Study of enhanced radio-resistance induced by hibernation

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Assemblea di Sezione - 04/02/2021

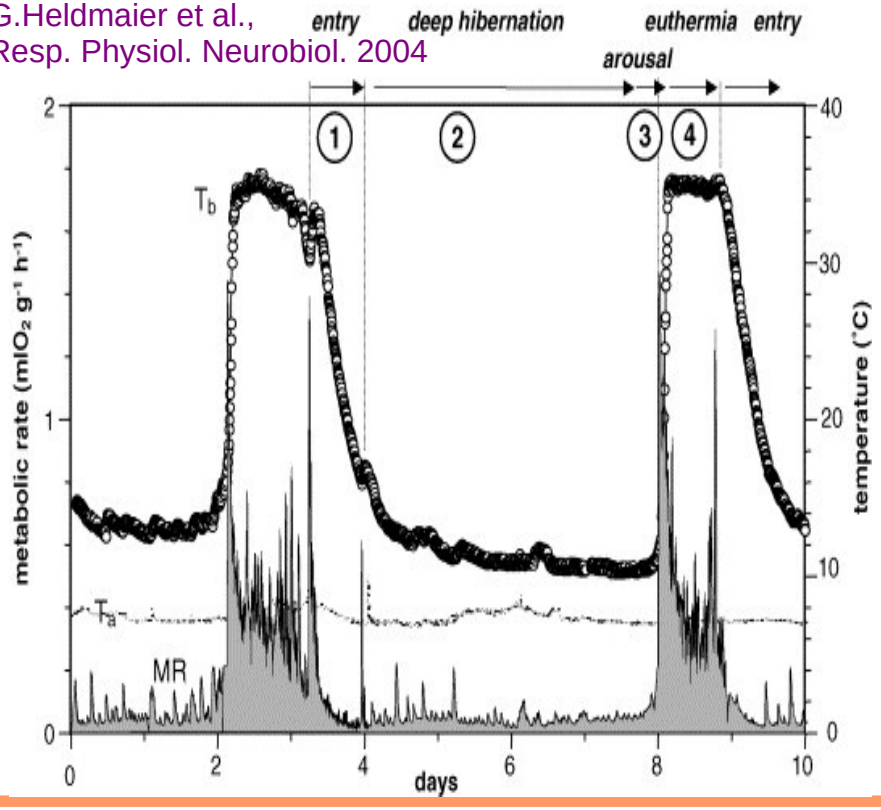
Hibernation

- Reduction of the metabolic rate
- Reduced oxygen consumption
- Decreasd heart rate
- Reduction of body temperature
- **Increased radioresistance**

Possible mechanisms:

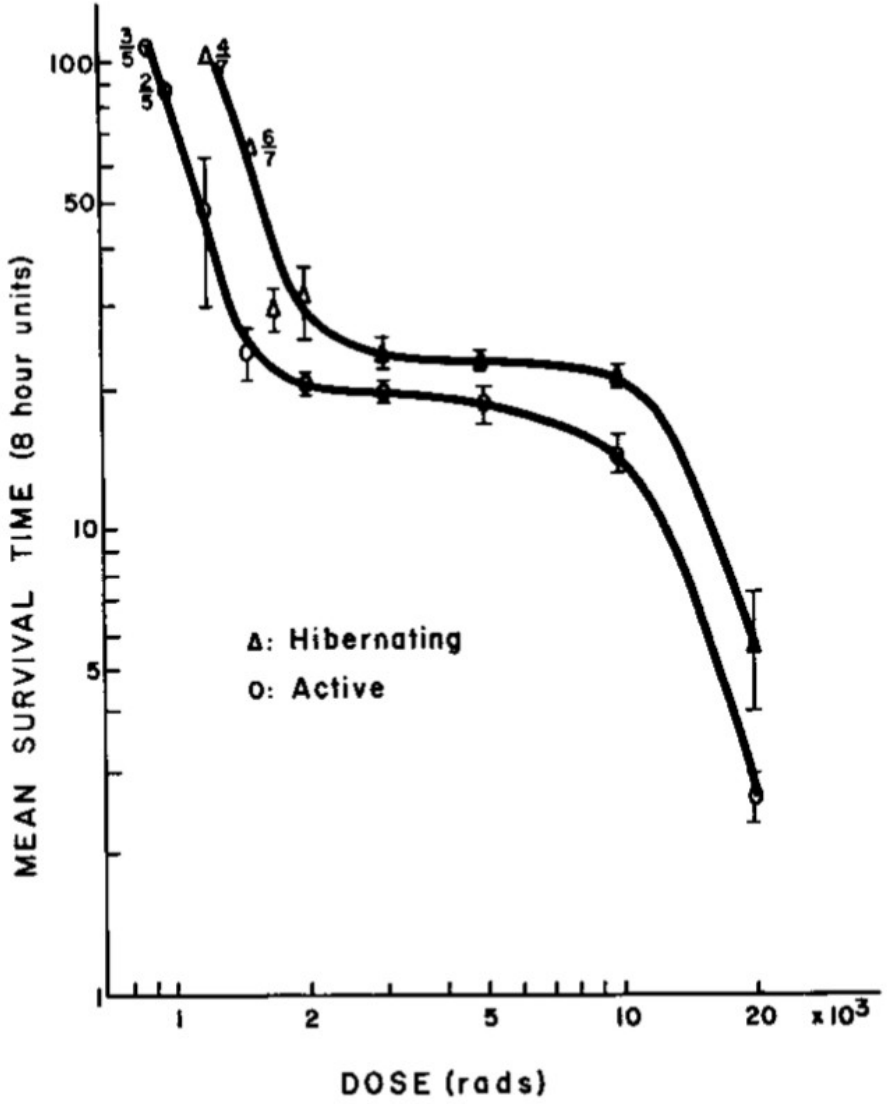
- Reduced mitotic activity during hibernation
- Stage of cell cycle when exposure occurs
  - Cells accumulate in G_1 during hibernation
- Tissue hypoxia
- Molecular mechanisms of cell self-protection
- Anti-oxidants
- Better repair mechanisms

