Radiobiological characterization of laser driven particles

Elke Beyreuther

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Outline

1. Research project onCOOPtics
2. In vitro experiments with laser-driven particles
3. Human tumor irradiation on mice
4. Optimization of the tumor model
5. Summary and outlook
1. Research project onCOOPtics

Aim: development of **compact ion therapy facility based on high-intensity laser** for radiotherapy of human cancer

- Technological progress in high power laser and optics
- Medical radiation research: investigation of the consequences of specific properties of laser driven particles on beam transport, radiation field formation, dosimetry and **radiobiological effects**

**Cell experiments**

**Animal studies**

Preclinical studies

Clinical application

Translational chain

Comparison to particle beams from conventional accelerators = medical devices: stable parameters and standard dosimetry
2. In vitro experiments with laser driven electrons

- JETI laser: 10 TW, 1 J, 80 fs, 10 Hz, multi-shot irradiation
- Electrons: 3…20 MeV
- Cell survival and DNA DSB ($\gamma$-H2AX foci, 24 h post irradiation) for several human tumour and normal tissue cell lines
- Reference radiation: 6 MeV clinical Linac

$\Rightarrow$ *No significant difference for cell survival, but significant lower number of foci for laser driven electron pulse irradiation of normal tissue*
2. In vitro experiments with laser driven protons

- DRACO laser: **150 TW**, 4 J, 25 fs, 10 Hz, multi-shot irradiation
- Protons: 6 … 18 MeV, 0.1 Hz
- Cell survival and DNA DSB (γ-H2AX foci, 24 h post irradiation) for human tumour cells
- Reference radiation: 10 MeV Tandem accelerator @ HZDR

\[\text{Surviving fraction / %} \]

\begin{tabular}{|c|c|}
\hline
\textbf{Dose / Gy} & \textbf{HNSCC tumour} \\
\hline
0 & \text{DRACO laser protons} \\
1 & \text{Tandem protons (reference)} \\
2 & \\
3 & \\
4 & \\
\hline
\end{tabular}

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\hline
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\hline
\end{tabular}

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\textit{No significant difference between laser-accelerated, ultra-short proton pulses and continuous Tandem proton beams}

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\[\text{Zeil et al. Appl Phys B 2013} \]
3. Transition from 2D to 3D irradiation

... requires new solutions for:

**Beam transport**
- Magnetic energy filtration ($E > 5$ MeV)
- Beam collimation and formation for homogeneous dose distribution
- Radiation shielding of mouse body

**Dosimetry and beam monitoring**

**Online monitoring**
- Faraday cup: dose rate independent absolute dose per pulse
- Ionization chamber: relative dose per pulse
- Scintillator: spatial dose and energy distribution

**Offline/Retrospective Dosimetry**
- Radiochromic film: dose rate independent absolute dose spatial (lateral, depth) dose distribution
3. Animal studies … additional requirements

Administration:
- Experiment proposal and permission from State Ministry
- Housing and maintenance according to animal welfare regulations
- Animal handling courses for all experimentalists

New small animal tumor model for laser driven particles
- Proton energies currently available at laser accelerators are too low (E ≤ 20 MeV) to penetrate standard tumors on mice legs
- New small animal tumor model established: human SCC FaDu on NMRI nude mouse ear

- Cartilage: natural demarcation to deeper layers
- Skin injection place
- Tumor
- Haematoxylin eosin staining
- Hoechst (perfusion)
- CD39 (vessels)
- Pimonidazole (hypoxia)

3. Tumor growth delay as first biological endpoint

Tumor growth delay (GD)
Difference between the mean time spans unirradiated and irradiated tumors need to achieve a certain rel. volume increase

\[ GD_{V_i} = t_{V_i,Dose} - t_{V_i,Control} \]

GD\(_{7\text{Gy}}\) \(\sim\) 16 days
GD\(_{14\text{Gy}}\) \(\sim\) 36 days

![Graph showing tumor growth delay for different radiation doses.](attachment:image.png)
3. In vivo study with laser accelerated electrons

... homogeneous dose delivery in 3D is easier with electrons

- JETI laser: 20 TW, 1.5 J, 80 fs, 10 Hz
- Electrons: 10 … 100 MeV, 5 Hz, multi-shot irradiation
- Real time and absolute dosimetry
- Radiation induced tumor growth delay: control, 0 Gy, 3 Gy, 6 Gy
- Reference irradiation: 21 MeV electrons (clinical LINAC)
- Full scale experiment (6 months, 300 mice)

Preparation and fixation of mice in mouse setup box
3. In vivo study with laser accelerated electrons

Mouse irradiation setup at JETI

Laser electrons: 10…100 MeV

Tumor position verification

Brüchner, Beyreuther et al. Radiat Oncol 2014;
3. Reference irradiation at a clinical Linac

- Radiation therapy in Dresden
- Linac: Oncor Impression, Siemens AG; $E_e = 21$ MeV
- JETI: $E_{e^-} = 20 – 150$ MeV, exponential
- Setup and handling similar to JETI campaign

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**Faraday Cup**

**Laser target chamber/collimator system**

**Mouse setup box**
3. Similar growth delay for laser driven and Linac electrons

Radiobiological effect: tumor growth delay
Full scale experiment

No significant difference in tumor growth delay due to ultra-short high-dose pulses of laser accelerated electrons

Proceeding with proton experiments, but …

Oppelt et al.: Radiat Environ Biophys 2015
4. The difference between “theory” and experiment

Establishment of the model & first tests

- Animal lab: 26°C, 50–60 % rel. humidity, 12-h light–dark cycle
- Qualified maintenance
- X-ray tube in lab, stable beam
- Tumor growing defines time point of treatment

| Application and planning of the experiment on basis of lab results |

Experiment at laser accelerator (& LINAC)

- Irradiation in a physics lab
- Heavy work load: animal care, exp. preparation in J and DD in parallel
- Beam loss and delay
- Beam time defines treatment time
  → Tumor take rate 60 – 90 %
  → Lower no. of treated animals

| Further reduction in follow up |

Model optimization before proton treatment required
4. Optimization of tumor model on mouse ear

Application of Matrigel® instead of PBS for tumor cell injection
- Gelatinous mixture of proteins e.g. laminin, collagen, growth factors
- Liquid at 4°C, polymerizes at 37°C
  → Reduce unintended flow of injected cells

Another tumor cell line of different origin
- Origin of HNSCC FaDu maybe too close to host position
- **Glioblastoma cell line LN229**
- Human prostate cancer cell line PC3
- Human adenocarcinoma cell line A549 (lung)

Relevant entities for proton treatment
4. Optimal mixture of Matrigel and FaDu cells

For results, please contact the authors!
4. Establishment of LN229 glioblastoma on mouse ear

For results, please contact the authors!
5. Summary: comparison of the tumor models

For results, please contact the authors!
5. Outlook: in vivo characterization of laser driven protons

Laser driven proton beam at Dresden laser acceleration source (DRACO)

VS.

Conventional proton beam at Universitäts Protonen Therapie/Dresden Universitätsklinikum Carl Gustav

courtesy of OncoRay
5. Experiment design

For information, please contact the authors!
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