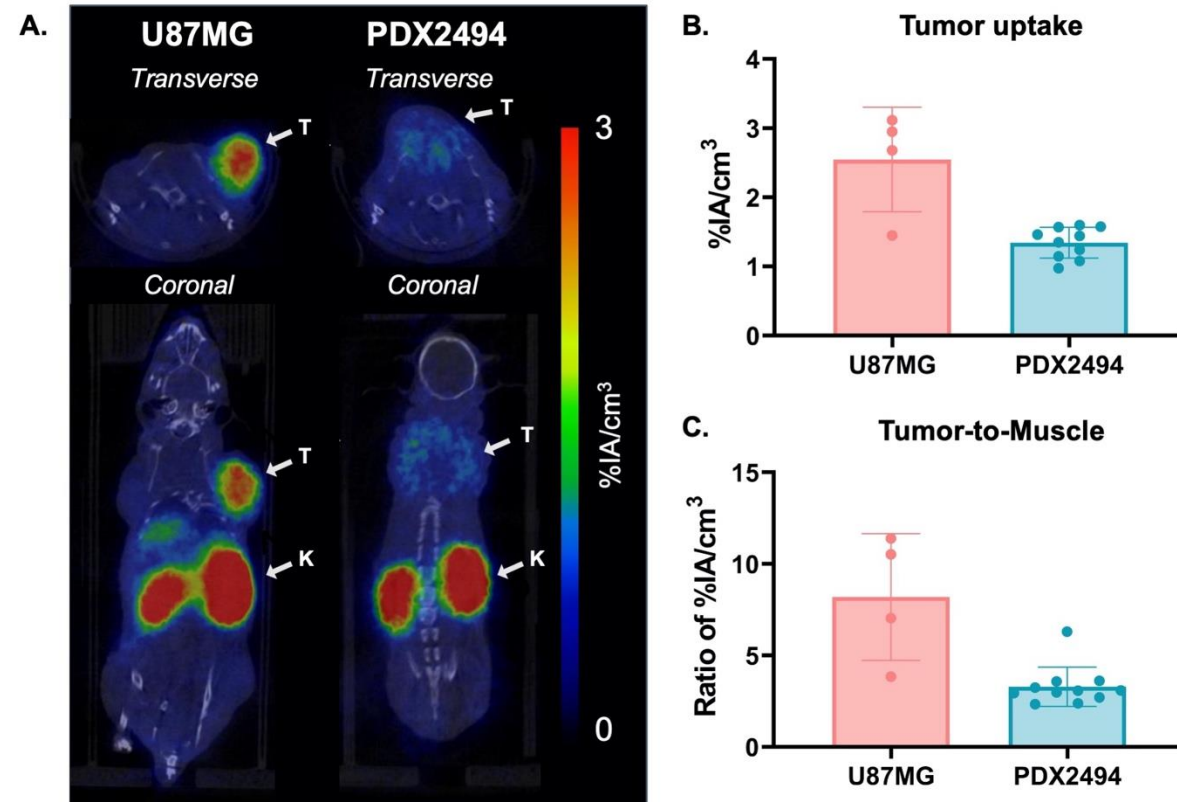
Identification of a murine model with FAP expression in the tumor microenvironment



