



# Investigating the Risk of Radiation-Induced Brain Necrosis Based on Ionization Detail (ID) Parameters in Proton Therapy for Skull Base Tumors

8th LIP/IDPASC PhD Students Workshop - 16.10.24 - 17.10.24

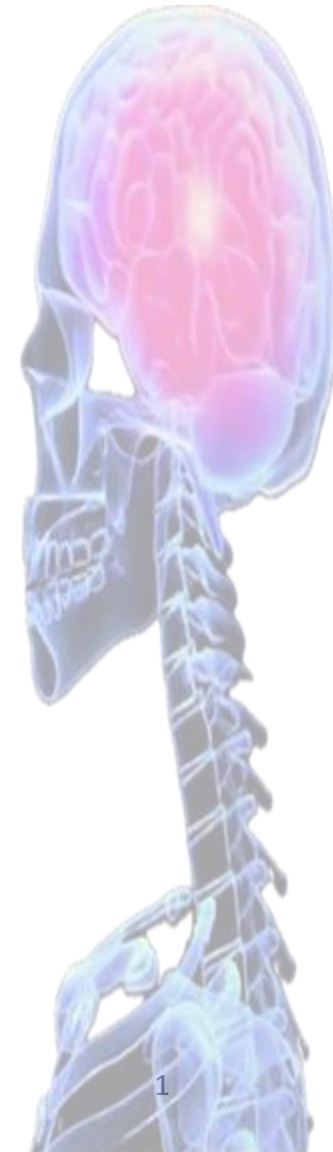
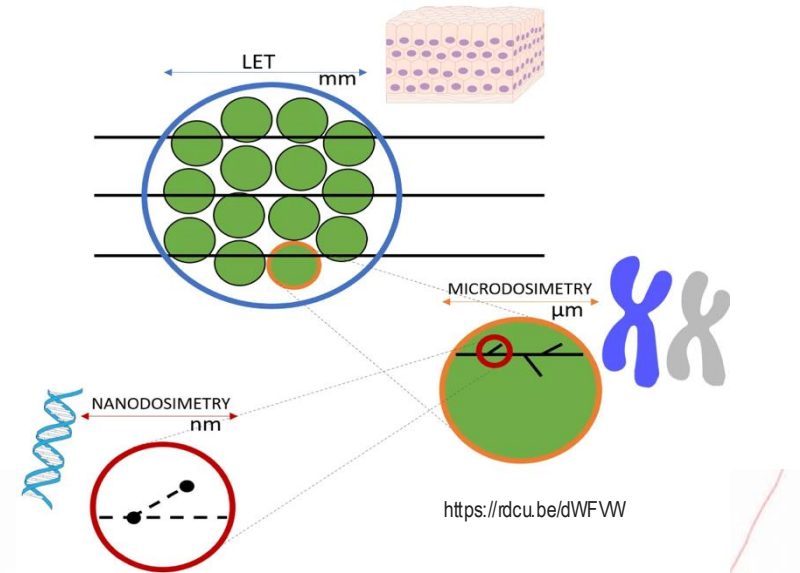
Khaled Katmeh

Supervision

Ana Belchior (C2TN) - Antoni Rucinski (IFJ PAN) - Reinhard Schulte (LLU)

