Time-dependent changes in expression of motility genes in prostate cancer cells after exposure to low- and high-LET radiation

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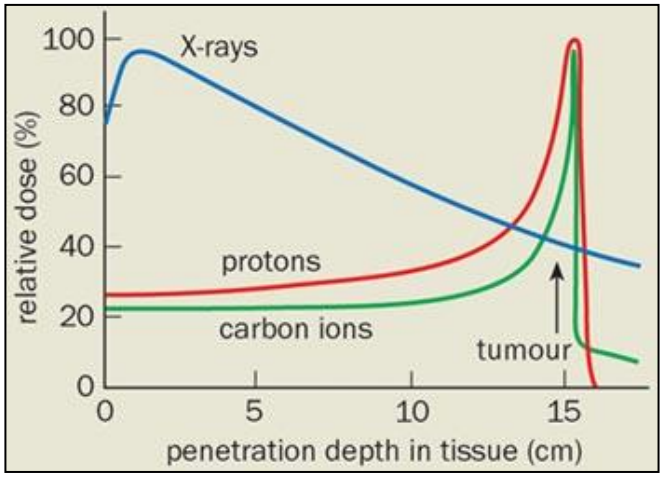
Radiotherapy for cancer

- Conventional: high energy photons



- Advanced = accelerated particle beams
  - Protons and carbon ions
  - Superior physical and biological properties

    - Precise localization of radiation dose

    - Useful for (radioresistant) tumors at critical locations

      e.g. H&N, NSLC, prostate cancer, …

    - Clinical trials: good local tumor control and survival rates

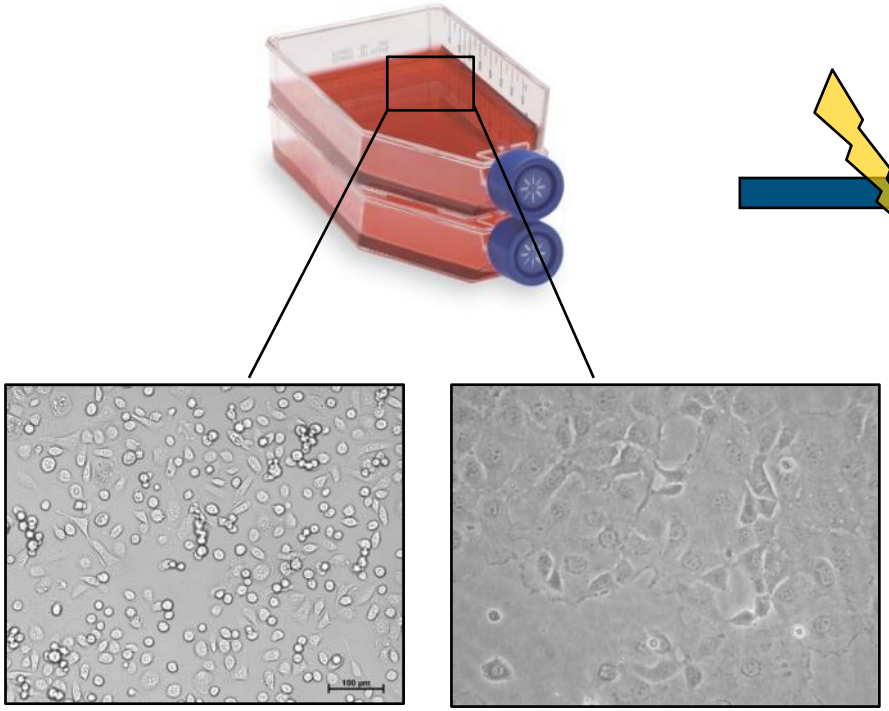
Objective

What is the impact of **different radiation qualities** on changes in **gene expression** in **cancer** cells?

