Challenges and opportunities for implementing biological optimization in particle therapy

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Date and Time: *Wednesday, August 3, 2016 from 1:45-3:45 PM*
Location: *Walter E. Washington Convention Center in Washington, DC*
Conflict of interest: Nothing to disclose

Yale SCHOOL OF MEDICINE

Overview of Talk

Biologically Guided Radiation Therapy (BGRT)

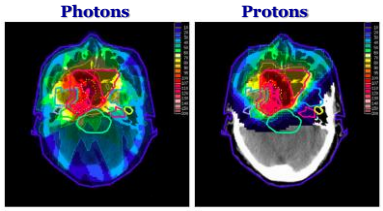
- Systematic method to derive prescription doses that integrate patient-specific information about tumor and normal tissue biology
- ***Problem*:** derived prescriptions may have large uncertainties
  - Uncertainties in physical and biological factors (experimental and clinical) that influence tumor and normal-tissue radiation response
  - Incomplete understanding of molecular and cellular mechanisms

- **Brief introduction of radiobiological concepts and RBE models**
  - Repair-misrepair-fixation (RMF) model: kinetic reaction-rate model relates DSB induction and processing to cell death → provides formulas linking LQ parameters to DSB induction and repair
- **Modeling RBE in proton, helium, and carbon ion RT**
  - RMF and Monte Carlo Damage Simulation (MCDS) models used to predict trends in biological response with particle type and energy
  - Derive practical estimates of the *RBE* for cell death for clinically-relevant charged particle therapy
  - Application of RBE-weighted dose (RWD): implementation and implications for particle therapy

Comparison of photons versus protons

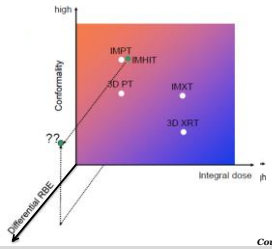
Protons allow reduction of integral dose and lower dose outside target:

Photons **Protons**



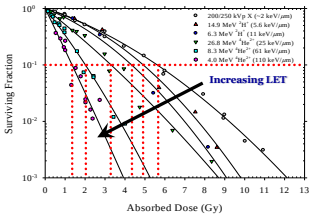
Taheri-Kadkhoda, Björk-Eriksson, Nill, Wilkens *et al.* Intensity-modulated radiotherapy of nasopharyngeal carcinoma: a comparative treatment planning study of photons and protons. *Radiation Oncology* 3:4 (2008).

Physical and Biological Aspects of Particle Therapy



Courtesy Prof. Uwe Oelfke (ICR, London)

Biological effects of radiation quality



Barendsen *et al.* (1960, 1963, 1964, 1966): *In vitro* cell survival data for human kidney T-1 cells

Definition of RBE:

$$\mathrm{RBE} = D_{\mathrm{photon}}/D_{\mathrm{ion}}$$

for same biological endpoint & effect

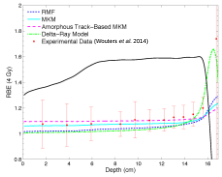
or

$$RBE = \frac{-\alpha_x + \sqrt{\alpha_x^2 + 4\beta_p\beta_x\left(\alpha_p + \beta_p d_p\right)}}{2\beta_x d_p}$$

Major Challenge: biological model selection

- How do we predict changes in biological effects in particle therapy?
  1. Empirical LET-based RBE models, e.g.,
     - Wilkens and Oelfke (2004)
     - Carabe *et al.* (2012)
     - Wedenberg *et al.* (2013)
     - McNamara *et al.* (2015)
  2. Mechanistic RBE models
     - Local effect model (LEMI-LEMIV)
     - Microdosimetric kinetic model (MKM)
     - Repair-misrepair-fixation model (RMF)
  3. Other physical surrogates such as dose-averaged LET [$\mathrm{LET_d}$] (may provide a reasonable approximation for protons)

Proton SOBP with 160 MeV max. E
RBE values for clonogenic survival of V79 cells

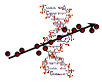


Polster *et al.* Extension of TOPAS for the simulation of proton radiation effects considering molecular and cellular endpoints. *PMB* 60: 5053–5070 (2015).

