

A new murine highly localized high-dose muscle radiation model: a tool to develop innovative countermeasures to treat radio-induced muscular lesions

Preliminary studies

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Nicolas JULLIEN, PhD

2nd International Conference on Biomedicines (ECB 2023)
Musculoskeletal Tissue Regeneration



CONTEXT

Manipulation of
nuclear weapons



Terrorist acts :
hidden source

Radiation
accidents



Cutaneous Radiation Syndrome (CRS)

Time



Erythema
Phlyctena

Latency
period



Dry and then wet desquamation
Extensive inflammation



Skin and muscle
necrosis

HIGH DOSES: PERSISTENT NECROSIS

**NEED TO DEVELOP NEW THERAPEUTIC STRATEGIES
TO IMPROVE POST-IRRADIATION TISSUE REPAIR**



IDENTIFICATION OF NEW REGENERATING PATHWAYS



ELSEVIER

Experimental Hematology 2010;38:945-956

**Experimental
Hematology**

Multipotent mesenchymal stem cell grafting to treat cutaneous radiation syndrome: Development of a new minipig model

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Late Effects of Radiation on Skeletal Muscle: An Open Field of Research

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Table 1. Studies investigating changes in cellular metabolism and protein degradation.

Author	Sample	Random	Radiation-dose	Local
Gerstner, HB. <i>et al.</i> 1953	frog $N = 28$ / rabbits $N = 5$	no	X-ray 100 KR/72KR	Gastrocnemius Muscle
Khan, M. <i>et al.</i> 1974	rabbits $N = 18$	yes	X-ray - 1130 Re 1300 R	Pectoralis major muscle
Ahlersová, E. <i>et al.</i> 1981	rats	no	X-ray - 2.39 Gy	Whole body
Horowitz, R. <i>et al.</i> 1986	rabbits	no	no - 1.5 Mrad	Psoas muscle
Schwenen, M. <i>et al.</i> 1989	rats	no	Gama - 15 Gy	Hind paw
Voitsitskiĭ, VM. <i>et al.</i> 1990	rabbits	no	X-ray - 0.21 C.kg ⁻¹	Hind paw
KhizhniakSV. <i>et al.</i> 1990	rabbits	no	X-ray - 0.21 C.kg ⁻¹	Hind paw
KhizhniakSV. <i>et al.</i> 1991	rabbits	no	X-ray - 0.24 C.kg ⁻¹	Hind paw
Fox, JB. Jr. <i>et al.</i> 1993	pigs	no	Gama - 0 - 10 kGy	no
Shtifman A <i>et al.</i> 2013	mice $N = 8$	yes	low-LET ¹ H- 90cGy high-LET ³⁶ Fe-15c Gy and Gama - 1 Gy	Whole body



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Gerstner, HP <i>et al.</i> 1953	frog N = 28/	no	X-ray	Gastrocnemius

Table 2. Studies that investigate repercussions on satellite cells.

Author	Sample	Random	Radiation-dose	Local
Khan, M. <i>et al.</i>				
Ahlersová, I	mice C57BL/6 males N = 32	yes	Gamma 2500 rad	Right hindlimb
Horowitz, R				
Phelan, JN. <i>et al.</i> 1997	rats N = 40	yes	Gama - 3000 rad	Right soleus muscle
Schwenen, J				
Voitsitskiĭ, I				
Caiozzo, VJ. <i>et al.</i> 2010	rats	no	Gama - 5 Gy	Cell culture hind paws
KhizhniakS				
Cho-Lim, JJ. <i>et al.</i> 2011	rats males	no	Gama - 1.2 e 5 Gy	Cell culture hind paws
Fox, JB. Jr.				
Jurdana, M. <i>et al.</i> 2013	human muscle tissue N = 3	no	X-ray- 2 to 8 Gy	Cultures of human myoblasts
Shtifman A				
McDonald AA. <i>et al.</i> 2014	mice C57BL/10 and dystrophic mdx: utrophin N = 4 to 8	no	Gama - 18Gy	Extraocular muscle and limb



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Ahlersová, I	mice C57BL/6 males			
Rosenblatt JD. 1993	N = 32	yes	Gamma 2500 rad	Right hindlimb
Horowitz, R				

Table 4. Studies that investigated the regeneration of muscle tissue.