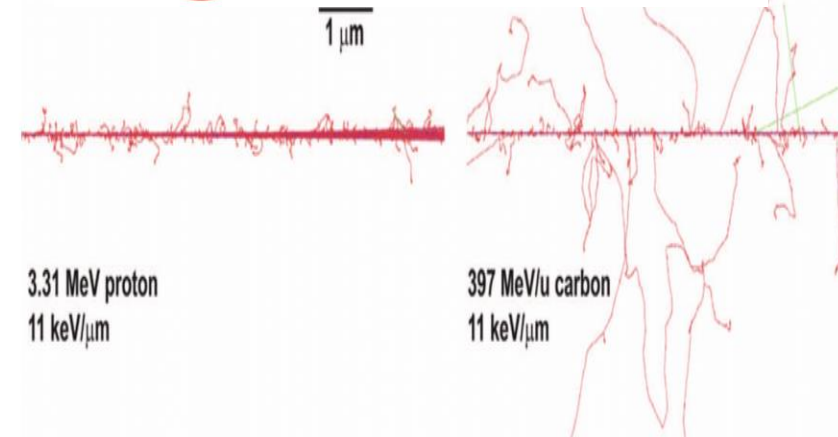
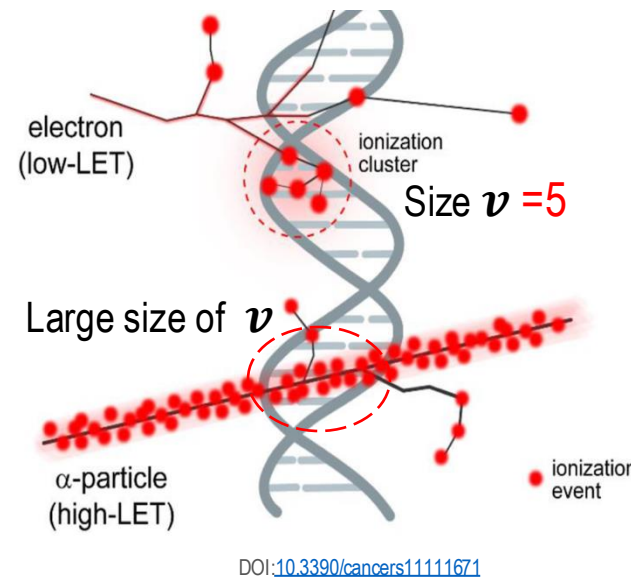
# Fundamentals

- **Absorbed dose** is weighted by RBE=1.
- Proton RBE varies from 0.9 to 1.7 and is influenced by LET at the microscopic scale
- **Biological effects** depend on dose, fluence, fractionation and **track structures**



# Supposition

- **Similar ionization clusters** result in **similar biological effects**
- **Cluster size  $\nu$**  correlates with **DNA lesion size**
- **Ionization clusters** in DNA segments cause **complex damage**



Same LET, different track structure

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# Post-proton therapy complications

Can LET and RBE predict the risk of brain necrosis in patients undergoing proton therapy? **No relationship was found**

## Brain Necrosis in Adult Patients After Proton Therapy: Is There Evidence for Dependency on Linear Energy Transfer?

Andrzej Niemierko, PhD,\* Jan Schuemann, PhD,\*  
Maximilian Niyazi, MD, MSc,\*<sup>†,‡,§</sup> Drosoula Giantsoudi, PhD,\*  
Genevieve Maquilan, MD,\* Helen A. Shih, MD,\*  
and Harald Paganetti, PhD\*

\*Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; <sup>†</sup>Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany; <sup>‡</sup>German Cancer Consortium, partner site Munich; and <sup>§</sup>German Cancer Research Center, Heidelberg, Germany

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**Purpose:** To investigate if radiographic imaging changes defined as necrosis correlate with regions in the brain with elevated linear energy transfer (LET) for proton radiation therapy treatments with partial brain involvement in central nervous system and patients with head and neck cancer.

**Methods and Materials:** Fifty patients with head and neck, skull base, or intracranial tumors who underwent proton therapy between 2004 to 2016 with a minimum prescription dose of 59.4 Gy (relative biological effectiveness) and with magnetic resonance imaging changes indicative of brain necrosis after radiation therapy were retrospectively reviewed. Each treatment plan was recalculated using Monte Carlo simulations to provide accurate dose distributions as well as 3-dimensional distributions of LET. To assess the effect of LET on radiographic imaging changes several voxel-based analyses were performed.

**Results:** In this patient cohort, LET adjusted for dose was not found to be associated with risk of brain necrosis.

**Conclusions:** A voxel-based analysis of brain necrosis as an endpoint is difficult owing to uncertainties in the origin of necrosis, timing of imaging, variability in patient specific radiosensitivity, and the simultaneous effect of dose and LET. Even though it is expected that the LET and thus relative biological effectiveness increases at the end of range, effects in patients might be small compared with interpatient variability of radiosensitivity and might be obscured by other confounding factors. © 2020 Elsevier Inc. All rights reserved.

