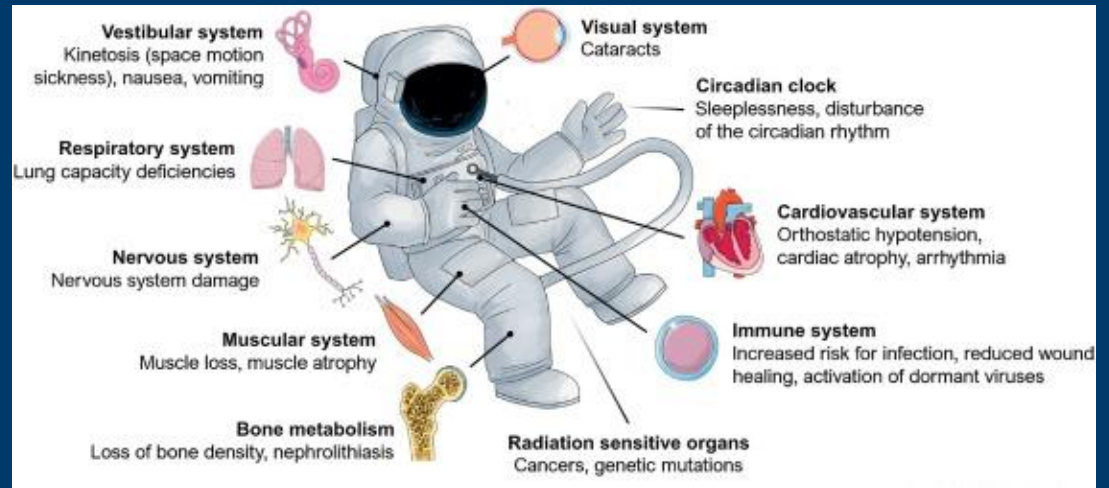


IMPIEGO DI MODELLI MURINI IN BIOMEDICINA PER LA RADIOBIOLOGIA SPAZIALE



Simonetta Pazzaglia (ENEA)

Moroni et al. *Trends in biotechnology* 2022, vol. 40, 398-411

15-17 March 2023, Simposio ASI "Biomedicina Spaziale per le Future Missioni di Esplorazione Umana dello Spazio: a Call to Action"





Team

Personale esperto in istopatologia, specializzato in processazione tissutale e tecniche molecolari per la valutazione di alterazioni patologiche e genetiche negli animali da esperimento.

Personale medico/veterinario per la cura degli animali



Progetti UE

DoReMi, ProCardio, CEREBRAD, Dark-Risk e OPERRA (6/7° PQ), LD-LensRad e SEPARATE (Horizon 2020)
Horizon Europe è partner di PIANAFORTE
Piattaforme europee: EURADOS e MELODI e NERIS

Obiettivi

Focus: aspetti meccanicistici delle alterazioni molecolari/cellulari responsabili dell'induzione di patologie da radiazioni a breve e lungo termine

Valutazione dei rischi da radiazioni

- Insorgenza di tumori
- Effetti «non-cancer» (cataratta, effetti neurologici, effetti metabolici, sull'intestino e microbioma)

Priorità in ambito aerospaziale

Effetti dell'esposizione a radiazioni cosmiche a livello sistemico e tessuto specifico, in particolare sulle ripercussioni a carico del sistema circolatorio e nervoso

Conoscenza approfondita dei meccanismi patogenetici delle radiazioni

Rischio da radiazioni sulla salute



CONTROMISURE

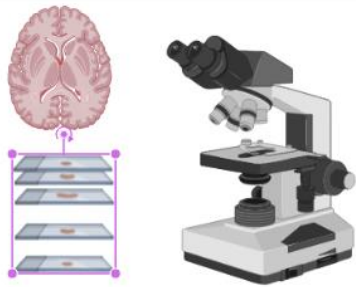


ENEA

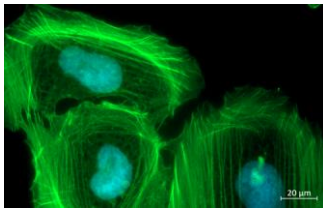
LABORATORIO DI TECNOLOGIE BIOMEDICHE



Modelli animali



Istologia



Microscopia

Raggi X



Raggi γ

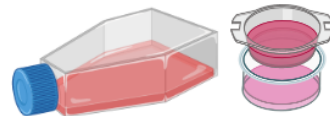


Neutroni

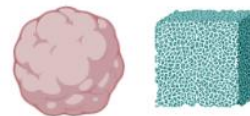
Protoni
(<70 MeV)



2D

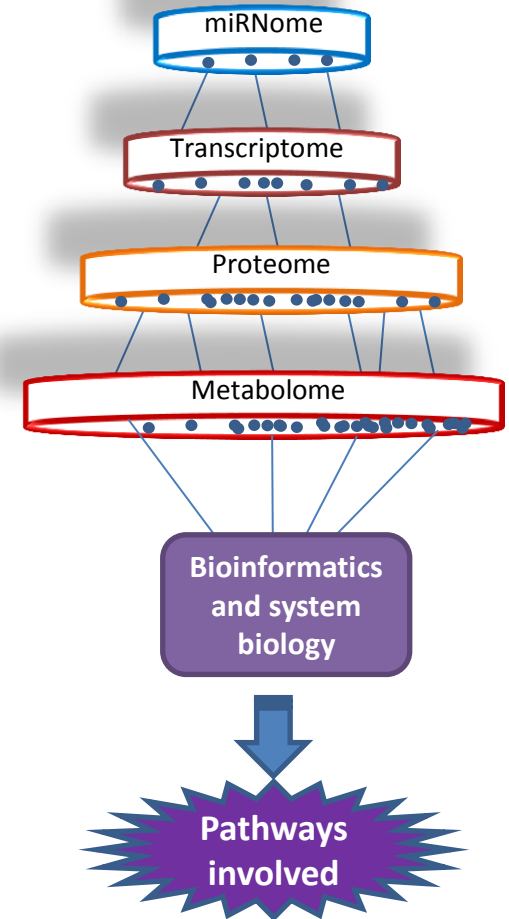


3D



Modelli *in vitro*

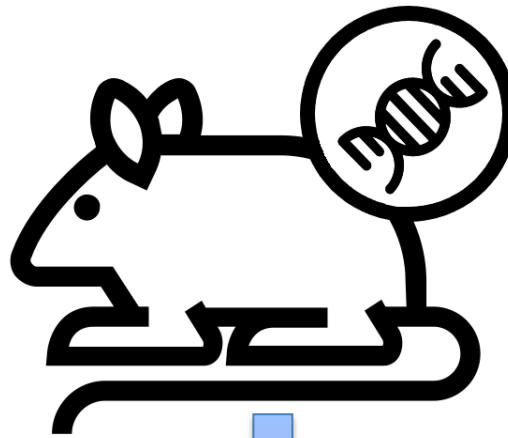
Analisi «omiche»