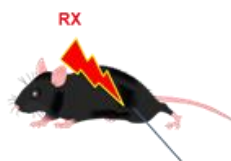
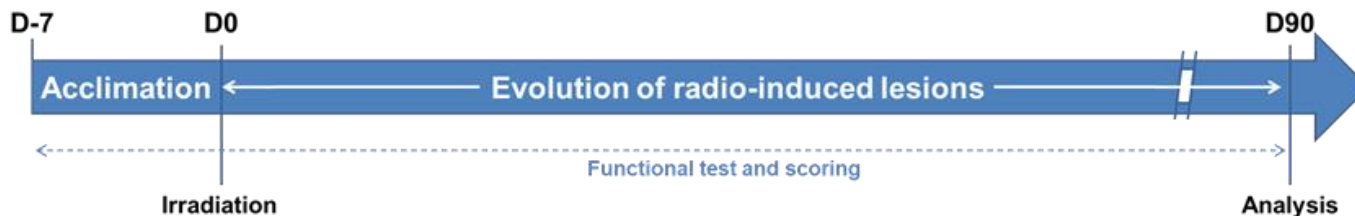
Author	Sample	Random	Radiation-dose	Local
Popova, MF. <i>et al.</i> 1978	rats	no	no -1000 R	Gastrocnemius Muscle
Wirtz, P. <i>et al.</i> 1982	mice strain Re 129 N = 30	no	no- 20 Gy	Plantaris, gastrocnemius and soleus muscle
Gulati, AK. 1987	rats	no	X-ray - 650, 2000 e 10.000 R	Extensor digitorum longus muscle
Popova, MF. <i>et al.</i> 1988	rats N = 64	no	X-ray - 20 - 30 Gy	Gastrocnemius Muscle
Rosenblatt JD. 1993	Rats males wistar N = 23	no	Gamma 25 Gy	Right hindlimb
Granata, Al. <i>et al.</i> 1998	Wild mice and mdx dystrophic mice N = 30	no	Gama/30Gy	Soleus muscle
Wernig, A. <i>et al.</i> 2000	mice N = 29	no	X-ray - 16 Gy	Soleus muscle

- Irradiation models are available but : large animals, whole leg exposure including bones, foot loss...
- Need to focus on muscle.