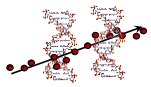
One- and two-track radiation damage

Lethal lesions are created by the actions of one or two radiation tracks

1 track damage
(∝ *D*)

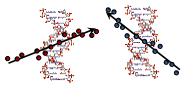


Lethal DSB misrepair, unrepairable damage



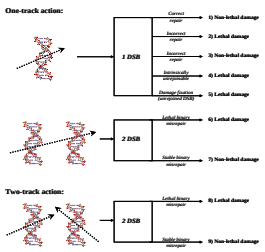
Pairwise interaction of two DSBs

2 track damage
(∝ D^2)



Pairwise interaction of two DSBs

Repair-misrepair-fixation (RMF) Model



Cell death related to fatal lesions:

$$S(D) = \exp[-F(\infty)] = \exp\left[-\left(\alpha D + \beta G D^2\right)\right]$$

1. Unrejoinable and lethal damage **3. Intra-track DSB interactions**

$$\alpha = (1 - f_R)\Sigma + \theta f_R \Sigma + [\eta/\lambda][\gamma - \theta]\varepsilon f_R \Sigma$$

2. Lethal misrepair and fixation

4. Inter-track DSB interactions

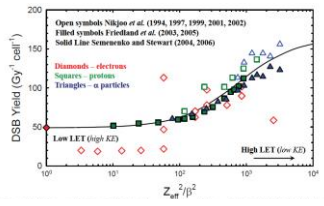
$$\beta = [\eta/(2\lambda)][\gamma - \theta](f_R \Sigma)^2$$

f_R = fraction of potentially rejoinable DSB
λ = rate of DSB repair ($\sim 10^{-1}$–$100\ h^{-1}$)
η = rate of binary misrepair ($\sim 10^{-5}$–$10^{-3}\ h^{-1}$)
$\varepsilon = z_D f_R \Sigma$ = # of DSB per track per cell

Σ = expected # of DSB (Gy^{-1}·cell^{-1})
θ = prob. DSB lethally misrepaired/fixed
γ = prob. exchange-type aberration lethal

Carlson DJ, Stewart RD *et al.* Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. *Radiat. Res.* 2008; 169: 447–459.

Monte Carlo Damage Simulation (MCDS)



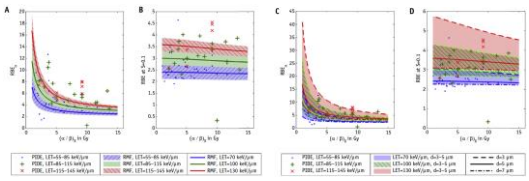
$$Z_{eff} = Z\left[1 - \exp(-125\beta Z^{-2/3})\right]$$ Effective charge (Barkas 1963)

$$\beta = \sqrt{1 - \left(1 + T/m_0c^2\right)^{-2}}$$ Speed of particle with kinetic energy (relative to *c*)

MCDS reproduces trends in DNA damage yields from more detailed track structure simulations for electrons, protons, and heavy ions over a wide range of energies

Semenenko V, Stewart RD, Fast Monte Carlo simulation of DNA damage formed by electrons and light ions, *Phys Med Biol*, 51 (2006) 1693-1706.
Stewart RD, Yu VK, Georgakilas AG, Koumenis C, Park JH, **Carlson DJ**. Monte Carlo simulation of the effects of radiation quality and oxygen concentration on clustered DNA lesions. *Rad. Res.* 2011; 176: 587–602.

Particle Irradiation Data Ensemble (PIDE)



- Comparison of RMF predictions with experimentally measured carbon ion RBE values reported by multiple institutions (www.gsi.de/bio-pide) for two biological endpoints (RBE_{10} and RBE at a survival level of S = 10%) and a range of LET and $(\alpha/\beta)_x$
- (A,B) Data calculated with d_{nuc} = 5 μm and a focus on LET variations, (C,D) range of cell nucleus diameters

Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, **Carlson DJ**. Fast biological modeling for voxel-based heavy ion therapy treatment planning using the mechanistic repair–misrepair-fixation (RMF) model and nuclear fragment spectra. *Int. J. Radiat. Oncol. Biol. Phys.* 93: 557–568 (2015).