Study of relationship between dose, LET and the risk of brain necrosis after proton therapy for skull base tumors



Magdalena Garbacz<sup>a,\*</sup>, Francesco Giuseppe Cordoni<sup>b,c</sup>, Marco Durante<sup>d,e</sup>, Jan Gajewski<sup>a</sup>, Kamil Kisielewicz<sup>f</sup>, Nils Krah<sup>g,l</sup>, Renata Kopeć<sup>a</sup>, Paweł Olko<sup>a</sup>, Vincenzo Patera<sup>h,i</sup>, Ilaria Rinaldi<sup>j</sup>, Marzena Rydygier<sup>a</sup>, Angelo Schiavi<sup>i</sup>, Emanuele Scifoni<sup>c</sup>, Tomasz Skóra<sup>f</sup>, Francesco Tommasino<sup>c,k</sup>, Antoni Rucinski<sup>a</sup>

<sup>a</sup>Institute of Nuclear Physics Polish Academy of Sciences, 31342 Krakow, Poland; <sup>b</sup>University of Verona, Department of Computer Science, Verona, Italy; <sup>c</sup>Trento Institute for Fundamental Physics and Applications, TIFPA-INFN, Trento, Italy; <sup>d</sup>GSI Helmholtzzentrum für Schwerionenforschung, Darmstadt, Germany; <sup>e</sup>The Technical University of Darmstadt, Germany; <sup>f</sup>National Oncology Institute, National Research Institute, Krakow Branch, Krakow, Poland; <sup>g</sup>University of Lyon, CREATIS, CNRS UMR5220, Inserm U1044, INSA-Lyon, Université Lyon 1, Centre Léon Bérard, France; <sup>h</sup>INFN - Section of Rome, Italy; <sup>i</sup>Department of Basic and Applied Sciences for Engineering, Sapienza University of Rome, Italy; <sup>j</sup>Department of Radiation Oncology (Maastrro), GROW School for Oncology, Maastricht University Medical Centre+, Maastricht, The Netherlands; <sup>k</sup>Department of Physics, University of Trento, Trento, Italy; <sup>l</sup>University of Lyon, Université Claude Bernard Lyon 1, CNRS/IN2P3, IP2I Lyon, UMR 5822, Villeurbanne, France

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### ABSTRACT

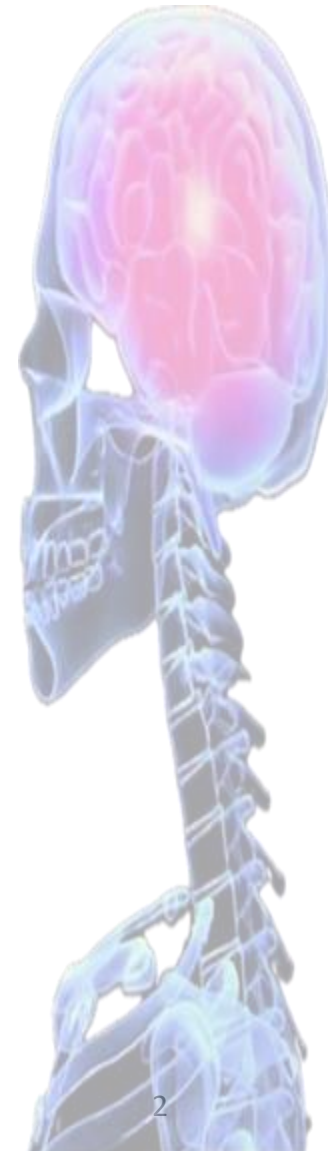
**Purpose:** We investigated the relationship between RBE-weighted dose (DRBE) calculated with constant (cRBE) and variable RBE (vRBE), dose-averaged linear energy transfer (LETd) and the risk of radiographic changes in skull base patients treated with protons.

**Methods:** Clinical treatment plans of 45 patients were recalculated with Monte Carlo tool FRED. Radiographic changes (i.e. edema and/or necrosis) were identified by MRI. Dosimetric parameters for cRBE and vRBE were computed. Biological margin extension and voxel-based analysis were employed looking for association of DRBE(vRBE) and LETd with brain edema and/or necrosis.

