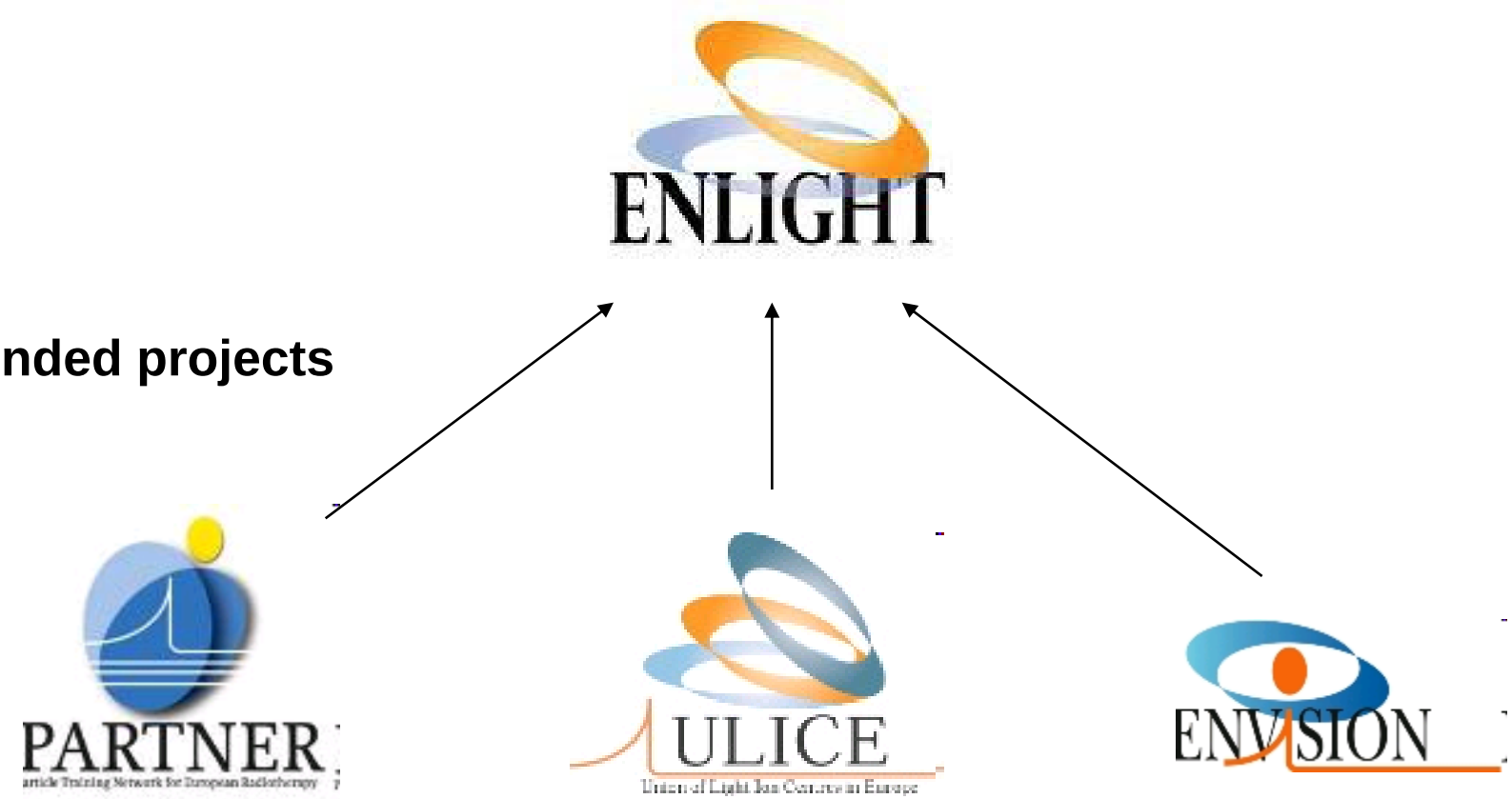
The **E**uropean **N**etwork for **LIG**ht ion **H**adron **T**herapy

The **E**uropean **N**etwork for **LIG**ht ion **H**adron **T**herapy

EU funded projects

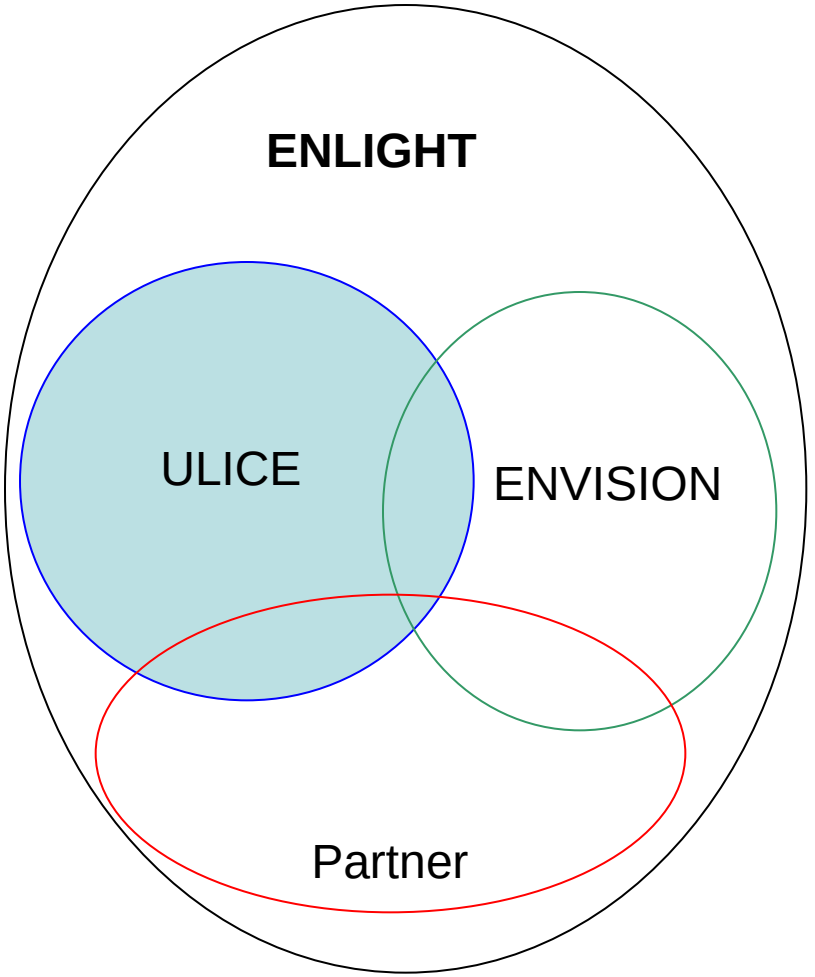


WP.8 Communication and dissemination for promoting hadron-therapy research facilities to end-users

In ENLIGHT 216 persons registered but only fraction of them participates in the projetcs

Tha aim of this part of work is to:

- communicate the ULICE achievements to ENLIGHT community
- information of ENLIGHT to ULICE



