How do different radiation qualities affect the Hedgehog signaling pathway?

Katrien Konings
Radiobiology Unit, SCK•CEN, Mol, Belgium
Laboratory of Experimental Radiotherapy, KU Leuven

kkonings@sckcen.be

KU LEUVEN

SCK•CEN
STUDIECENTRUM VOOR KERNENERGIE
CENTRE D'ETUDE DE L'ENERGIE NUCLEAIRE

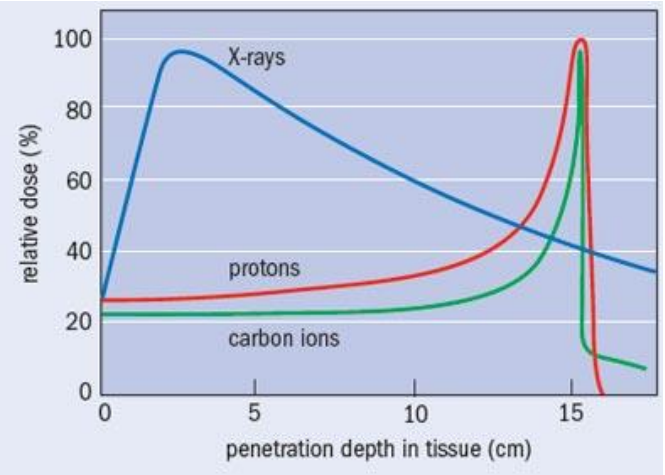
BHTC

Overview

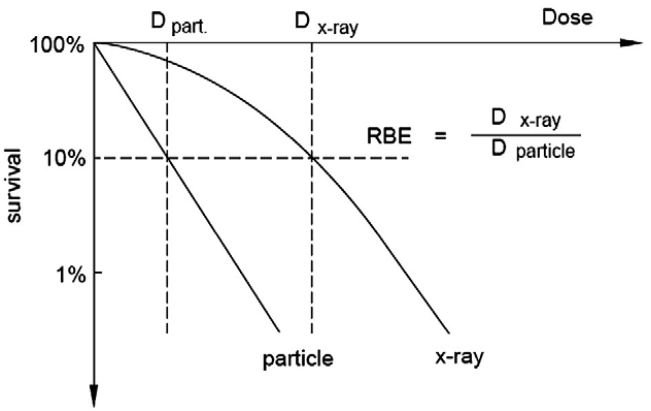
- Introduction
- Aims of the PhD project
- Results
- Conclusions
- Future perspectives
- Acknowledgements

Introduction

- Radiotherapy
  - ±50% of cancer patients
  - Conventional radiotherapy
    - Photons (X-rays)
  - Particle therapy
    - Protons or carbon ions
    - Physical and biological advantages
    - Specific clinical indications
      - Children
      - Brain tumours
      - …



Relative biological effectiveness (RBE)



Introduction

- Photons ⟷ particles
  - Different biological effects
    - DNA damage
    - Migration
    - Gene expression
      - Previously published data
        (Suetens et al., Int J Oncol, 2014 and Suetens et al., J Radiat Res, 2015)

→ Hedgehog (Hh) signaling pathway

- Aberrant expression in cancer
  - Tumor growth, survival and progression
  - Therapy resistance