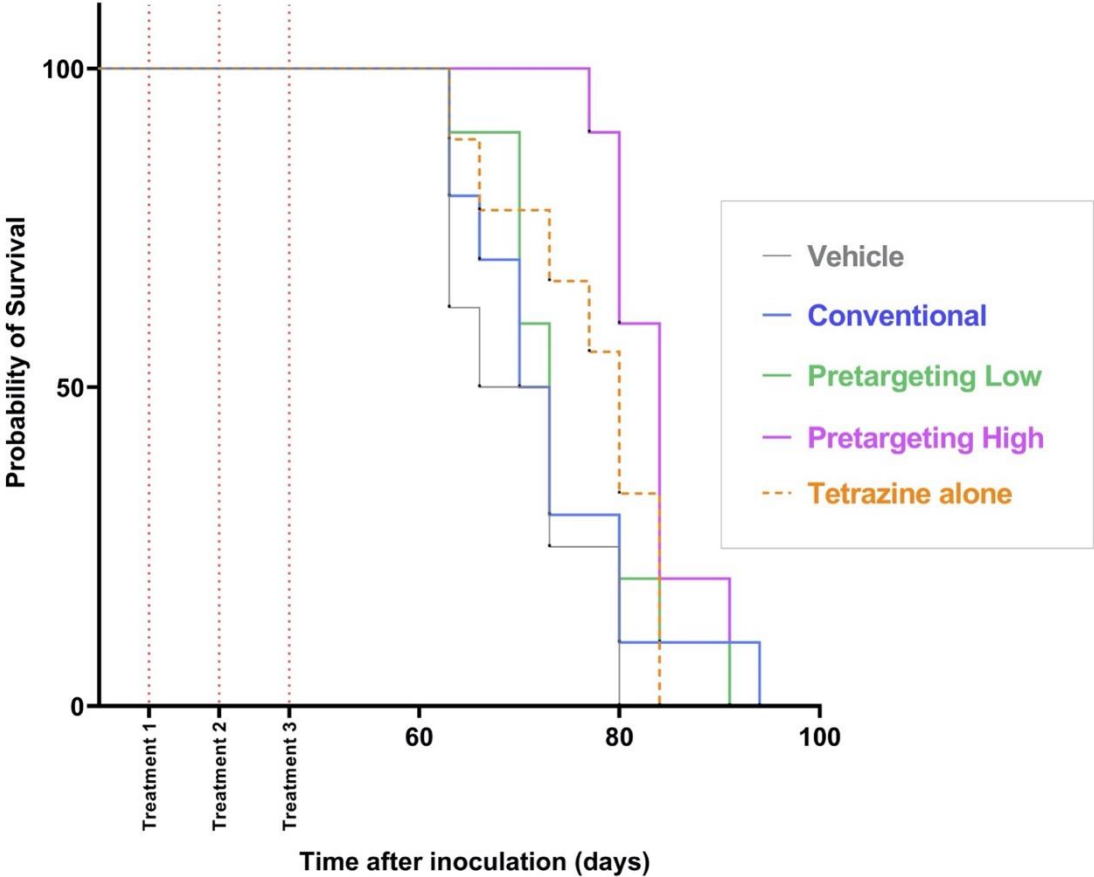
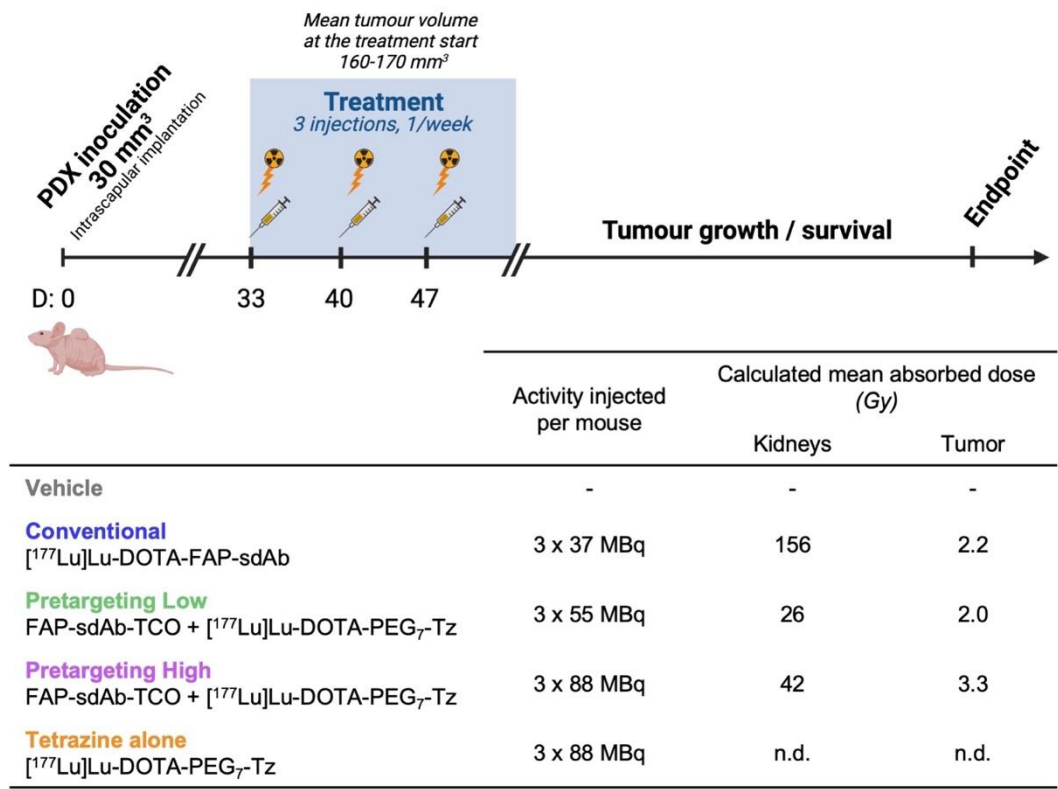
Identification of a murine model with FAP expression in the tumor microenvironment