WP.8 Communication and dissemination for promoting hadron-therapy research facilities to end-users

This report on:

1) Construction of proton radiotherapy centers in Central Europe

- Praha (CZ),
- Ruzemberok (SK)
- Kraków (PL)

2) Announcement of the 2nd Workshop of Romanian Society of Hadrontherapy, Sibiu, 12-14 November, 2010

3) Summary on the progress in ENLIGHT partners: Radiobiology

New Proton Therapy Centers in Central Europe

Central Military Hospital, Ruzemberok, Slovakia

The name of facility: Centrum Protonovej Terapie

- **Accelerator:** 230 MeV synchrotron developed at Physical-Technical Center of Lebedev Physical Institute of the Russian Academy of Sciences (PTC LPI)
- **Consultant**: Dan Jones, ITEMBA lab, South Africa
- **Status:** opened on April 4, 2010
- Proton beam available
- **First patient:** planned in the first half of 2011

http://www.uvn.sk

New Proton Therapy Centers in Central Europe

Proton Therapy Center Czech s.r.o

- **Location:** Prague, Czech Republic
- **Investor:** private
- **Accelarator:** IBA C-235 cyclotron
- **Treatment facilities:** 3 gantries
- **Construction:** started in 2009
- **First patient :** end of 2012

www.ptc.cz

New Proton Therapy Centers in Central Europe

Protontherapy of eye at IFJ PAN Kraków

- **Location:** Kraków, PL, Insitute of Nuclear Physics Polish Academy of Sciences
- **Accelarator:** AIC-144 60 MeV proton cyclotron**,** developed at IFJ
- **Treatment facilities:** eye treatment room
- **Construction:** completed
- **Medical partner:** Clinic of Ophthalmology Kraków UJ University
- **First patient :** end of 2010

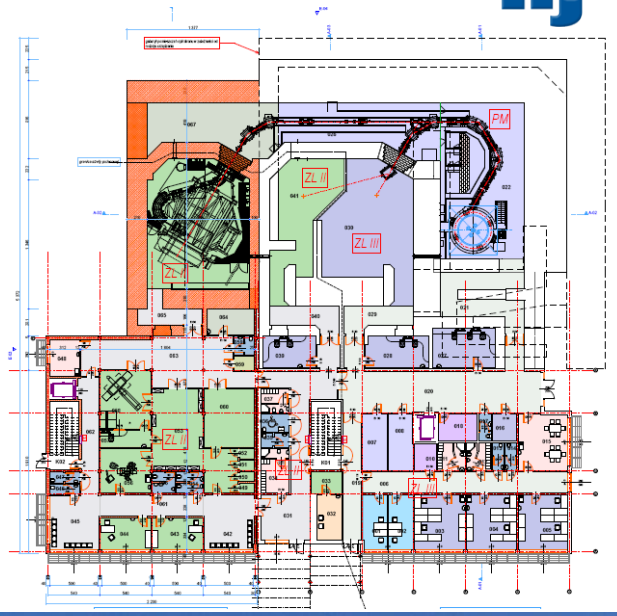
www.ifj.edu.pl

New Proton Therapy Centers in Central Europe

Protontherapy at IFJ PAN Kraków

- **Location:** Kraków, PL, Insitute of Nuclear Physics Polish Academy of Sciences
- **Accelarator:** IBA Proteus C-235
- **Treatment facilities:** horizontal beam for eye, one gantry
- **Construction:** contract signed August 2, 2010
- **Financed:** EU structural funds (85%)
- **First patient :** end of 2013

www.ifj.edu.pl



The 2nd Workshop of Romanian Society of Hadrontherapy

Titele **Hadrontherapy, knowledge and evidences**

Place: **Sibiu, Romania**

Time: **12-14 November, 2010**

www.rsh.ro

Organizer: **Dr. Nicolae Ioan Verga**
Societatea Romana de Hadronotherapie

GOALS

o hadrontherapy of different type of cancers;
o evaluation of the educational, economical and technological aspects of hadrontherapy;
o the new directions in the accelerated ions radiotherapy research;
o the related fields

WP.8 Communication and dissemination for promoting hadron-therapy research facilities to end-users

The European Network for LIGht ion Hadron Therapy

TOPICS and CONVENERS

1. Clinical Studies and medical training	**Roberto ORECCHIA Jürgen DEBUS**
2. Radiobiology	**Wilma WEYRATHER-KRAFT Annelie E. MEIJER**
3. Treatment planning and biological optimization of Intensity Modulated Particle Therapy	**Hanitra SZYMANOWSKI Johanna KEMPE**
4. Adaptive image guided ion therapy and treating moving organs	**Dietmar GEORG David SARRUT**
5. Novel in-beam PET systems and in vivo tumour response imaging	**Wolfgang ENGHARDT Madjid BOUTEMEUR**
6. Importance and feasibility study for innovative gantry designs	**Marco PULLIA François KIRCHER**
7. Information and Communication Technologies and networking in hadron therapy	**Thomas AUBERGER Hans Falk HOFFMANN**

WP.8 Communication and dissemination for promoting hadron-therapy research facilities to end-users

The European Network for LIGht ion Hadron Therapy

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WP.8 Communication and dissemination for promoting hadron-therapy research facilities to end-users

RADIOBIOLOGY

Convener: Wilma WEYRATHER-KRAFT

CONTENT

Pavel Kundrát	Probabilistic Two stage model. Towards applications in treatment planning in hadron radiotherapy
Michael Beuve	Experimental study of the LEM Theoretical study of the LEM
Mira Maalouf	Different mechanisms of cell death in radiosensitive and radioresistant p53 mutated head and neck squamous cell carcinoma cell lines exposed to carbon ions and x-rays.
Bleddyn Jones	The apparent increase in the ß-parameter of the linear quadratic model with increased linear energy transfer during fast neutron irradiation.
Lara Barazzuol	Evaluation of combined ion beam therapy and chemotherapy in glioblastoma cell lines A mathematical model of brain tumour response to radiotherapy and chemotherapy
Thilo Elsässer	Quantification of the Relative Biological Effectiveness for Ion Beam Radiotherapy: Direct Experimental Comparison of Proton and Carbon Ion Beams and a Novel Approach for Treatment Planning
Carola Hartel	Chromosomal aberrations in peripheral blood lymphocytes of prostate cancer patients treated with IMRT and carbon ions.
Burkhard Jakob	Live cell microscopy analysis of radiation-induced DNA double-strand break motion.
Daniele Alloni	A Monte Carlo study of the radiation quality dependence of DNA fragmentation spectra.
Chitralekha Mohanty	Comparative Analysis of Cellular and Molecular Responses of Tumor Cells towards High and Low LET Radiation

Probabilistic two-stage model

Pavel Kundrát
Institute of Physics, Academy of Sciences of the Czech Republic, Na Slovance 2,
CZ-182 21 Praha 8, Czech Republic