- Whole-genome profiling after irradiation
- *Time-, dose- and cell type-dependent changes in motility related genes*
- *Potential clinical relevance of motility genes*

Experimental set-up

In vitro model



PC3 human prostate cancer cell line

Caco2 human colon cancer cell line

Irradiation

- **Carbon:** C-ions (75 MeV/u; LET = 33.4 keV/µm)
- **X-ray:** Pantak HF420 RX (250 kV, 15 mA, 1mmCu, 1.2 mm Al dose rate: 0,25 Gy/min)

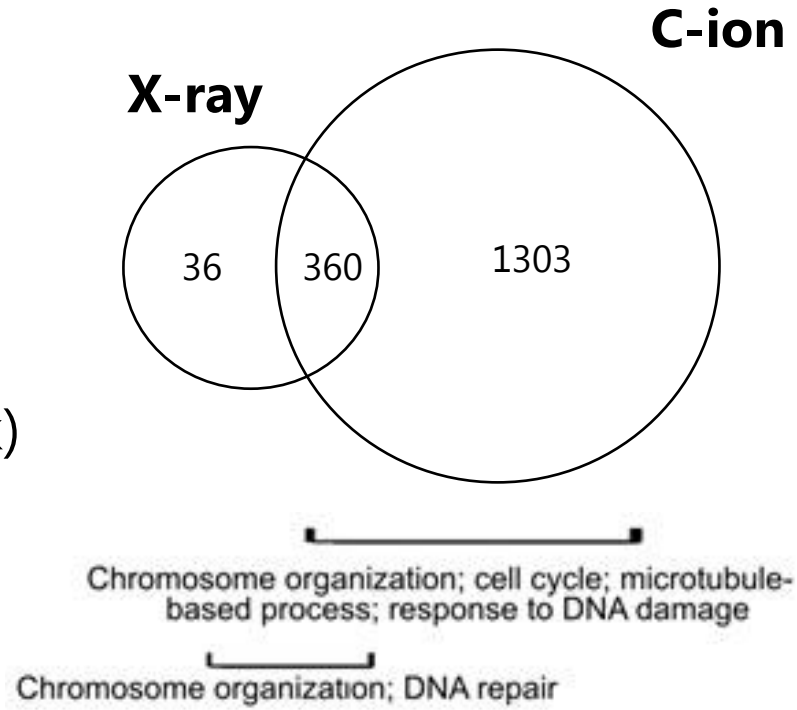
→ Doses: 0, 0.5 and 2 Gy

→ Timepoints: 2-8-24 h

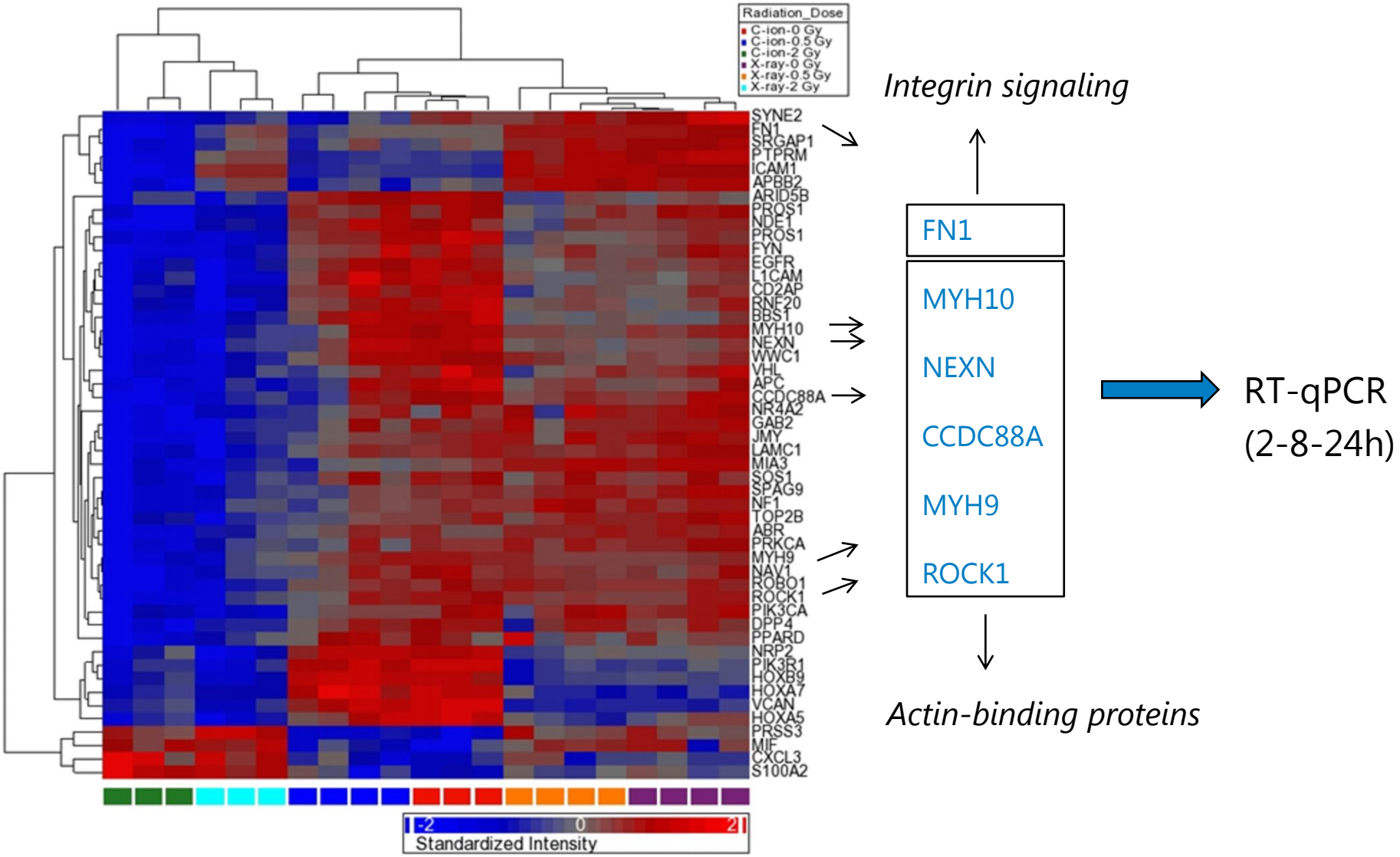
RNA collection

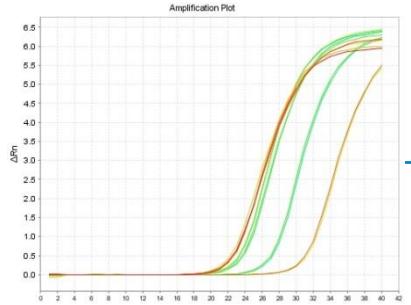
Whole-genome expression profiling

- RNA extraction of **PC3** cells
  - Doses: 0, 0.5, 2 Gy
  - 8 h timepoint
- Microarray + data analysis (Partek)
  - Gene expression profiles
    - FC (≥ |2| with FDR ≤ 0.05 (2 Gy))
  - Gene ontology
    - Specific biological processes