Validation with [^{68}Ga]Ga-DOTA-FAP-sdAb imaging
(18-22 MBq, 0.4-0.5 nmol)
Imaging 1-hour post-iv injection



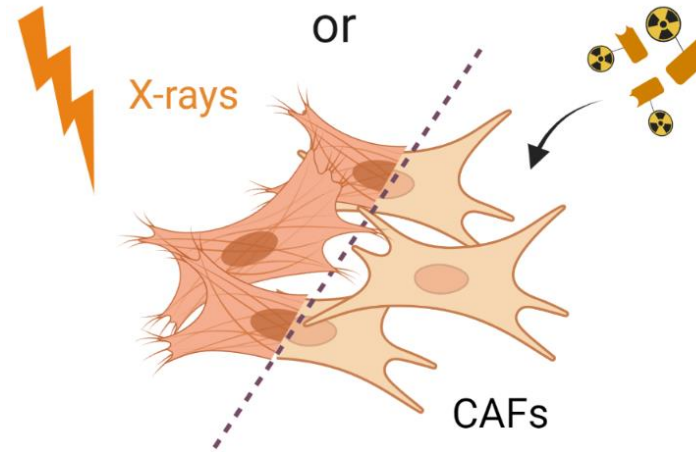
Beyond pancreatic cancer neoplasm



Beyond pancreatic cancer neoplasm

X-RT = senescence

- Persistent DNA damages
- No proliferation
- Cell cycle arrest
- β -galactosidase activity increase
- LaminB1 expression decrease
- p21 increases



anti FAP-TRT $\neq$ senescence

- DNA damages repair
- Proliferation slow down
- No cell cycle arrest
- No β -galactosidase activity
- LaminB1 expression no change



