Geant4 Monte Carlo microdosimetry for Tumor Anti-vascular Alpha Therapy

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Targeted Alpha Therapy (TAT)

Alpha emitter
Chelator
Antibody

Kill the cell
Binder
Target cancer cell

Alpha-immunoconjugate (AIC)
Systemic TAT for metastatic melanoma in phase 1 clinical trial

Original size by blue ring

H&E stain negative for melanoma
Tumor Anti-vascular Alpha Therapy (TAVAT)

Leaky capillary endothelial cells diffuse into perivascular space.
Alphas kill endothelial cells.
Capillaries shut down, deprive oxygen & nutrition.
Tumor regression.

AICs target cancer cells and kill endothelial cells.
Objective

- Quantitatively analyze TAVAT hypothesis
- Determine whether the lethal dose to tumor capillaries is safe for normal tissue capillaries and lymphocytes
Current status of microdosimetric modelling

- Solid State Dosimeter
  - minimum detectable energy
  - the shape and the dimensions of the sensitive volume
  - The non-tissue-equivalence of the detector

- Monte Carlo Simulation
  - Energy cut off go down to sub eV in Geant4 DNA
  - Direct modeling of the targeted volume
  - Direct modeling of defined material
Radiobiology Modeling Process

- Biological Assumptions
- Mathematical Expressions

INPUT: Mathematical Manipulation

OUTPUT: Mathematical Results

The MC Calculation

Biological Consequences

Steve P. Lee  UCLA
10th Asia-Oceania Congress of Medical Physics
Taipei, 16th Oct, 2010
Biological Assumptions

- Cell survival curves are relatively insensitive to the cell cycle or oxygen status with alpha hits.
- The activity is uniformly distributed in tissue or blood.
- Capillary endothelial cell is simplified as a tube.
- Lymphocyte is modeled as an ellipsoid at a first approximation.
Modeling Process

- **Biological Assumptions**
- **Mathematical Expressions**
- **Mathematical Manipulation**
- **Mathematical Results**
- **The MC Calculation**
- **Biological Consequences**

**INPUT**

**OUTPUT**
Geometry for the capillary

- Capillary is modeled as a tube with a ellipsoid cell nucleus in the centre
- $^{213}$Bi was set as the source
1: Perivascular Model

- AICs diffuse through leaky tumor endothelial cells, target cancer cells and pericytes and saturate receptors in the perivascular space.

- In the case of the melanoma clinical trial: $9.2.27^{-213}\text{Bi} -> \text{MCSP antigen}$
2: Intralumen model

- AICs are confined in the healthy endothelial cells
- Background dose needs to be low enough to keep patient safe
3: lymphocyte model

- Lymphocyte was model as two eccentric ellipsoids
- The lymphocyte was placed in the centre of a 50 μm long capillary
- AICs were random arising from blood in the capillary

![Diagram showing lymphocyte model with dimensions 6.2 μm and 7.33 μm]
Modeling Process

- Biological Assumptions

 Mathematical Expressions → Mathematical Manipulation → The MC Calculation → Mathematical Results → Biological Consequences

INPUT

OUTPUT
Geant4

- Geant4 9.3 and Low Energy Electromagnetic physics models with threshold of production for secondary particles of 250 eV
- Geant4 9.4 DNA - Region
- Results of Very Low Energy package (eV scale) is on the way
Physics list

- **e-**
  - G4eMultipleScattering
  - G4eIonisation
  - e-_G4DNAExcitation
  - e-_G4DNAIonisation
  - e-_G4DNAAttachment
  - e-_G4DNAVibExcitation

- **proton**
  - G4hMultipleScattering
  - G4hIonisation
  - proton_G4DNAExcitation
  - proton_G4DNAIonisation
  - proton_G4DNAChargeDecrease

- **hydrogen**
  - hydrogen_G4DNAIonisation
  - hydrogen_G4DNAExcitation
  - hydrogen_G4DNAChargeIncrease

- **alpha**
  - G4hMultipleScattering
  - G4alphaIonisation
  - alpha_G4DNAExcitation
  - alpha_G4DNAIonisation
  - alpha_G4DNAChargeDecrease

- **alpha+**
  - G4hMultipleScattering
  - G4hIonisation
  - alpha_G4DNAExcitation
  - alpha_G4DNAIonisation
  - alpha_G4DNAChargeDecrease
  - alpha+_G4DNAChargeIncrease

- **helium**
  - helium_G4DNAExcitation
  - helium_G4DNAIonisation
  - helium_G4DNAChargeDecrease

- **GenericIon**
  - theRadioactiveDecay
  - G4hMultipleScattering
  - G4hIonisation
Quantities of interest

- Energy deposition in each event
- Specific energy (SE)
- Lineal Energy Transfer (LET)
- Mean chord length
- Probability of hit
Modeling Process