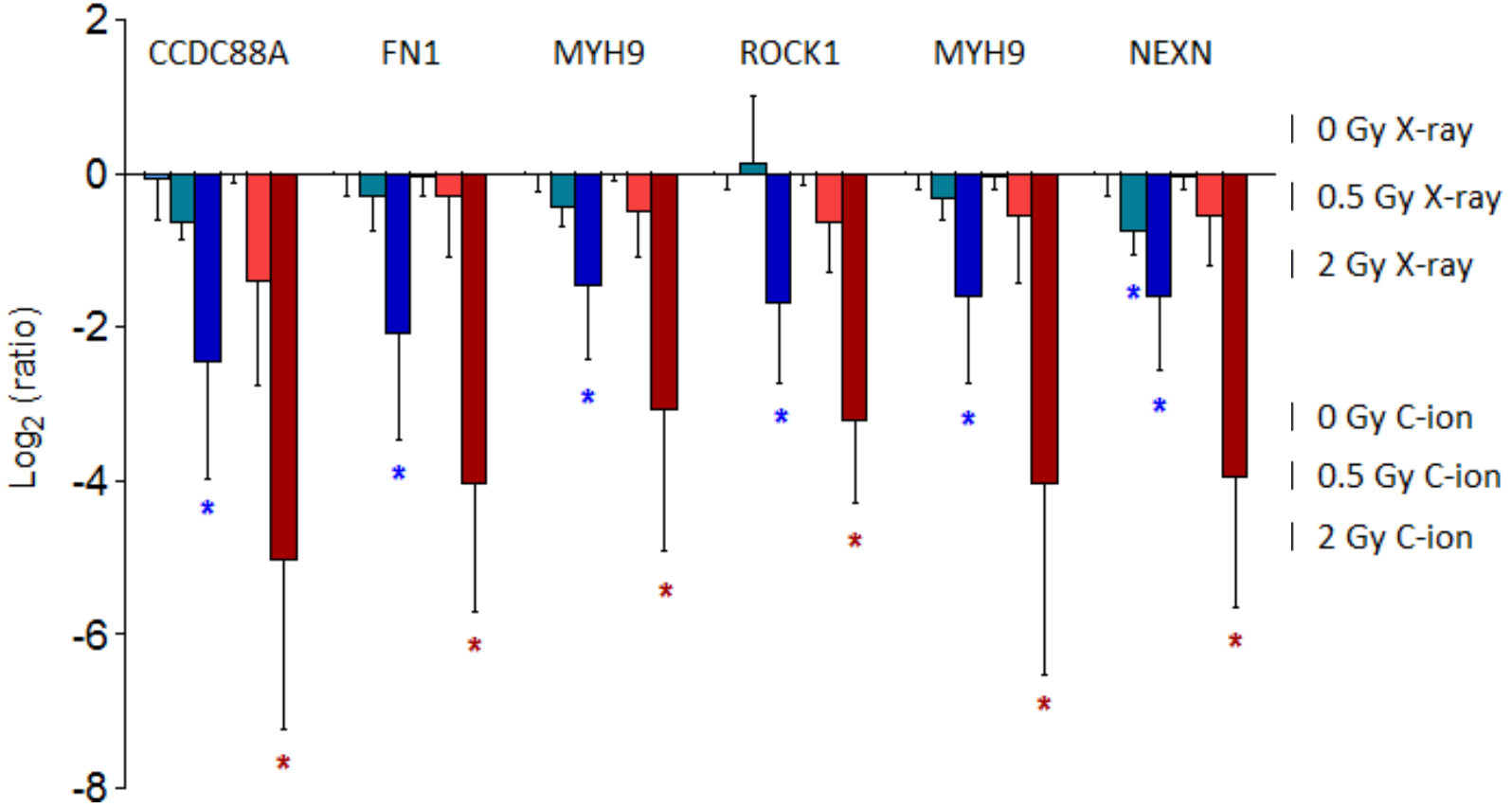


GO set: motility genes





Dose-dependent changes in motility genes



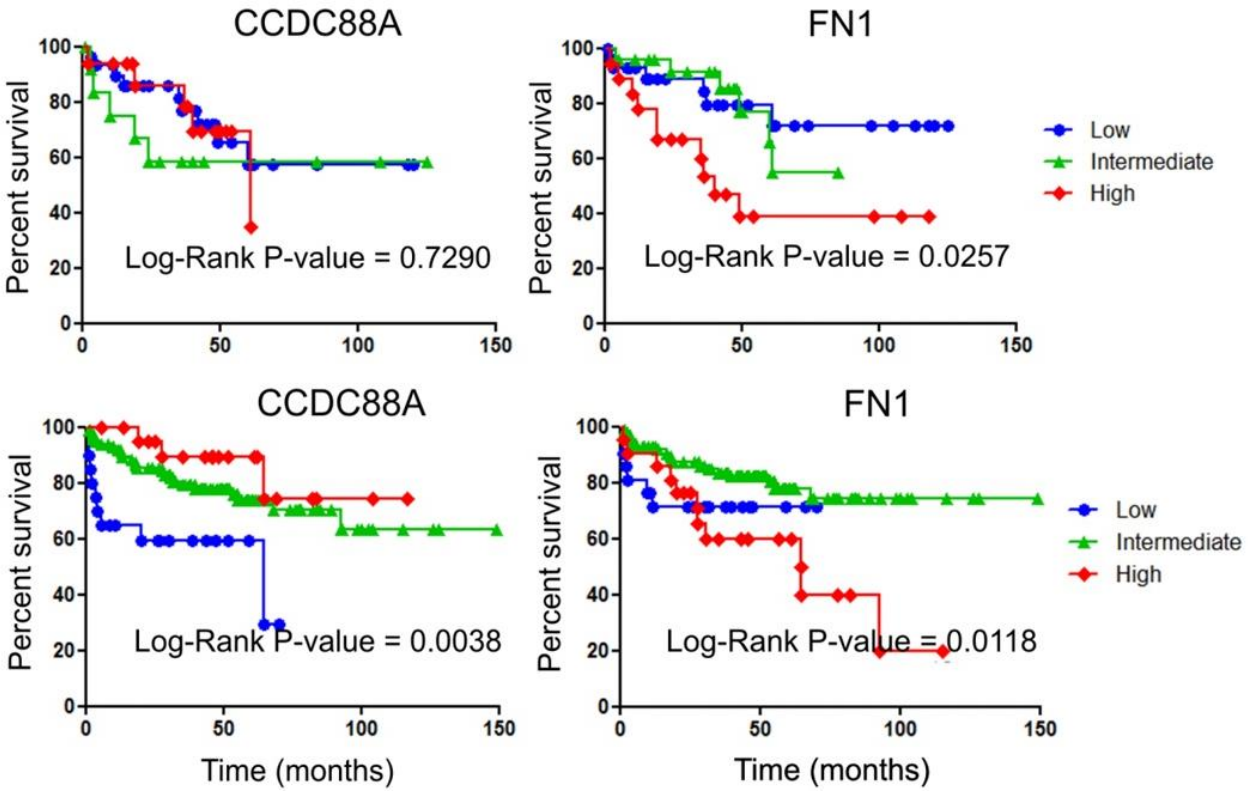
- * marks significantly altered gene expression compared to CTRL samples (p-value ≤ 0.05) based on one-tailed Mann Whitney tests.