**Results:** When using vRBE, Dmax in the brain was above the highest dose limits for 38% of patients, while such limit was never exceeded assuming cRBE. Similar values of Dmax were observed in necrotic regions, brain and temporal lobes. Most of the brain necrosis was in proximity to the PTV. The voxel-based analysis did not show evidence of an association with high LETd values.

**Conclusions:** When looking at standard dosimetric parameters, the higher dose associated with vRBE seems to be responsible for an enhanced risk of radiographic changes. However, as revealed by a voxel-based analysis, the large inter-patient variability hinders the identification of a clear effect for high LETd.

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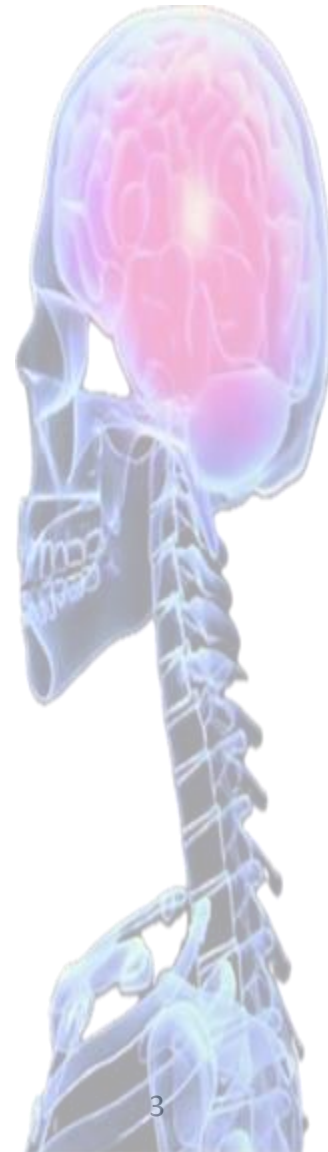
ProtoTera

# Challenge

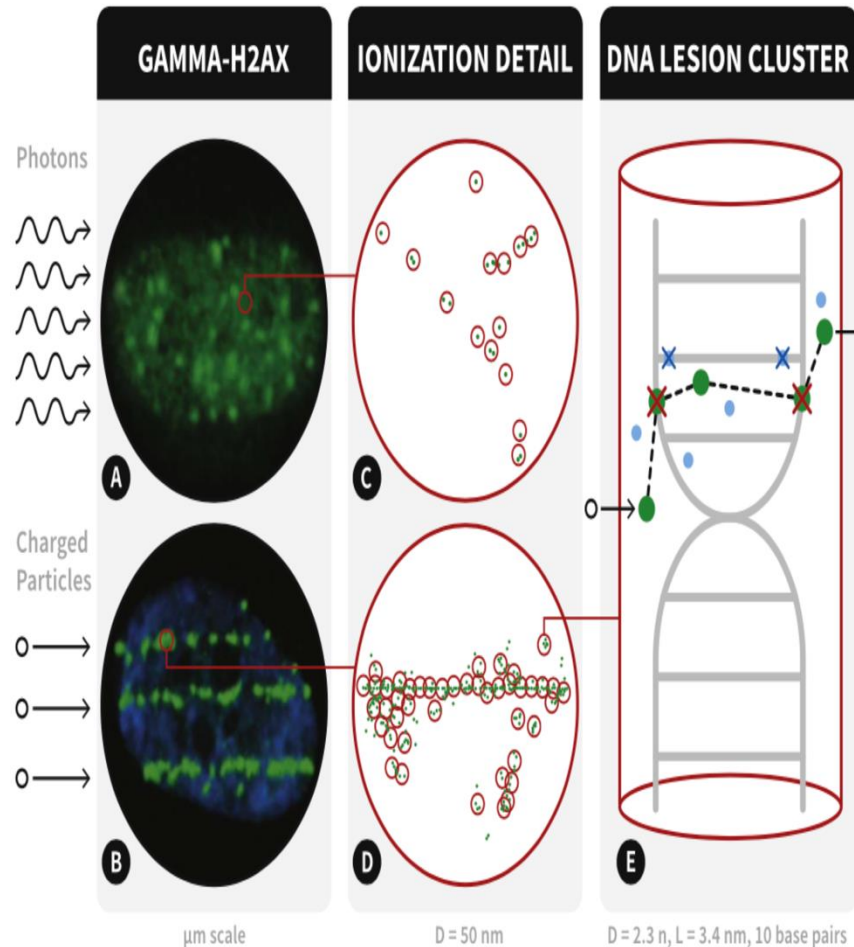
- The relationship between dose and biological effects is complicated
- Particle therapy uses RBE models or dose weighted LET
- Ionization detail on the nanometer level is neglected