- Damage induction: single-track (per-track probability) – a; combined – b
- Repair of damage: success probabilities r_{ij}
- Number of tracks: Poisson distribution, mean h~D
- Cell survival $s(D)=\Sigma_k P_k(D) q_k$,

$$q_k = \sum_{i=0}^{k} \binom{k}{i} a^i (1-a)^{k-i} \sum_{j=0}^{k-i} \binom{k-i}{j} b^j (1-b)^{k-i-j} r_{ij} \quad , \quad r_{00} \equiv 1 \equiv r_{01}$$

- For independent repair of individual lesions (no onset, no saturation), $r_{ij}=(r_a)^i(r_b)^j$:

$s(D) = \exp[-\theta_1 D]\,[1+\theta_2 D]$ $\qquad$ $-\ln s(D) = \theta_1 D - \ln(1+\theta_2 D)$

$\theta_1 = h(1-ar_a-(1-a)(br_b+1-b))$ $\qquad$ $\theta_2 = h(1-a)b(1-r_b)$

Unrepaired ("residual") damage only: $r_{00}=r_{01}=1$, all other r=0

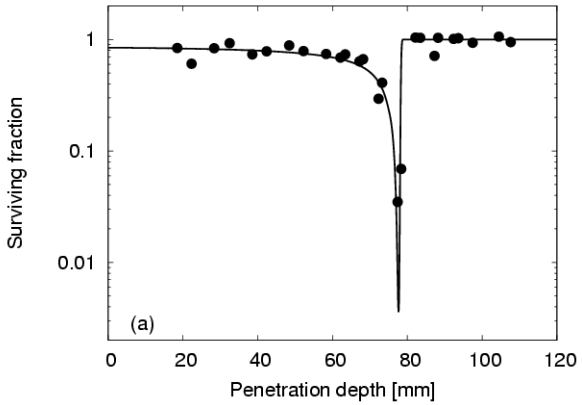
$\theta_1 = h(a+b(1-a))$ $\qquad$ $\theta_2 = h(1-a)b$

- Similar to $s(D)=\exp[-\theta_1 D]\,[1+\theta_2 D]^{\theta_3}$ predicted by lethal-potentially lethal and repair-misrepair model
- Logarithmic + linear behaviour, can be described as 'linear-quadratic-linear'
- Contrary to linear-quadratic model, does not suffer from unrealistic predictions for very high doses (note that these have to be artificially removed in local effect model)
- Applied to cell killing by p, He, C, O ions (Kundrát, Phys Med Biol 2005, 2006; Appl Radiat Isotopes 2009)

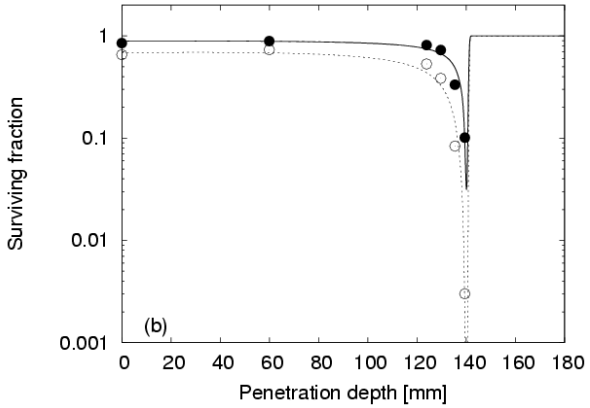
Towards applications in treatment planning in hadron radiotherapy

Pavel Kundrát
Institute of Physics, Academy of Sciences of the Czech Republic, Na Slovance 2, CZ-182 21 Praha 8, Czech Republic

- Simple physical model of Bragg peak
  - Energy loss & straggling
  - Nuclear reactions: reducing fluence of primary particles
  - Secondary particles not followed
- Radiobiological model
  - Damage probabilities a(LET), b(LET) from data on survival of CHO cells irradiated by mono-energetic C ions (Weyrather et al Int J Radiat Biol 1999)
  - Average damage along Bragg peak:
    weighting over LET spectrum
    (and different ion species – not considered in this work)
- Predicted biological efficiency in agreement with data, indicating potential applications of the model in hadron radiotherapy (Kundrát, Phys Med Biol 2007)



CHO cells, 187 MeV/u C, 2×10^7 cm^{-2}



CHO cells, 264 MeV/u C, 2 and 5×10^7 cm^{-2}

Data: Scholz et al, Radiat Environ Biophys 1997
Kraft et al, Radiat Environ Biophys 1999

Experimental study of the LEM

– Only after fitting the parameter D_t [1]

Michael Beuve

Université de Lyon, Université Lyon 1, CNRS, UMR 5205, LIRIS, Laboratoire d'InfoRmatique en Images et Systèmes d'information, Villeurbanne, F69622, France

- Consequences for TPS
  - Cell survival to X-rays cannot simply be extrapolated to cell survival to ions.
  - As for the other models (MKM, ion-kill γ-kill model, HIMAC approach), for each cell line (tissue, patient), data with high-LET ions are pre-required to get predictions and therefore dose optimization [2].

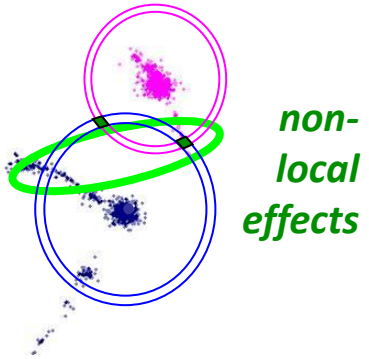
[1] Beuve M. et al. Int. J. Rad. Onc. *Biol. *Phys. 71 635-642 (2008)
[2] Beuve M. et Rodriguez-Lafrasse C. Int. J. Rad. Onc. *Biol. *Phys., 72(1) 303 (2008)

Theoretical study of the LEM

Michael Beuve
Université de Lyon, Université Lyon 1, CNRS, UMR 5205, LIRIS, Laboratoire d'InfoRmatique en Images et Systèmes d'information, Villeurbanne, F69622, France

- +++ Local effects
  - The LEM interestingly introduces the notion of local Effect
  - Local effect = point-like lethal event (i.e. cluster of DNA damage)

- - - - we showed
  - A pure theory of local effects cannot predict shoulders in cell survival even for low-LET ions [3]
  - The shoulders predicted by the LEM arise from expected quantities used inconsistently with regard to radiation physics and biology [4]



- Conclusion
  - Fitting D_t allows however to get interesting predictions
  - An explicit introduction of non-local effects in the LEM could improve the principles and predictions of the LEM [4]

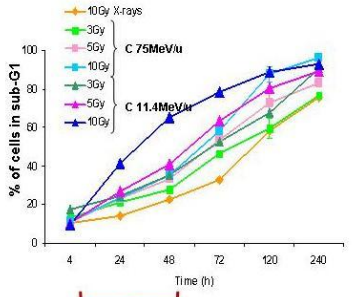
[3] Beuve M. Rad. Res 172(3) 394-402 (2009)
[4] Beuve M. Rad. Res 173(6) 856-858 (2010)

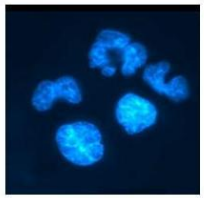
Different mechanisms of cell death in radiosensitive and radioresistant p53 mutated head and neck squamous cell carcinoma cell lines exposed to carbon ions and x-rays.