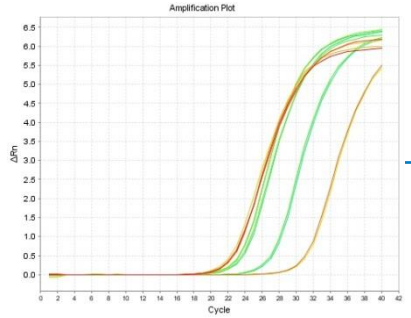
Clinical relevance?

- Publicly accessible microarray data (**prostate** cancer patients)
  - Kaplan-Meier survival analysis

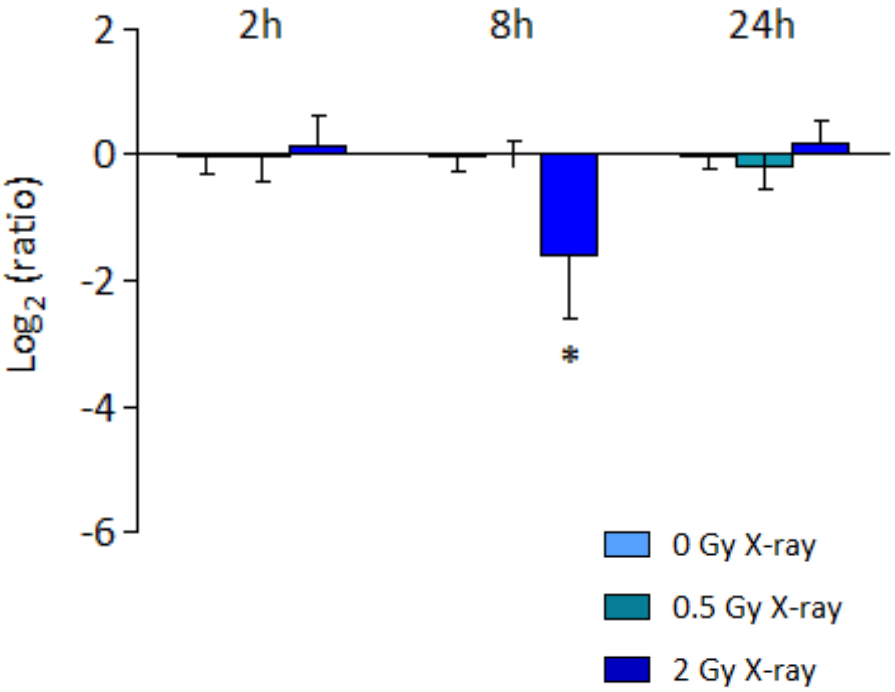
Taylor *et al*. 2010

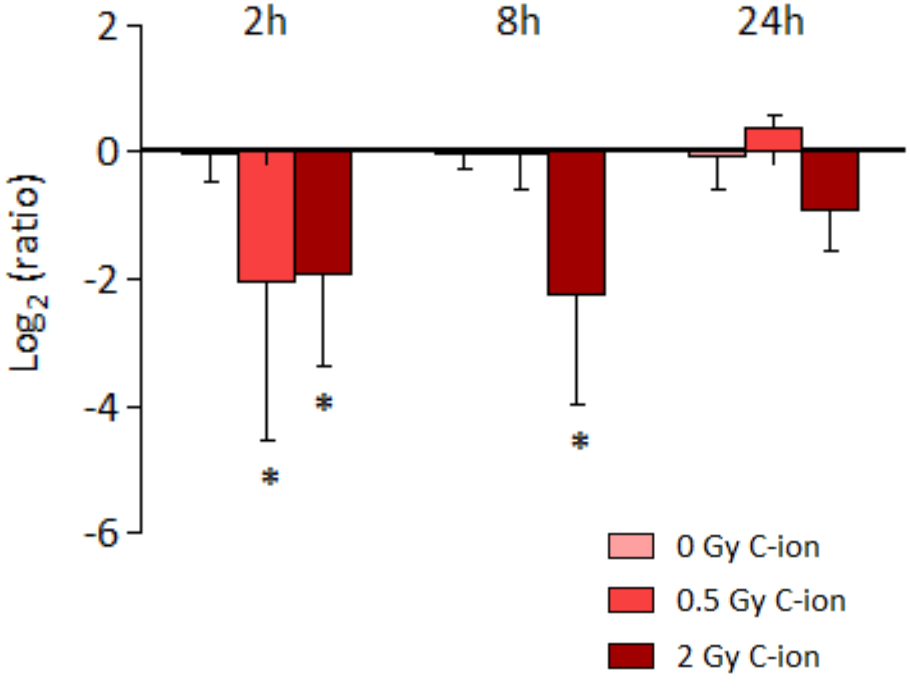
Gulzar *et al*. 2012