# Solution

- The current PhD work focuses on correlating the frequency of large ionization cluster per unit of mass (cluster dose) with clinically important endpoint such as brain necrosis



# Nanodosimetric Ionization Detail (ID) and Formalism ( $I_p^c$ )



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Particle class  $\mathbf{c}$  : Type and energy

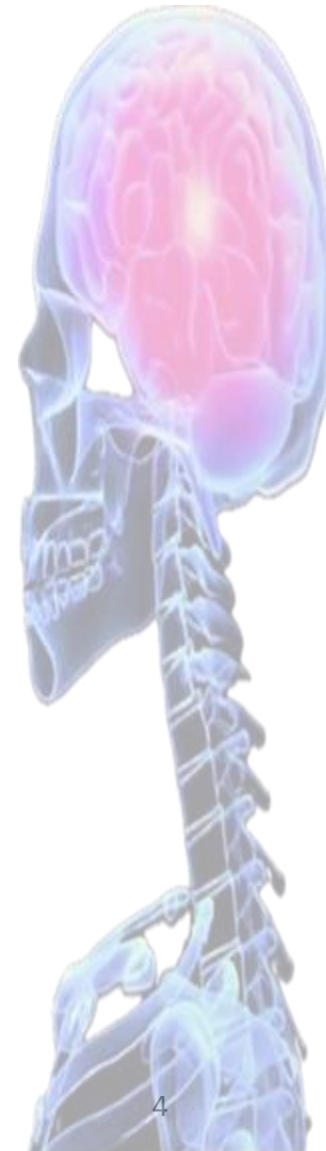
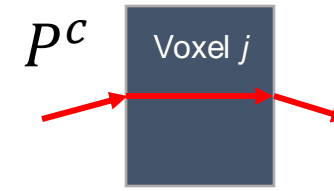
Frequency ICSD,  $f^c(v)$