Method to determine RBE for cell killing

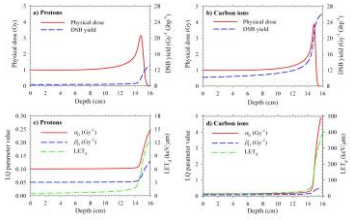
- RMF-derived predictions of α and β are used to estimate the RBE for cell killing in clinically-relevant ion therapies

1. Estimate cell-specific model constants: $\kappa = \frac{2\beta_x}{\Sigma_x^2}$ $\theta = \frac{\alpha_x}{\Sigma_x}\left[1 - \frac{2\overline{z}_F}{(\alpha/\beta)_x}\right]$
2. Calculated radiosensitivity parameters for ion of given energy E_i:
$\alpha_i = \theta\Sigma_i + \kappa\overline{z}_F^2\Sigma_i^2$ $\beta_i = (\kappa/2)\Sigma_i^2$
3. Calculate dose-averaged mean values of α and β as a function of penetration depth for a mixed field of ions of different energy
$\alpha_D = \frac{1}{D}\sum_{i=1}^{N} D_i\alpha_i$ $\sqrt{\beta_D} = \frac{1}{D}\sum_{i=1}^{N} D_i\sqrt{\beta_i}$
4. Calculate RBE for cell killing relative to reference treatment (simply an isoeffect calculation using D_x=$RBE \times D$):
$$RBE(\alpha_x, \beta_x, \alpha, \beta, D) = \frac{\sqrt{\alpha_x^2 + 4\beta_x(\alpha_D D + \beta_D D^2)} - \alpha_x}{2\beta_x D}$$

Clinically-relevant pristine Bragg peaks

Physical and biological properties of proton and carbon ion pristine Bragg peaks:

- Dose & LET calculated using analytical approximations (Bortfeld 1997,Wilkens and Oelfke 2003)
- DSB yields simulated with MCDS
- α and β calculated assuming chordoma reference parameters
- All calculations include Gaussian particle spectrum



Frese MC, Yu VK, Stewart RD, **Carlson DJ**. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; 83: 442–450.

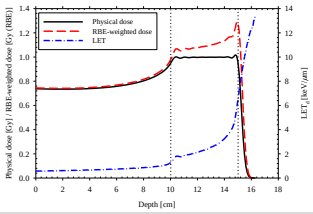
RBE for cell killing in Proton SOBP

Conditions:
1. Normoxic chordoma cells: α_x= 0.1 Gy^{-1}, $(\alpha/\beta)_x$=2.0 Gy
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 0.3 cm
5. # of Bragg peaks: 17

Results:
1. Entrance RBE ~1.0
2. RBE ranges from 1.03 to 1.34 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP is ~1.11

Potential for biological hot and cold spots within proton SOBP

Dose, energy, and LET calculated using analytical approximation proposed by Bortfeld (1997) and Wilkens and Oelfke (2003)

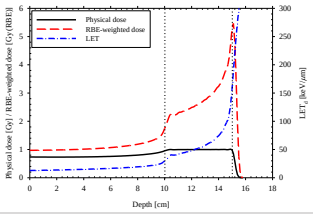


RBE for cell killing in Carbon Ion SOBP

Conditions:
1. Normoxic chordoma cells: α_x= 0.1 Gy^{-1}, $(\alpha/\beta)_x$=2.0 Gy
2. Proximal edge of SOBP: 10 cm
3. Distal edge of SOBP: 15 cm
4. Distance between Bragg peaks: 0.3 cm
5. # of Bragg peaks: 17

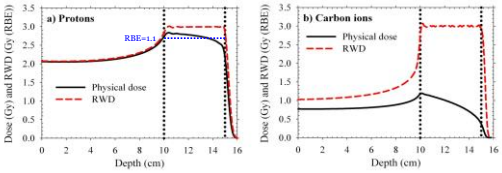
Results:
1. Entrance RBE ~1.3
2. RBE ranges from 1.8 to 5.4 from proximal to distal edge of the SOBP
3. Mean RBE across SOBP is ~2.8