MODELLI MURINI di interesse in ambito radioprotezionistico



Stabulario



KO mice per geni
del riparo al DNA,
• DNA-PK^{-/-}
• Rad54^{-/-}
• PARP1^{-/-}

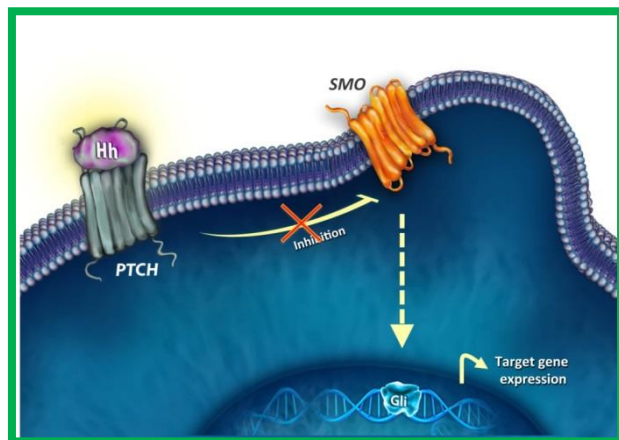
Topi ApoE^{-/-}

Topi wild type

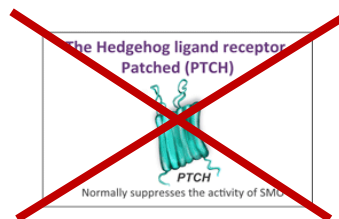
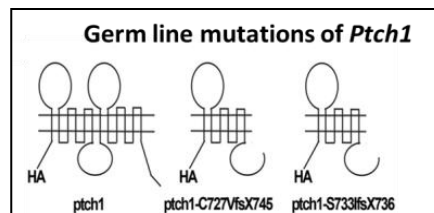
Topi *Patched*^{+/-}

MODELLO MURINO *PATCHED1* (*Ptch1*^{+/-})

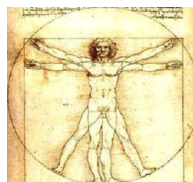
The Shh signaling pathway



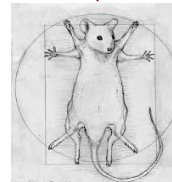
The Shh signaling pathway is an important regulator of cell growth and differentiation in a wide array of tissues during normal embryonic development



Ptch1 mutations in humans and mice



Gorlin syndrome



Ptch1^{+/-} mice model of the Gorlin syndrome

Common features

Developmental defects

Generalized overgrowth

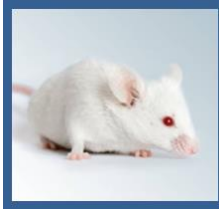
Polydactily

Radiation hypersensitivity

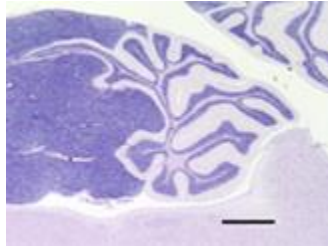
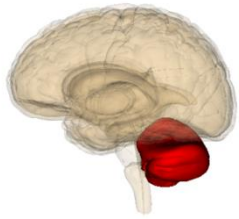
Tumor predisposition

Topi *Ptch1*^{+/-} per lo studio di patologie radioindotte

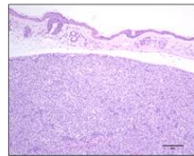
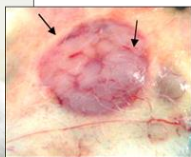
CANCER



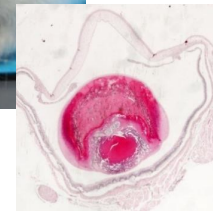
NON-CANCER



Induzione di medulloblastoma



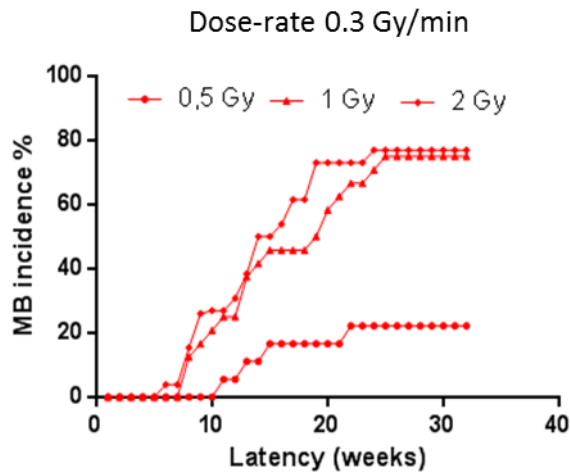
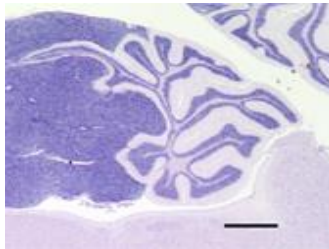
Induzione di BCC



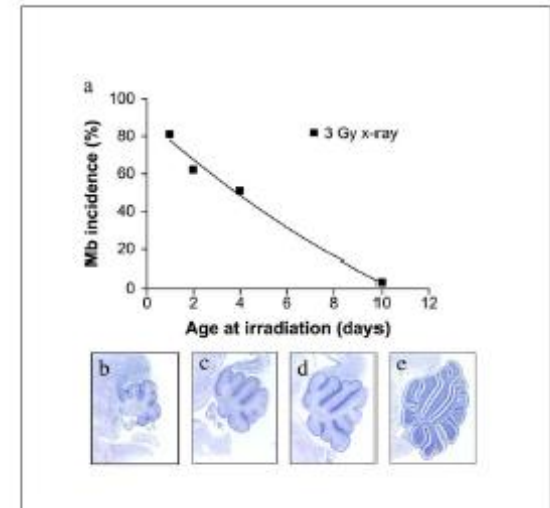
Induzione di cataratta

Topi *Ptch1*^{+/-}: INDUZIONE DI MEDULLOBLASTOMA (Raggi- γ)

- ✓ Medulloblastoma (MB) è il tumore cerebrale pediatrico più maligno
- ✓ Circa il 30% dei MB sporadici mostra attivazione del pathway di Shh
- ✓ 7% dei topi *Ptch1*^{+/-} sviluppa spontaneamente MB