Input

- Biological Assumptions
- Mathematical Expressions

Mathematical Manipulation

The MC Calculation

Output

- Mathematical Results
- Biological Consequences
LET Spectrum (one million $^{213}\text{Bi}$ decay)

**Definition**

LET = $\frac{dE}{dx}$

**Average LET for $\alpha$**

95 keV/um
Specific Energy Spectrum of two capillary models

Definition: $D = \frac{\Delta\varepsilon}{\Delta m}$

SI Unit: 1 Gy = 1 J/kg

Dose per radioactive decay:
- PeriVascular model: 0.5 cGy
- Intraluminal model: 1.1 cGy
Lymphocyte background dose in different diameter vessels

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Traversal number</th>
<th>Specific energy (cGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriole (30 μm)</td>
<td>0.29</td>
<td>15.1</td>
</tr>
<tr>
<td>Capillary (8 μm)</td>
<td>0.05</td>
<td>2.5</td>
</tr>
<tr>
<td>Venule (20 μm)</td>
<td>0.19</td>
<td>9.6</td>
</tr>
</tbody>
</table>
Modeling Process

- Biological Assumptions
- Mathematical Expressions
- Mathematical Manipulation
- Mathematical Results
- Biological Consequences

INPUT: The MC Calculation
OUTPUT:
Cell survival rate in perivascular model

- In the clinical trial, the maximum administered dose activity is 3.2 mCi/mg
- 40 cancer cells around one capillary endothelial cell, there would be ~800 AICs in the perivascular space.
- 0.5 cGy per radioactive decay from G4
- The perivascular dose to the endothelial cell nucleus is 4 Gy or 20 RBE Gy
- Less than 1% survival rate for tumor endothelial cell
Cell survival rate for background models

- Every $^{213}$Bi in the blood would give the nucleus a background dose of 0.011 Gy
- In the clinical trial, 25 mCi were systemically injected into patient, then each capillary nucleus would receive $7 \times 10^{-6}$ Gy
- 2.5 cGy to 15.1 cGy lymphocyte dose corresponds to 87% ~ 92% survival rates for lymphocytes
- ~99% survival rate for normal capillary endothelial cell.
Adopt Geant4 result for biological endpoints

- Cytokinesis-blocked micronucleus (MN) assay allows the evaluation of radiation induced cytogenetic damage to lymphocytes after radiation.
- Number of MN can be acted as a biological dosimeter for radiotherapy.
- Specific energy to lymphocyte nucleus was calculated by lymphocyte model of Geant4.

Figure 4. Lymphocytes with one MN (A) and three MN (B).

### Relate number of MN with G4 result

<table>
<thead>
<tr>
<th>Activity of $^{213}$Bi (kBq/mL)</th>
<th>Average MN</th>
<th>Total specific energy (Gy)</th>
<th>RBE dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>38</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>30</td>
<td>70</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>60</td>
<td>69</td>
<td>0.4</td>
<td>1.5</td>
</tr>
<tr>
<td>90</td>
<td>164</td>
<td>0.6</td>
<td>2.3</td>
</tr>
<tr>
<td>120</td>
<td>210</td>
<td>0.8</td>
<td>3.1</td>
</tr>
<tr>
<td>150</td>
<td>220</td>
<td>1.0</td>
<td>3.8</td>
</tr>
<tr>
<td>300</td>
<td>391</td>
<td>1.9</td>
<td>7.6</td>
</tr>
<tr>
<td>600</td>
<td>676</td>
<td>3.8</td>
<td>15.3</td>
</tr>
</tbody>
</table>

Biology experiment setup

MNMs were counted under microscope

SE were calculated with Geang4

RBE factor = 4
RBE dose and micronucleus (MN) response relationship

$$RBE = MN^2 + 0.01MN - 0.14$$

Biological dosimeter to the patient
Future Perspectives

- Modeling three models from cellular level to DNA level – physics process at the eV scale

- The background dose to bone marrow stem cell toxicity would be significant
Conclusions

- Intraluminal, PeriVascular and Lymphocyte microdosimetry models were examined for TAVAT with Geant4.

- The therapeutic dose to tumor endothelial cell nucleus is 4 Gy or 20 RBE Gy corresponding to ~1% survival rate.

- The background dose to normal capillary endothelial cells corresponding to 99% survival rate and 87% ~ 92% survival rates for lymphocytes.

- A quadratic fitting function of RBE dose to lymphocyte and number of micronuclide was established. It can be used as biological dosimeter.

- These results show that TAVAT holds promise to deliver a lethal dose to the tumor capillary endothelial cells while preserving the function of normal capillaries and lymphocytes.
Thank you for your attention

Comments are welcome!