A NEW LOCALIZED HIGH-DOSE MUSCLE IRRADIATION MODEL

Murine model : Female C57Bl/6J mice
 12 week-old

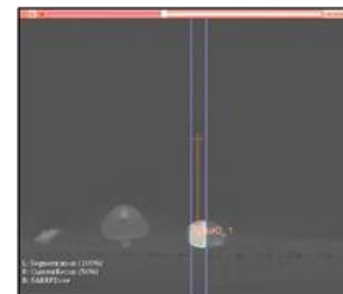
MUSCULOCUTANEOUS model



Left G/S muscles
 Radiation dose: 60 Gy



Left G/S muscles
 Non IR control 0 Gy



5 mice

5 mice

NO EFFECT OF RADIATION ON MICE GENERAL CONDITION



Behavior +



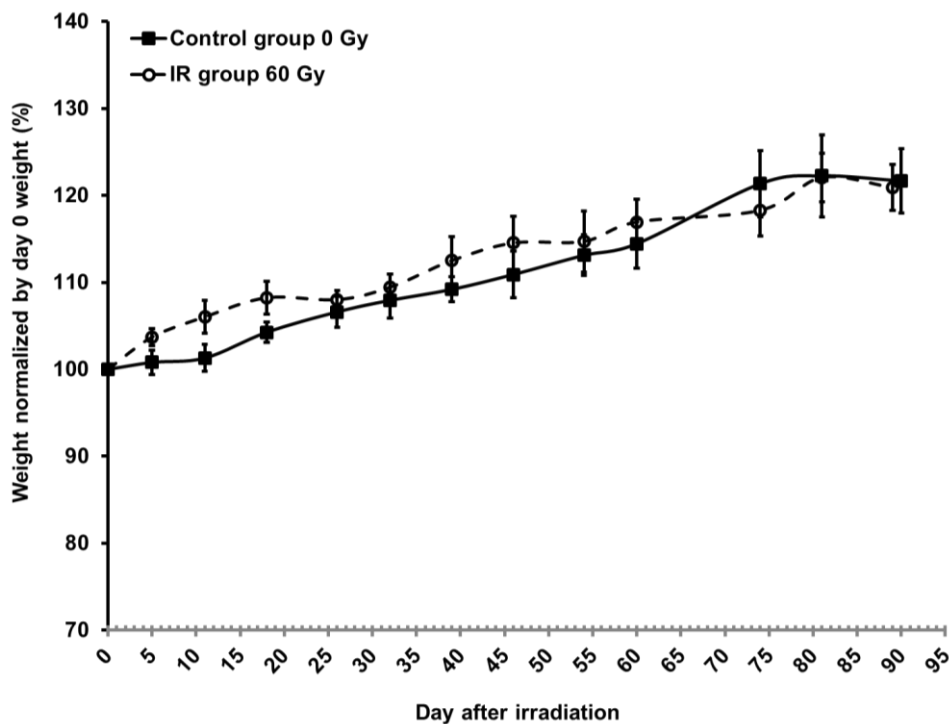
Appearance +



Locomotion +

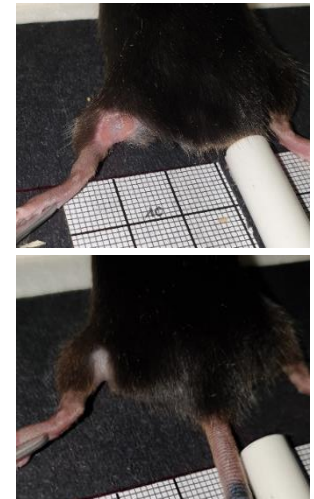
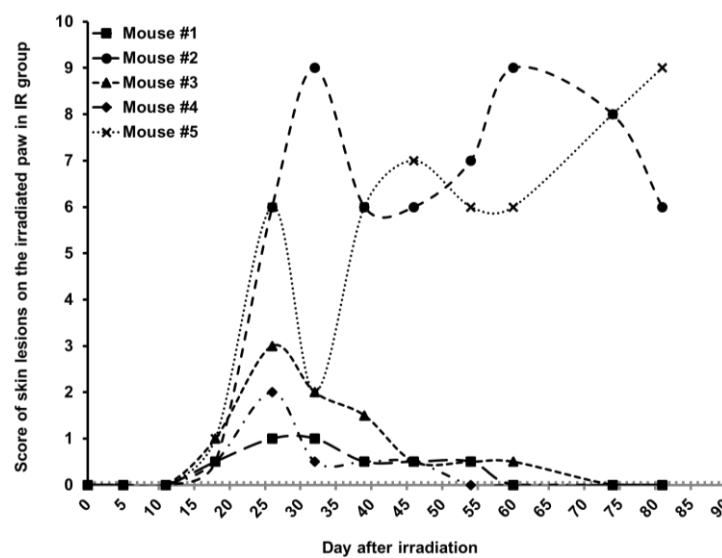
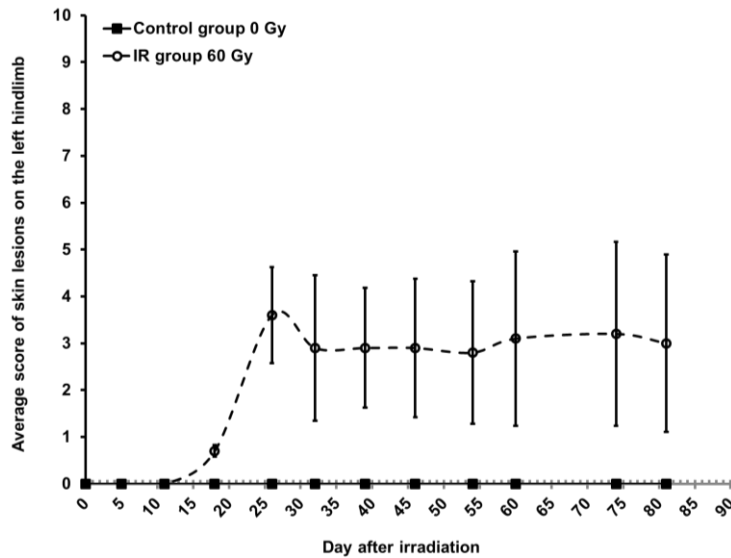