Dose, energy, and LET calculated using analytical approximation proposed by Bortfeld (1997) and Wilkens and Oelfke (2003)



Physical dose optimization

Clinical objective is to deliver a uniform biological effect (RWD)

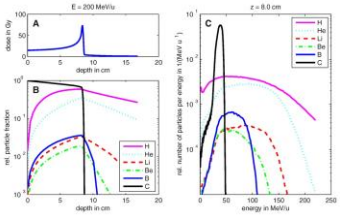


Spread out Bragg peaks consisting of pristine Bragg peaks whose fluences were optimized to yield a constant RBE-weighted absorbed dose of 3 Gy (RBE) using method of Wilkens and Oelfke (2006)

Frese MC, Yu VK, Stewart RD, **Carlson DJ**. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2012; 83: 442–450.

Challenge: accurate physics modeling of fragments

- Simulation of clinical carbon ion beam line using Monte Carlo code FLUKA (Parodi *et al.* 2012)
- In our example, 32 carbon ion beams with energies from 90 to 400 MeV/u in 10 MeV/u steps in a homogenous water phantom
- **Panel A:** characteristic depth-dose dependency (Bragg peak) of carbon ions for an initial energy of 200 MeV/u
- **Panel B:** relative number of particles. H and He are most prominent fragments
- **Panel C:** spectra of six considered fragments at a depth of 8 cm, close to the Bragg peak, where the impact of fragmentation is highest



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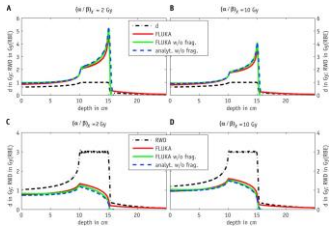
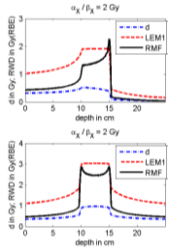
Impact of nuclear fragmentation on RBE for carbon

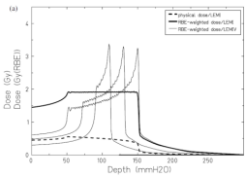


- **RMF predictions of RBE-weighted dose w/ and w/o FLUKA-generated nuclear fragments and an analytical approach w/o fragmentation (Frese et al. 2012)**
- **SOBPs optimized for target in water at depth of 10-15 cm for RWD= 3 Gy(RBE)**
  - **Squared-differences optimization (Wilkens and Oelfke 2006)**
- **RBE is over-estimated when neglecting nuclear fragments (especially in distal edge of SOBP)**
- **If fragments are neglected, estimated physical dose required to obtain a constant RWD could be underestimated by up to 33%**

Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, **Carlson DJ**. Fast biological modeling for voxel-based heavy ion therapy treatment planning using the mechanistic repair-misrepair-fixation (RMF) model and nuclear fragment spectra. *Int. J. Radiat. Oncol. Biol. Phys.* 93: 557–568 (2015).

Comparison to LEM1 and LEM4





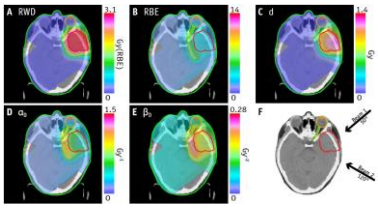
(Grün *et al.* 2012, PMB)

Kamp F, *et al.* Fast biological modeling for voxel-based heavy ion therapy treatment planning using the mechanistic repair-misrepair-fixation (RMF) model and nuclear fragment spectra. *Int. J. Radiat. Oncol. Biol. Phys.* 93: 557–568 (2015).