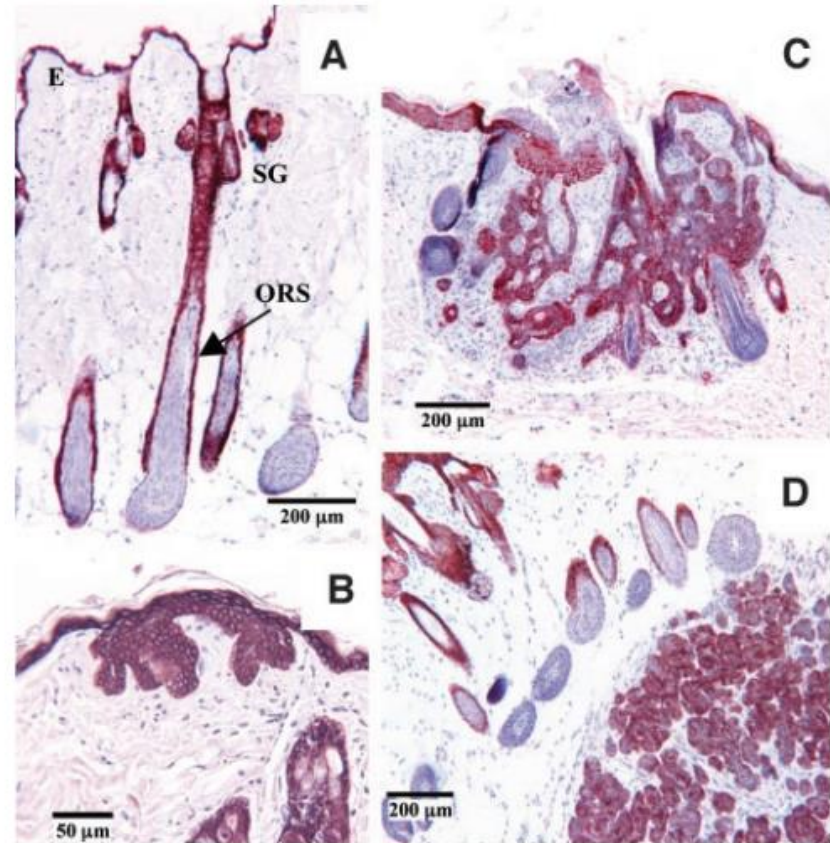
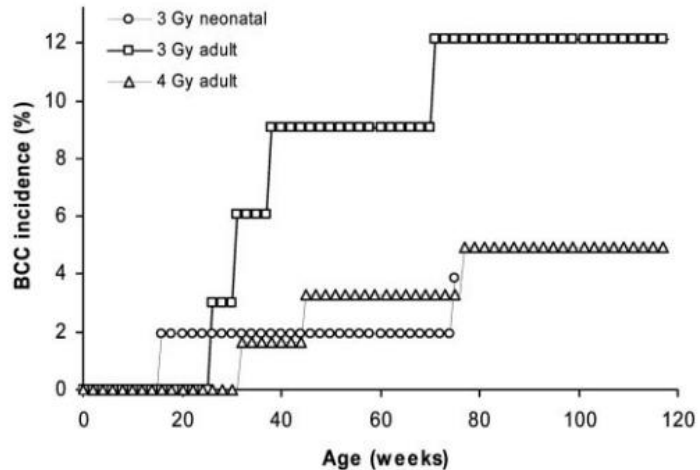
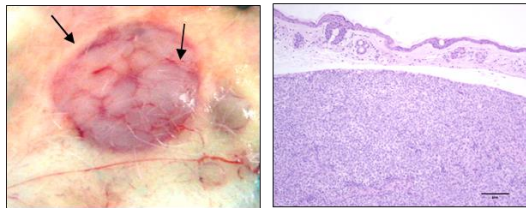


Anche dopo irraggiamento con 0.5 Gy, topi *Ptch1*^{+/-} mostrano un aumento significativo dell'induzione di MB ($P = 0.018$)



La possibilità di indurre MB dopo irraggiamento è limitata all'età neonatale

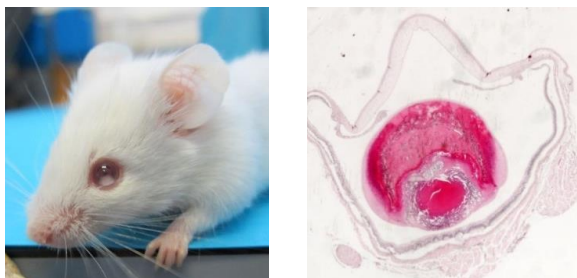
Topi *Ptch1*^{+/-}: INDUZIONE DI BCC DA RADIAZIONI



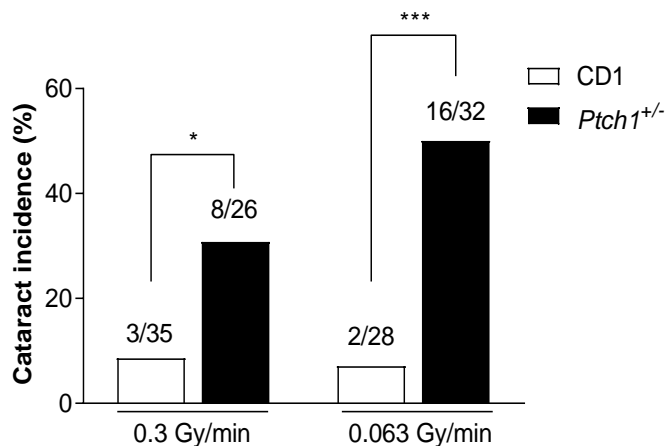
Anti-CK14-staining of skin lesions

Topi *Ptch1*^{+/-}: induzione di cataratta (Raggi- γ)

Role of genetic background in controlling the induction of lens opacity in *Ptch1*^{+/-} and WT mice



2 Gy



Incidence of macroscopic cataract in 2 Gy irradiated *Ptch1*^{+/-}/CD1 and CD1 WT mice

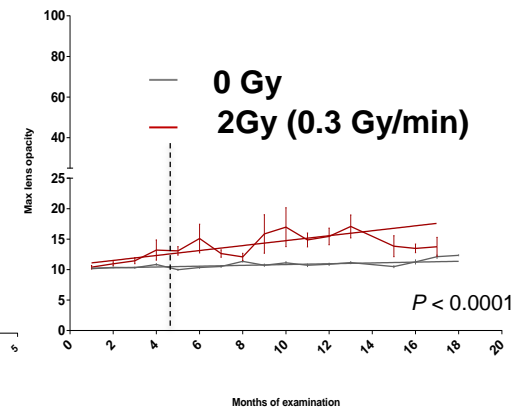
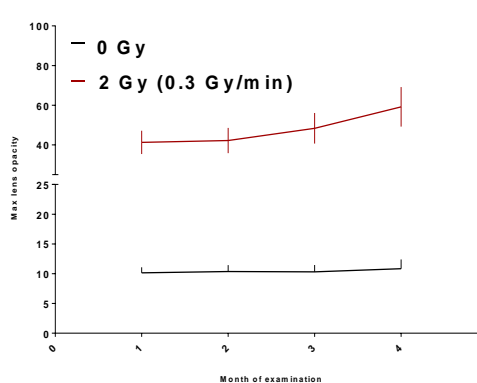
Age-dependency for radiation-induced cataract in *Ptch1*^{+/-}/CD1 mice



Neonatal irradiation (P2)