Number of ionizations in clusters of  $k$  or more ionizations

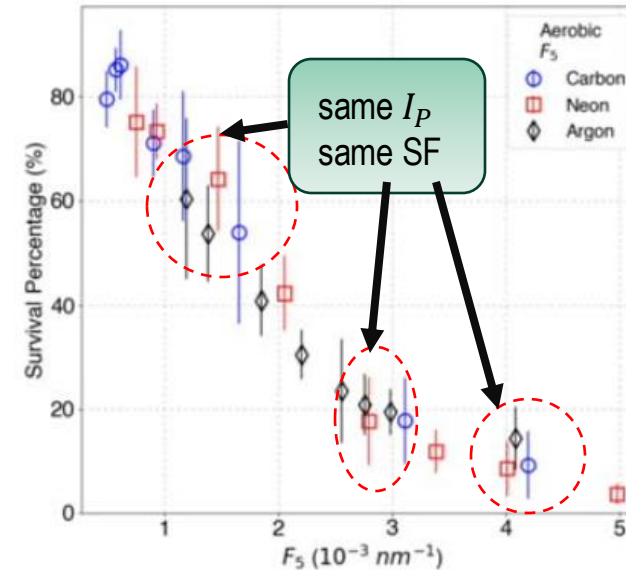
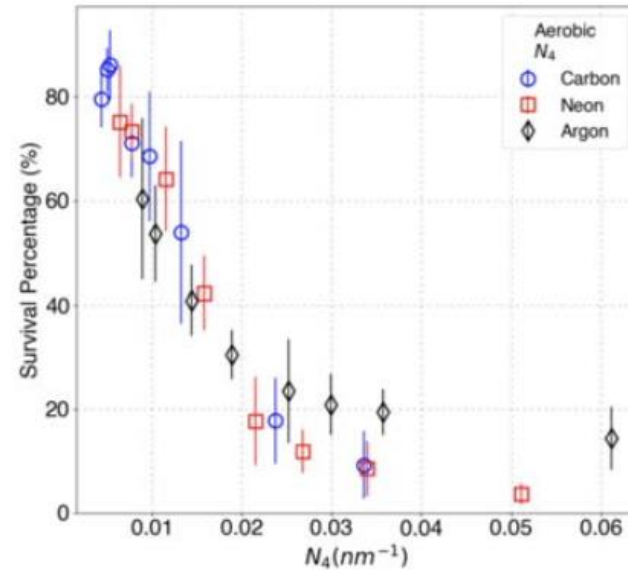
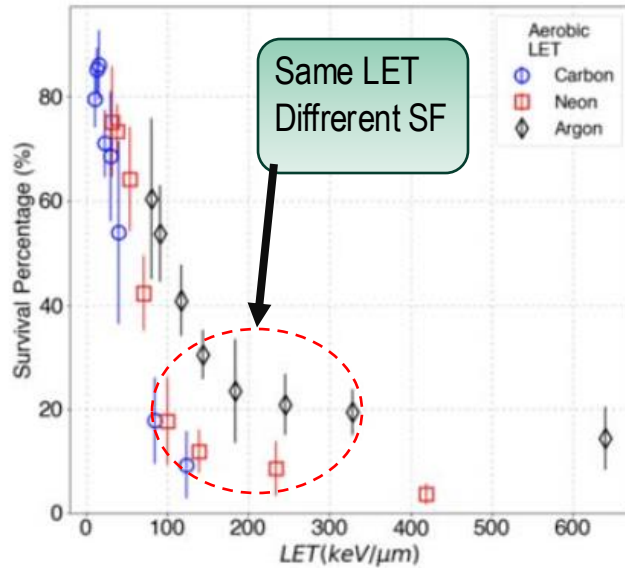
$$N_k^c = \sum_{v=k}^{v_{\max}} v f^c(v) \quad [1/\text{length}]$$

Number of clusters of  $k$  or more ionizations

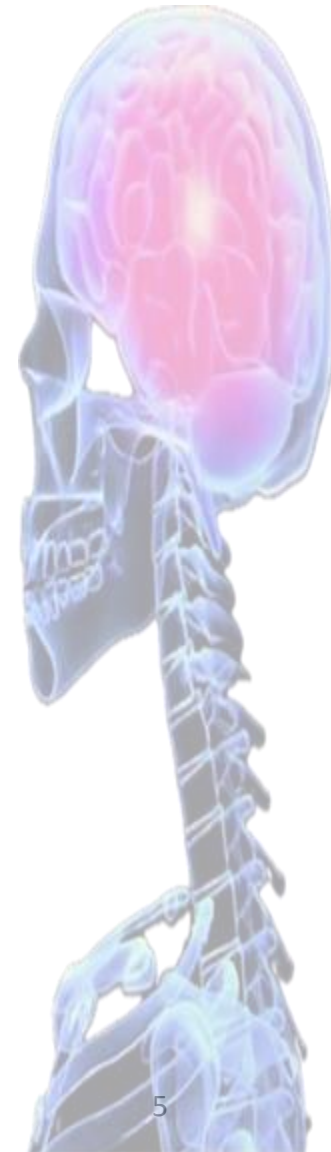
$$F_k^c = \sum_{v=k}^{v_{\max}} f^c(v) \quad [1/\text{length}]$$