Maalouf M, Alphonse G, Colliaux A, Beuve M, Trajkovic-Bodennec S, Battiston-Montagne P, Testard I, Chapet O, Bajard M, Taucher-Scholz G, Fournier C, Rodriguez-Lafrasse C.

Int J Radiat Oncol Biol Phys. 2009 May 1;74(1):200-209

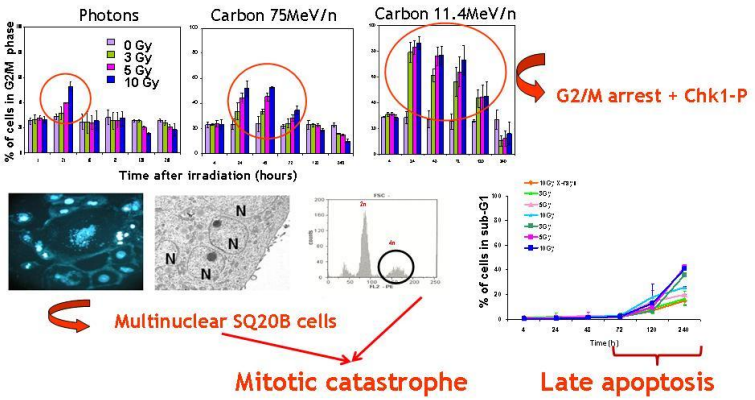
SCC61 radiosensitive cells :





Early apoptotic cell death increasing with time and LET

SQ20B radioresistant cells :



- G2/M phase arrest associated with Chk1 activation
- Cell death by mitotic catastrophe followed by late apoptosis

By comparison to photon irradiation :

- Carbon ion irradiation does not modify the type of cell death involved, but triggers it earlier and amplifies it.
- In SCC61radiosensitive cells : Induction of early apoptosis
- In SQ20B radioresistant cells :
- - G2/M phase arrest associated with Chk1 activation
- - Mitotic catastrophe followed by late apoptosis
- - Escape to mitotic catastrophe for a subpopulation of SQ20B cells which continue to proliferate
- Resistance of HNSCC to carbon irradiation = cancer stem cells ?

Current Studies

- Characterization of the role of the ceramide-dependent p53-independent pathway in the triggering of apoptosis (Coll. C. Fournier and G. Taucher-Scholz (GSI) and A. Meijer (Karolinska))
- Isolation and characterisation of the sub-population of SQ20 cells resistant to irradiation
- **Criteria of selection of the proliferating « stem–like cancer cells » :**
  - CD44 expression
  - Hoechst exclusion
  - Tumorisphere formation
  - In vivo tumor formation

Response of human normal and tumour brain cells to anti-glioma treatments

Specific aims :

- To assess and predict the specific response of gliomas and normal brain cells to anti-cancer treatment (X-rays, carbon ions, temozolomide), and their association, in terms of ceramide production, telomere status, cell death and signalling
- 11 glioma cell lines with different radiosensitivity and p53 status and 5 normal brain cell lines

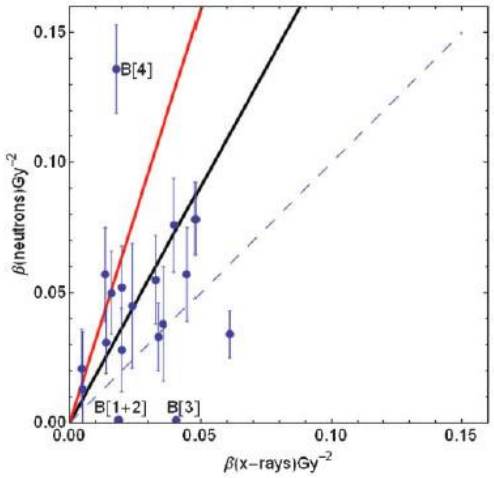
Preliminary results :

- In glioma cells, high and low LET irradiation induce mitotic catastrophe followed by late apoptosis
- Temozolomide do no sensitize glioma cells to photon or carbon ion (compared to TMZ alone)

The apparent increase in the ß-parameter of the linear quadratic model with increased linear energy transfer during fast neutron irradiation.

Bleddyn Jones
Gray Institute for Radiation Oncology and Biology, University of Oxford, Headington
British Journal of Radiology 83, 433-436 (2010)

The β radiosensitivity parameter of the LQ model increases with LET,but not as much as the α parameter.



Additional Calculations

- The change in RBE with dose per fraction is highly dependent on the low LET α/β ratio, so that the largest RBE values are predicted to occur at low dose in cellular or tissue systems that have a low α/β such as brain, spinal cord. In contrast, cellular or tissue systems that have a high α/β such CHO-V79 cells and many other in vitro systems, as well as acute reacting in vivo systems, show little change in RBE with dose per fraction.
- Scaling of these results for proton RBE`s suggest that the acute reacting in vitro and in vivo assays published by Paganetti et al 2002 would not show significant changes in RBE with dose per fraction. This suggests that further tissue experiments are necessary to find the most appropriate values of RBE for tissue with low α/β such as the brain and spinal cord.
- At high doses per fraction there is very little difference between the RBE values for different α/β value systems.

We are also investigating:

- Adaptation of the LQ model to produce increasing linearity of the survival curve with dose as a continuous function, which might be useful in the context of the Local Effect Model.
- Other approaches for the prediction of changes in RBE with LET and the influence of mixed quantities of low and high LET given simultaneously to cells.
- Displays of malignant induction probabilities in 3-D.
- The potential bio-effects of ultra short laser generated charged particles.

Evaluation of combined ion beam therapy and chemotherapy in glioblastoma cell lines

L. Barazzuol[a], J. C. Jeynes[a], M. Merchant[a], K. J. Kirkby[a], R. Jena[b], N. F. Kirkby[c]
[(a)] Ion Beam Centre, University of Surrey, Guildford Surrey GU2 7XH, United Kingdom, [(b)] Oncology Centre, Addenbrooke's Hospital, P.O. Box 193, Cambridge CB20QQ, United Kingdom, [(c)] Faculty of Engineering & Physical Sciences, University of Surrey, Guildford Surrey GU2 7XH, United Kingdom

Cell survival with X-rays and TMZ

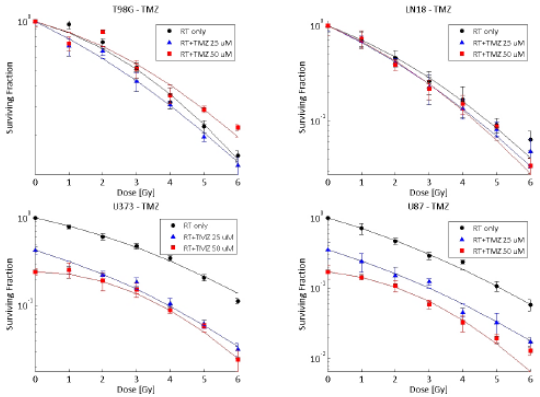


Figure 5: Cell survival curves of MGMT-positive T98G and LN18 cells (top), and MGMT-negative U373 and U87 cells (bottom). Cells received X-rays only (black), X-rays plus 25 μM TMZ (blue) and X-rays plus 50 μM TMZ (red). Symbols represent mean $\pm$ standard error of at least three independent experiments.