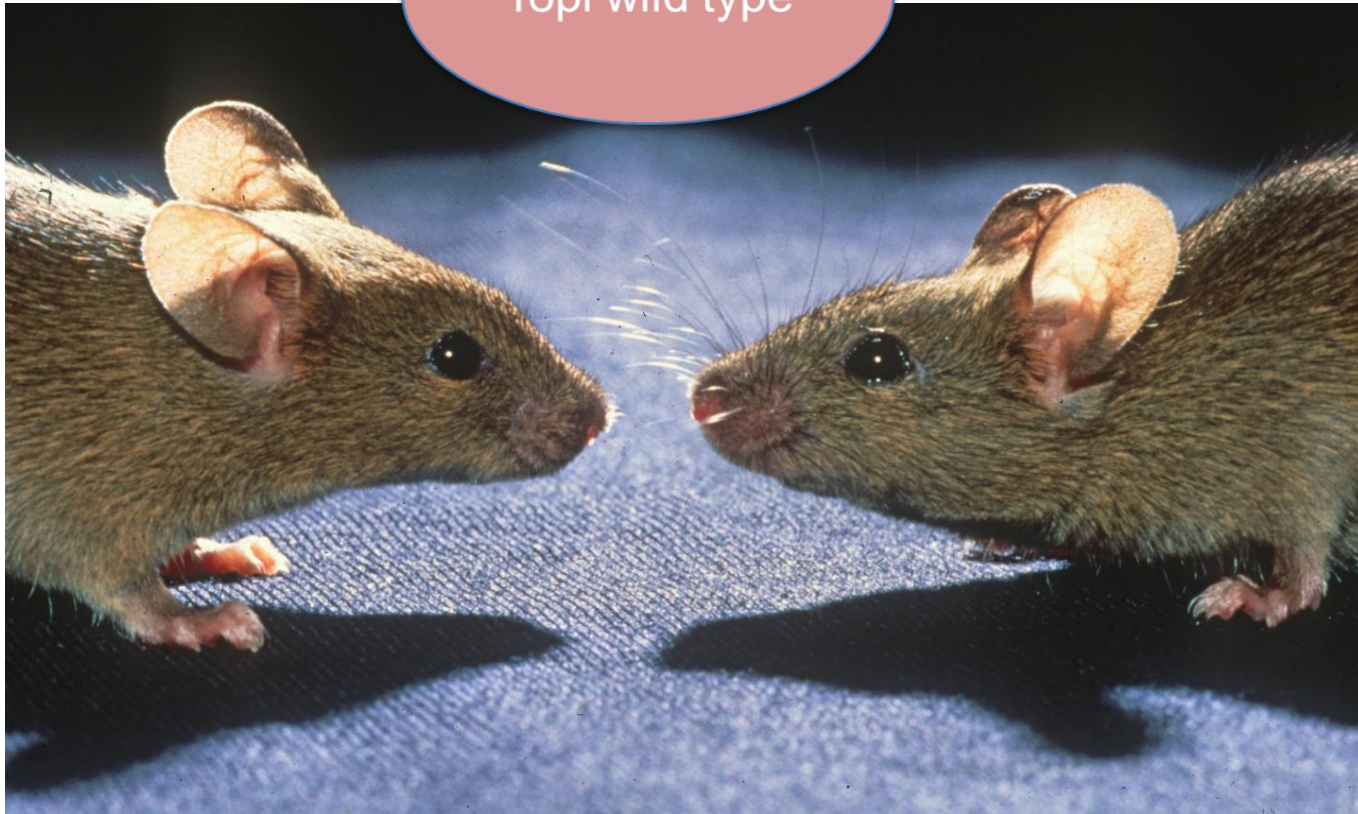
Adult irradiation (10W)



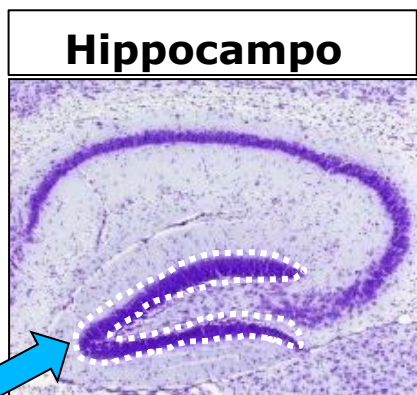
Strong decrease in sensitivity to radiation-induced lens opacity with increasing of mouse age at irradiation

Effetti indotti dalle radiazioni ionizzanti in vari tessuti di topi WT

Topi wild type

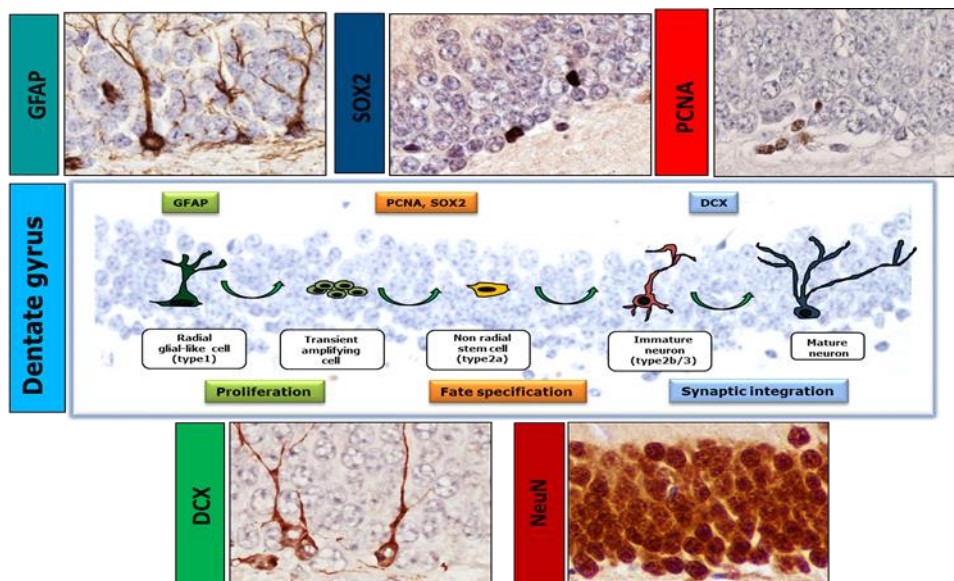


Neurogenesi dell'ippocampo

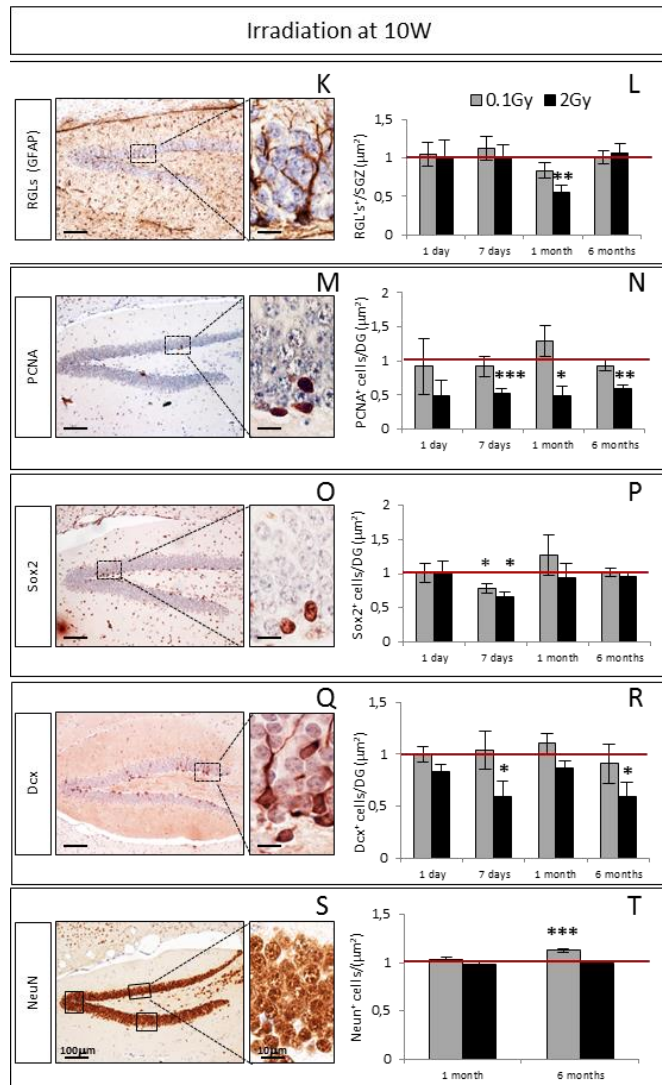


Il giro dentato (DG) dell'ippocampo è una delle strutture del sistema nervoso centrale dove la neurogenesi è osservata per tutta la vita e la maggioranza dei neuroni è generata postnatalmente.