Weight gain +

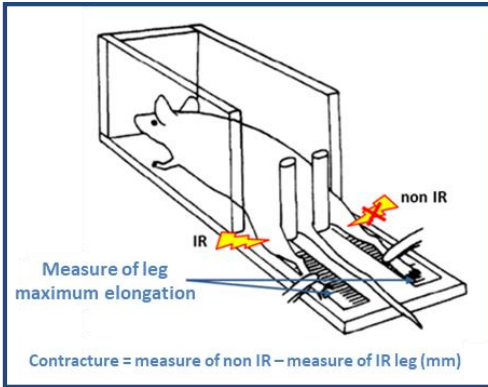


Weekly scoring of skin lesions

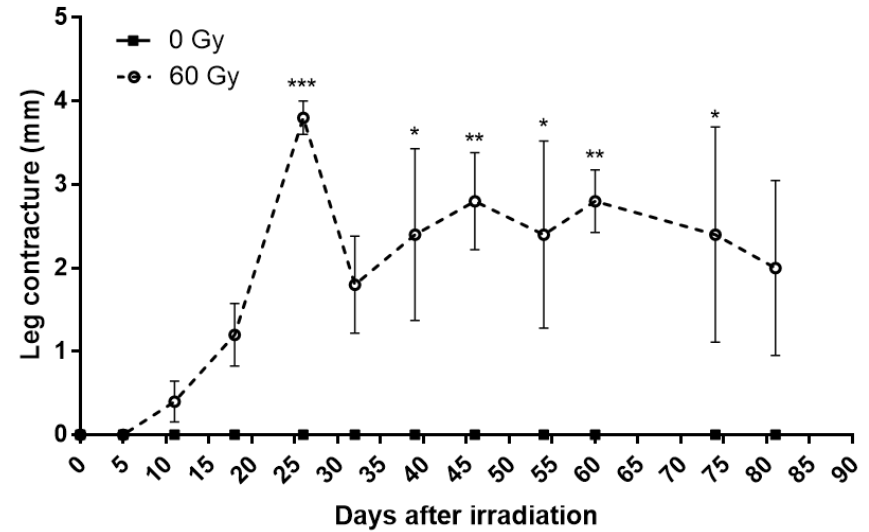
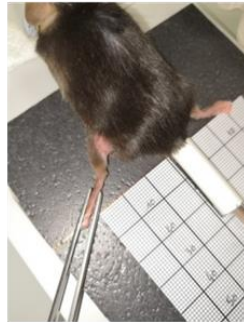
	Score						
	0	0.5	1	2	3	4	5
Depilation	none	slight	pronounced				
Erythema	none		slight redness	redness	pronounced redness	intense redness	burgundy to purple redness
Edema	none		minor bulge	slight swelling	pronounced swelling	major swelling	phlyctena
Exudation	none		slightly moist wound	oozing	marked exudation	impregnated hair around the wound	superinfection
Ulcer/Necrosis	none					shallow ulcer / small necrosis	deep ulcer / significant necrosis
Tendency to spread	same or smaller area than at previous examination				moderate extension (<50% of the area at previous examination)		significant extension (>50% of the area at previous examination)



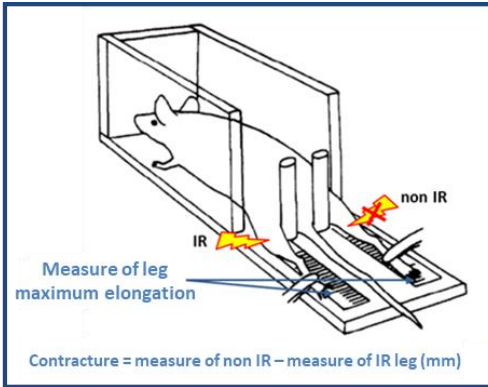
Weekly evaluation of leg contracture



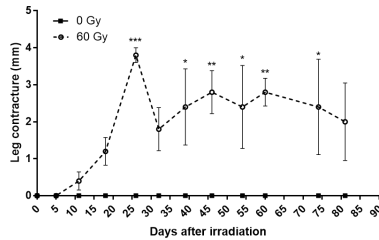
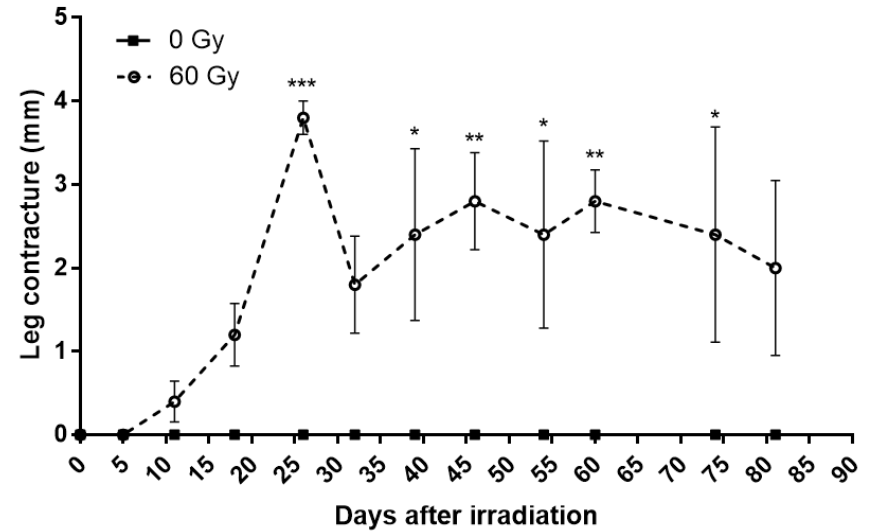
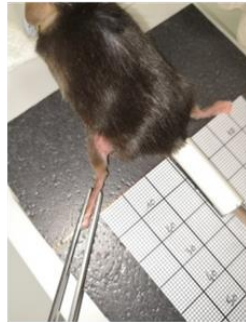
From Stone HB, 1984



