Modelling of different types of radiation-induced cell deaths following exposures to low linear energy transfer (LET) photons and high LET accelerated ions

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Aims of the project:

The aim of this project is to *in vitro,* in human normal and tumour cells with different origin and gene-status investigate and compare:

- the sensitivity of low linear energy transfer (LET) radiation exposure on clonogenic cell survival and different types of cell death, e.g. apoptosis, necrosis, mitotic catastrophe, autophagy and senescence

- the sensitivity of high LET proton, carbon and nitrogen ion exposures on clonogenic cell survival and different types of cell deaths

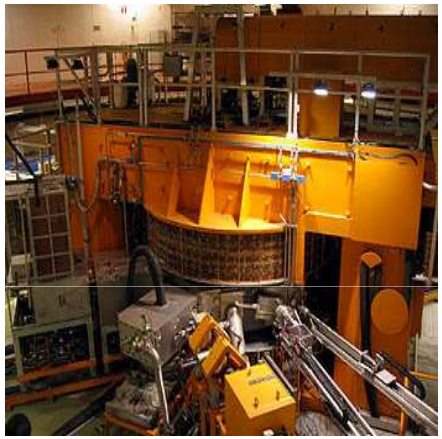
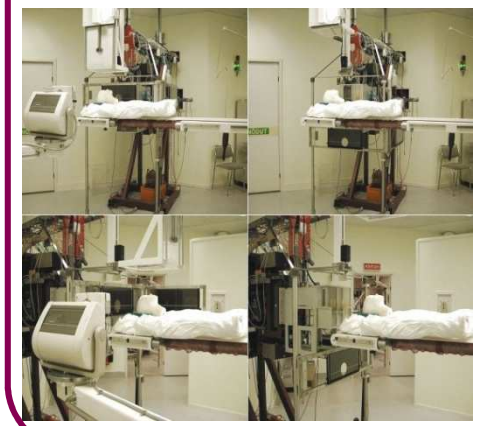
Aims of the project:

- the relative biological effectiveness (RBE) of protons, carbon and nitrogen ions in comparison with low LET photons with regard to clonogenic cell survival and different types of cell deaths using and developing different mathematical models

