6th European Congress of Aerospace Medicine

Cancer & Health Research in Space (CHRIS)
A Study on Glioblastoma in Microgravity

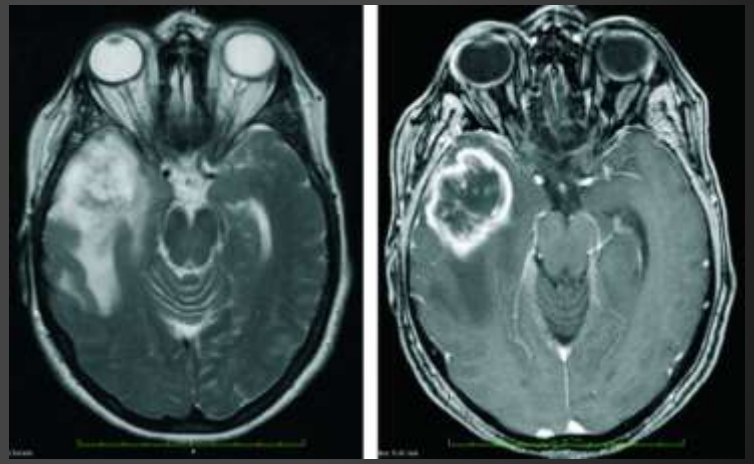
Lydia Johnson Kolaparambil Varghese
University of Perugia
European Society of Aerospace Medicine (ESAM)
Space Medicine Group, Cologne, Germany

What is Glioblastoma (GBM)?

GBM (grade IV, WHO 2016) is the most frequent primary malignant brain tumor in adults, representing about 60% of central nervous system (CNS) tumors.

GBM is characterized by:

- Uncontrolled proliferation
- Massive angiogenesis
- Cell infiltration
- High genomic instability
- Resistance to radio and chemotherapy
- High frequency of relapses



Schreiber S et al. *BMC Cancer* (2010)

Features of Glioblastoma

Macroscopically:

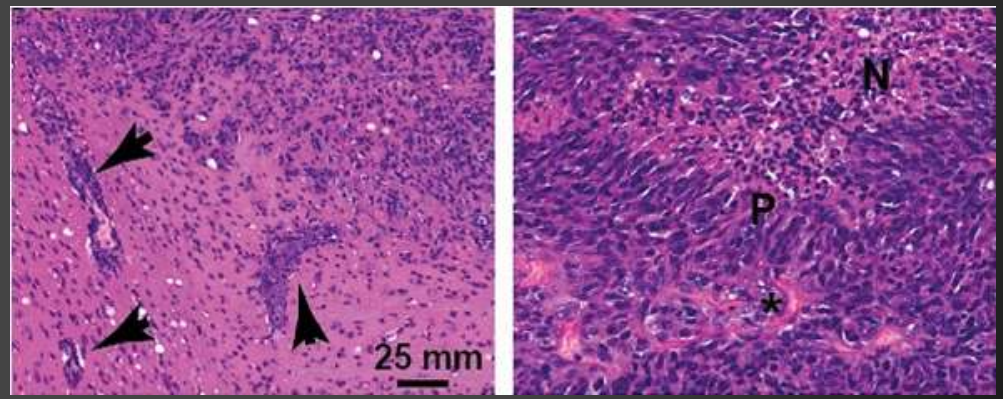
- Multiforme
- Regions of necrosis
- Haemorrhage

Microscopically:

- Regions of pseudopalisading necrosis
- Pleomorphic nuclei
- Cells and microvascular proliferation

Genetically:

- Deletions
- Amplifications
- Point mutations
- Copy number variations



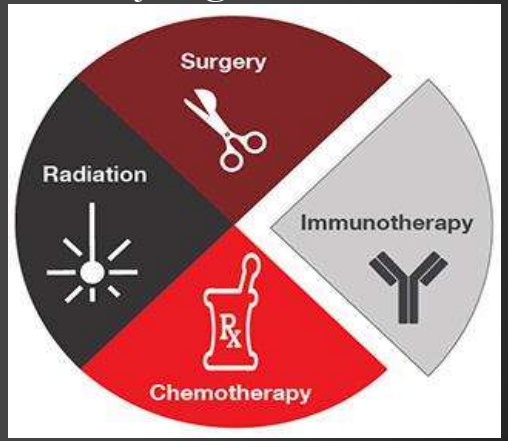
Prognosis

- Median survival: 14 months
- Median time to recurrence of the disease after standard therapy: 6.9 months
- Median survival <5% after five years from the diagnosis.