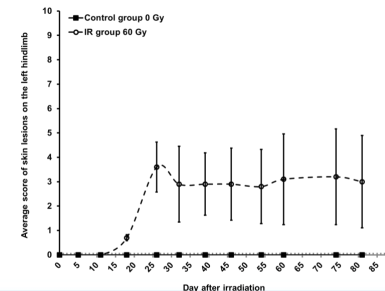
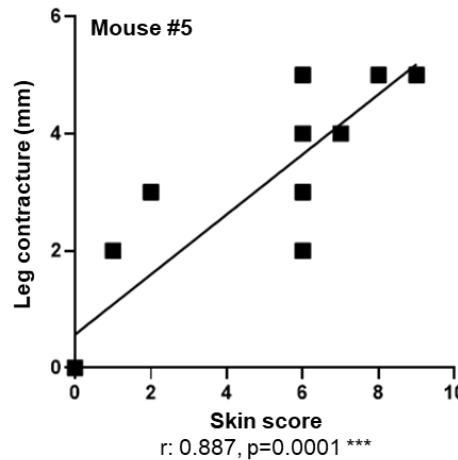
Weekly evaluation of leg contracture



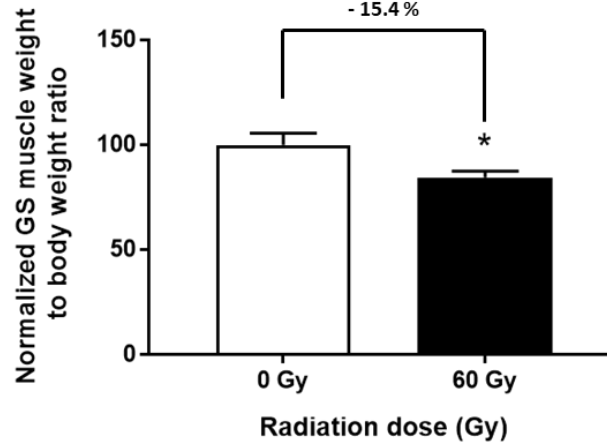
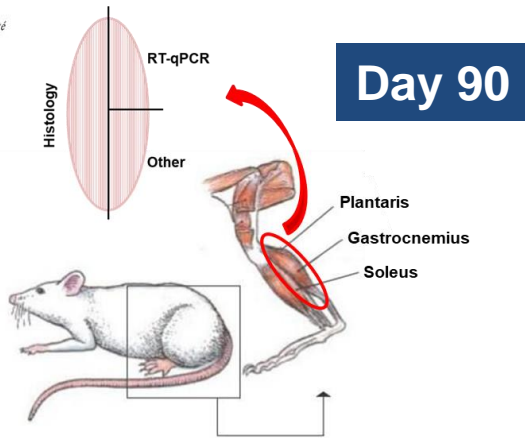
From Stone HB, 1984



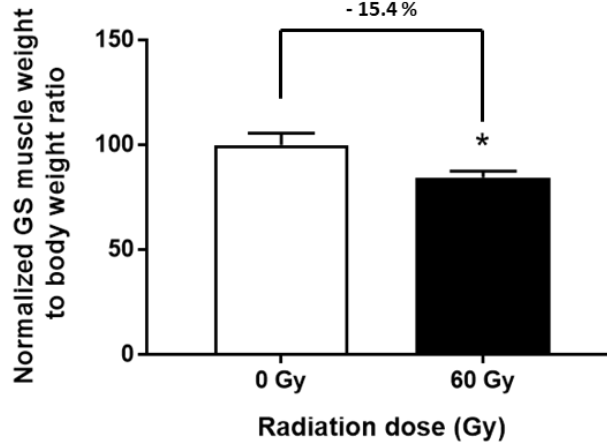
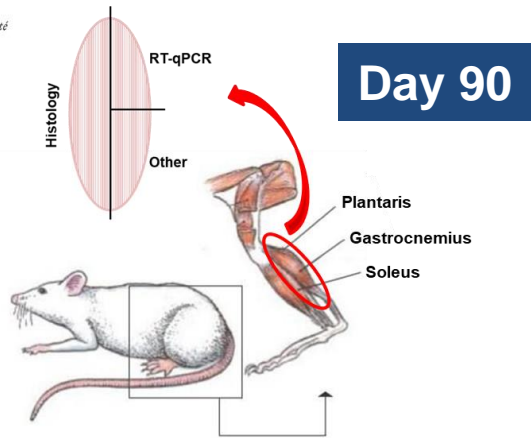
Significant positive correlation between leg contracture and skin score (4 mice/5)



