



RADIOBIOLOGY

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Preclinical phase

Radiobiological beam characterization



Proton beams
In vitro



Carbon ion beams
In vitro
In vivo

As part of a large program of clinical commissioning before treating patients

- to estimate biologic RBE values in order to evaluate whether the CNAO beams work in safe and optimal conditions for the clinic
- to make beam intercomparison among different facilities and to allow transferring radiobiological information from beam to beam

Active collaboration

INFN
radiobiology
groups



Uni-PV
(Dept. Biology and Biotechnology,
Interdepartmental Centre of Services
for the Unified Management of
Stabling and Radiobiology for mice
housing and care,
The Ethics Committee for Animal
Testing)

NIRS
(National Institute of
Radiological Sciences,
Chiba, Japan)

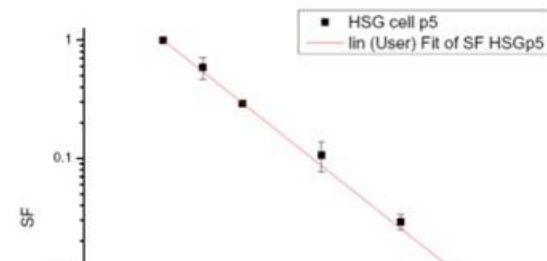
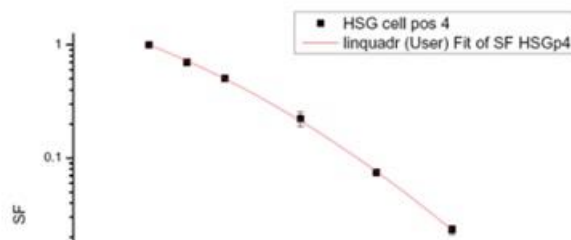
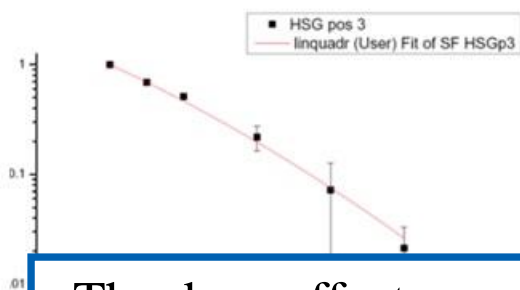
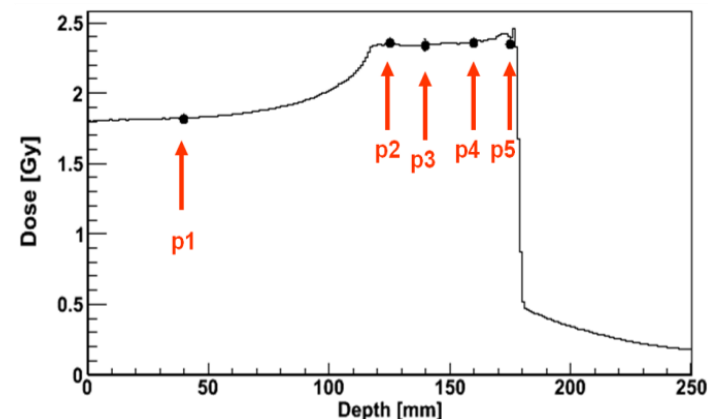
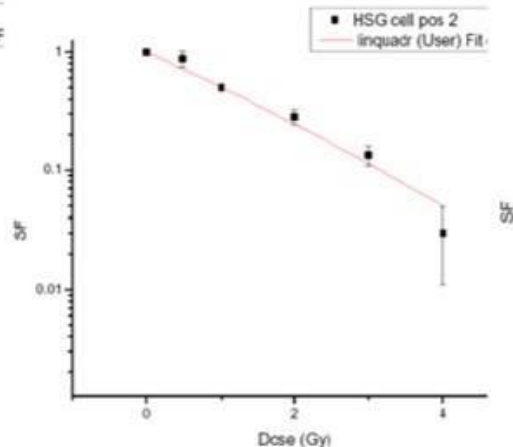
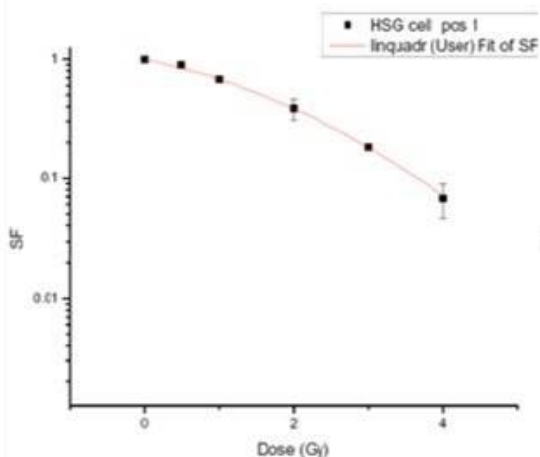
***In vitro* (protons and carbon ions)**