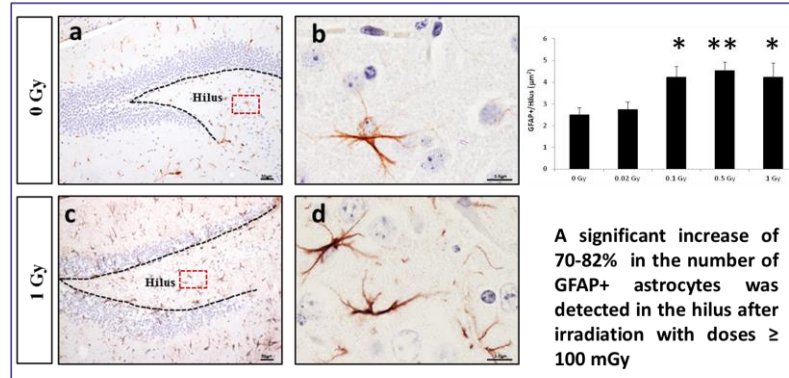
L'esposizione alla radiazioni ionizzanti è nota rallentare la neurogenesi dell'ippocampo.



Effetti delle radiazioni sulla neurogenesi dell'ippocampo di topi wt



Microenvironment is another critical player in hippocampal neurogenesis



Chronic inflammation may alter hippocampal neurogenesis causing defects in cognitive function

www.impactjournals.com/oncotarget/

Oncotarget, Vol. 7, No. 19

Age-related effects of X-ray irradiation on mouse hippocampus

Arianna Casciati¹, Katalin Dobos², Francesca Antonelli¹, Anett Benedek², Stefan J. Kempf^{3,8}, Montserrat Bellés³, Andrea Balogh², Mirella Tanori¹, Luis Heredia², Michael J. Atkinson^{4,5}, Christine von Toerne⁶, Omid Azimzadeh⁴, Anna Saran¹, Geza Sáfrány², Mohammed A. Benotmane⁷, M. Victoria Linares-Vidal³, Soile Tapio⁴, Katalin Lumniczky², Simonetta Pazzaglia¹

Kempf et al. *Molecular Neurodegeneration* 2014, 9:57
<http://www.molecularneurodegeneration.com/content/9/1/57>



RESEARCH ARTICLE

Open Access

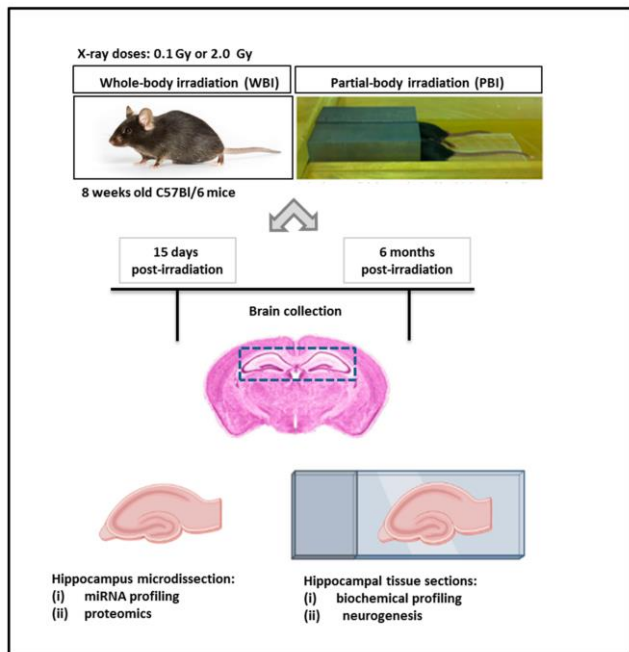
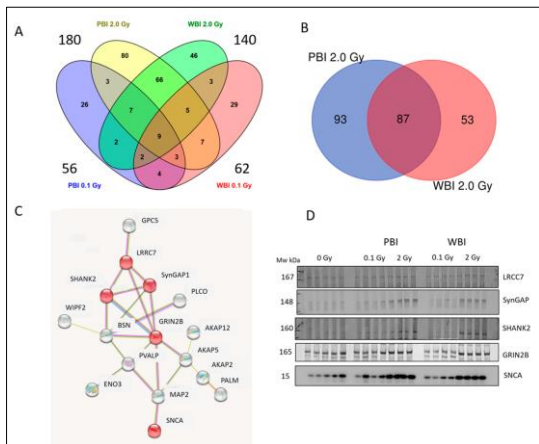
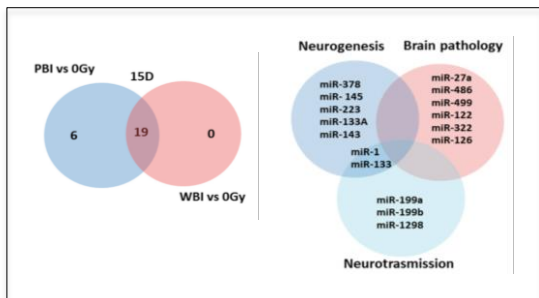
The cognitive defects of neonatally irradiated mice are accompanied by changed synaptic plasticity, adult neurogenesis and neuroinflammation

Stefan J Kempf¹, Arianna Casciati^{2†}, Sonja Buratovic^{3†}, Dirk Janik⁴, Christine von Toerne⁵, Marius Ueffing⁵, Frauke Neff⁶, Simone Moertl¹, Bo Stenerlöw⁶, Anna Saran⁷, Michael J Atkinson^{1,2}, Per Eriksson³, Simonetta Pazzaglia³ and Soile Tapio¹*