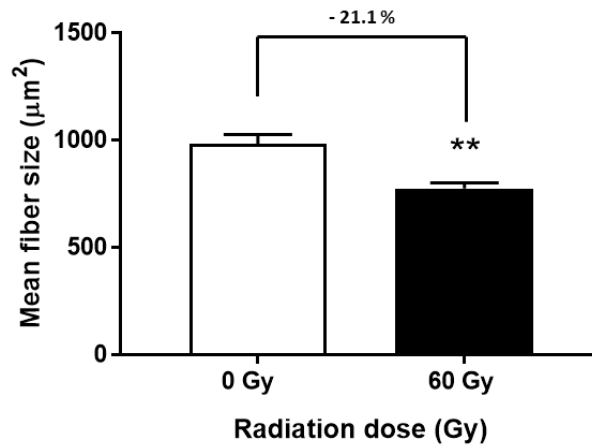
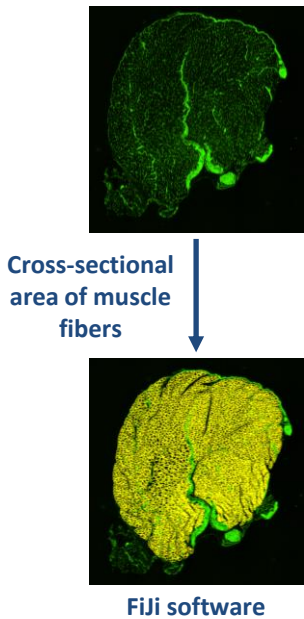
RADIATION-INDUCED DAMAGE TO THE MUSCLE STRUCTURE



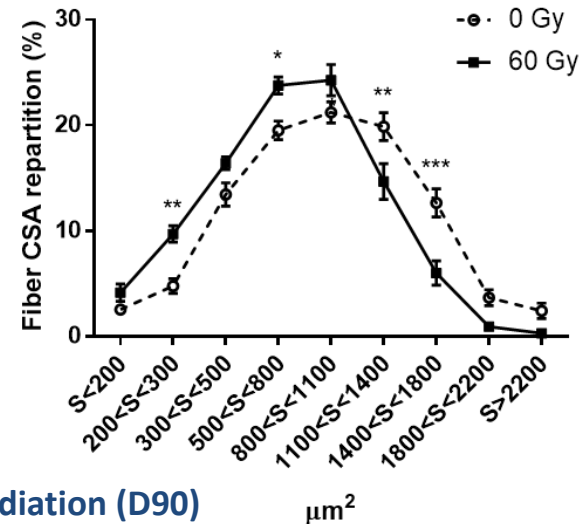
Decrease of GS muscle mass
after irradiation



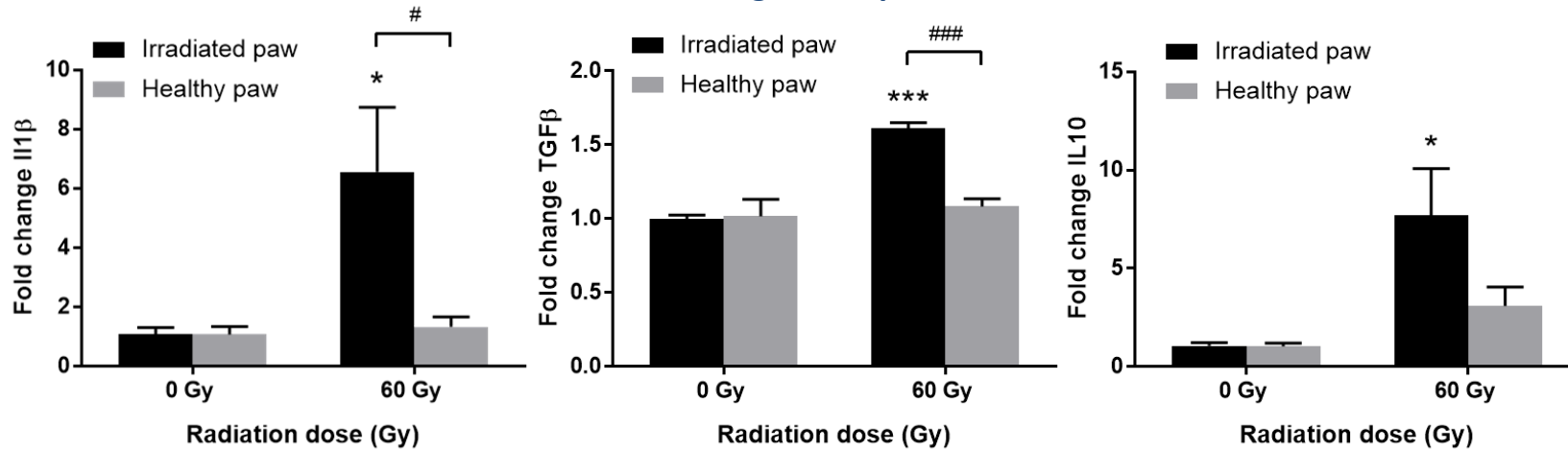
Decrease of GS muscle mass after irradiation