Cell survival curves from 3 different cell lines:

- **HSG (Human salivary gland tumor)** - reference cell line for the pre-clinical activities used at various hadrontherapy centres
- **T98G (human glioblastoma)** - a radio-resistant cell line widely used as *in vitro* model in various radiobiology studies
- **V79 (Chinese hamster lung fibroblast)** - a radiobiology reference cell line of which a significant amount of data exist in literature

**INFN Legnaro National Laboratories (Coordinator),
Milan University Physics Department, Naples University Physics
Department, Rome 3 University Biology Department, ISS - Istituto
Superiore di Sanità in Rome.**

In vitro



The dose-effect curves thus obtained were found to be in good agreement with those obtained with other beams and RBE values calculated in different positions of the SOBP are within the ranges of values published

In vivo

Intestinal crypt regeneration in mice : a biological system for quality assurance in non-conventional radiation therapy

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André Wambersie^a and Vincent Grégoire^{a,b}

^a Laboratory of Radiobiology and Radioprotection, Department of Medicine, Catholic University of Louvain, Belgium

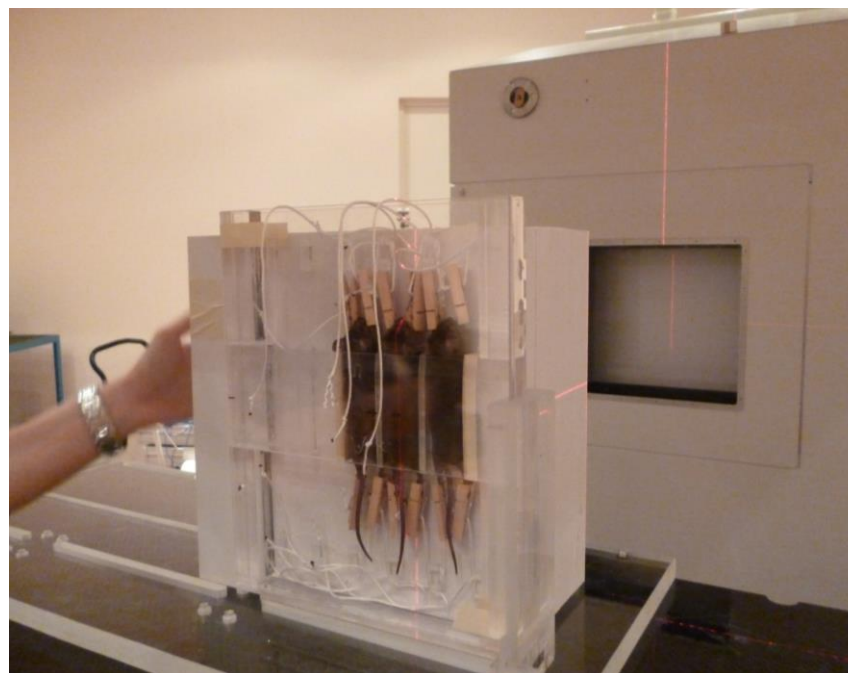
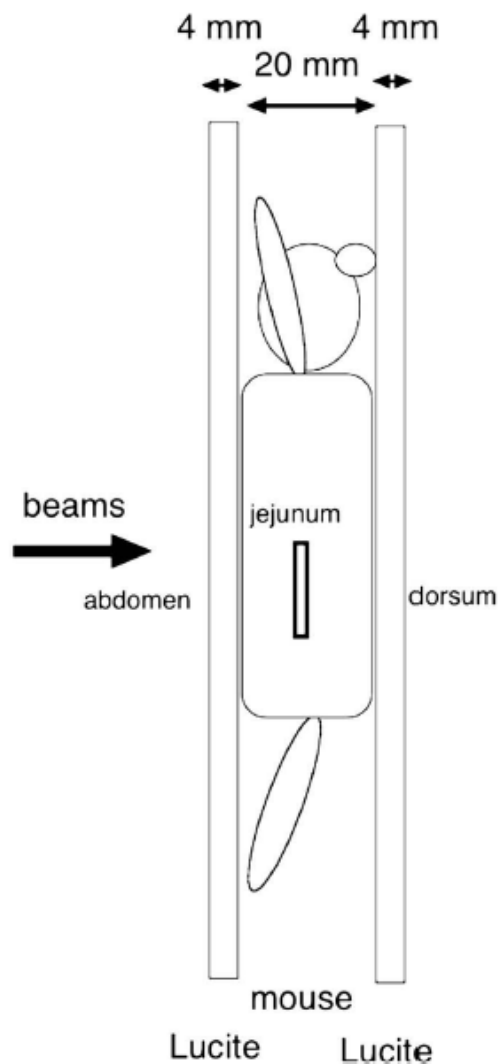
^b Radiation Oncology Department, University Hospital St-Luc, Catholic University of Louvain, Belgium