IN SUMMARY: NOT AT ALL GOOD FOR THE PATIENT

Current Treatments

- Surgical resection ↠ Radiation and adjuvant chemotherapy with **Temodal®**, an oral alkylating agent.
- **Bevacizumab (Avastin®):** a humanized monoclonal antibody against vascular endothelial growth factor.
- Immunotherapy
- Gene therapy

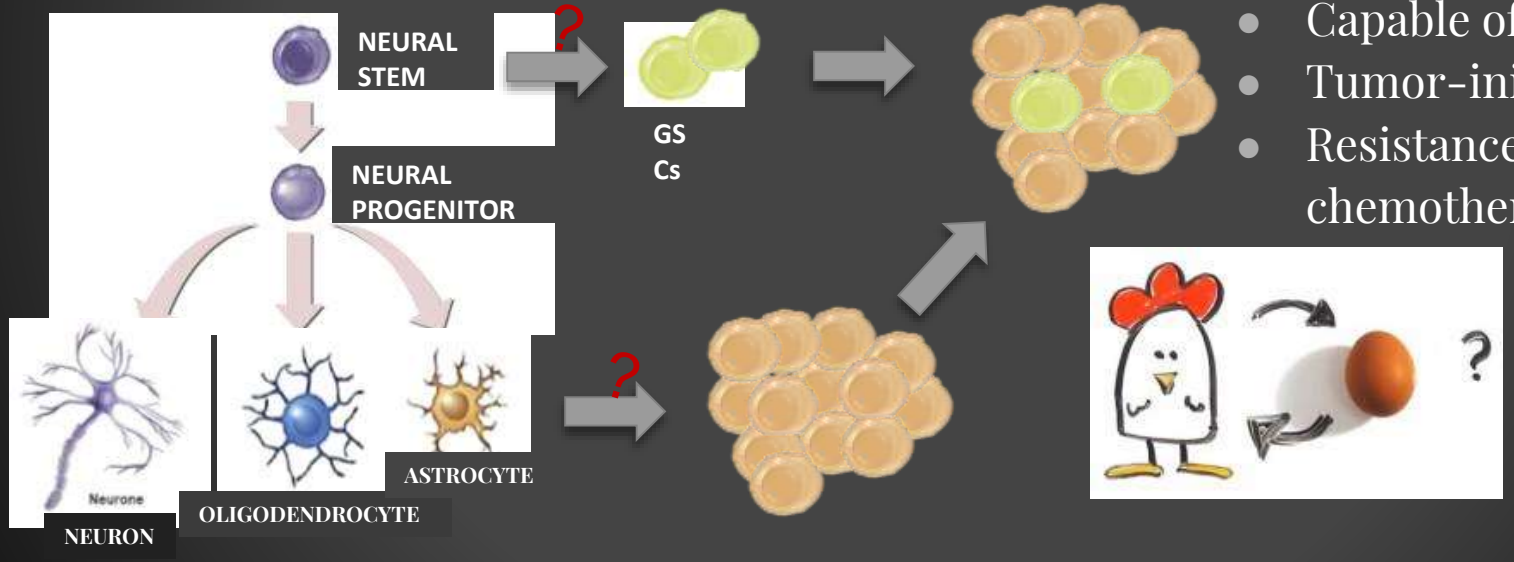


Despite current therapies, **GBM is still incurable**.

Glioblastoma Stem Cells (GSCs)

- A small percentage of tumor cells within a tumor mass
- Through their capacity for self-renewal, GSCs give rise to uncontrolled amplification of tumor cell populations with altered molecular and cellular phenotypes

- Multipotent cells
- Capable of self-renewal
- Tumor-initiating ability
- Resistance to radio- and chemotherapies



Why microgravity?

GLIOSAT: A PROJECT TO STUDY THE COMBINED EFFECT OF IONIZING RADIATION AND MICROGRAVITY ON GLIOBLASTOMA MULTIFORME CELLS

Chantal Cappelletti, Cgiamtsi Cappelletti, Angelo Notarangelo, Claudio Cappelletti, Filippo Graziani

ORIGINAL PAPER

Eur. J. Histochem. 46: 209-214, 2002
© Luigi Pozzio e figlio - Editori in Pavia

Microgravity-induced apoptosis in cultured glial cells

B.M. Uva[1], M.A. Masini[1], M. Sturla[1], F. Bruzzone[1], M. Giulinni[1], G. Tagliafierro[1], and F. Strollo[2]