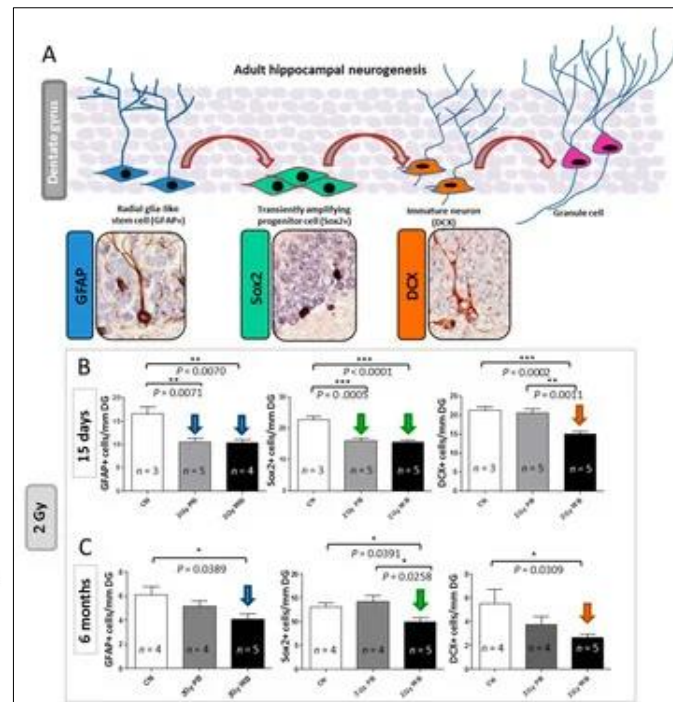
Article
Long-Term Effects of Ionizing Radiation on the Hippocampus: Linking Effects of the Sonic Hedgehog Pathway Activation with Radiation Response
 Francesca Antonelli^{1*}, Arianna Casciati¹, Montserrat Bellés², Noemi Serra², Maria Victoria Linares-Vidal², Carmela Marino¹, Mariateresa Mancuso¹ and Simonetta Pazzaglia^{1*}

EFFETTO BYSTANDER INDOTTO DALLE RADIAZIONI NELL'IPPOCAMPO

Analisi «omiche»



Istologia

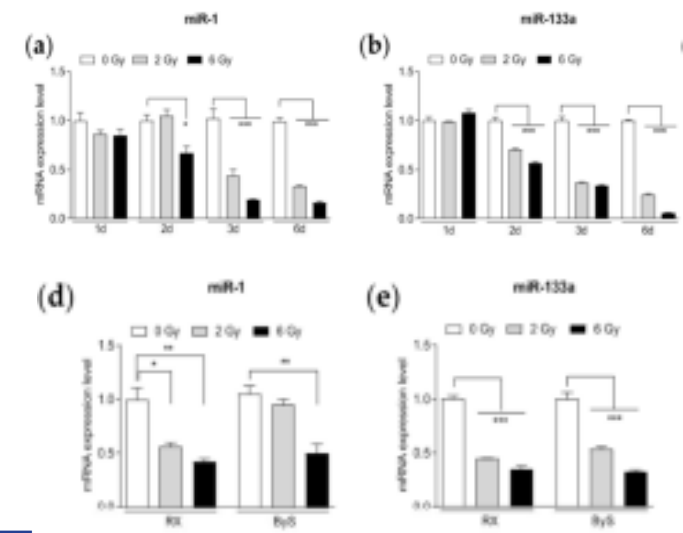
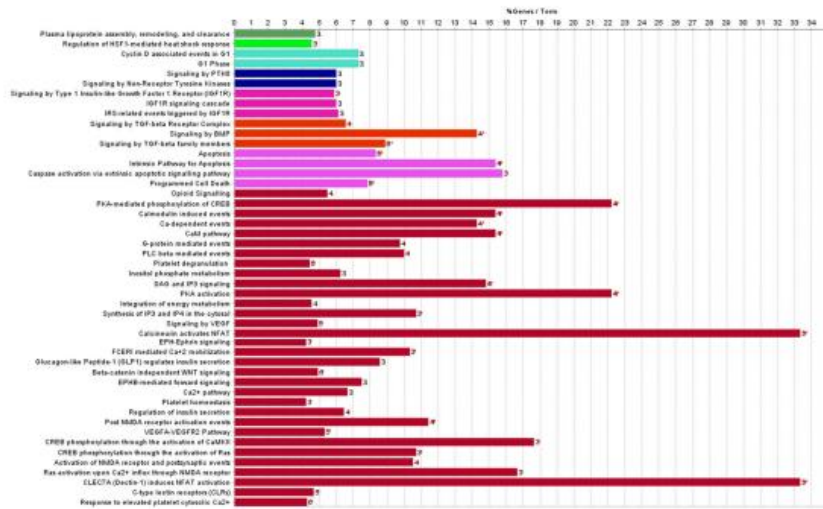
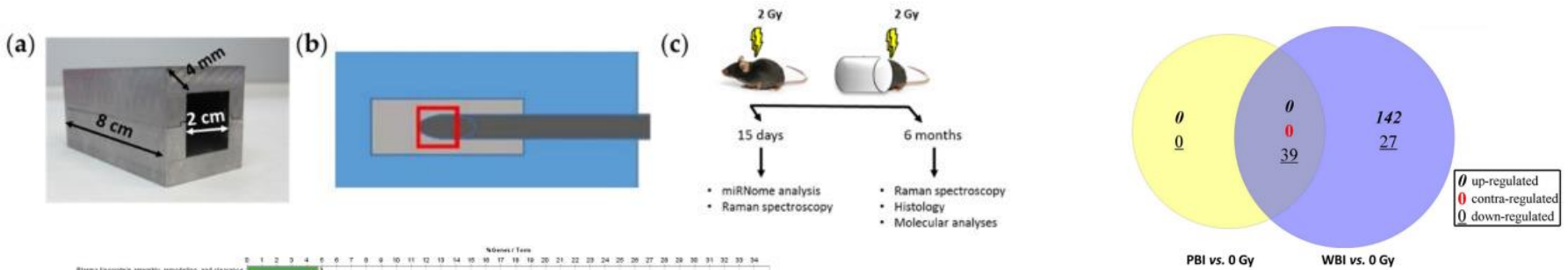


Article

Out-of-Field Hippocampus from Partial-Body Irradiated Mice Displays Changes in Multi-Omics Profile and Defects in Neurogenesis

Simonetta Pazzaglia^{1,*}, Barbara Tanno¹, Francesca Antonelli¹, Paola Giardullo¹, Gabriele Babini^{2,3,†}, Prabal Subedi^{4,5}, Omid Azimzadeh^{4,5}, Zohaib N. Khan⁴, Kateryna Oleksenko⁴, Fabian Metzger^{6,†}, Christine von Toerne⁶, Damien Traynor⁷, Dinesh Medipally⁷, Aidan D. Meade⁷, Munira Kadhim⁸, Fiona M. Lyng⁷, Soile Tapio⁴, Anna Saran¹ and Mariateresa Mancuso^{1,†}

I MiRNA MEDIANO L'EFFETTO BYSTANDER INDOTTO DALLE RADIAZIONI NEL CUORE



✓ Mir-1 and miR-133a, membri della famiglia dei myomiR, erano altamente deregolati dopo analisi NGS eseguita a 15 days postirradiation nei cuori WBI e PBI



