Mechanisms and Clinical Significance of Particle RBE

Variable RBE (vRBE) Models are the Future of Particle Therapy Treatment Planning

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Disclaimer

- Co-investigator on a Research Collaboration Agreement with RaySearch Inc.
- Have an unapologetic bias towards the use of vRBE models for outcome assessment and plan optimization
Learning Objectives

- Understand the relationship between the RBE for DNA double strand break (DSB) induction ($RBE_{DSB}$) and the RBE for reproductive cell survival

- Gain an appreciation for the strengths and weaknesses of RBE modeling as useful predictive tools for the analysis of laboratory and clinical studies
  - Do mechanism-inspired RBE models capture more biology than LET-based models? From a clinical perspective, do we care more about LET or biology?

- Provoke discussion and debate on forward-looking strategies to more fully exploit the potential of hadron therapy using RBE-based plan optimization
  - Is plan optimization based on LET more accurate and less risky than robust planning using a mechanistic RBE model?
RBE for DSB Induction (\( RBE_{DSB} \))

DSB are the most critical form of initial molecular damage created by ionizing radiation.

Pairs of mis-rejoined DSB create chromosome aberrations that are often lethal or highly mutagenic.

\( RBE_{DSB} \) closely related to the RBE for cell survival.

Published models for \( RBE_{DSB} \) are in good agreement with each other for a wide range of particle types and energies.

Monte Carlo models reflect and synthesis a large body of measurements, i.e., they are the “gold standard” for \( RBE_{DSB} \).

Figure adapted from data presented in Stewart et al. (2011, 2015, and 2018). Open and filled symbols are published data from track structure simulations. Solid lines are for the Monte Carlo Damage Simulation (MCDS).
Track-end radiobiology and $RBE_{DSB}$

Monte Carlo models are in very good agreement for $^1$H$^+$ and $^4$He$^{2+}$ ions with even a sub-millimeter range.

$RBE_{DSB}$ only exceeds 1.1 in the last 2 mm of a proton track–track-end effects only have an impact on a few tens or hundreds of cells per proton (i.e., it's a small volume effect)!

For therapeutic protons, $RBE_{DSB}$ only exceeds 1.4 well beyond the tip of a pristine Bragg peak (range ~ 1-2 mm).

Figure adapted from data presented in Stewart et al. (2011, 2015, and 2018). Filled symbols are published data from track structure simulations. Solid lines are for the Monte Carlo Damage Simulation (MCDS).
Is $RBE_{DSB}$ Predictive of Trends in Cell Survival with LET?

Repair-Misrepair-Fixation (RMF) Model (Carlson et al. 2008, Stewart et al. 2018)

1. Estimate $\alpha_R$ and $(\alpha/\beta)_R$ from a fit to kV x-ray data (red filled circles)
2. Use MCDS to compute ion- and energy-specific value for $RBE_{DSB}$
3. Compute ion-specific value for $\alpha_{ion}$ and $\beta_{ion}$ using RMF formula

$$\alpha_{ion} = \alpha_R \cdot RBE_{DSB} \left(1 + \frac{2\bar{\zeta}_F \cdot RBE_{DSB}}{(\alpha / \beta)_R}\right) \quad \bar{\zeta}_F \approx LET / \rho d^2$$

$$\beta_{ion} = \beta_R \cdot RBE_{DSB} \cdot RBE_{DSB}$$

$d$ is effective diameter of cell nucleus (~ few $\mu$m)

4. Compute cell survival: $S(D) = \exp\left(-\alpha_{ion} D - \beta_{ion} D^2\right)$

(dashed lines in figure are predictions and not fits!)

RBE_{DSB} \rightarrow \text{RBE for Reproductive Cell Survival}

In the MCDS + RMF system of models, the RBE for cell survival is always greater than or equal to the RBE for DSB induction.

**Low dose RBE:** \( RBE_{LD} = \frac{\alpha_{ion}}{\alpha_R} = RBE_{DSB} \left( 1 + \frac{2 \varepsilon_F RBE_{DSB}}{(\alpha / \beta)_R} \right) \geq RBE_{DSB} \)

**High dose RBE:** \( RBE_{HD} = \sqrt{\frac{\beta_{ion}}{\beta_R}} = RBE_{DSB} \geq 1. \)

For ion dose \( D \), RBE for cell survival only depends on \((\alpha/\beta)_R\) and the asymptotic value for \( RBE_{LD} \) and \( RBE_{HD} \).

\[
RBE(D) = \frac{(\alpha / \beta)_R}{2D} \left\{ -1 + \sqrt{1 + \frac{4D}{(\alpha / \beta)_R} \left( 1 + \frac{D}{(\alpha / \beta)_R} \left( \frac{RBE_{HD}}{RBE_{LD}} \right)^2 \right) RBE_{LD}} \right\}
\]

For protons, the RBE for cell survival is in good agreement with \( RBE_{DSB} \) (red squares and yellow triangles are within a few %). For \(^4\text{He}^{2+}\) and other massive ions, \( RBE_{LD} \) can be much larger than \( RBE_{DSB} \).

Is LET an effective alternative to RBE modeling?

Laboratory studies provide overwhelming evidence that molecular and cellular damage tends to (1) increase with increasing LET, (2) decreases with increasing dose, and (3) increases with decreasing tumor and tissue ($\alpha/\beta$)

- LET-based approach of Unkelback et al. (2016) is effectively the same as plan optimization using a Monte Carlo model (Stewart et al. 2011, 2015) for proton RBE$_{DSB}$
- Optimization based on LET and RBE$_{DSB}$ does not capture the dose-dependence nor the tissue-specific aspects of particle RBE
  - Parameter “k” depends on ($\alpha/\beta$) and dose.
  - Neglecting the dose- and tissue-specific aspects of particle RBE is potentially more risky than robust planning (e.g., Kamp presentation) using RBE models that capture fundamental molecular and cellular mechanisms.

Representative plan optimized for dose (RBE = 1.1), track-end avoidance in a critical OAR, and RWD (= dose × RBE\textsubscript{DSB})
Conclusions

- Mechanism-inspired RBE models for the endpoint of cell survival may not capture all of the relevant biology. *But...* they do capture more fundamental molecular and cellular biology than LET-based methods
  - LET-based approach of Unkelback *et al.* (2016) is effectively the same as using $RBE_{DSB}$ for plan optimization, if selective applied to contoured (critical) OAR
  - Track-end based optimization is much more aggressive about pushing biological hot spots out of contoured critical OAR and into adjacent (non-specific) tissue than global RBE-based optimization. *Which approach is more risky?*

- RBE modeling has been effective for high LET carbon ions and fast neutron therapy – Why not use it for proton plan optimization too?
  - Uncertainties in vRBE modeling can be mitigated through robust planning (e.g., Kamp presentation). Plans could also be re-scaled to ensure tumor coverage is not compromised.

- RBE-based plan optimization is no more risky than LET-based optimization and, regardless, arguably superior to a constant clinical RBE = 1.1 for plan optimization.