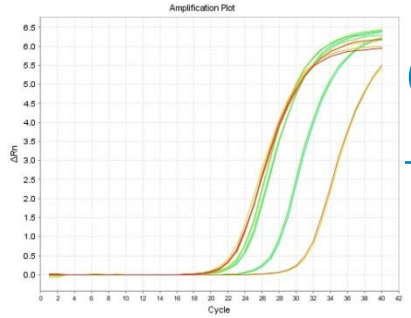


Time-dependent changes in motility genes





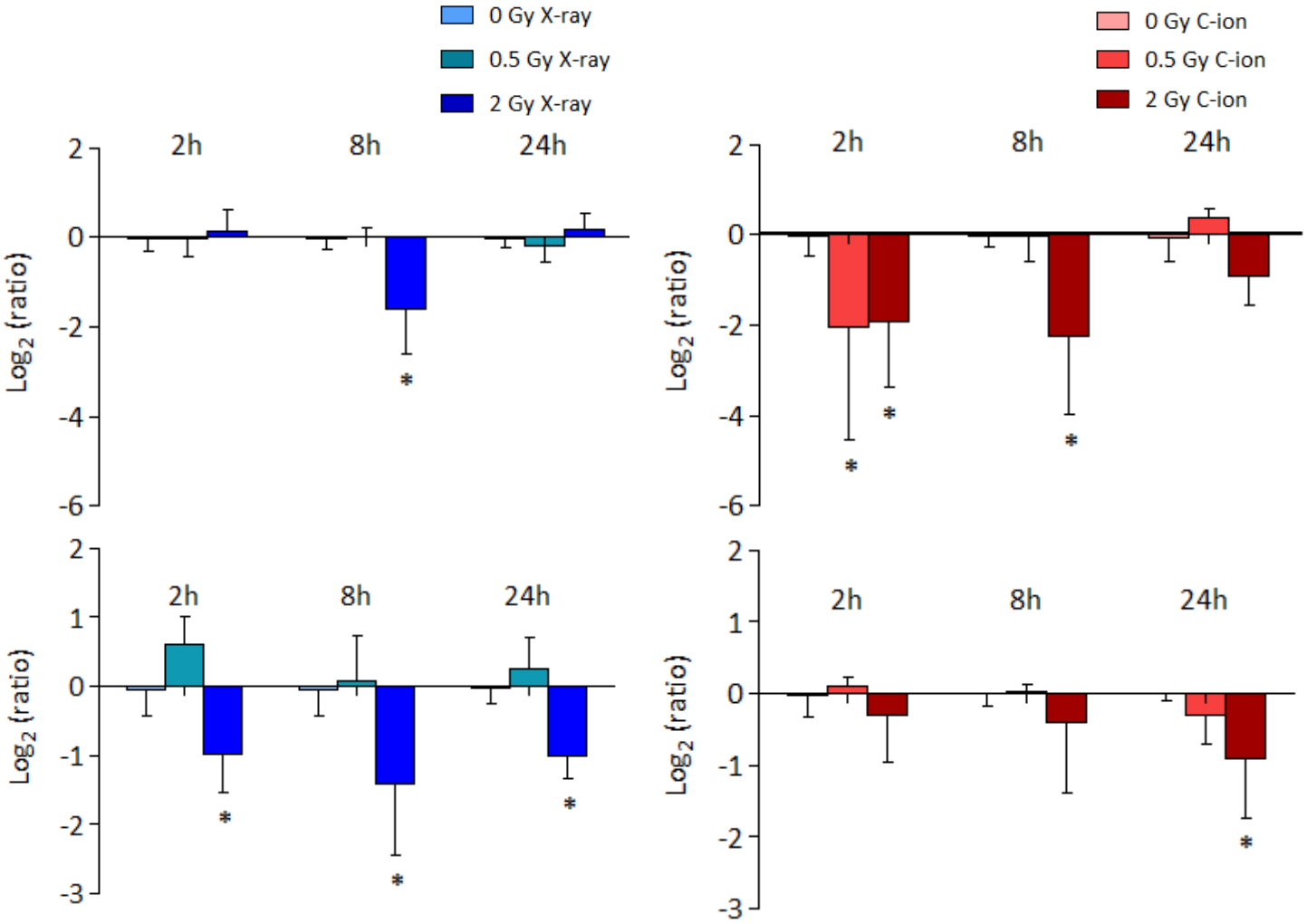
- FN1 gene expression in PC3 cells
- * marks significantly altered gene expression compared to CTRL samples (p-value ≤ 0.05) based on one-tailed Mann Whitney tests.