- cell survival after micro-beam carbon and nitrogen ion exposure

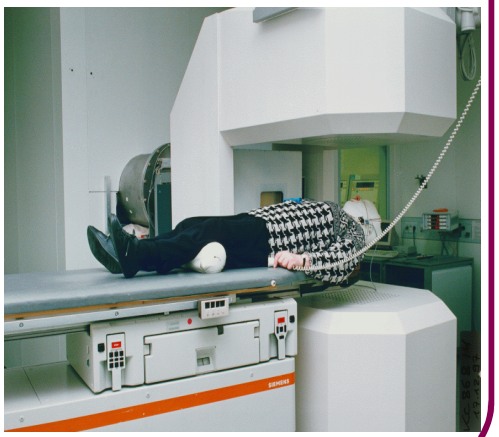
Radiation facilities

The Svedberg Laboratory, Uppsala, Sweden

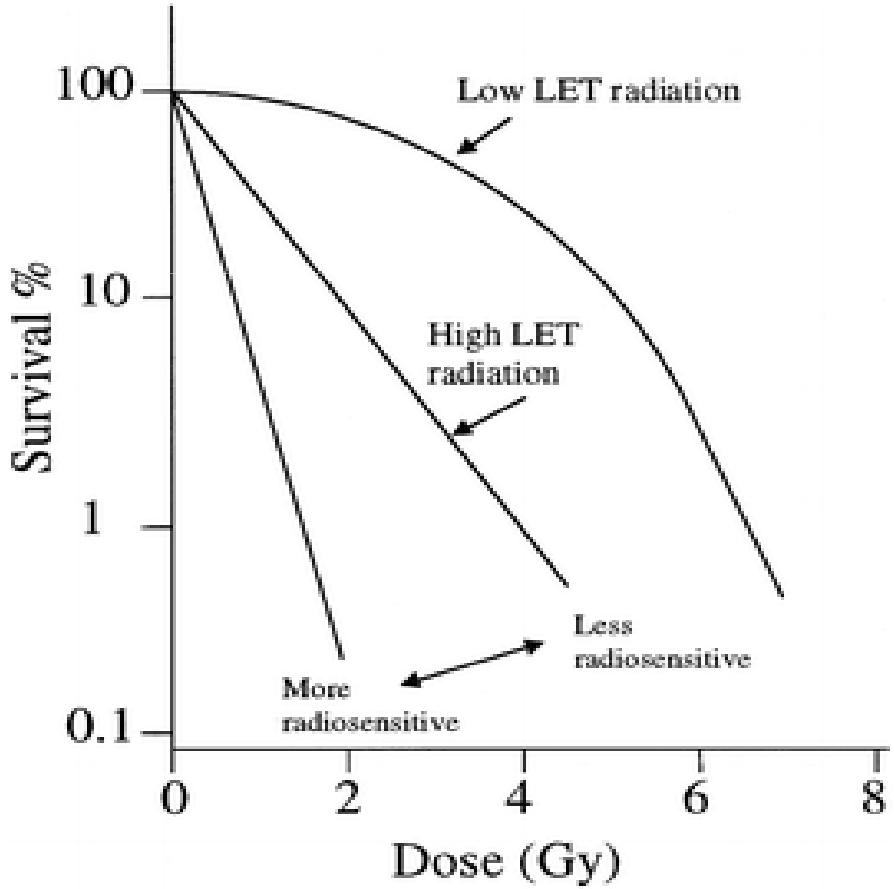

GSI, Centre for Heavy Ion Research, Darmstadt, Germany



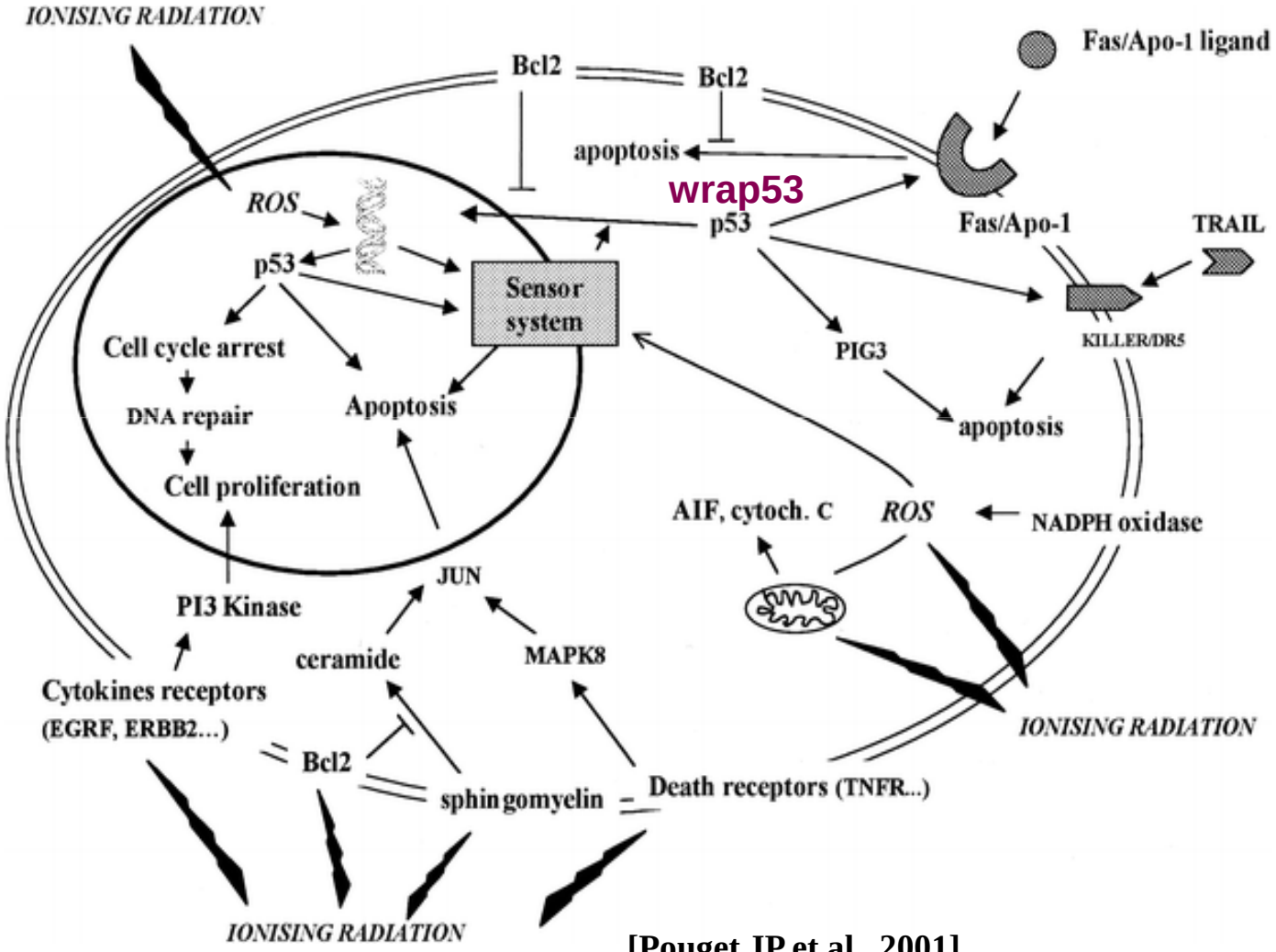
Methods

Dose response curves for clonogenic cell survival will be established and analysis of different modes of cell death will be studied following different LET irradiations.