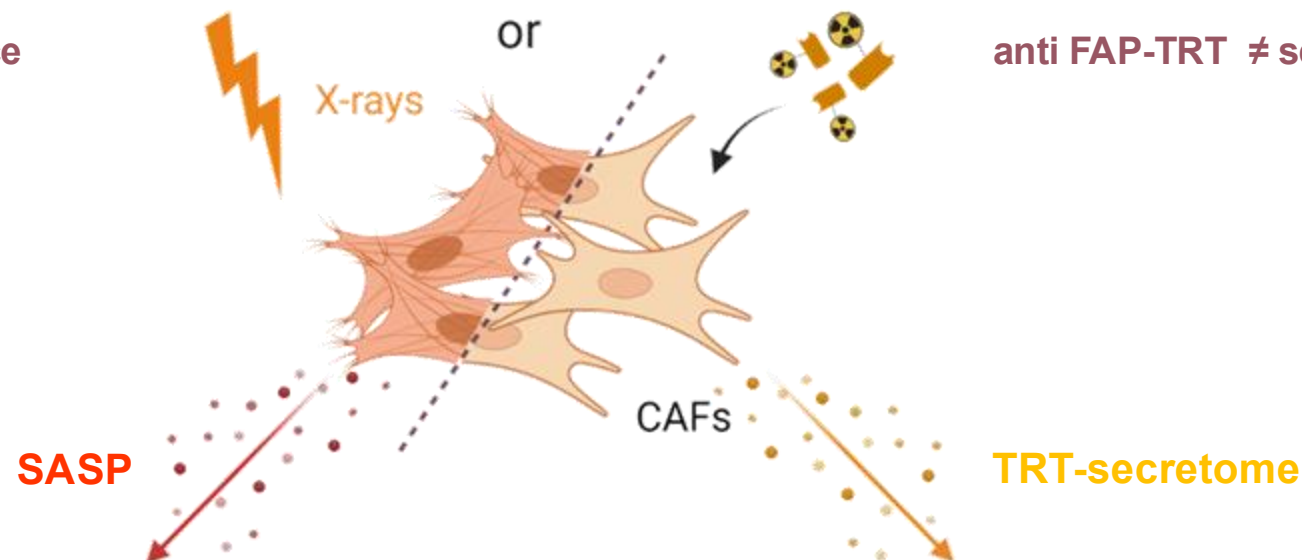
Laura Ordas
PhD student



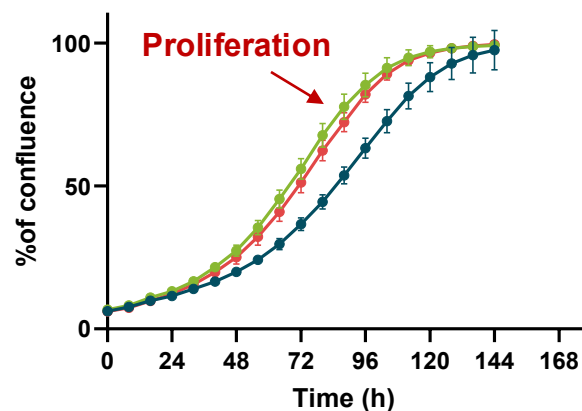
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X-RT = senescence

