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• Director, Division of Mathematical Oncology

• Ph.D. Applied Mathematics, University of Washington, Seattle

• Mathematical Modeling of:
  – Cancer progression, response to therapy
  – Medical imaging (MRI, PET)
  – Radiation therapy

• Focus: translation of mathematics into the clinic
Optimizing treatment with radionuclide therapy and immunotherapy

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OUTLINE

• What is radioimmuno therapy (RIT)
• What is CAR T-cell immunotherapy

• Combination therapies and challenges of RIT + CAR T-cell immunotherapy

• Mathematical modeling to address challenges of combo therapy
  – Mathematical models can incorporate:
    • RIT decay, dose, tumor response, toxicity constraints
    • CAR T cell effect, proliferation, exhaustion
    • Provide a framework to optimize: dose, sequence, timing
    • Make predictions and give dynamic quantifications of response

• Examples of mathematical modeling and analysis of:
  – $^{225}$Ac, $^{177}$Lu RIT + CAR T cells in preclinical multiple myeloma model
Radio-immunotherapy (RIT)

- Targeted Radionuclide therapy with antibodies (Ab)
- Renewed interest in alpha emitters in RIT ($\alpha$RIT), ex. $^{225}$Ac

$\alpha$RIT is high LET radiation

Chimeric Antigen Receptor (CAR) T-cell Therapy

Combination therapies in cancer

• Combination therapy approaches are challenging:
  
  – How to determine Dose, timing, sequence of therapies is not clear

• RIT and CAR Ts are a new, potentially important combo therapy, however this presents unique challenges:
  
  □ αRIT – radiobiology, toxicity
  
  – CAR Ts – nonstandard PK/PD, living therapy with cell dynamics and kinetics

• Mathematical modeling can help address these challenges
Multiple Myeloma

Estimated New Cases in 2020: 32,270
% of All New Cancer Cases: 1.8%

Estimated Deaths in 2020: 12,830
% of All Cancer Deaths: 2.1%

5-Year Relative Survival: 53.9%
2010–2016

Death Rate per 100,000 Persons by Race/Ethnicity & Sex: Myeloma

U.S. 2013–2017, Age-Adjusted

Percent of New Cases by Age Group: Myeloma

Myeloma is most frequently diagnosed among people aged 65–74.
Median Age At Diagnosis: 69
Daratumumab (Darzalex, Dara)

- CD38 is a multifunctional ectoenzyme which is essential for the regulation of intracellular Ca^{2+} and subsequent signal transduction.

- Daratumumab (Dara), is a human anti-CD38 IgG_{1} (κ subclass) antibody against the receptor CD38, is now considered the last FDA approved treatment option for MM patients at relapse.

- Since CD38 is a highly expressed surface protein on PCs, the main anti-MM effect of Dara has been attributed to its associated antibody-dependent cellular cytotoxicity (ADCC), complement dependent cellular cytotoxicity (CDC), and antibody-dependent cellular phagocytosis activities (Phipps et al., 2015).

- Clinical results obtained with Dara have been impressive (Dimopoulos, 2016), but unfortunately most MM patients relapse.


Multiple Myeloma is a disseminated disease

We want the model to capture
• **Effect of cell kill of radiation**
• **Decay of radionuclide**
• **Proliferation of tumor cells**
• **Clearance of dead cells from system**

Consider the hazard function
\[
\frac{dSF}{dt} = -h(t)SF(D(t))
\]

**Lea-Catcheside Dose protraction factor**
\[
h(t) = \alpha R_0 e^{-\lambda_p t} + \frac{2\beta R_0^2}{\gamma - \lambda_p} \left( e^{-2\lambda_p t} - e^{-(\lambda_p + \gamma)t} \right)
\]