Cell survival with low-energy protons, alpha-particles, and TMZ

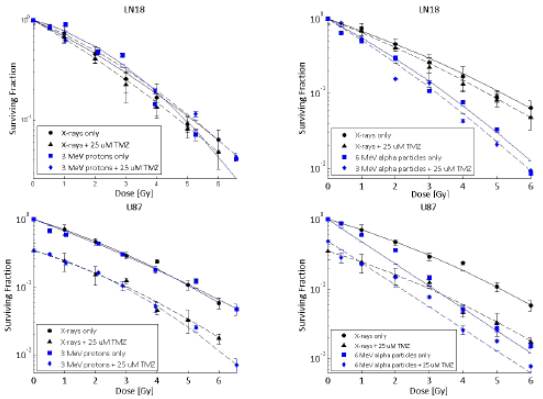


Figure 7: Cell survival curves of MGMT-positive LN18 cells (top) and MGMT-negative U87 cells (bottom) irradiated with 3 MeV protons (left, blue lines) and 6 MeV alpha-particles (right, blue lines). Cells also received concomitant TMZ (dashed lines). Survival curves with 300 kV X-rays were used as comparison (black lines). Error bars indicate the standard error of at least three independent experiments.

Goal:

- To assess the potential role of temozolomide (TMZ) chemotherapy and to explore its synergistic contribution in addition to X-rays, and low energy protons (3 MeV) and alpha-particles (6 MeV)
- four glioma (MGMT-expressing T98G and LN18 cells, and MGMTdeficient U373 and U87 cells.) cell lines
- Cells were exposed to TMZ for 2 h, including 1 h before irradiation.

Results:

- No difference in radiosensitivity to X-rays and protons, whereas a higher RBE value was found when cells were irradiated with alpha-particles.
- The combination of TMZ with X-rays, protons and alpha particles is at best additive in MGMT-deficient U373 and U87 cell lines. For MGMT-expressing T98G and LN18 cell lines no significant difference.

A mathematical model of brain tumour response to radiotherapy and chemotherapy

L. Barazzuol[a], N. G. Burnet[b], R. Jena[b], K. J. Kirkby[a], N. F. Kirkby[c]
[a] Ion Beam Centre, University of Surrey, Guildford Surrey GU2 7XH, United Kingdom
[b] Oncology Centre, Addenbrooke's Hospital, P.O. Box 193, Cambridge CB20QQ, United Kingdom
[c] Faculty of Engineering & Physical Sciences, University of Surrey, Guildford Surrey GU2 7XH, United Kingdom

Scenario 1: TMZ as a radiosensitizer

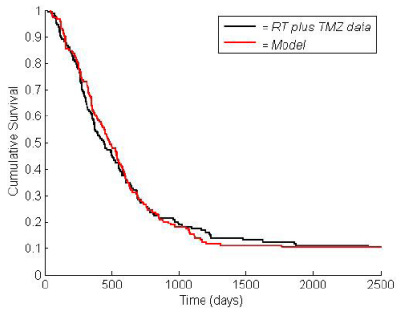


Figure 1: Kaplan-Meier survival plot for radiotherapy alone plus TMZ data, and fitted model, assuming pure radiosensitization by TMZ.

Scenario 2: TMZ as a cytotoxic agent

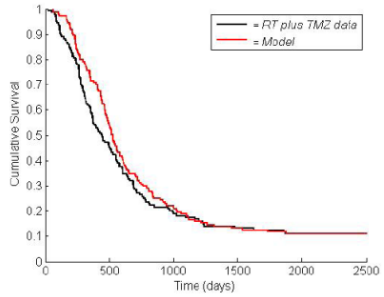


Figure 2: Kaplan-Meier survival plot for radiotherapy plus TMZ data, and fitted model, assuming that the effect of TMZ is entirely due to direct cytotoxicity.

Goal:

- To revise the existing model, mostly addressed to radiotherapy, to develop a new module to asses the potential role of TMZ from clinical data, and to explore its synergy with radiation.
- The model has also been extended to include the linear-quadratic equation

Chemo-radiotherapy model
Consideration of two potential scenarios to describe the effect of TMZ:
Scenario 1, TMZ as a radiosensitizer
Scenario 2, TMZ as a cytotoxic drug.

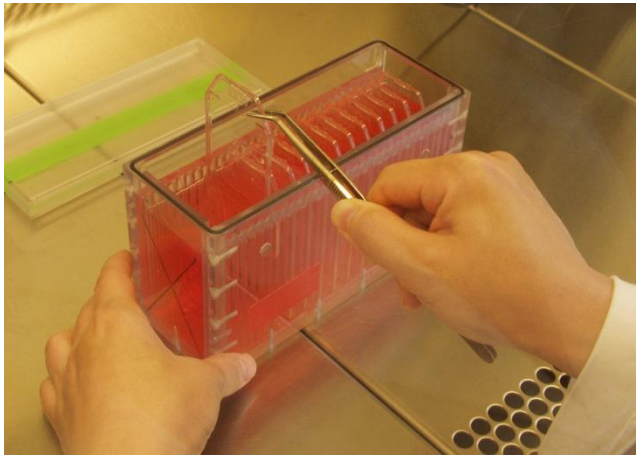
Results:

- The comparison of the *in silico survival curve with the real data demonstrates that the* model can qualitatively represent the clinical reality
- The results indicate that the model achieves an excellent fit to the clinical data, with the assumption that TMZ given concomitantly with RT synergistically increases radiosensitivity.
- The addition of concomitant TMZ appears to change the radiobiological parameters. This aspect of results suggests possible treatment developments.