G.Heldmaier et al.,
Resp. Physiol. Neurobiol. 2004

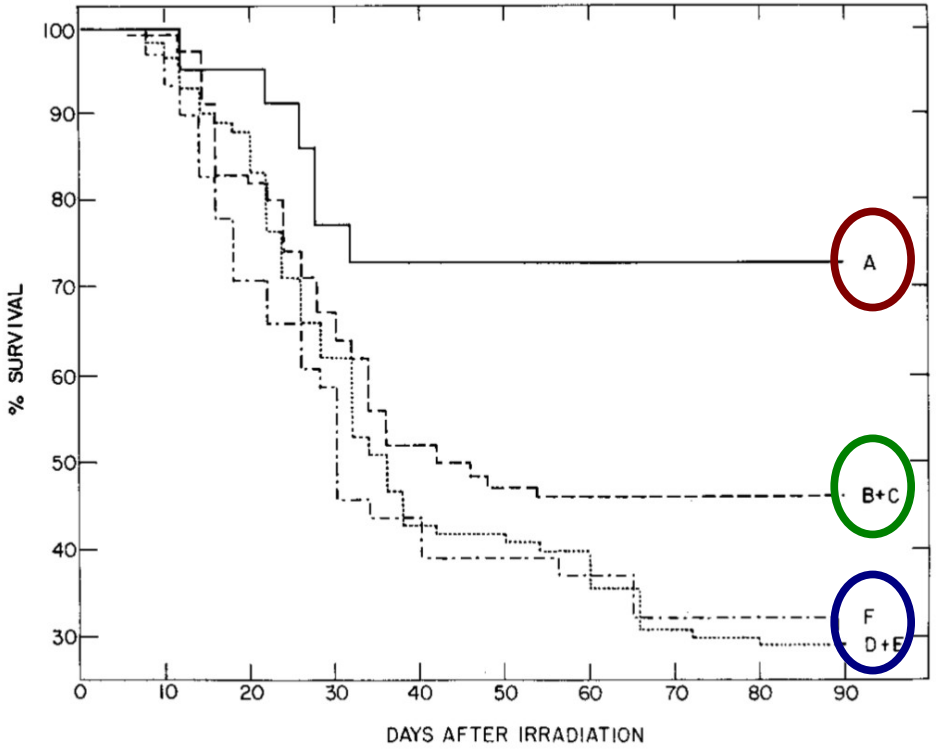


Hibernation and radioresistance

Barr and Musacchia
Radiation Research 33, 348-356 (1968)



Jaroslow et al
Radiation Research 38, 379-388 (1969)



2 dose fractions (668 rad each, 6 hrs apart):
A) kept in cold for 20 hrs after both irradiations
B+C) returned to warm room right after 2nd irradiation
D+E) returned to warm room after 1st irradiation
F) outside hibernation for both irradiation

Overview of results in the literature

Life Sciences in Space Research 11 (2016) 1–9

Contents lists available at ScienceDirect

Life Sciences in Space Research

journal homepage: www.elsevier.com/locate/lssr

Review Article

Hibernation for space travel: Impact on radioprotection

Matteo Cerri[a,b], Walter Tinganelli[c], Matteo Negrini[b], Alexander Helm[c], Emanuele Scifoni[c], Francesco Tommasino[c,d], Maximiliano Sioli[b,e], Antonio Zoccoli[b,e], Marco Durante[c,*]