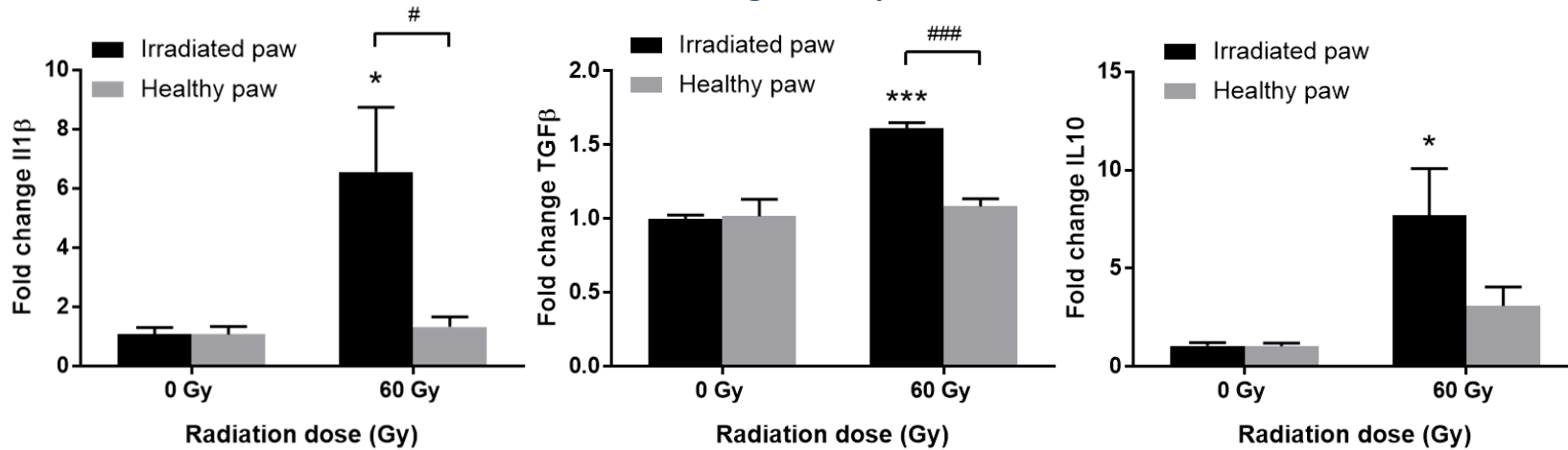
Redistribution of myofiber sizes after irradiation (D90)



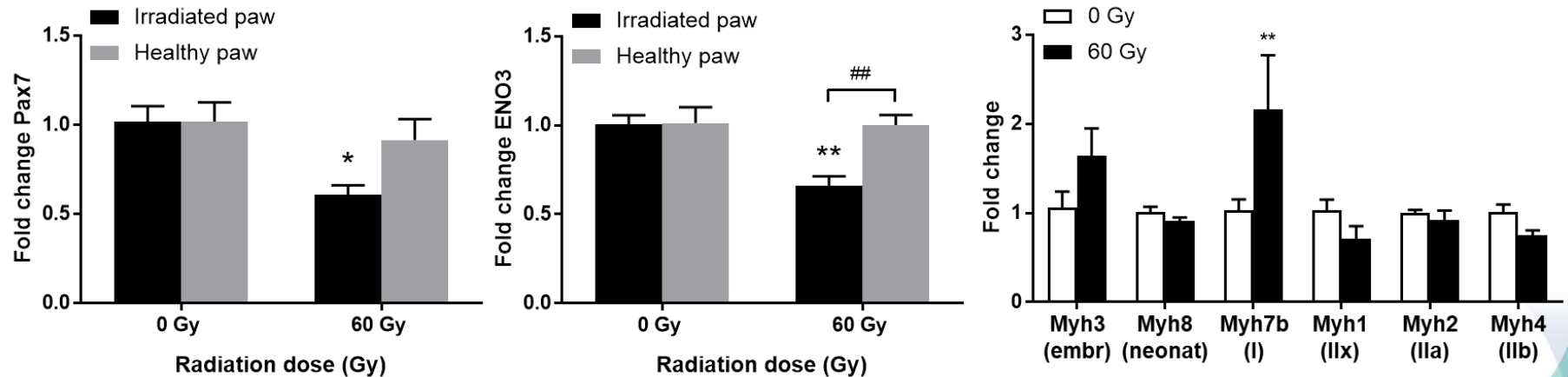
Increase of inflammation and fibrotic genes expression