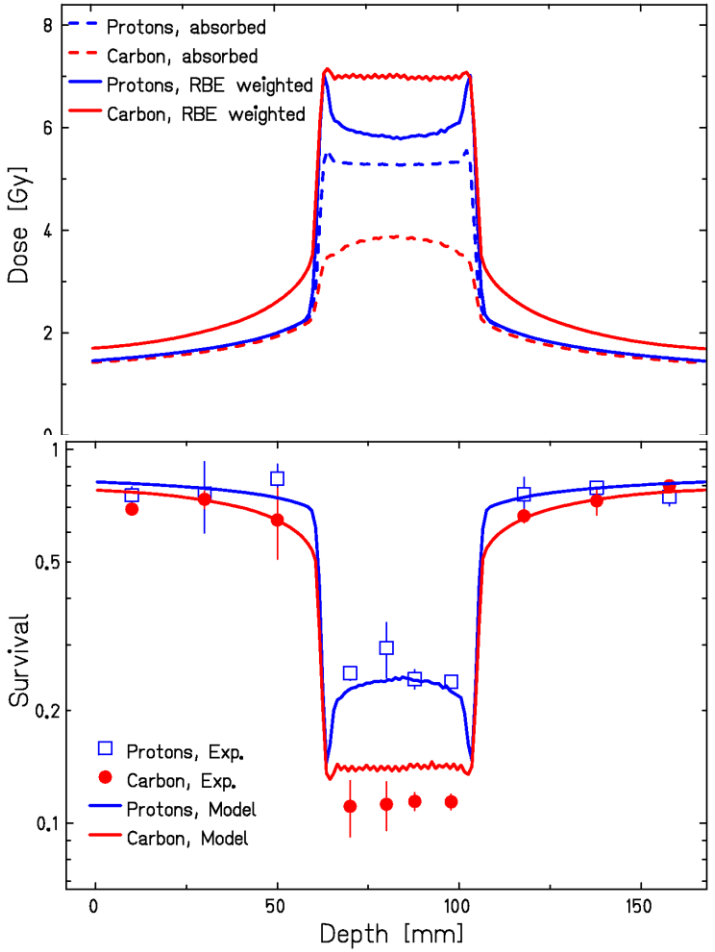
Quantification of the Relative Biological Effectiveness for Ion Beam Radiotherapy: Direct Experimental Comparison of Proton and Carbon Ion Beams and a Novel Approach for Treatment Planning

Thilo Elsässer, Wilma K. Weyrather, Thomas Friedrich, Marco Durante, Gheorghe Iancu, Michael Krämer, Gabriele Kragl, Stephan Brons, Marcus Winter, Klaus-Josef Weber, Michael Scholz

Int. J. Radiation Oncology Biol. Phys. In Press, Available online 21 August 2010



- Chinese hamster ovary cells
- Two port irradiation
- Three-dimensional phantom
- Pencil beam scanning technique
- Direct experimental *in vitro* comparison of proton and carbon irradiation
- Comparison to model predictions (LEM, TRiP)

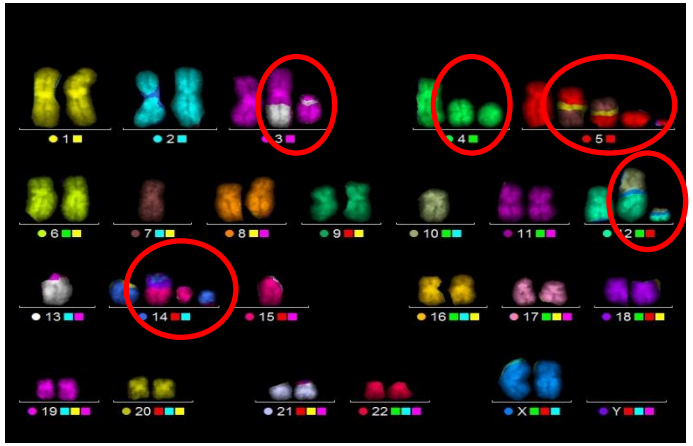


Chromosomal aberrations in peripheral blood lymphocytes of prostate cancer patients treated with IMRT and carbon ions.

Hartel C, Nikoghosyan A, Durante M, Sommer S, Nasonova E, Fournier C, Lee R, Debus J, Schulz-Ertner D, Ritter S.

Radiother Oncol. 2010 Apr;95(1):73-8. Epub 2009 Sep 30

- 22 patients treated for prostate cancer.
- Chromosomal aberrations in peripheral blood lymphocytes (representing the normal tissue)
- C-ion boost + photon IMRT or solely IMRT.
- multiplex fluorescence in situ hybridization technique (mFISH).
- Four blood samples per patient during radiotherapy course and 1 year follow-up.
- *In vitro* irradiation (X-rays and C-ions) performed in addition.
- Comparison of aberration yield after the C-ion boost and comparable doses IMRT
  → C-ion irradiation induces less aberrations in the peripheral blood lymphocytes than IMRT.

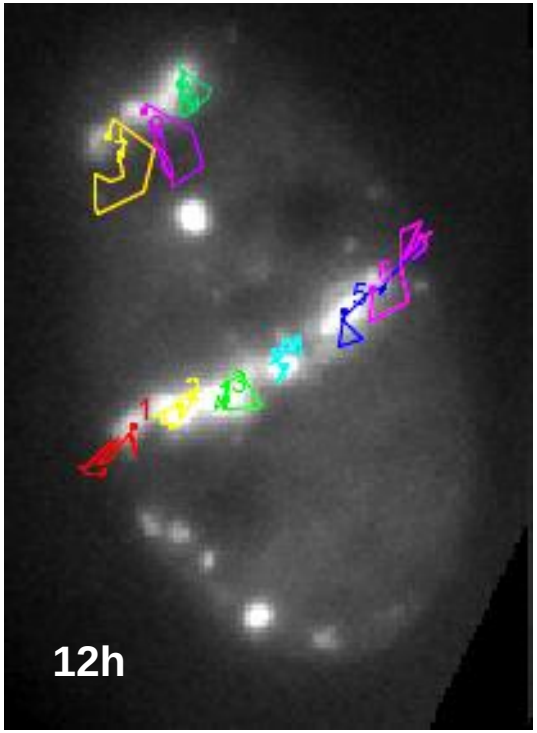


In vitro, 4Gy 100 MeV/u C-ions

In vivo, after therapy

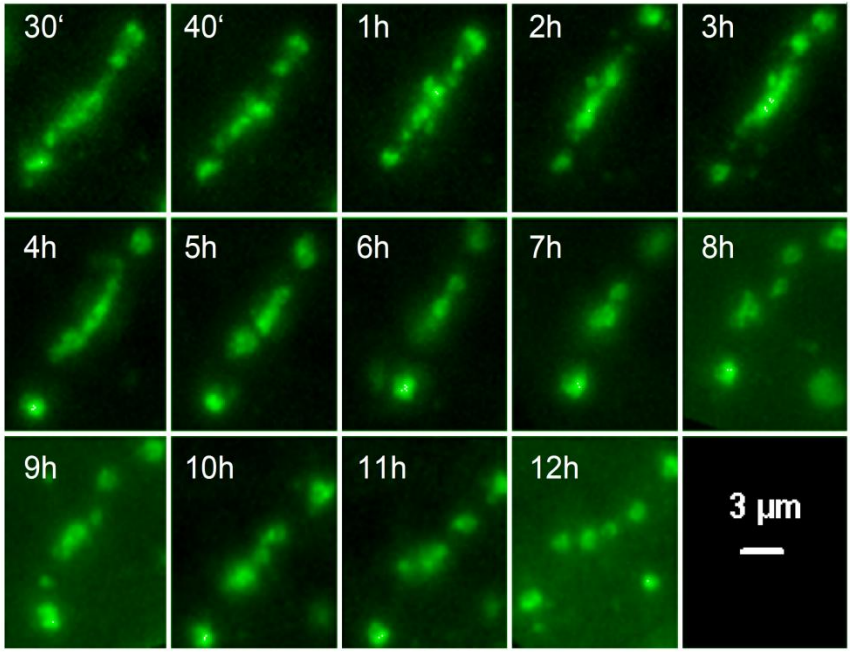
Live cell microscopy analysis of radiation-induced DNA double-strand break motion.