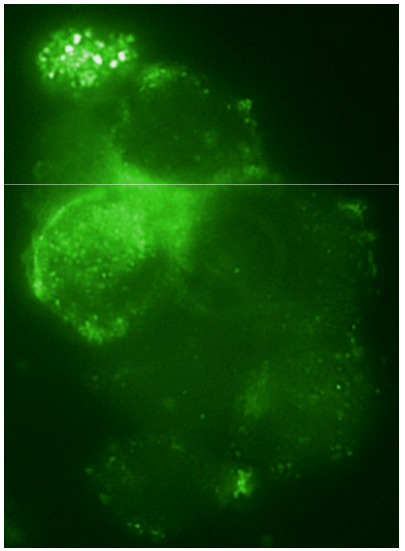
Typical cell survival curves from low- and high-LET radiation [Pouget JP et al., 2001]

Some of the mechanisms influencing the cellular choice between life and death after exposure to ionising radiation.



[Pouget JP et al., 2001]

AIF is involved in the early induction of high LET radiation-induced apoptosis in human glioma cells



M059K cells 3 h after exposure to 4 Gy of high LET nitrogen ions (140 keV/µm).

[Meijer AE et al.]

It has been reported that a variety of charged particles are more effective in inducing apoptosis than low linear energy transfer (LET) in cells with different origin and gene status (Meijer *et al.* 1998, 2001, 2005; Coelho *et al.* 2001; Holgersson *et al.* 2003).

However, there are several reports on that accelerated ions with high LET induce apoptosis independently of the p53 gene status of the tumour, but there are also some results suggesting the involvement of p53 in high LET radiation-induced responses (Yamakawa *et al.* 2008; Mori *et al.* 2009).

Methods:

(1) morphological examinations of cells in microscope after staining with different dyes and immunochemistry,

(2) measurements of apoptotic bodies using flow cytometry and microscopy,

(3) enzymatic DNA-fragmentation by gel-electrophoresis analysis (DNA-ladders).

For clonogenic cell survival different cell survival models (e.g. LQ, RCR and LEM) will be used and the underlying molecular mechanisms will be investigated using Western Blot, ELISA and array techniques.

Ion- and LET dependent relative biological effectiveness (RBE) for cell survival and different types of cell death will be determined in chosen cancer cell lines.

Significance of the project:

- Improved knowledge and understanding of the effects of agents that induce different types of cellular damage, e.g. low and high LET radiation, and thereby also different types of cell death pathways, could lead to new and better treatment forms for (radio)resistant tumours.

- Improving the quality of life for patients with cancers by optimising the radiation therapy treatment using ions.

WP7. Milestones and Deliverables

No.	Name	Expected date	Nature
7-D1	**Research plan**	**m3**	**Report-PP**
7-M1	Effectiveness of photons on clonogenic cell survival and modes of cell death	m12	Irradiations at CCK, Stockholm, Sweden
7-D2	Effects of photon irradiations on cell survival	m12	Report-PP
7-M2	Effectiveness of one ion species on clonogenic cell survival and modes of cell death. RBE and LET effects	m24	Irradiations with protons, carbon and/or nitrogen ions at TSL, Uppsala, Sweden
7-M3	Effectiveness of the same ion species as above on clonogenic cell survival and modes of cell death. RBE and LET effects	m18	Irradiations with carbon ions at GSI, Darmstadt, Germany
7-D3	Effects of carbon ions on cell survival	m18	Report-PP
7-M4	Effectiveness of another ion species on clonogenic cell survival and modes of cell death. RBE and LET effects	m24	Irradiations with other ions at e.g. GANIL, Caen, France
7-D4	Effects of a other ions on cell survival	m24	Report-PP
7-M5	Effectiveness of micro-beams on modes of cell death	m36	Irradiations with micro-beams at the University of Surrey, UK
7-D5	Effects of micro beams on cell survival	m36	Report-PP
7-M6	Finishing thesis and publications	m42	
7-D6	Publications and thesis	m42	Report-PP