INFN-Bologna participants in the project

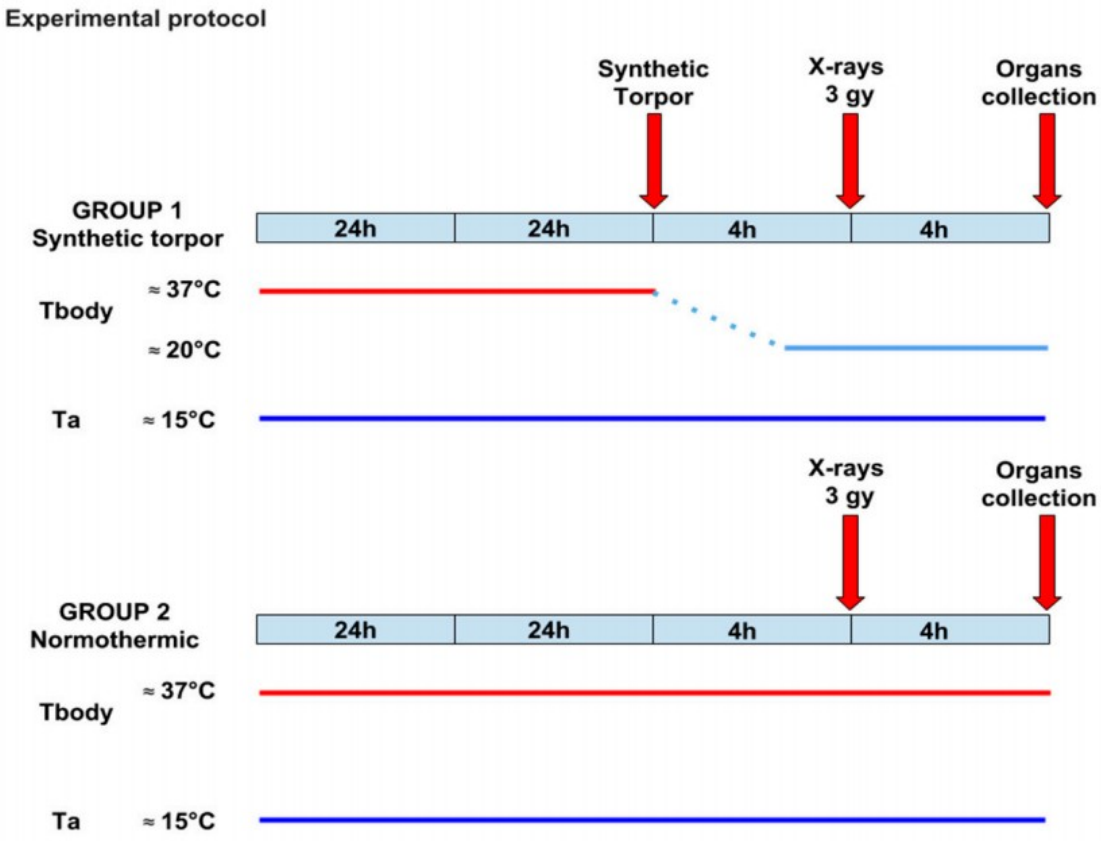
The HIBRAD experiment

Goal: Perform a proof of concept experiment to investigate the molecular mechanism of the hibernation induced radioresistance

