The Increased Biological Effectiveness of Heavy Charged Particle Radiation:

From Cell Culture Experiments to Biophysical Modelling

Michael Scholz
GSI Darmstadt
Advantage of ion beams for therapy:

Physical aspects:
• Inverted depth dose profile
• Defined penetration depth
• Reduced lateral scattering

Biological aspects:
• Increased effectiveness
• Reduced oxygen effect
Inverted Depth Dose Profile

Bragg Peak

![Graph showing relative dose vs depth in water for different particle types and energies. The graph includes data for photons (21 MeV), $^{12}$C (270 MeV/u), and protons (148 MeV/u).]
Biological Advantage: Increased Effectiveness

Carbon 195 MeV/u

Differential Effect:

\[
\text{RBE(Depth)} > \text{RBE(Entrance)}
\]

Kraft-Weyrather et al.
Cell Survival

V79 Chinese Hamster Cells

Survivor:

1 cell $\rightarrow$ $\geq$ 50 cells
(t=0)    (t=7d)

„Colony forming“

G. Böhrnsen/
I. Katayama

$\Delta t=15\text{min}$

$T_{ges}=85\text{h}$
Survival after Photon Irradiation

G. Böhrnsen

\[ S = \frac{N_{col}}{N_{seed}} = e^{-(\alpha D + \beta D^2)} \]
Survival after Carbon Ion Irradiation

- Increasing effectiveness with decreasing energy
- Saturation effects at very low energies (<10 MeV/u)
- Transition from shouldered to straight survival curves
Definition of Relative Biological Effectiveness

\[
RBE = \frac{D_\gamma}{D_{\text{Ion}}} |_{\text{Isoeffect}}
\]
RBE depends on LET

![Graph showing RBE vs LET, Energy, and Remaining range for CHO-Cells, Carbon Ions]

W. Kraft-Weyrather
RBE depends on Dose

- RBE decreases with dose
- Dose dependence more pronounced for lower energies

W. Kraft-Weyrather
RBE depends on **Cell Type**

Increase of effectiveness is more pronounced for resistant tumors compared to sensitive tumors

W. Kraft-Weyrather
RBE depends on Cell Type

RBE is higher for resistant (repair proficient) cell types.

W. Kraft-Weyrather
RBE depends on Ion Species

- RBE maximum is shifted to higher LET for heavier particles
- The shift corresponds to a shift to higher energies

\[ \text{LET [keV/\mu m]} \]

\[ \sim 1 \text{ MeV/}u \sim 15 \text{ MeV/}u \]
Explanation of increased effectiveness

M. Krämer

Cell nucleus

10 µm
Cells are able to repair radiation induced DNA damage.
Cellular DNA Damage Response Pathways

Transition $G_1 \rightarrow S$-Phase

Transition $G_2 \rightarrow M$-Phase
The Role of non-coding DNA

J.S. Mattick, Spektrum d. Wissenschaft 3/2005
Can we model it from first principles?

>100 (free?) parameters!

Precision ????
Radial Dose Profile of Particle Tracks

Radial Dose Profile:
\( D(r) \): Expectation value

\[ D(r) \sim \frac{1}{r^2} \]

\[ R_{\text{Track}} \sim E^c \]
Microscopic Local Dose Distribution
Visualization of Local Biological Response

CDKN1A/p21: green
DNA: red
Pb-ions, 3.1 MeV/u, 3x10^6/cm^2

Cell Nucleus

p21 response

Tracks in CR39

Ca-ions, 10.1 MeV/u, 2x10^6/cm^2

B. Jakob et al.

M. Scholz et al.
Basic Assumption:
Increased effectiveness of particle radiation can be described by a combination of the photon dose response and microscopic dose distribution + RBE!
Local biological effect:

\[ S = e^{-N_{\text{lethal}}} \]

Low-LET dose response:

\[ \bar{N}_{\text{lethal}}(D) = -\ln S_X(D) = \alpha D + \beta D^2 \]

Event density:

\[ \nu(D) = \frac{\bar{N}_{\text{lethal}}(D)}{V_{\text{Nucleus}}} \]

\[ \bar{N}_{\text{lethal}} = \int \frac{-\ln S_X(d(x, y, z))}{V_{\text{Nucleus}}} dV_{\text{Nucleus}} \]

M. Scholz et al.
Input Parameters

• Radial Dose Distribution:
  Monte-Carlo (M. Krämer), Analytical Models (Katz, Kiefer), Experimental Data
  \[ D(r) \propto \frac{1}{r^2} \quad R_{\text{Track}} \propto E^{1.7} \]

• X-ray Survival Curves:
  Experimental data according to LQ; additional assumption:
  Transition from shoulder to exponential shape at high doses
  \[ S = e^{-(\alpha D + \beta D^2)}, \quad D < D_t \]
  \[ S = e^{-s_{\text{max}}(D-D_t)}, \quad D \geq D_t \]

• Target Size (Nuclear Size):
  Experimental Data
Algorithms

- **Exact calculation:**
  - Monte-Carlo method for determination of ion impact parameters
  - Numerical integration (taking into account overlapping tracks in detail)

- **Approximation:**
  - Exact calculation of single particle effects (corresponding to initial slope of survival curve)
  - Estimation of $\beta$-term from boundary condition:
    Max. slope of HI curve = max. slope of photon dose response curve
Comparison with experimental data

Data: Kraft-Weyrather et al.
Comparison with experimental data

Data: Weyrather et al., IJRB 1999
Summary

- Biological advantage of ion beams in tumor therapy: increased effectiveness in Bragg peak region
- Increased effectiveness depends on factors like dose, ion species & energy, cell type, ...
- Complex dependencies require modeling for treatment planning in ion tumor therapy
- Modeling cannot be based on first principles
- Empirical approaches based on a link to the photon dose response curves allow high quantitative precision