Increase of inflammation and fibrotic genes expression

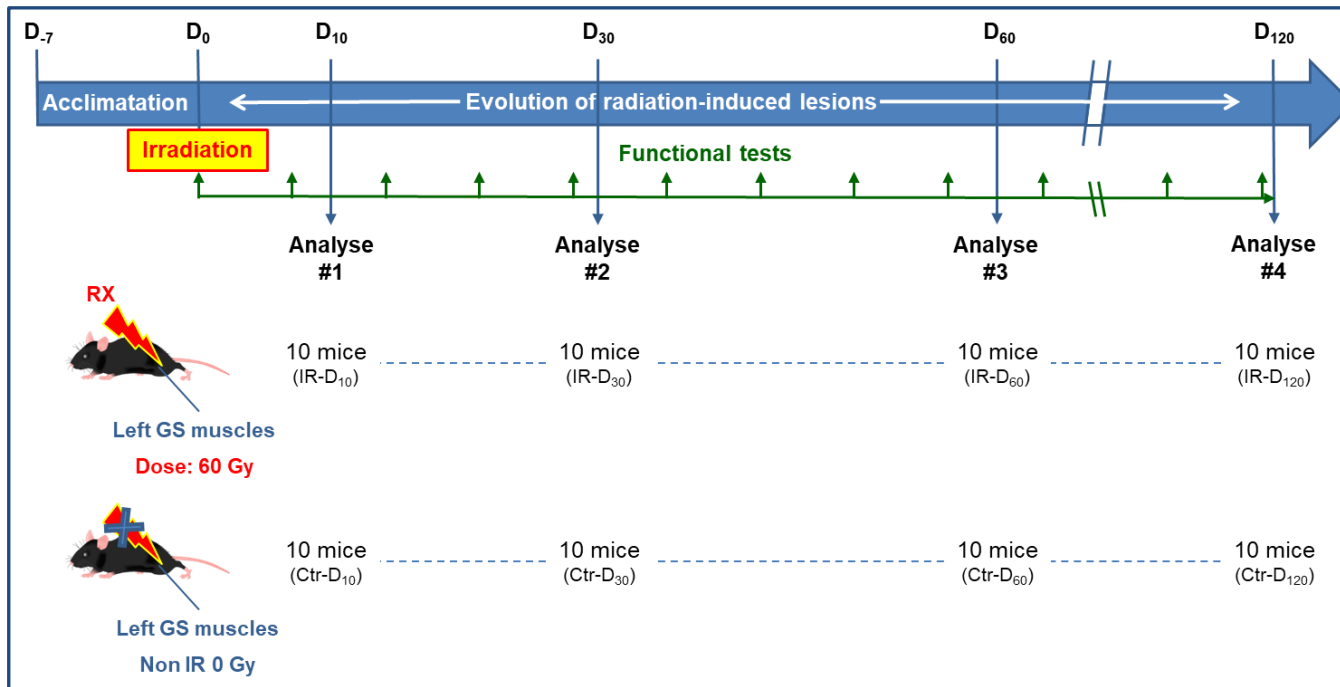


Modulation of myogenesis genes expression



- After a localized 60 Gy X-rays irradiation:
- Functional impairment of GS muscles
 - Decrease of GS muscles mass
 - Modification of the distribution of myofibers
 - Deregulation of inflammatory/fibrotic and myogenic markers

Need to acquire longitudinal data:



Identification of new therapeutic targets and evaluation of medical countermeasures to treat radiation-induced muscle damage.



From IRBA Radiobiology Unit:
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Diane RICCOBONO
Sabine FRANCOIS
Michel GAUTHIER
Emmanuelle ROTA-GRAZIOSI

**THANK YOU
FOR YOUR ATTENTION**

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