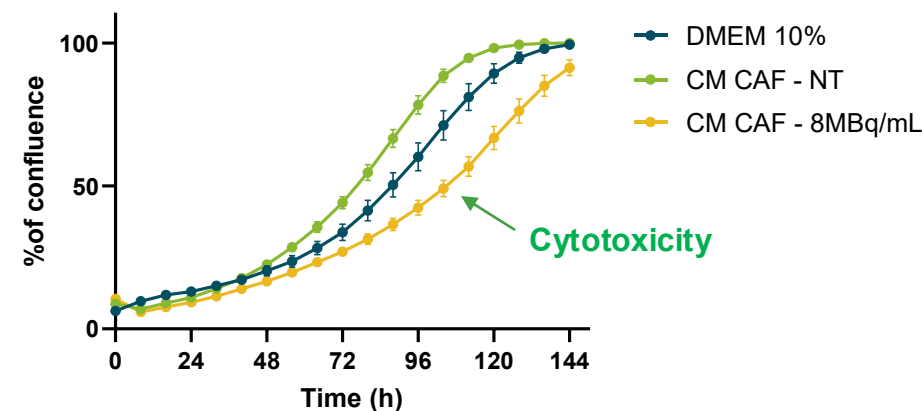
anti FAP-TRT ≠ senescence



PDAC cancer cell

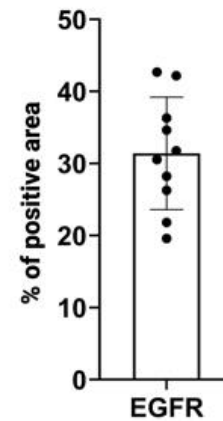
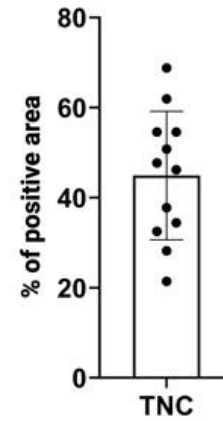
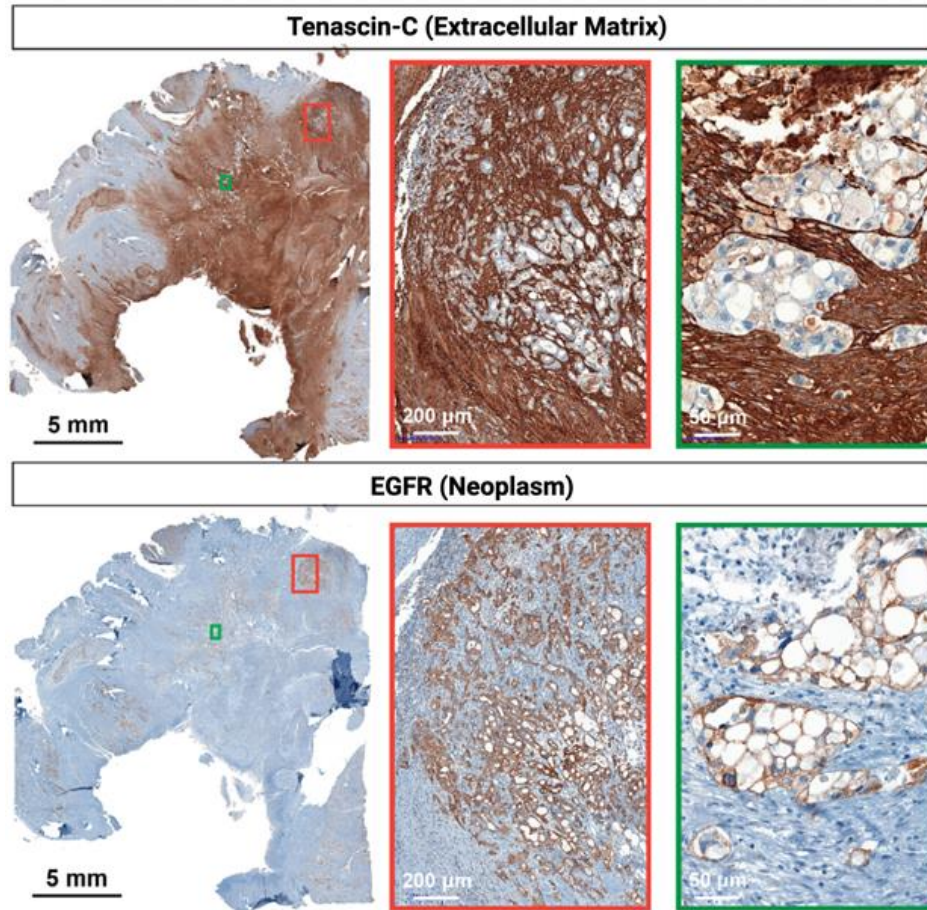