Jakob B, Splinter J, Durante M, Taucher-Scholz G.
Proc Natl Acad Sci U S A. 2009 Mar 3;106(9):3172-7. Epub 2009 Feb 12



Motional trajectories of foci inside ion tracks

- Live cell imaging of ion-induced double-strand breaks: positional stability over 12h, only diffusion-compatible undirected motion, no large scale migration.
- Implicates that DSB proximity is needed for chromosomal translocations.



A Monte Carlo study of the radiation quality dependence of DNA fragmentation spectra.

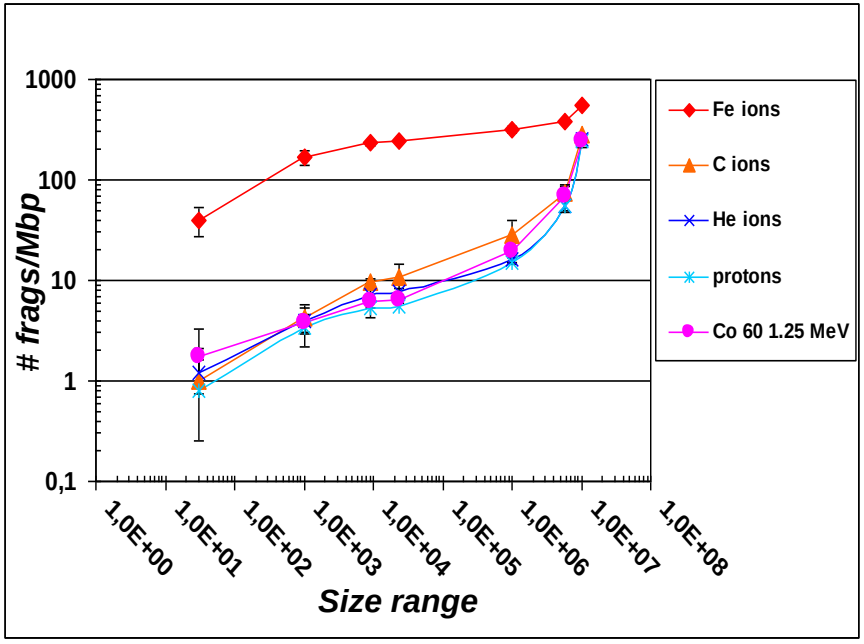
UNIPV-DFNT

D. Alloni, A. Campa, M. Belli, G. Esposito, A. Facoetti, W. Friedland, M. Liotta, L. Mariotti, H. G. Paretzke, and A. Ottolenghi

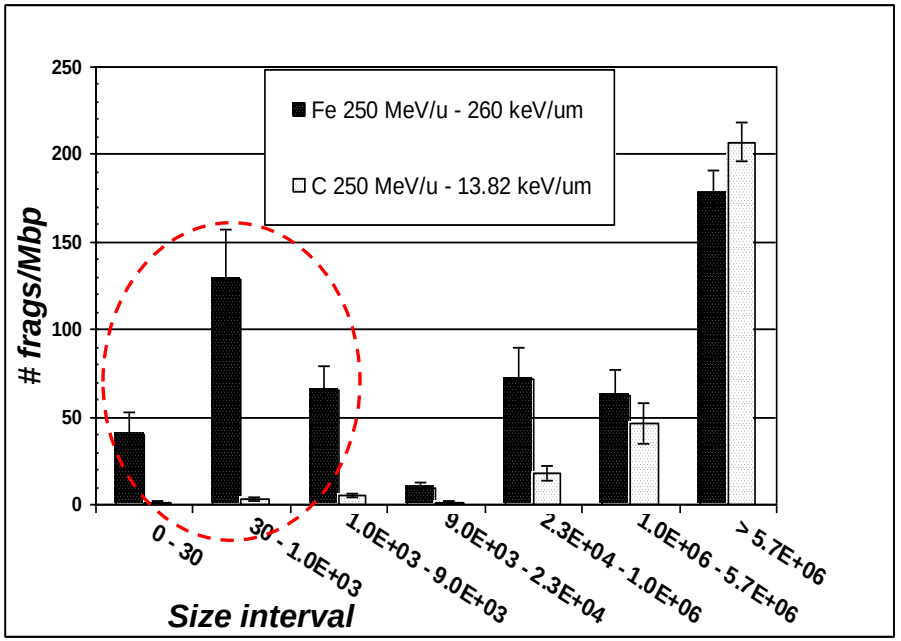
Radiation Research 173(3):263-271. 2010

EXAMPLE: same specific energy

Cumulative DNA fragment distributions ions 250 MeV/u - 5 Gy



Iron vs. Carbon 250 MeV/u - 5 Gy



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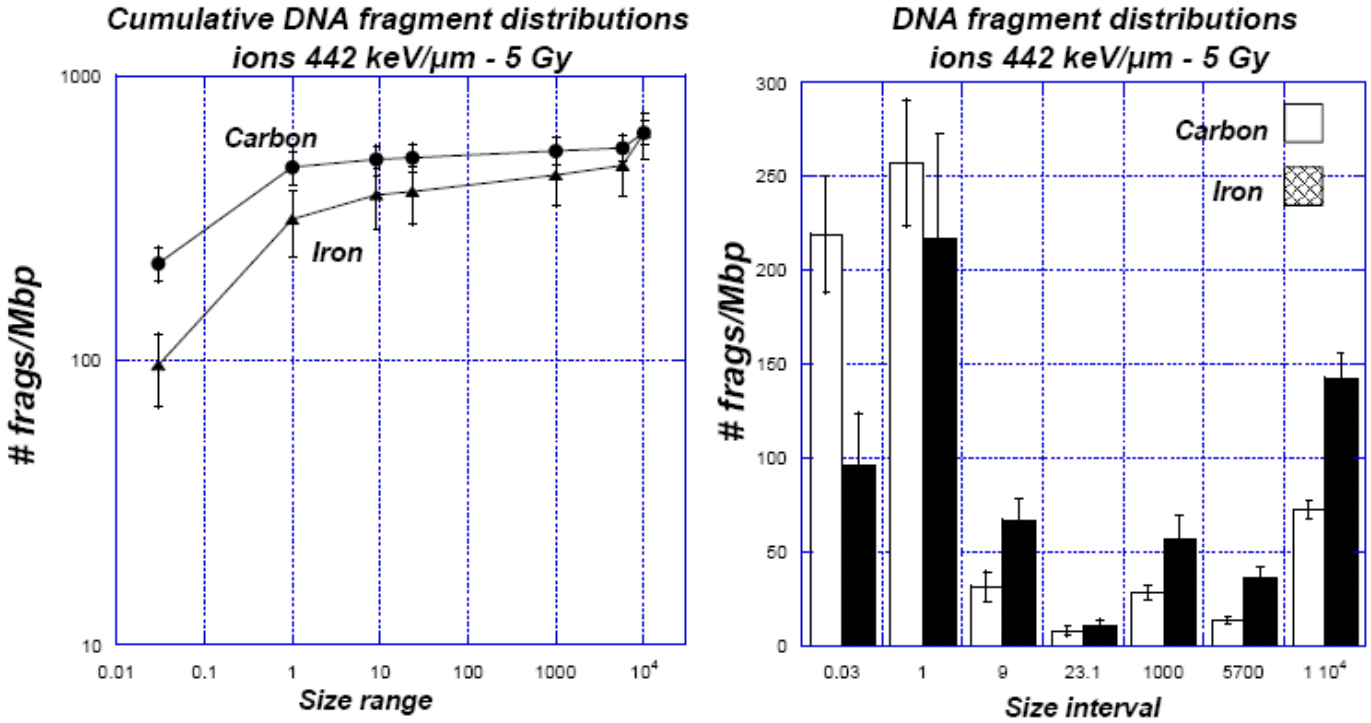
EXAMPLE:

same LET



The ion with the lower charge (and thus with lower specific energy for the same LET) generates δ rays with an energy distribution shifted towards lower energies. In terms of track structure this results in a "narrower" track and a lower mean free path, with an enhanced production of smaller fragments.

Comparative Analysis of Cellular and Molecular Responses of Tumor Cells towards High and Low LET Radiation

Chitralekha Mohanty

The proposed research works aims to *in vitro,* in human tumour and normal 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.
- differences in **cell cycle alterations** and **molecular responses** after exposures to low LET photon and **high LET** carbon ions.
- comparison of cellular and molecular responses after exposure to other ions.
- the **intra cellular targets** for specific types of cell death and cell cycle regulation; micro-beam studies e. g. on carbon ions

Comparative Analysis of Cellular and Molecular Responses of Tumor Cells towards High and Low LET Radiation

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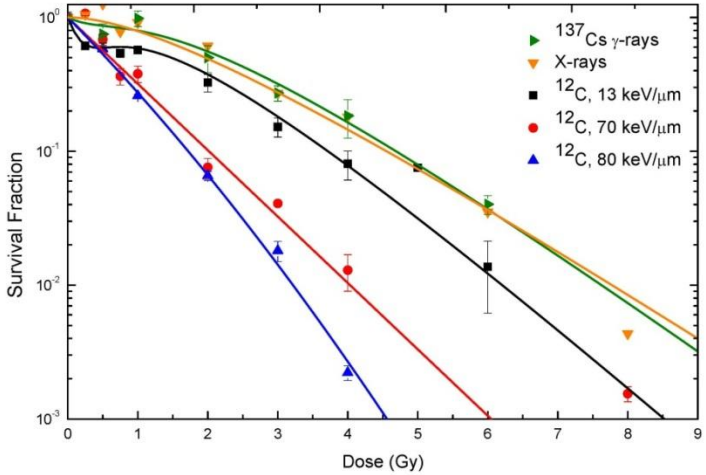
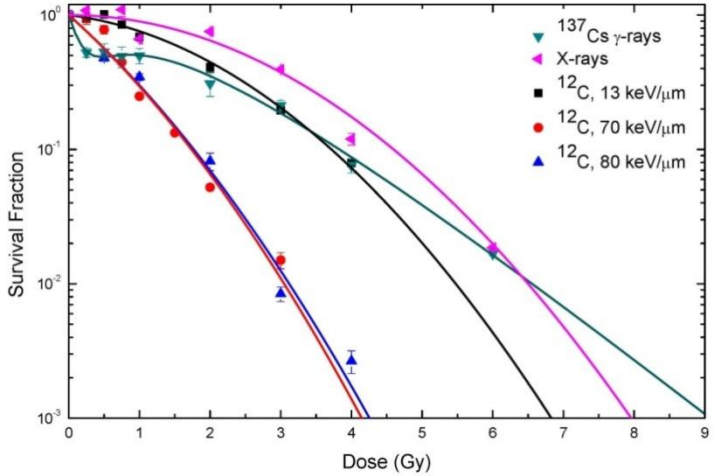
DU-145



PC3



The CCK, Stockholm, Sweden
The TSL, Uppsala, Sweden

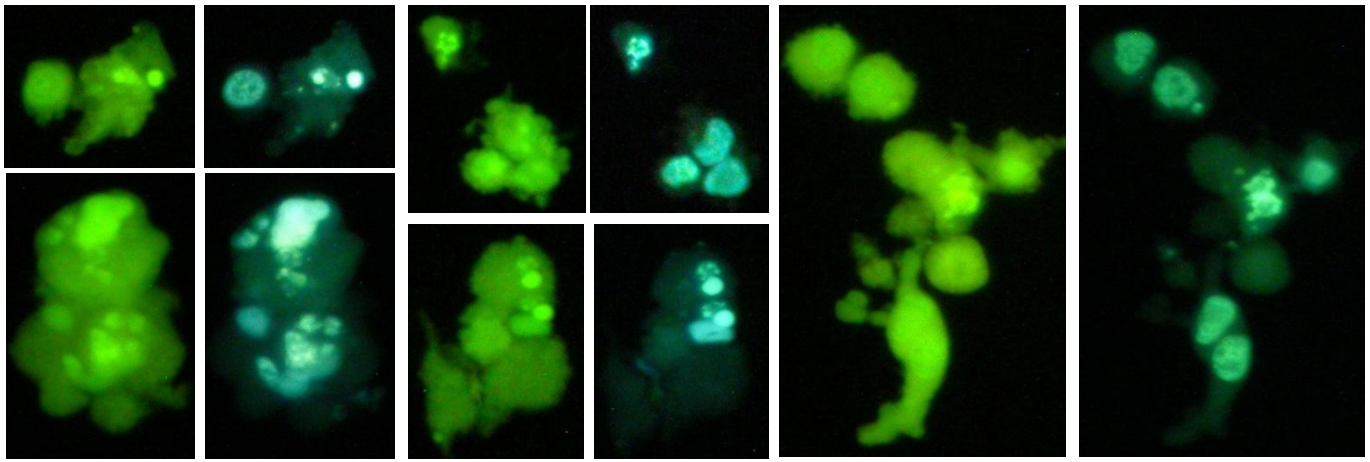
The HIMAC, Chiba, Japan
The NIRS, Chiba, Japan

The International Open Laboratory (IOL)

National Institute of Radiological Sciences
独立行政法人 放射線医学総合研究所

Progress and Future work

Chitralekha Mohanty



PC3 cells exposed to photons and carbon ions of different LET

Cell cycle analysis

Senescence, Ki67, β-galactosidase assay

Molecular responses