Cell type-dependent changes in motility genes

FN1 expression in PC3 cells

FN1 expression in Caco2 cells



- * marks significantly altered gene expression compared to CTRL samples (p-value ≤ 0.05) based on one-tailed Mann Whitney tests.

Low dose effects on motility genes

- Literature
  - Sub-lethal doses X-irradiation induce migration
  - General trend for heavy ion irradiation reduced migration
    - However with exceptions (PANC-1, Fujita et al., 2012)

➡ Will gene expression analysis bring more insight?

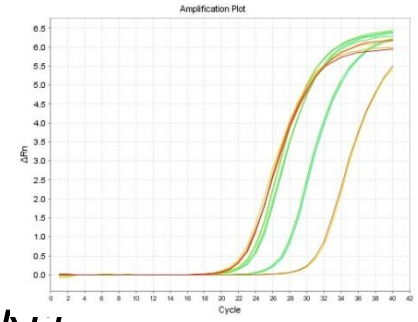
- Preliminary results
  - X-ray and nickel ion irradiation
    -> upregulating trend in Caco- cells but not in PC3 cells

- Future experiments
  - X-ray irradiation at SCK•CEN
  - Proton irradiation at LARN, Namur

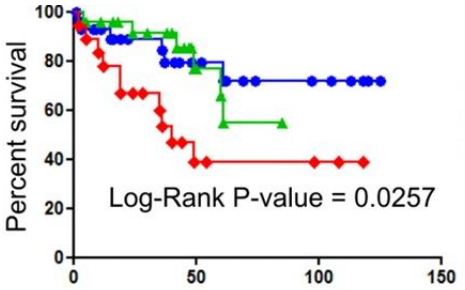
Conclusions & future perspectives

- Genomic profiling of prostate cancer cells (C-ion / X-rays)
  - C-ion >>> X-rays (# genes, magnitude)
  - Genes of several interesting pathways are regulated

- Radiation-induced changes in motility genes (C-ion / X-rays)
  - Dose-dependent downregulation (8h)
  - Time-dependent changes depending on radiation quality
  - Cell type-dependent changes



- Use of motility genes as potential biomarkers → *FN1*



- Future perspectives
  - *In vitro* cell behaviour: invasion – adhesion assay
  - Involvement of actin-binding proteins in cell cycle

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