Gamma irradiation
Dose: **3 Gy total body**
Animal: **rat**

4 study groups / 8 animals per group

Group	Hibernation	Irradiation
1	YES	YES
2	NO	YES
3	YES	NO
4	NO	NO



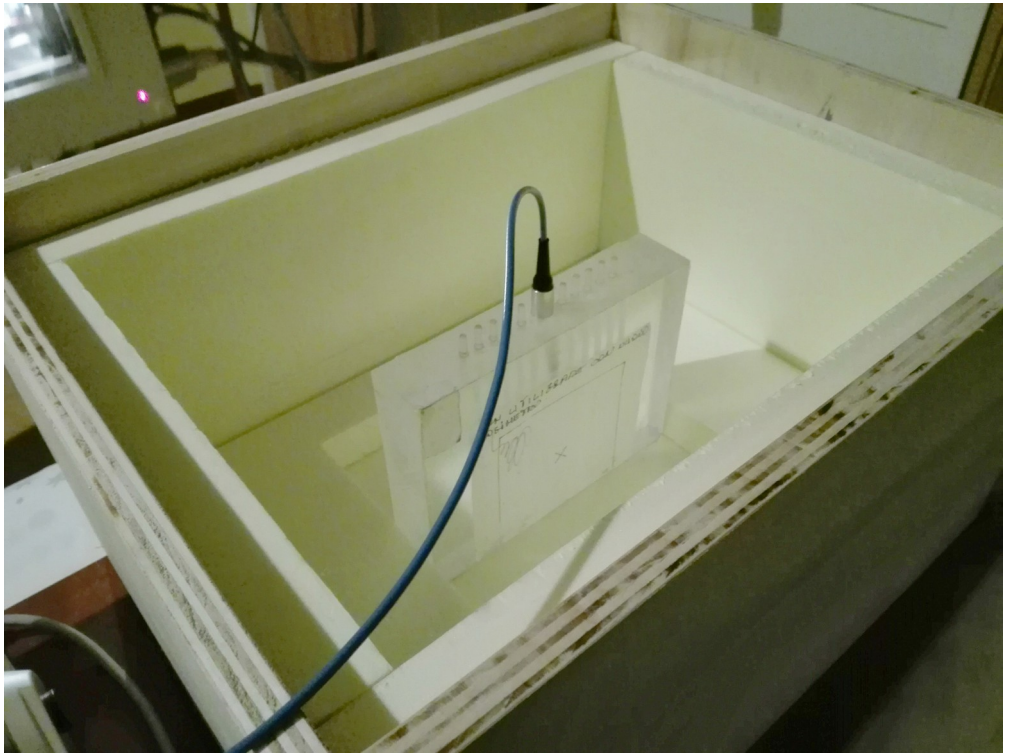
Tissues analysis (4 animals per group):

- Gene expression (array)
- Histology

Calibration of irradiaton setup

Calibration of irradiation setup with ionization chamber:

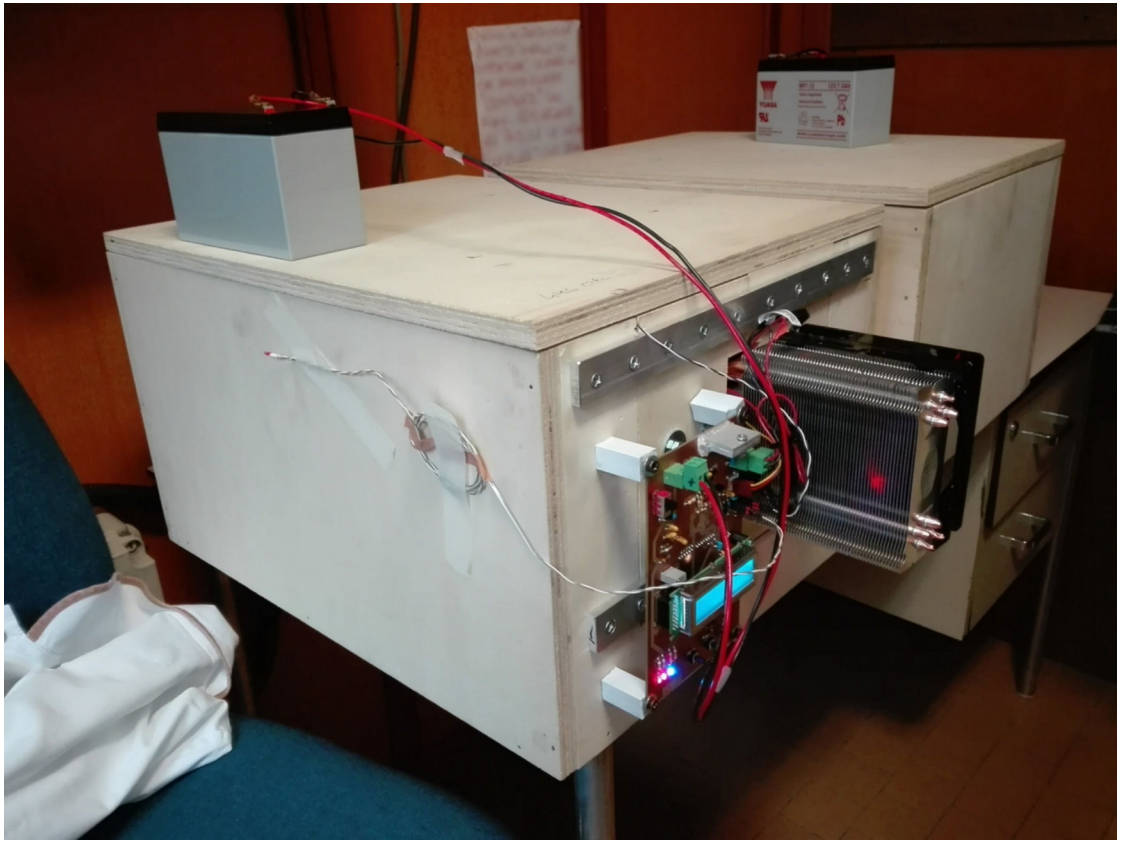
- Tube potential: 220 kV
- Irradiation field dimension: 20 cm x 20 cm
- Dose rate: 60 cGy/min → 5 min irradiation time