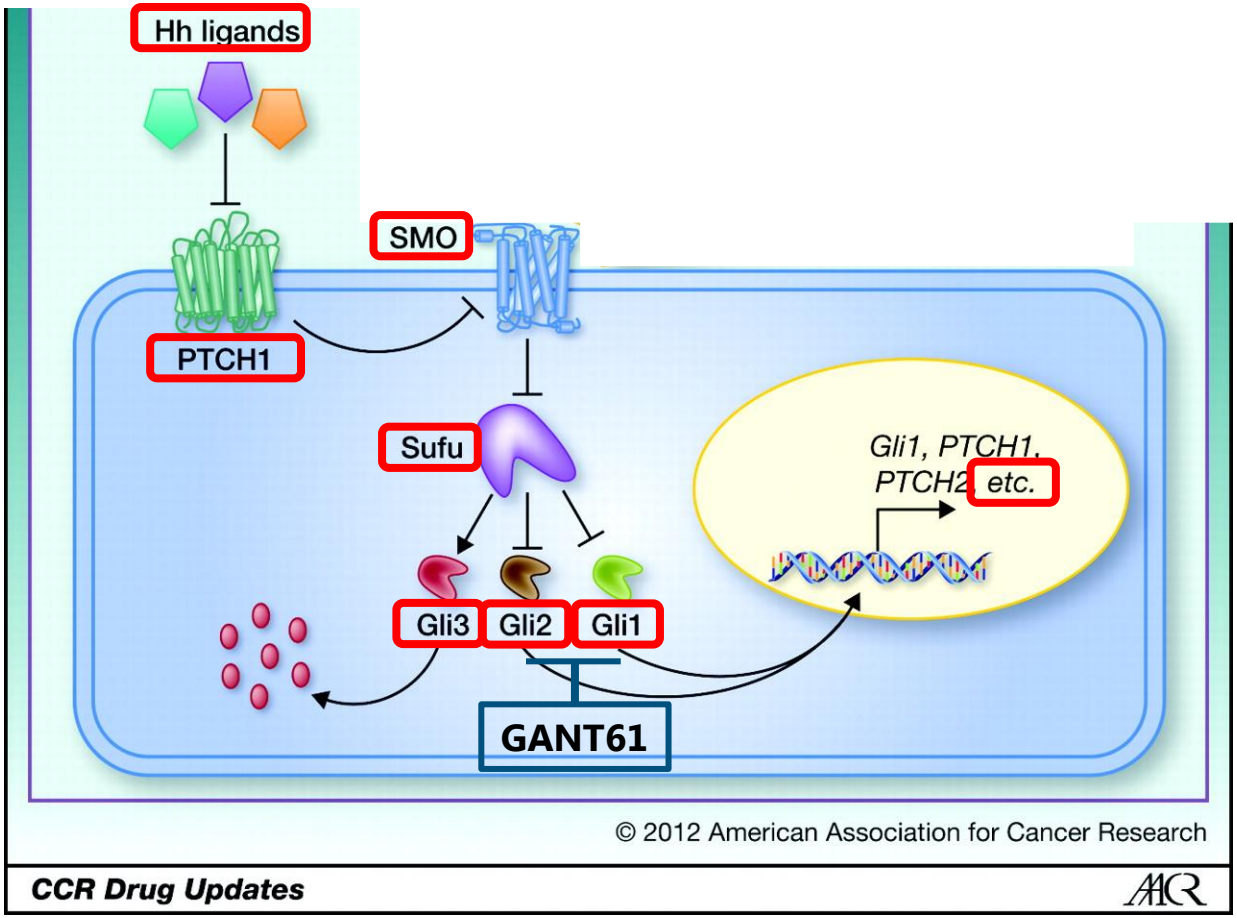
Hh pathway can become activated after photon irradiation

→ radioresistance of tumor

→ effect after particle irradiation unknown

Introduction

- Hedgehog pathway
  - SHH
  - PTCH1
  - SMO
  - SUFU
  - GLI1, 2, 3
  - CCND1
- Hh inhibitor:
  - GANT61



Aims of the PhD project

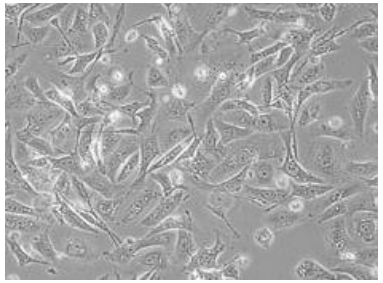
1) Investigate the effect of different radiation qualities on the cellular and molecular response of cancer cells

2) Investigate the effect of Hh inhibitors in combination with different radiation qualities on cancer cells