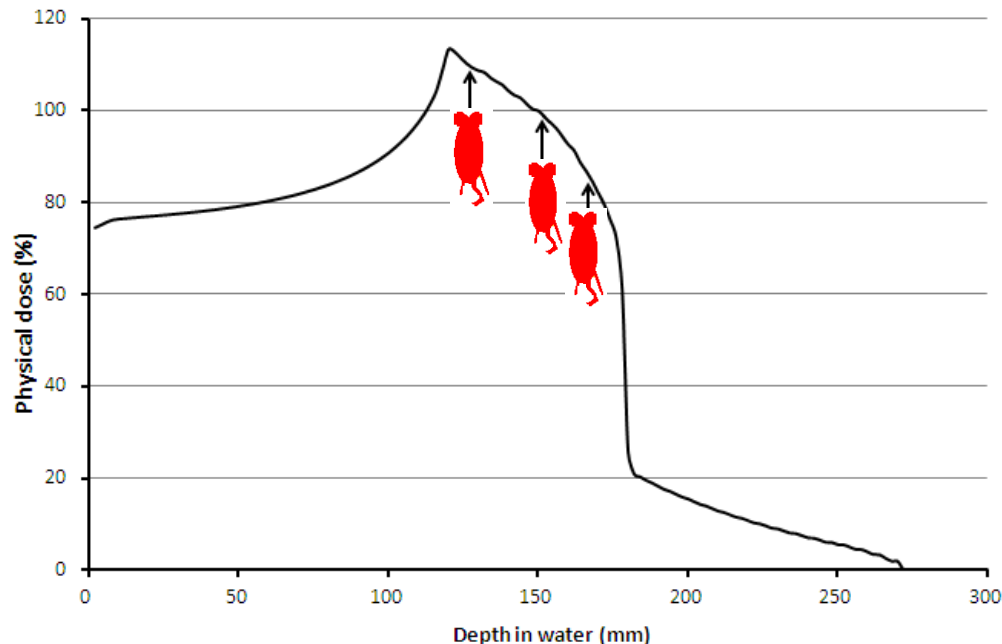
Radiother Oncol. 2004

Irradiation set up

The jig was positioned perpendicularly to the beam axis in order to irradiate mice in abdomen-dorsum direction