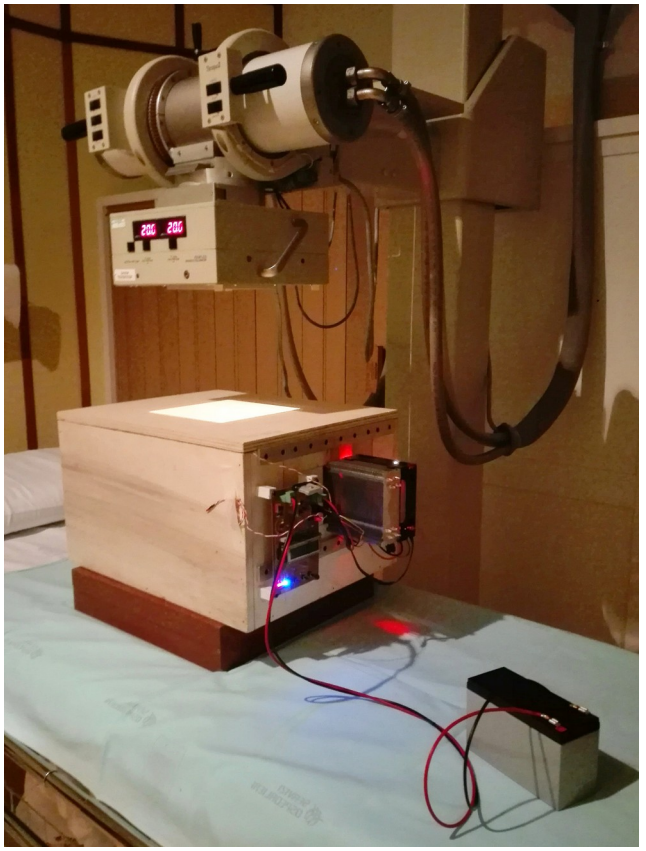


Thermostatic cage

- Transportable thermostatic cage (transportation to irradiation site)
- Homogeneous walls for irradiation homogeneity

INFN+UNIBO Patent requested





HIBRAD: first results

Int. J. Mol. Sci. **2019**, *20*, 352; doi:10.3390/ijms20020352

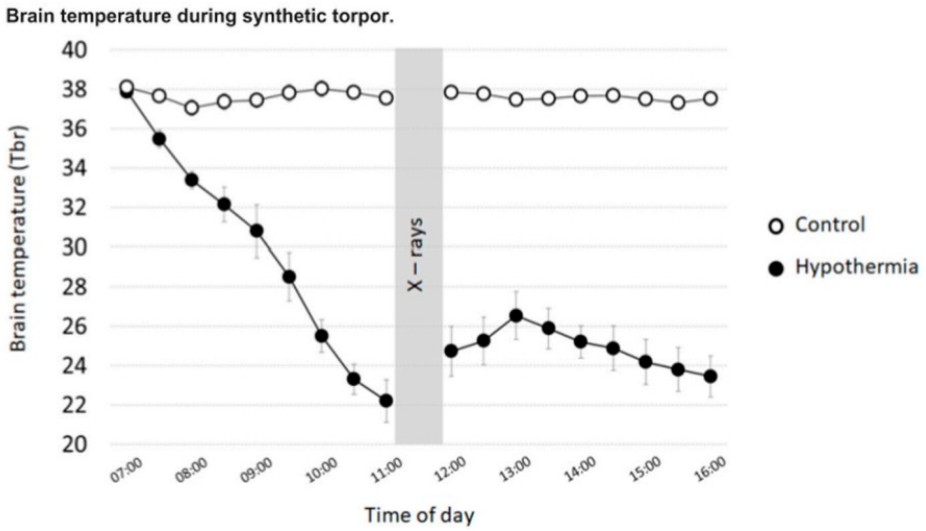
International Journal of *Molecular Sciences*

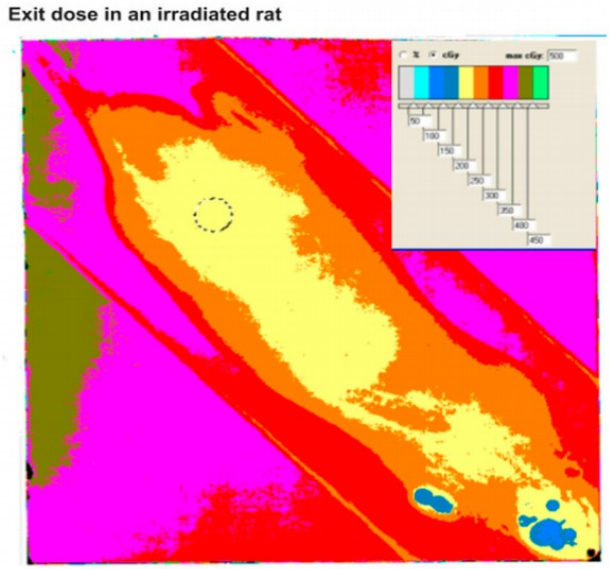
MDPI

Article

Hibernation and Radioprotection: Gene Expression in the Liver and Testicle of Rats Irradiated under Synthetic Torpor