[1]Dipartimento di Biologia Sperimentale, Ambientale ed Applicata, Università di Genova, V.le Benedetto XV n. 5, 16132 Genova, Italy and [2]Unità Endocrinologica, "INRCA" Università "La Sapienza" via Cassia, 00189, Roma, Italy

The influence of simulated microgravity on proliferation and apoptosis in U251 glioma cells

Jiao Zhao[1] · He Ma[2] · Leitao Wu[1] · Liang Cao[1] · Qianqian Yang[2] · Haijun Dong[1] · Zongren Wang[1] · Jing Ma[1] · Zhen Li[2]

In Vitro Cell.Dev.Biol.—Animal (2017) 53:744–751
DOI 10.1007/s11626-017-0178-6

Modeled microgravity suppressed invasion and migration of human glioblastoma U87 cells through downregulating store-operated calcium entry

Zi-xuan Shi [a, 1], Wei Rao [b, 1], Huan Wang [c], Nan-ding Wang [d], Jing-Wen Si [a], Jiao Zhao [a], Jun-chang Li [a, *], Zong-ren Wang [a, *]

Biochemical and Biophysical Research Communications 457 (2015) 378–384

EFFECTS OF SIMULATED MICROGRAVITY ON PROLIFERATION AND CHEMOSENSITIVITY IN MALIGNANT GLIOMA CELLS

Kaoru Kurisu, MD, PhD, Masaaki Takeda, MD, PhD, Takahito Okazaki, MD, PhD, Yumi Kawahara, PhD, and Lous Yuge, PhD; Graduate School of Biomedical and Health Sciences, Hiroshima University

Neuro-Oncology 16:iii23–iii41, 2014.
doi:10.1093/neuonc/nou208.50

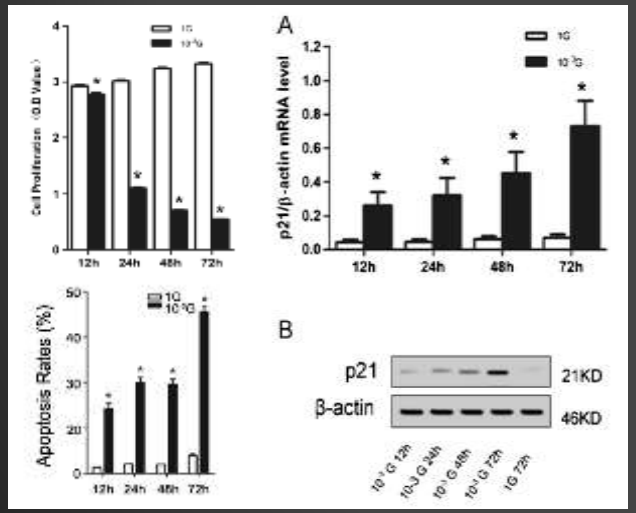
Proceedings of the International Astronautical Congress, IAC
Volume 1, 2012, Pages 482-488
63rd International Astronautical Congress 2012, IAC 2012; Naples; Italy; 1 October 2012 through 5 October 2012; Code 98825

Study of glioblastoma cancer cells behaviour inside space shuttle (Conference Paper)

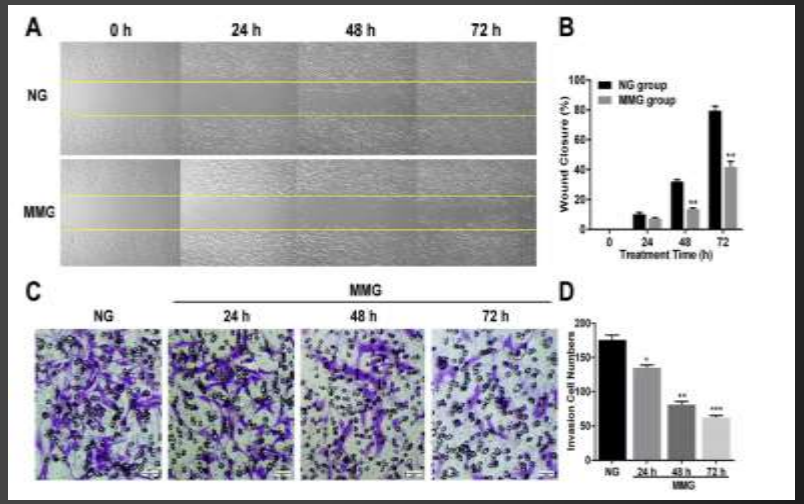
Cappelletti, C., Notarangelo, A., De Moss, D.