Groups of 3 mice were kept in a Lucite jig especially designed and irradiated together





SOBP 6 cm, 120-180 mm

Proximal (13 cm)

Central (15 cm)

Distal (17 cm)

- ✓ Reference radiation was represented by ^{60}Co gamma rays from Japan.
- ✓ Animals were sacrificed 84 ± 4 hours after the end of the irradiation

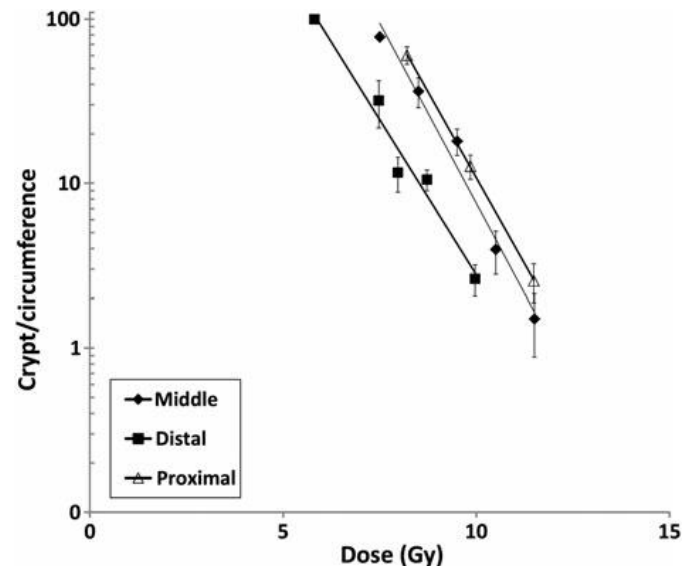
Results - RBE

beam intercomparison

Table 2. RBE ratio of CNAO with NIRS and GSI for RBE₁₀ and RBE₃₀.

Beam position in SOBP	Facility	RBE ₁₀ ratio	RBE ₃₀ ratio
Proximal	CNAO/NIRS	1.05	1.04
	CNAO/GSI	1.03	1.04
Middle	CNAO/NIRS	0.97	0.95
	CNAO/GSI	0.93	0.94
Distal	CNAO/NIRS	0.97	0.98
	CNAO/GSI	0.97	1.00

Mean ratio for RBE₁₀: CNAO/GSI = 0.97; CNAO/NIRS = 0.99. Mean ratio for RBE₃₀: CNAO/GSI = 0.99; CNAO/NIRS = 0.99^(5, 11).



Facoetti A et al, Rad Prot Dosimetry, 2015



Formal approval of the Health Ministry

PAST (...but also PRESENT)

Radiobiology groups (INFN, UniPV, Istituto Nazionale Tumori, UTS Texas...)