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Mathematical modeling: RIT

We want the model to capture
- Effect of cell kill of radiation
- Decay of radionuclide
- Proliferation of tumor cells
- Clearance of dead cells from system

\[
\frac{dV_T}{dt} = \rho V_T - k_{Rx} V_t \\
k_{Rx} = \alpha R_0 e^{-\lambda_p t} + \frac{2\beta R_0^2}{(\gamma - \lambda_p)} (e^{-2\lambda_p + \gamma} t) \gamma \lambda_p \\
\frac{dV_R}{dt} = k_{Rx} V_T - k_{cl} V_R
\]

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<thead>
<tr>
<th>parameter</th>
<th>description</th>
<th>unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\rho)</td>
<td>Tumor cell proliferation rate</td>
<td>time(^{-1})</td>
</tr>
<tr>
<td>(k_{Rx})</td>
<td>Rate of tumor cells being irradiated</td>
<td>time(^{-1})</td>
</tr>
<tr>
<td>(k_{cl})</td>
<td>Clearance rate of irradiated tumor cells</td>
<td>time(^{-1})</td>
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Mathematical modeling: RIT

We want the model to capture
- Effect of cell kill of radiation
- Decay of radionuclide
- Proliferation of tumor cells
- Clearance of dead cells from system

\[
\begin{align*}
\frac{dV_T}{dt} &= \rho V_T - k_{Rx} V_t \\
\alpha R_0 e^{-\lambda_p t} + \frac{2\beta R_0^2}{(\gamma - \lambda_p)} \left( e^{-2\lambda_p t + \gamma t} \right) \gamma \lambda_p \\
\frac{dV_R}{dt} &= k_{Rx} V_T - k_{cl} V_R
\end{align*}
\]

A. \( R_0 \)
B. \( \alpha \)
C. \( \rho \)
D. \( k_{cl} \)
225Ac-DOTA vs 177Lu-DOTA-Daratumumab

225Ac-DOTA vs 177Lu-DOTA-Daratumumab

CAR T-cell Predator-Prey Mathematical Model

\[
\frac{dV}{dt} = \rho V \left(1 - \frac{V}{K}\right) - \kappa_1 VC
\]

\[
\frac{dC}{dt} = \kappa_2 VC - \theta C
\]

\(V(t)\): tumor cells
\(C(t)\): CAR T–cells

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<tr>
<td>(\rho)</td>
<td>cancer cell net growth rate</td>
<td>day(^{-1})</td>
</tr>
<tr>
<td>(K)</td>
<td>carrying capacity</td>
<td>cell</td>
</tr>
<tr>
<td>(\kappa_1)</td>
<td>CAR T-cell killing rate</td>
<td>day(^{-1}) cell(^{-1})</td>
</tr>
<tr>
<td>(\kappa_2)</td>
<td>net rate of proliferation and exhaustion of CAR T-cells when stimulated by cancer cells</td>
<td>day(^{-1}) cell(^{-1})</td>
</tr>
<tr>
<td>(\theta)</td>
<td>CAR T-cell death rate (persistence)</td>
<td>day(^{-1})</td>
</tr>
</tbody>
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CAR T-cell model potential PK/PD

CAR T-cell killing dynamics

CAR T-cell + αRIT Combination therapy in MM

1. Unpublished data.
CAR T-cell + αRIT Combination therapy in MM

\[
\frac{dV_T}{dt} = \rho V_T - \delta(t - \tau_{Rx})k_{Rx}V_R - \delta(t - \tau_C)\kappa_1 V_T C
\]

\[
\frac{dV_R}{dt} = \delta(t - \tau_{Rx})(k_{Rx}V_R - k_{cl} V_R) - \delta(t - \tau_C)\kappa_1 V_R C
\]

\[
\frac{dC}{dt} = \kappa_2 (V_T + V_R)C - \theta C
\]
Summary

• Combination therapies and challenges of RIT + CAR T-cell immunotherapy

• Mathematical modeling to address challenges of combo therapy
  – Mathematical models can incorporate:
    – RIT decay, dose, tumor response, toxicity constraints
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Thank you

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