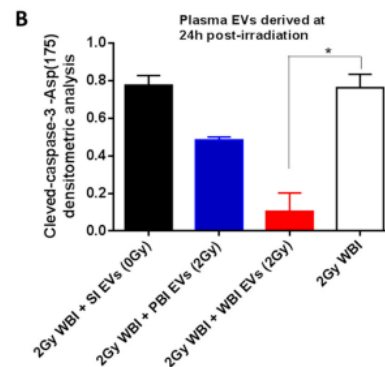
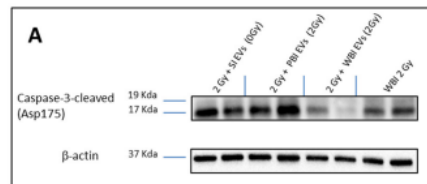
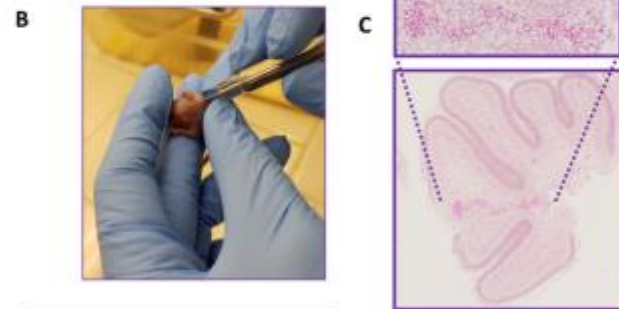
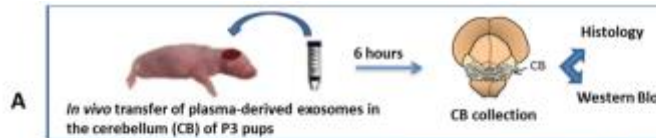
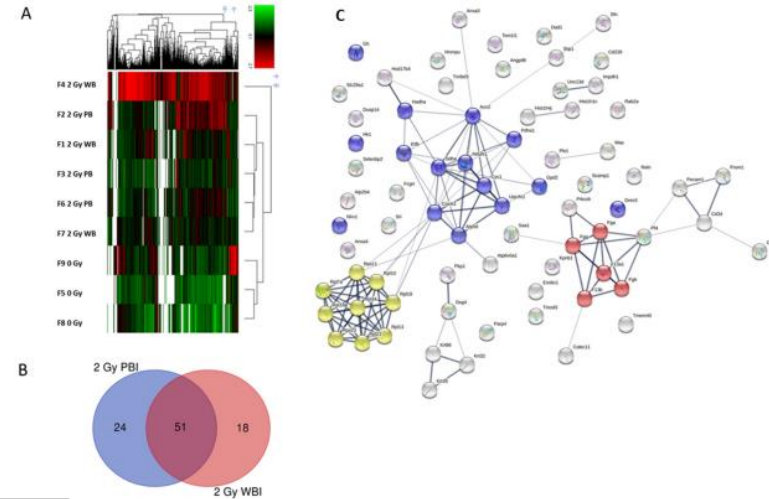
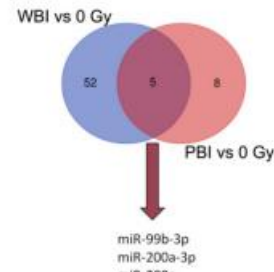
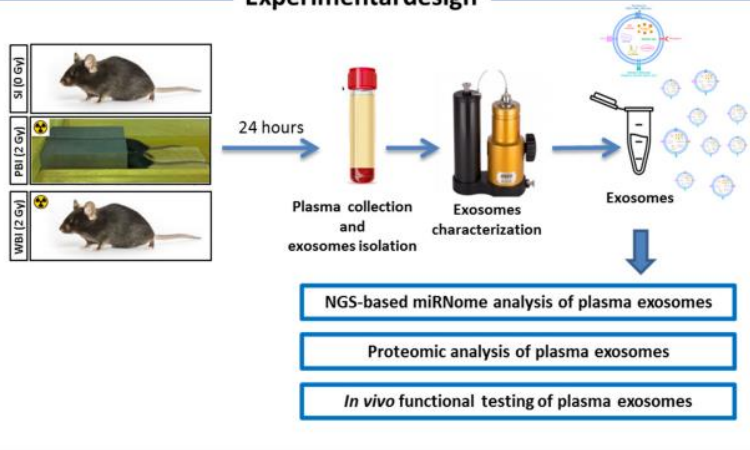
Article MiRNA-Mediated Fibrosis in the Out-of-Target Heart following Partial-Body Irradiation

Barbara Tanno ^{1,*}, Flavia Novelli ¹, Simona Leonardi ¹, Caterina Merla ¹, Gabriele Babini ^{2,†}, Paola Giardullo ¹, Munira Kadhim ³, Damien Traynor ⁴, Dinesh K. R. Medipally ¹, Aidan D. Meade ⁴, Fiona M. Lyng ⁴, Soile Tapio ⁵, Luca Marchetti ^{1,6}, Anna Saran ^{1,7}, Simonetta Pazzaglia ¹ and Mariateresa Mancuso ^{1,*}



Micro-RNA and Proteomic Profiles of Plasma-Derived Exosomes from Irradiated Mice Reveal Molecular Changes Preventing Apoptosis in Neonatal Cerebellum

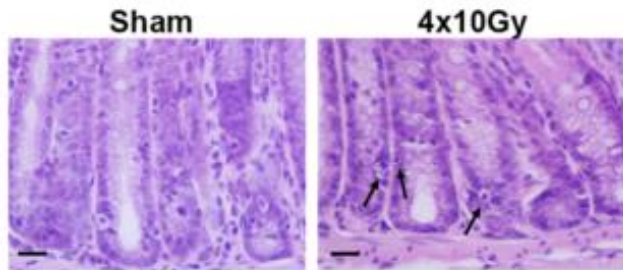
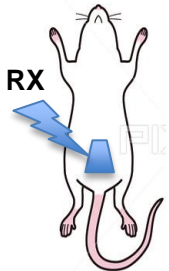
Experimental design



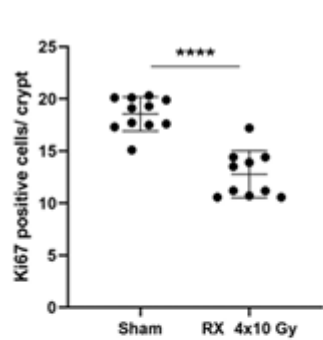
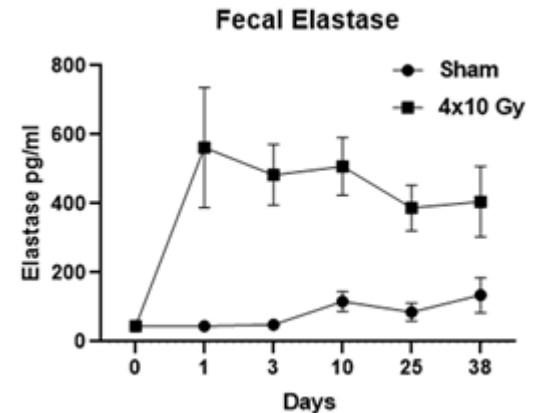
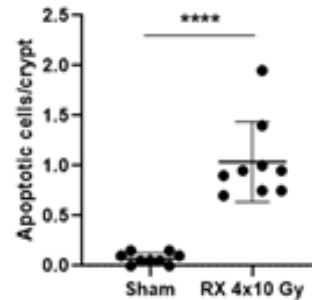
Micro-RNA and Proteomic Profiles of Plasma-Derived Exosomes from Irradiated Mice Reveal Molecular Changes Preventing Apoptosis in Neonatal Cerebellum