Implementation of 3-D treatment plan optimization

Multi-field biological optimization with RMF for carbon ion RT in extension of research treatment planning platform CERR (Deasy et al. 2003)

- Astrocytoma plan with 2 carbon ion fields optimized on 3 Gy(RBE)
- Spot scanning, dose-to-water pencil beam algorithm for dose calculation → pre-calculated reference tables of depth-dose, lateral spread, α_D and β_D for 32 initial carbon ion energies
- Initial carbon ion energy range covers < 27 cm in water (with mean distance of 8 mm between single Bragg peaks)
- Simplified range shifter used to generate necessary peaks in between



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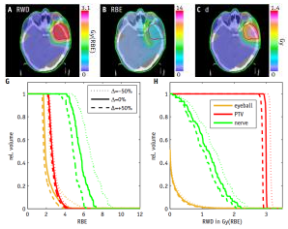
Biological dose-volume histograms (DVHs)



- PTV shown in red
- Organs : LT optic nerve (green), LT eye (orange)
- RBE in PTV ranges from 2.2 to 4.9 (mean 2.8)
- RBE, α_D, and β_D increase with depth (lower particle E) toward distal edge of PTV w/ max. values outside PTV at target edge
- α_X = 0.1 Gy^{-1}, β_X = 0.05 Gy^{-2} for optimization
- Sensitivity analysis performed by changing $(\alpha/\beta)_X$ = 2 Gy by ±50%
  - Biological model is decoupled from physical dose
  - Extremely fast changes of α_x and β_X (full biological modeling in 1-4 ms)

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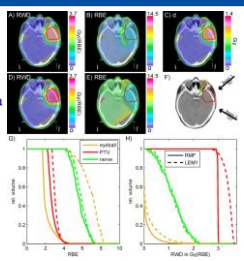
Comparing model predictions

RMF

LEM1

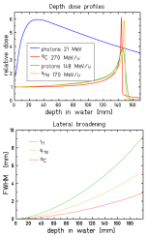


- RBE predictions by LEM1 are generally larger than the RMF model predictions as expected
- Deviations between the two implemented models are large but not surprising given the uncertainties in the biological modeling process
- Disagreement is reduced when comparing RMF to LEM4 version (not shown)
- Differences in RBE and RWD of the OARs need to be carefully evaluated in order to apply dose constraints for OARs and to predict normal tissue complication probabilities
- More 3-D model comparisons are necessary

Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, **Carlson DJ**. Fast biological modeling for voxel-based heavy ion therapy treatment planning using the mechanistic repair–misrepair-fixation (RMF) model and nuclear fragment spectra. *Int. J. Radiat. Oncol. Biol. Phys.* 93: 557–568 (2015).

Is there a more optimal particle type for RT?

- Potential advantages and disadvantages depend on interplay of physical and biological properties
  - For protons:
    - No observable fragmentation tail ⇧
    - Larger lateral scattering ⇩
    - Wider Bragg peak ⇩
  - For carbon ions:
    - Decreased lateral scattering and narrower Bragg peak ⇧
    - Higher entrance to peak dose ratio ⇩
    - Higher and longer nuclear fragmentation tail ⇩
    - Lateral dose halo effect is greater than other ions ⇩
  - What about helium ions?
    - Less lateral scattering than protons *and* smaller fragmentation tail than carbon ions



Guan F, Titt U, Bangert M, Mohan R. In Search of the Optimum Ion for Radiotherapy. *Med. Phys.* 40: 320 (2013).
Grün R, Friedrich T, *et al.* Assessment of potential advantages of relevant ions for particle therapy: a model based study. *Med Phys.* 2015 42: 1037-1047 (2015).

Potential of helium ion radiotherapy

Biologically optimized helium ion plans: calculation approach and its *in vitro* validation

A Mairani[1,2], I Dokic[2,3,4], G Magro[1], T Tessonnier[2,5], F Kamp[3], D J Carlson[6], M Ciocca[7], F Cerutti[8], P R Sala[9], A Ferrari[8], T T Böhlen[10], O Jakel[2,4], K Parodi[2,3,4], J Debus[2,3], A Abdollahi[2,3,4] and T Haberer[1]

Mairani A, Dokic I, Magro G, Tessonnier T, Kamp F, **Carlson DJ**, *et al.* Biologically optimized helium ion plans: calculation approach and its in vitro validation. *Phys. Med. Biol.* 93: 557–568 (2016).