Walter Tinganelli [1,2,†], Timna Hitrec [3,†], Fabrizio Romani [4], Palma Simoniello [5], Fabio Squarcio [3], Agnese Stanzani [6], Emiliana Piscitiello [3], Valentina Marchesano [2], Marco Luppi [3], Maximiliano Sioli [7,8], Alexander Helm [1], Gaetano Compagnone [4], Alessio G. Morganti [9], Roberto Amici [3], Matteo Negrini [7], Antonio Zoccoli [7,8], Marco Durante [1,10,*] and Matteo Cerri [3,7,*]

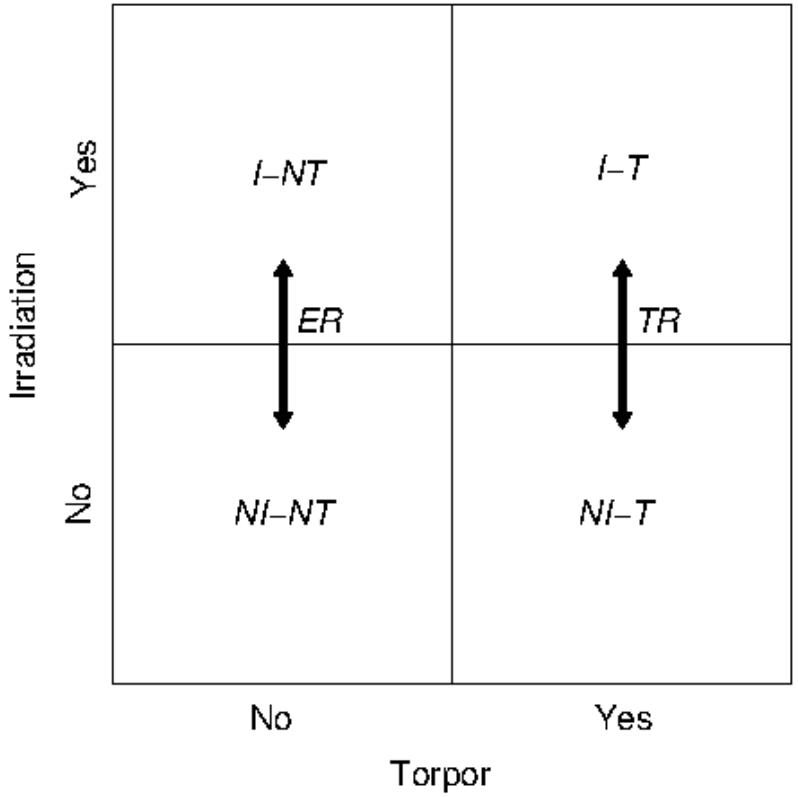




HIBRAD: Gene expression

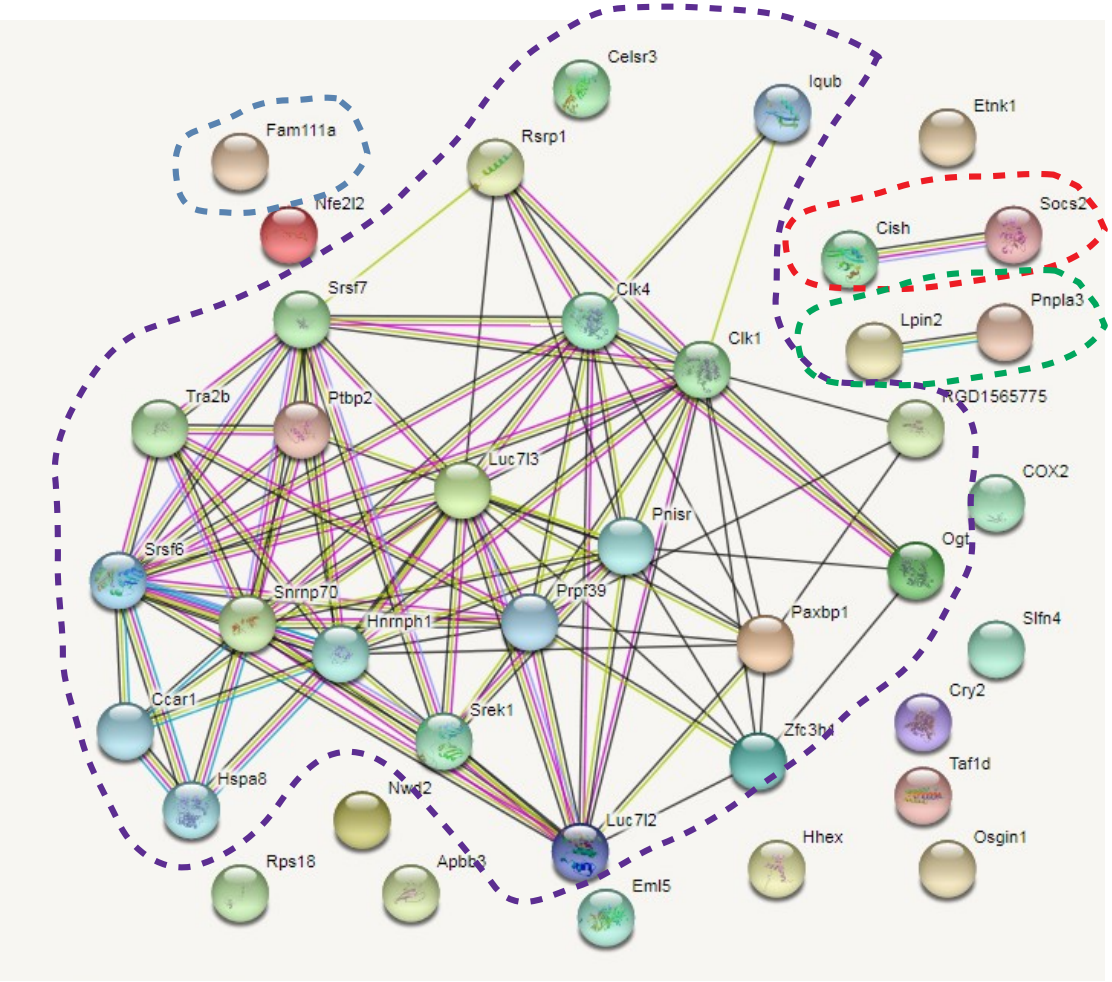
The identification of the gene response to radiation during torpor can be obtained by comparison with control groups, irradiated at normal temperature (warm)

Even without irradiation, the gene expression during torpor is different from the one at normal temperature → a meaningful comparison requires 4 study groups, for the identification of the gene response to radiation in both metabolic states



Comparison between:
ER: Gene response to radiation in warm-irradiated vs warm
TR: Gene response to radiation in cold-irradiated vs cold

HIBRAD: preliminary results



- Preliminary results presented at SIF2020 (selected among best communications)
- Publication in preparation

Visualization of genes that are up-regulated only when irradiation occurs during torpor

- Circles: genes that are up-regulated in TR but not in ER.
- Lines: known/predicted interactions.

HIBRAD is looking at early cell response (few hrs after irradiation):

- Genome activation → activation of mechanisms of DNA expression
- Suppression of inflammation → damage reduction
- Activation of fat acid metabolism → activation of energetic supplies
- FAM111A: Stabilization of replication process in case of DNA damage
  Nature Communications 11, 1318 (2020)