Simonetta Pazzaglia ^{1,*}, Barbara Tanno ¹, Ilaria De Stefano ¹, Paola Giardullo ¹, Simona Leonardi ¹, Caterina Merla ¹, Gabriele Babini ^{2,†}, Seda Tuncay Cagatay ³, Ammar Mayah ³, Munira Kadhim ³, Fiona M. Lyng ⁴, Christine von Toerne ⁵, Zohaib N. Khan ⁵, Prabal Subedi ⁵, Soile Tapio ⁵, Anna Saran ¹ and Mariateresa Mancuso ^{1,*}

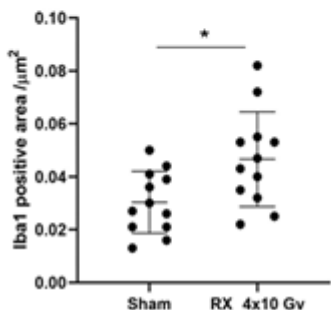
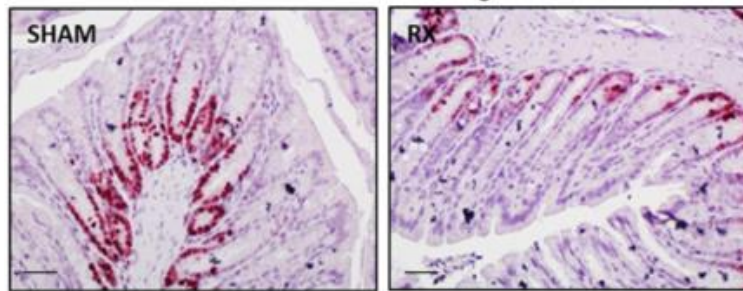
Radioenterite da radiazioni



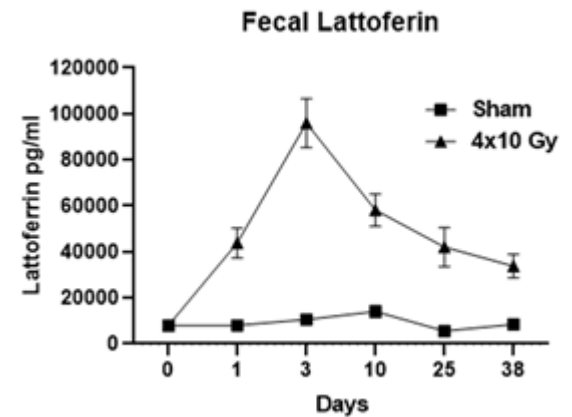
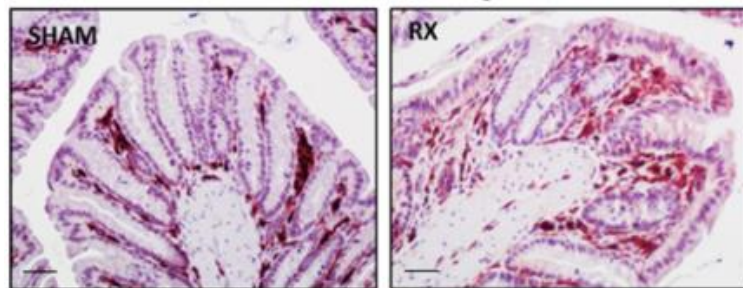
3 h post-irradiation



Ki67 immunostaining



Iba1 immunostaining



Quantitative analysis of intestinal inflammatory fecal markers Elastase and Lactoferrin

38 days post-irradiation

CONCLUSIONI



- I nostri modelli murini, estremamente ben caratterizzati per la risposta alle radiazioni in molti tessuti rilevanti per la radiobiologia spaziale, permettono di valutare l'efficacia di contromisure *in vivo*, come ad esempio valutare se il rallentamento dello stato metabolico di un organismo può mitigare gli effetti dannosi delle radiazioni.

- L'identificazione dei meccanismi patogenetici delle radiazioni è cruciale per lo sviluppo di metodi per mitigare il rischio da radiazioni.

LAB TECS

M Mancuso
A Casciati
E Colantoni
I De Stefano
S Leonardi
E Pasquali
F Palone
B Tanno
M Tanori
R Vitali



Simonetta Pazzaglia
simonetta.pazzaglia@enea.it



Francesca Antonelli



Grazie per l'attenzione



Emiliano Fratini



HORIZON EUROPE

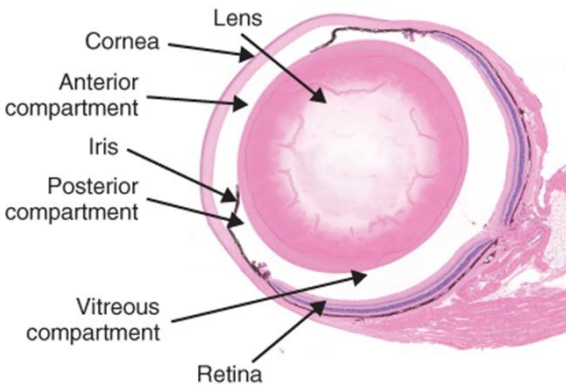


Daniela Giovannini

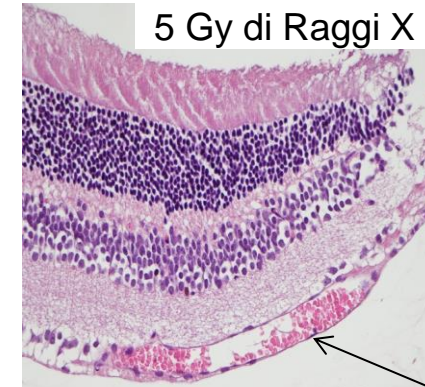
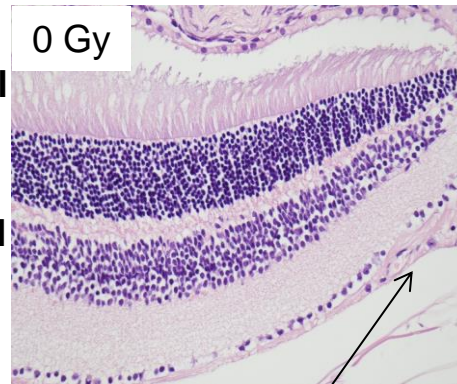


Effetti dell'irraggiamento sulla retina wi topi WT

Topi CD1 WT a 4 settimane post RX



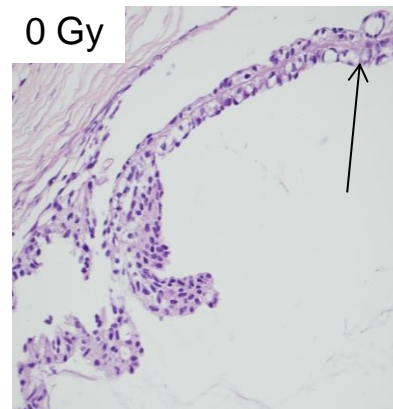
gcl
inl
onl



Retiniti da radiazioni

- ✓ Aumento volume vasi superficiali periferici
- ✓ Diminuzione del numero di cellule dei gangli (RCG) nella retina sensoriale

iride



Glucoma neovascolare

- ✓ Aumento numero e volume dei vasi nell'angolo anteriore dell'occhio-iride