PDAC cancer cell

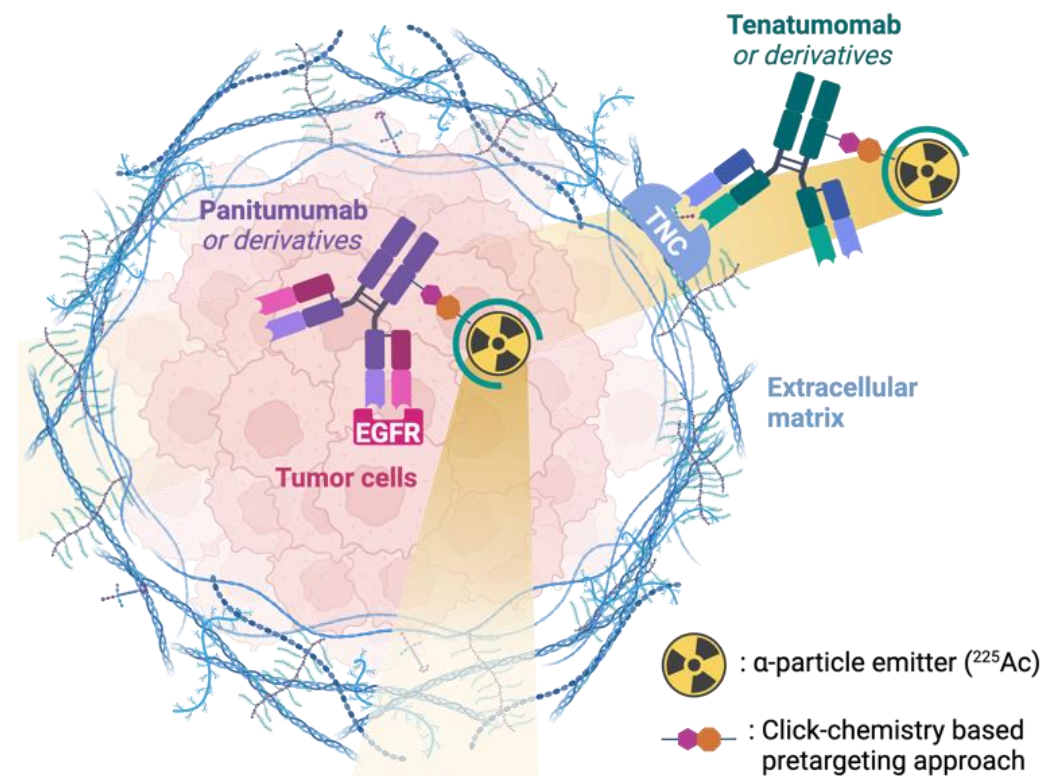
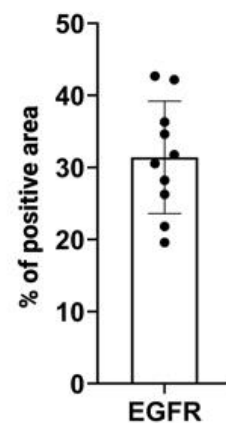
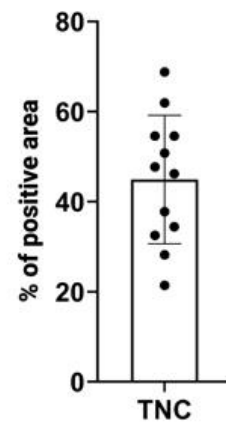
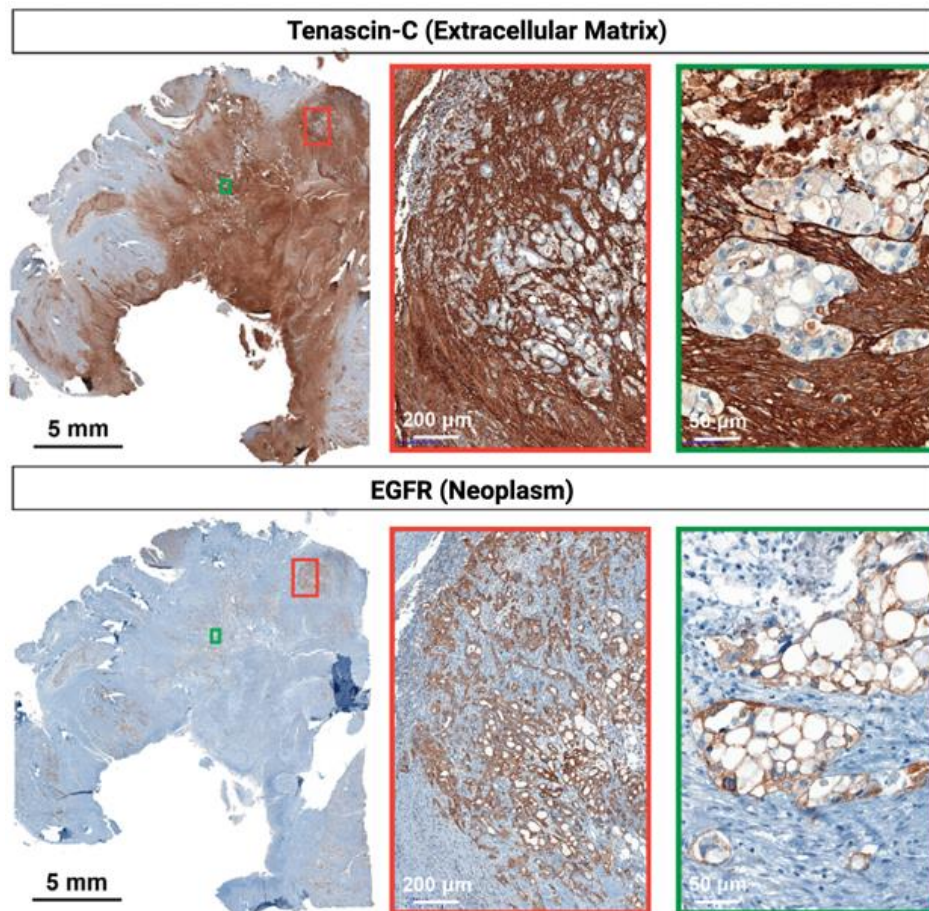


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Radiopharmaceuticals, Imaging
Theranostics and Multimodality

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