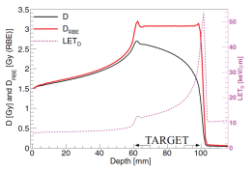
Helium ions for radiotherapy? Physical and biological verifications of a novel treatment modality

Michael Krämer [1] Emanuele Scifoni, Christoph Schuy, and Marta Rovituso
Walter Tinganelli
Andreas Maier, Robert Kaderka, and Wilma Kraft-Weyrather
Stephan Brons and Thomas Tessonnier
Katia Parodi
Marco Durante

Kramer M, Scifone E, Schuy C, Rovituso M, Tinganelli W, Maier A, Kaderka R, *et al.* Helium ions for radiotherapy? Physical and biological verifications of a novel treatment modality. *Med. Phys.* 43: 1995–2004 (2016).

Biologically optimized helium ion plans

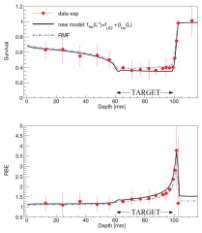
- **Objective:** to perform studies on biological effect of raster-scanned helium ion beams with experimental verification before clinical application
- Integration of data-driven biological models into Monte Carlo treatment planning (MCTP) tool based on FLUKA (Mairani *et al.* 2013)
- Consider primary He-4 ions and secondary particles: He-3 and He-4 (Z=2) fragments, and protons, deuterons, and tritons (Z=1)
- 4 cm SOBP optimized and delivered at Heidelberg Ion Beam Therapy Center (HIT)



Optimized D_{RBE}, FLUKA simulated absorbed dose D, and LET_D values plotted as a function of the depth in water

Mairani A, Dokic I, Magro G, Tessonnier T, Kamp F, **Carlson DJ**, *et al.* Biologically optimized helium ion plans: calculation approach and its in vitro validation. *Phys. Med. Biol.* 93: 557–568 (2016).

Predicting RBE effects in helium ion therapy



Summary of mean survival absolute deviation (μS) between model predictions and experimental data

RBE model	μ_{SA} (%)
$\beta_{ph} + \beta_{hh}(L)$	9.8 ± 1.3
RBE = 1.3	18.8 ± 4.3
LEM $D_t = 10.8$ Gy	4.5 ± 0.8
LEM $D_t = 15$ Gy	6.7 ± 1.5
RMF	5.8 ± 1.1
New $\beta_{LET} + \beta_{hh}(L)$	5.3 ± 0.9
New $\beta_{LET} + \beta_{hh} = \beta_{ph}$	6.5 ± 0.9

RMF model not fit to data or adjusted using other helium ion data

- Human lung adenocarcinoma cells A549 (α_x=0.173 Gy^{-1}, β_x=0.032 Gy^{-2})
- Cell survival and RBE as function of the depth in water for the forward re-calculated plan using the RMF model and an empirical approach
- Implementation of RMF model only needed α_x and β_x as input parameters → not previously adjusted to match light ion data

Mairani A, Dokic I, Magro G, Tessonnier T, Kamp F, **Carlson DJ**, *et al.* Biologically optimized helium ion plans: calculation approach and its in vitro validation. *Phys. Med. Biol.* 93: 557–568 (2016).

Conclusions and Future Opportunities

- **Biological models can be used for optimization in particle therapy**
  - RMF model, combined with independently benchmarked MCDS, provides quantitative & mechanistic method to efficiently predict RBE-weighted dose distributions in carbon ion RT in real patient cases
  - RMF and MCDS approach can also be used to investigate oxygenation effects
- **Limitations of existing RBE models**
  - May not explicitly capture many important biological factors, e.g., low dose hyper-radiosensitivity, possibility of other biological targets (e.g., vasculature and immune responses, etc.)
  - Uncertainty in experimental data, variation in patient radiosensitivity, and differences between RBE model predictions present real challenges for the heavy ion therapy community
  - Need reliable methods to quantify patient variability in radiosensitivity and RBE as function of genomic heterogeneity (e.g., DNA repair defects could result in enhanced RBE)
- **Best to practice evidence-based medicine**
  - Clinical data is gold standard → must be skeptical of simplified models and understand limitations
  - Potential to improve outcomes in particle RT through optimization based on biological objective functions in addition to dose-based surrogates

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