Experiments conducted on GBM cell lines showed that microgravity (MG) is able to:

- Decrease cell proliferation
- Increase apoptosis
- Attenuate invasion and migration potential
- Stimulate the overexpression of tumor suppressor p21



Zhao et al. *In Vitro Cell Dev Biol Anim* (2017)



Shi et al. *Biochemical and Biophysical Research Communications* (2015)

SMG VS RMG

-Simulating microgravity lasts only for several seconds (repeated in cycles) in comparison to a prolonged RMG

- Interaction with the Earth magnetic field introduce effects in addition to SMG

-SMG is about 10^-2 g but RMG (LEO) is in the range of 10^−9-10^−5 g (Cappellettti et al. 2012)

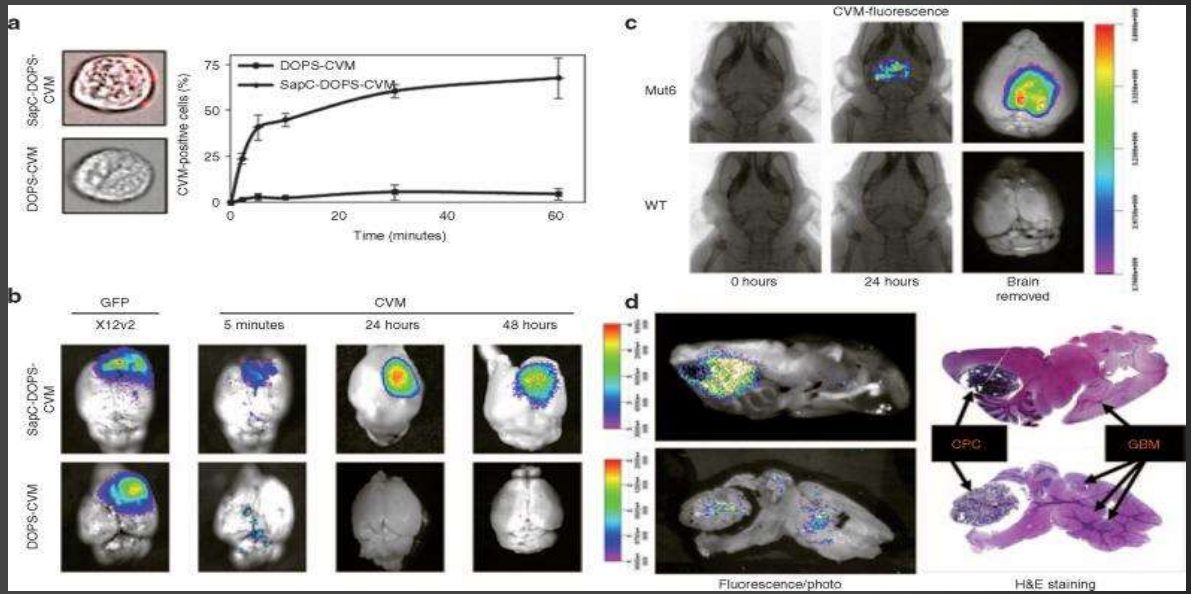
-RMG is accompanied with ionizing radiations

Aim of the study

- Investigate the effect of microgravity and ionising radiation on GBM in vivo mouse model
- Implications in therapy
- Translation of results to on-ground therapy
- Enquire future Space Colonization effect

Innovation

The innovative point of this project consists on the possibility to study cancer models *in vivo*, rather than *in vitro*, on the ISS.



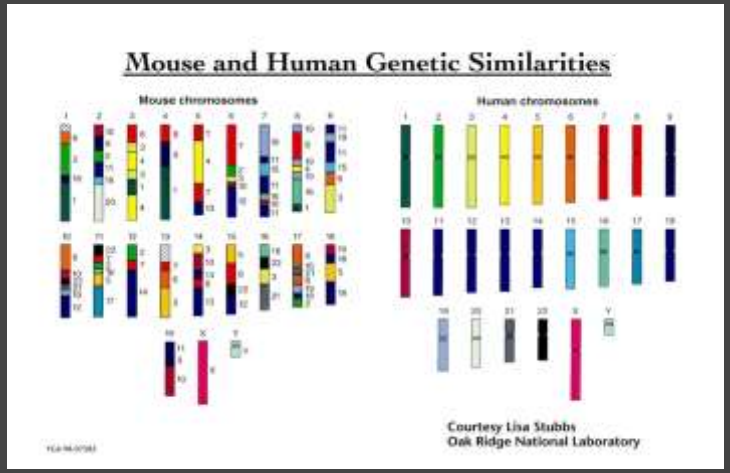
Wojton et al. *Molecular Therapy* (2013)