Experimental set-up

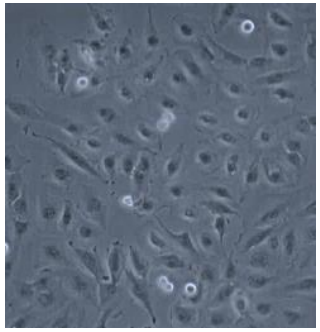
In vitro cancer cells lines

PC3



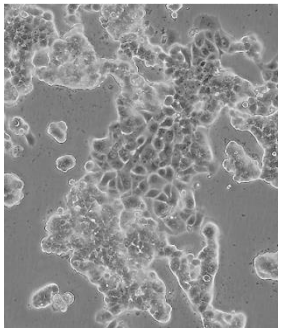
Prostate cancer

DAOY



Pediatric
Medulloblastoma

MCF-7



Breast cancer

X-rays
Protons
Carbon ions

± Hh inhibitor
GANT61

1) Cell survival

2) Gene expression of Hh pathway

3) Migration – invasion

Different radiation qualities

- X-rays
  - SCK•CEN
  - XStrahl 320 kV generator
  - 250 kV, 12 mA, 1.4 mmCu, 3.8 mm Al
  - Dose rate: 0,5 Gy/min
  - Doses: 0, 0.5, 2, 4 and 6 Gy

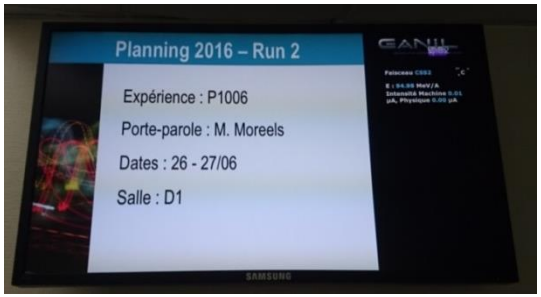
- Protons
  - NARILIS, UNamur (Prof. Stéphane Lucas)
  - ALTAÏS accelerator
  - LET = 25 keV/µm
  - Dose rate: 0,5 Gy/min
  - Doses: 0, 0.5, 2, 4 and 6 Gy

- Carbon ions (^{12}C)
  - GANIL, Caen, France
  - Beam energy = 95 MeV/u
  - LET = 73 keV/µm
  - Doses: 0, 0.5, 1, 2, 3 and 4 Gy

Experiment @ GANIL

- 27th of June 2016
- 1,5 UT of carbon ion beam time (12 hours)
- Beam energy: 95 MeV
- LET: 73 keV/µm
- PC3, DAOY and MCF-7 cell lines:
  - Colony survival assay (+/- GANT61)
  - Gene expression (+/- GANT61)
  - Migration assay: Boyden chamber

→In total 248 samples were irradiated



Conclusion

- Colony survival assay
  - Particle irradiation is more effective in cell killing compared to X-irradiation
- Migration assay
  - Dose-dependent decrease in cell migration, more pronounced after carbon ion irradiation
- Gene expression of the Hh pathway
  - Components of the Hh pathway are differently affected by different radiation qualities
  - More pronounced changes after carbon ion irradiation in DAOY and PC3 cells compared to X-irradiation

Future experiments

Further investigate the impact of different radiation qualities for the different cell lines (increase number of replicates)

- Colony survival assay
- Gene expression analysis
- Migration assay

} ± Hh inhibitors

- X-irradiation experiments at SCK•CEN (ongoing)
- Proton irradiation experiments at NARILIS, UNamur (ongoing)
- Submitted project for proton beam time at iThemba (South-Africa-, collaboration with RDC).
- Carbon ion irradiation at GANIL, France

Acknowledgements

- SCK•CEN
  - Prof. Sarah Baatout
  - Dr. Marjan Moreels
  - Niels Belmans
  - Merel van Walleghem
  - Thomas Bielen
  - Arlette Michaux
  - Kevin Tabury
  - RDC
- GANIL
  - Dr. Yannick Saintigny
  - Dr. Florent Durantel
- KU Leuven
  - Prof. Dr. Karin Haustermans
  - Dr. Sofie Isebaert
  - Annelies Gonnissen
- UNamur
  - NARILIS
  - Prof. Stéphane Lucas
  - Dr. Anne-Catherine Heuskin
- BHTC
  - Prof. Frank Deconinck