# ID Parameters – Association with Cell Survival



Biol. 68 (2023) 175013



# Cluster Dose $g_j^{(I_p)}$ in Voxel $j$

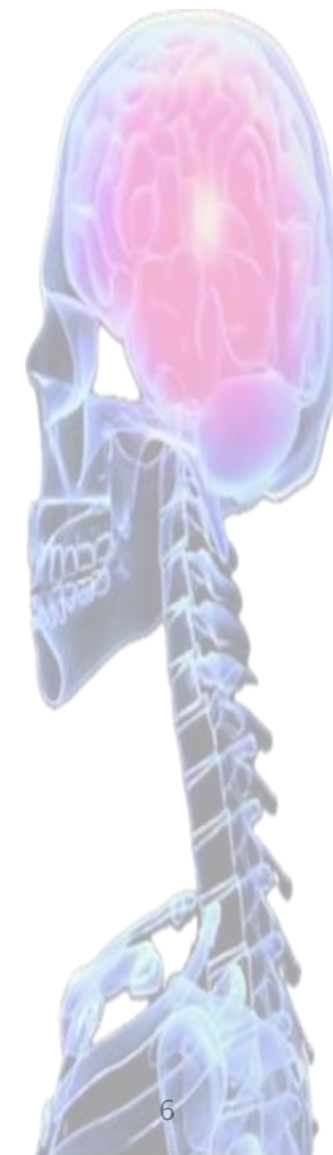
- The same cluster dose is expected to result in the same biological outcome, regardless of particle type
- Different particle types with the same  $I_p$  are expected to produce the same biological outcome
- Different ion beams with identical local fluence and  $I_p$  are expected to yield the same biological effect

$$g_j^{(I_p)} = \frac{1}{\rho_0 V_j} \sum_{c \in C_j} t_j^c I_p^c \quad [1/\text{mass}]$$

$t_j^c$  cumulative track segment length of particle class  $c$  in voxel  $j$

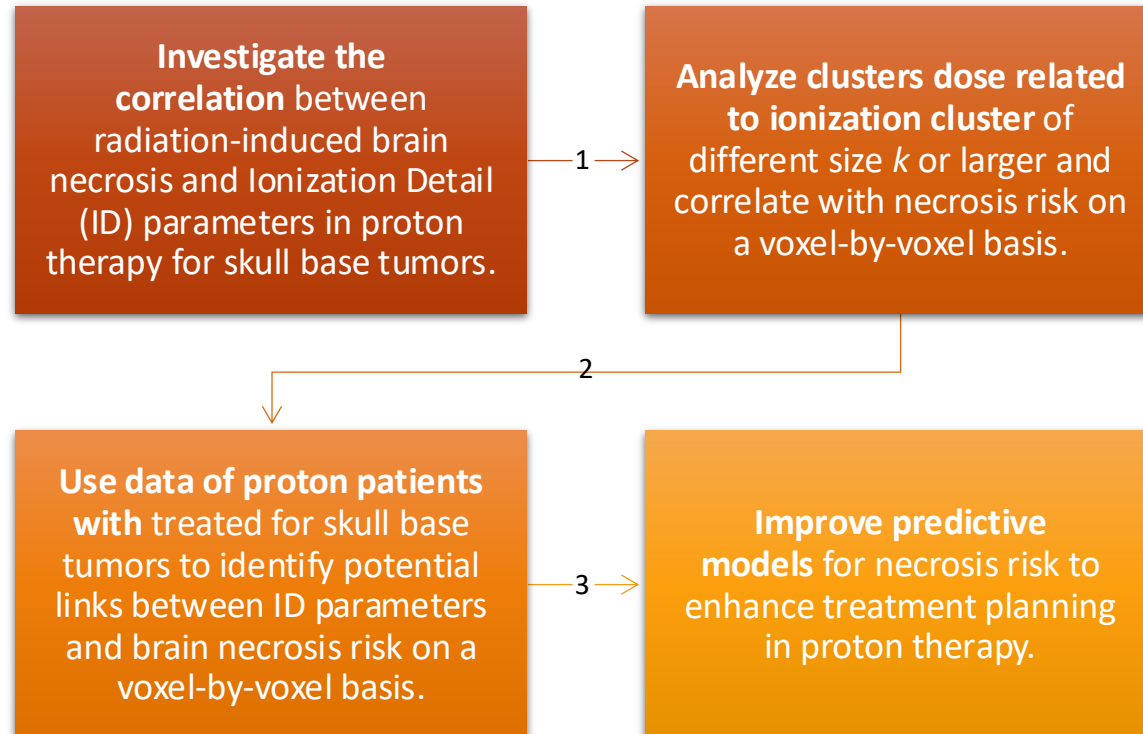
$$\Phi_j^c = \frac{t_j^c}{V_j}$$

$$g_j^{(I_p)} = \frac{1}{\rho_0} \sum_{c \in C_j} \Phi_j^c I_p^c \quad [1/\text{mass}]$$



# PhD Objective

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I appreciate your attention!