In vivo VS *In vitro*

-Different sensibility grade to veliparib and TMZ *in vivo* in comparison to *in vitro*

- *In vitro* studies are not able to reproduce 3D effects and growth

-*In vivo* murine models share 85% of human genome



Methods

Isolation and characterization of **patient-derived GSCs**

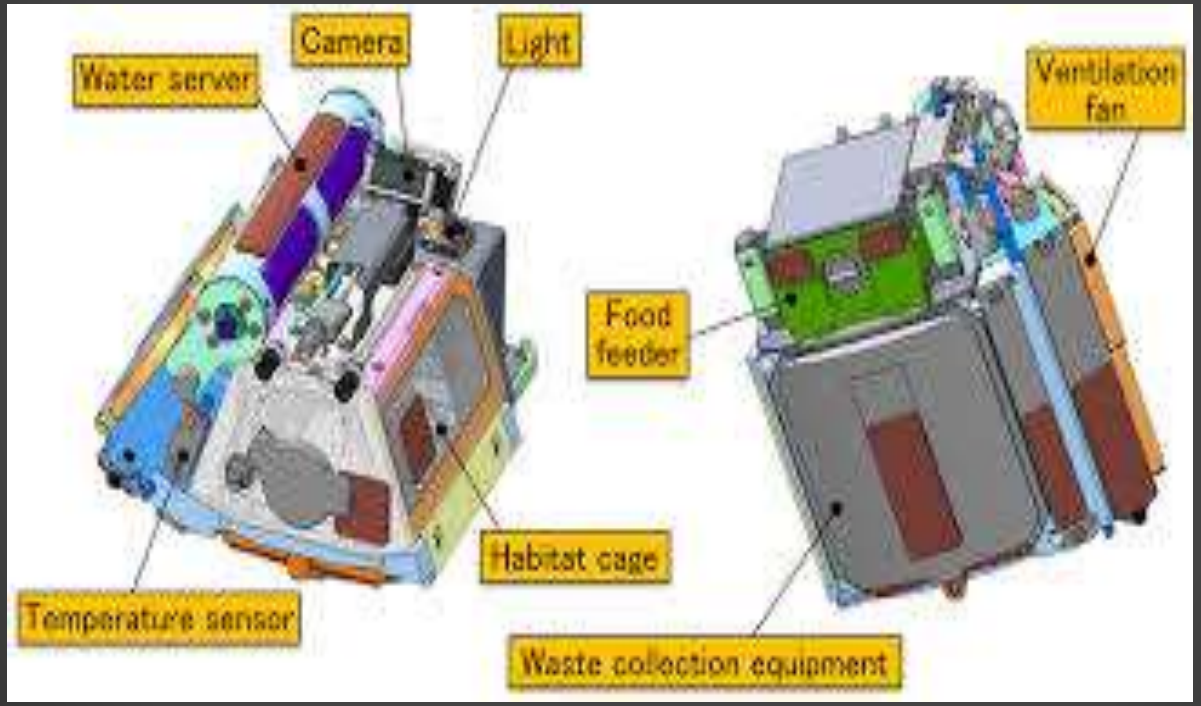
Inoculation of GSCs into mice brain

Study groups on the **ISS**:
- **Healthy** mice
- Mice with **GBM untreated**
- Mice with **GBM treated with TMZ**

Study groups on the **on-ground**:
- **Healthy** mice
- Mice with **GBM untreated**
- Mice with **GBM treated with TMZ**

- Behavioral tests through our specifically projected maze to evaluate cognitive abilities
- Magnetic Resonance Imaging to rate growth and vascularization of the tumor mass
- Morphological, cellular, molecular, and genetic analyses

JAXA and cages



On the ISS board, mice will be kept in special cages used previously by JAXA

Conclusions

The innovative concept of this research project:

- Possibility of conducting microgravity experiments
- Make improvements in the treatment of GBM
- Improve our knowledge about GBM behaviour and progression
- Develop new therapeutic strategies
- Improve GBM clinical outcome
- Increase overall survival

The current project status

Problems:
-Financial Aid
-Launching

ONGOING...

Acknowledgements

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