Effect of hypometabolic state after irradiation

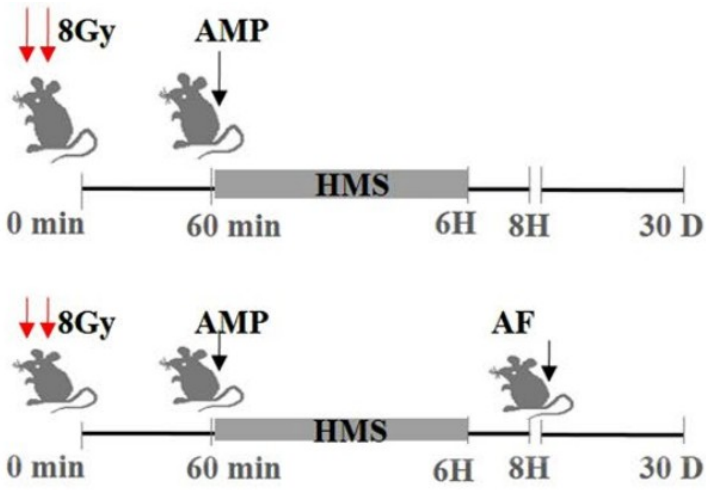
SCIENTIFIC REPORTS

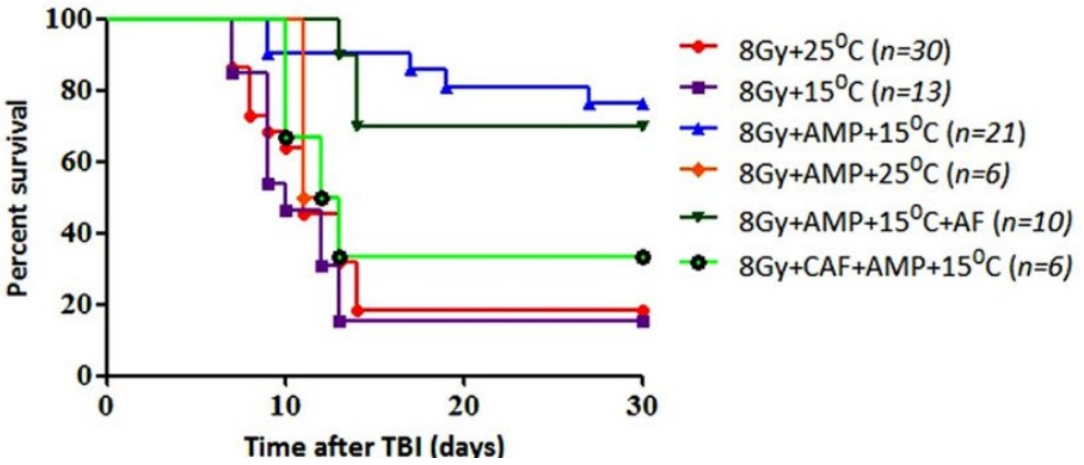
OPEN

Received: 27 June 2017
Accepted: 19 October 2017
Published online: 02 November 2017

Pharmacologically induced reversible hypometabolic state mitigates radiation induced lethality in mice

Subhajit Ghosh[1,2], Namita Indracanti[1], Jayadev Joshi[1,2], Jharna Ray[2] & Prem Kumar Indraganti[1]





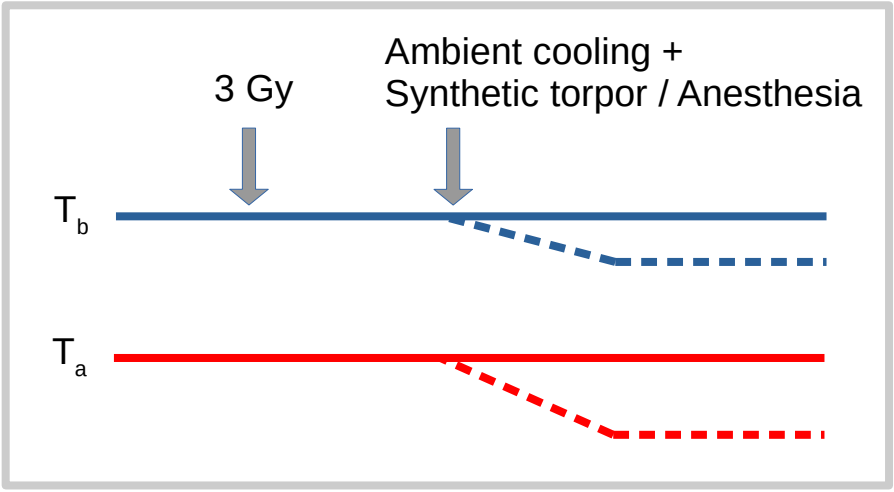
Radioprotective effect of hypometabolic state induced after irradiation (up to 3 hrs)

The HYPORAD experiment

Investigating the possible radioprotective mechanisms of synthetic torpor and hypothermia induced after irradiation.

Same animal model/dose as in HIBRAD to allow comparisons

- 3 Gy total body irradiation
- Synthetic torpor / hypothermia 1 hr after irradiation
- 4 irradiated + 4 non-irradiated study groups. 4 animals per group.
  - Synthetic torpor: T_{body}=35°C, $T_{ambient}$=30°C
  - Synthetic torpor: T_{body}=25°C, $T_{ambient}$=15°C
  - Hypothermia: T_{body}=35°C, $T_{ambient}$=30°C
  - Hypothermia: T_{body}=25°C, $T_{ambient}$=15°C
- Gene expression analysis: liver and kidneys



- Experiment approved by INFN CSN5 for 2020.
- Experimental phase concluded in December 2020 (some delays caused by COVID19).
- Tissue analysis ongoing.

Summary

- HIBRAD: proof of concept for the investigation of the mechanisms of the enhanced radio-resistance induced by hibernation.
  Proved feasibility for future experiments.
- HYPORAD: testing the presence of the such mechanisms if torpor or hypothermia is induced after irradiation.
  One step towards human applications.
- Main results:
  - first complete screening of irradiation-induced gene expression in animal in synthetic torpor, paving the way to the identification of the molecular pathway responsible for the torpor-induced increase in radioprotection
  - preliminary indications of different repair mechanisms induced by hibernation, as response to high radiation
- Highly multidisciplinary, at the cutting-edge of radiobiology research
- Possible benefits to other fields:
  - Spare healthy tissues in radiotherapy
  - Reduce radiation risk in space exploration