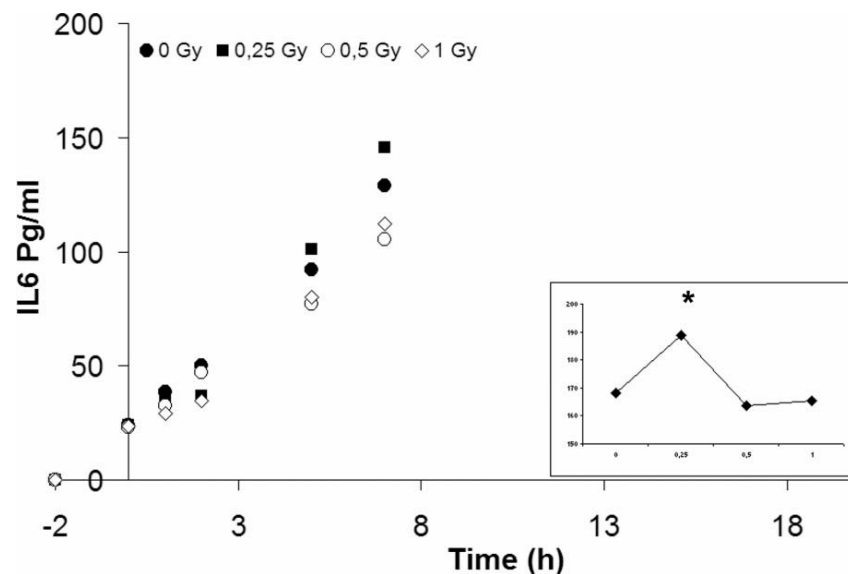
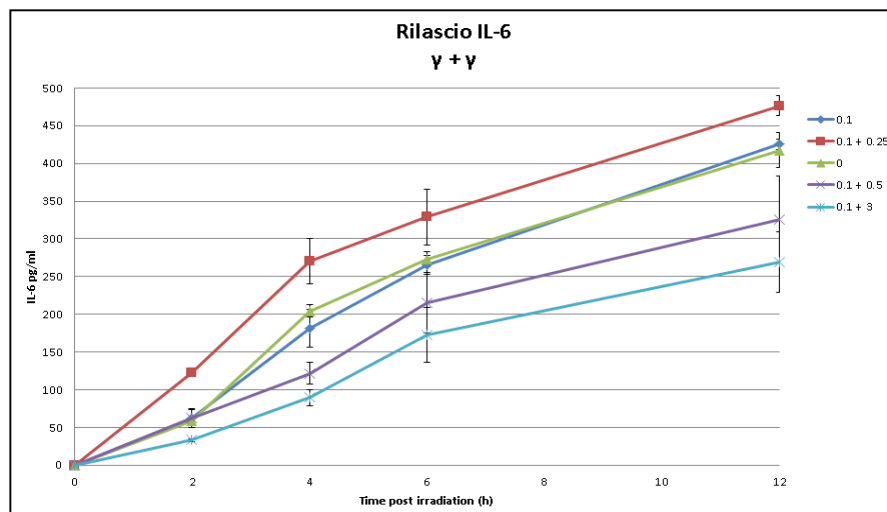


- ✓ Effects of radiosensitizing drugs on tumor cells after proton or carbon ion irradiation
- ✓ Cellular premature senescence in normal human cell lines exposed to carbon ion beams
- ✓ Normal and cancer stem cells
- ✓ Head and Neck cancer cells response to Carbonions
- ✓ ...

2014: INFN-founded project TANTARA (LNL coordinator)

→ to contribute to improve the understanding of the mechanisms underlying the “low-dose non-targeted effects”, with particular emphasis on the IR “adaptive response”), in cells exposed to combined IR beams.

→ → We investigated a pre-exposure to low doses of gamma rays may affect the release of IL-6 by irradiated normal fibroblasts (with gamma-rays or protons).



Present

INFN-founded Research project 2015-2017

ETHICS

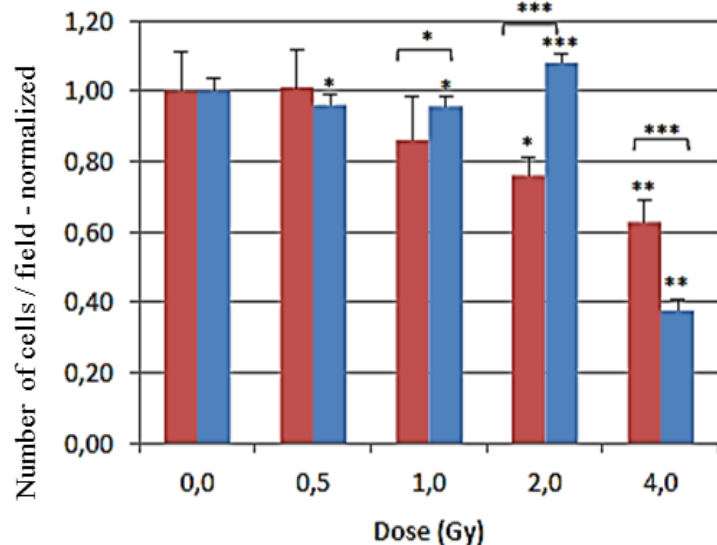


Pre-clinical experimental and theoretical studies to improve treatment and protection by charged particles

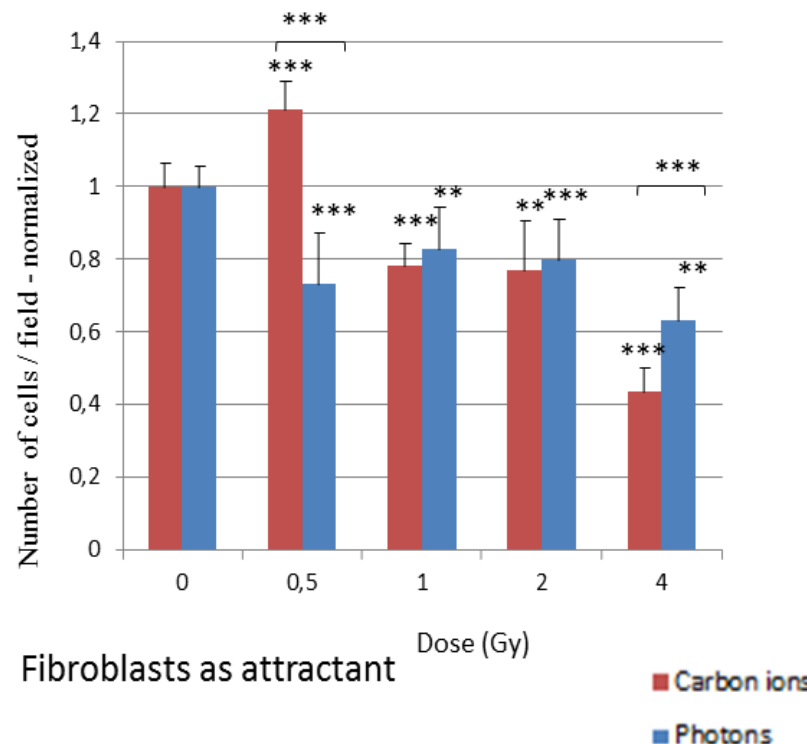
Understanding the underlying action mechanisms on normal cells by charged particles used in medicine to reduce the risks for human health

→ The experimental activity of the CNAO Unit is dedicated to the evaluation of the effects of sublethal doses of different radiation qualities on the stroma mechanisms regulating cell adhesion and migration (risk metastasis).

ETHICS - Experimental activity of the CNAO Unit



Completed medium as attractant



Fibroblasts as attractant

■ Carbon ions
■ Photons

- ✓ Evaluation of the migration capability of pancreatic tumour cells following irradiation with varying radiation quality
- ✓ Effects of paracrine diffusible factors secreted by fibroblasts irradiated with varying radiation quality on the adhesion, proliferation, migration and invasion of pancreatic cancer cells

*Collaboration activity with National Tumor Institute of Milan :
Dissecting the role of microRNAs in the radiation response
of human prostate cancer*

✓ AIRC grant (Approved)

Identification of microRNAs functionally involved in the response to photon/carbon ion irradiation and the dissection of their underlying molecular mechanisms using a panel of prostate cancer (PCa) cell lines with distinct radiosensitivity profiles that carry genetic alterations relevant to the disease.

CIPHER pancreatic trial in collaboration with UT southwestern center

Basic, translational, and clinical radiobiological research in pancreatic cancer

Collection of patient specimens from which we would try to develop some insight into patient response to carbon therapy

- Tumor specimens for dna sequencing
- Blood sample for cfDNA sequencing, exosomal capture and analysis
- Pancreatic cancer Cell lines carbonion radiobiological characterization
- ...

Hot topics for radiobiological research in CNAO



- ✓ Mechanisms of radioresistance (cancer stem cells)
- ✓ Healthy tissues and microenvironment response
- ✓ Immunomodulation radiation
- ✓ Effects of existing and/or new radiosensitising agents with high LET radiations
- ✓ Migration and invasion
- ✓ ...





Thanks for your attention!