A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth

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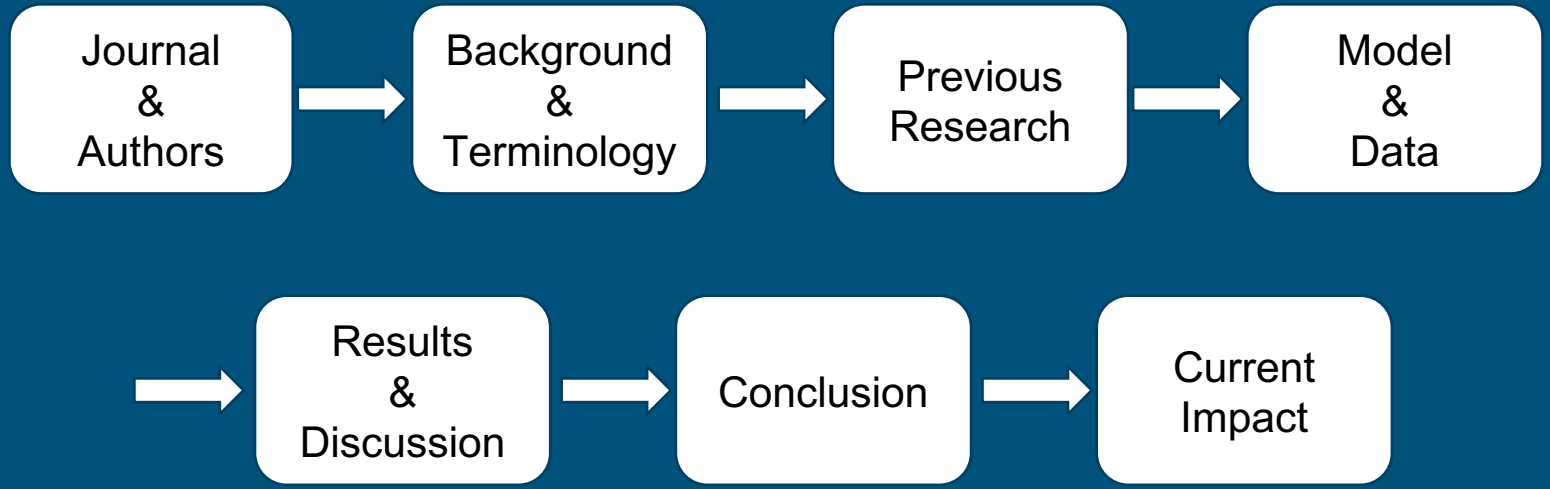
Overview


Journal & Authors
Background & Terminology
Previous Research
Model & Data
Results & Discussion
Conclusion
Current Impact

Journal and Article

Journal

- Scope: The pathobiological (disease biology) foundations of cancer and the translational study of cancer to inform public health action
- Impact factor: **12.701**
- Frequency: Biweekly issues, 1 volume/year

Article

- Title: "A Validated Mathematical Model of Cell-Mediated Immune Response to Tumor Growth"
- Publication date: September 1, 2005
- Citations: **314**

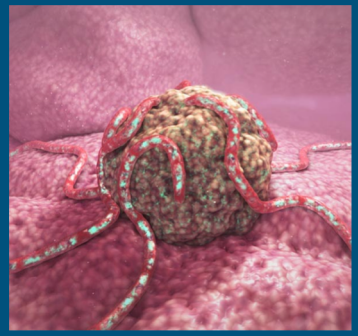
Authors

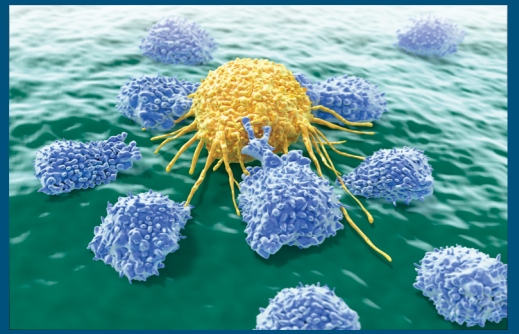
- First Author: Dr. Lisette G. de Pillis
  - Biomathematician
  - Research interests: Applications of math to solve real-life problems in biology with a focus on cancer and HIV
  - Affiliation: Mathematics Professor, Harvey Mudd College

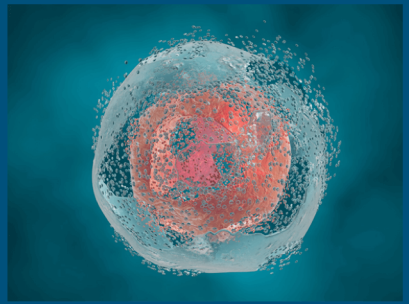
- Co-Authors
  - Ami E. Radunskaya, Biomathematician
  - Charles L. Wiseman, Oncologist

Background

- Tumor:
  - Cells grow and divide uncontrollably
- Immune response
  - Natural killer cell (NK cell):
    - Belongs to innate immunity
    - kill tumor cells independent of prior exposure
  - $CD8^+$ T cell
    - Belongs to specific immunity
    - Recognize cancer cells and kill them
- Lysis
  - Plasma Membrane of cell break down







Scope and Purpose of Research

1. Determine the dynamics of tumor rejection
    - Interaction between tumor and immune response

2. Determine the specific role of NK cell and $CD8^+$ T cell in suppressing tumor cells
    - Efficacy of NK cell impairs tumor growth
    - Efficacy of $CD8^+$ T cell impairs tumor growth

Literature Review

Year	Article	Accomplishment
1986	Coldman AJ, Goldie JH. A stochastic model for the origin and treatment of tumors containing drug resistant cells. Bull Math Biol 1986;48:279–92. Simulation in cancer research.	• Using stochastic model to understand the tumor growth with chemotherapy, including the factor of drug-resistant reaction
2001	de Pillis L, Radunskaya A. A mathematical tumor model with immune resistance and drug therapy: an optimal control approach. Journal of Theoretical Medicine 2001;3:79–100.	• Model tumor growth with chemotherapy and immune system response • Find the optimal cancer treatment
2004	Lin AH. A model of tumor and lymphocyte interactions. Discrete and Continuous Dynamical Systems-Series B 2004;4:241–66.	• Using predator-prey model to analysis the tumor growth and immune system response

Originality

- New functional form for $CD8^+$ T cell tumor kill term
  - Represented by D

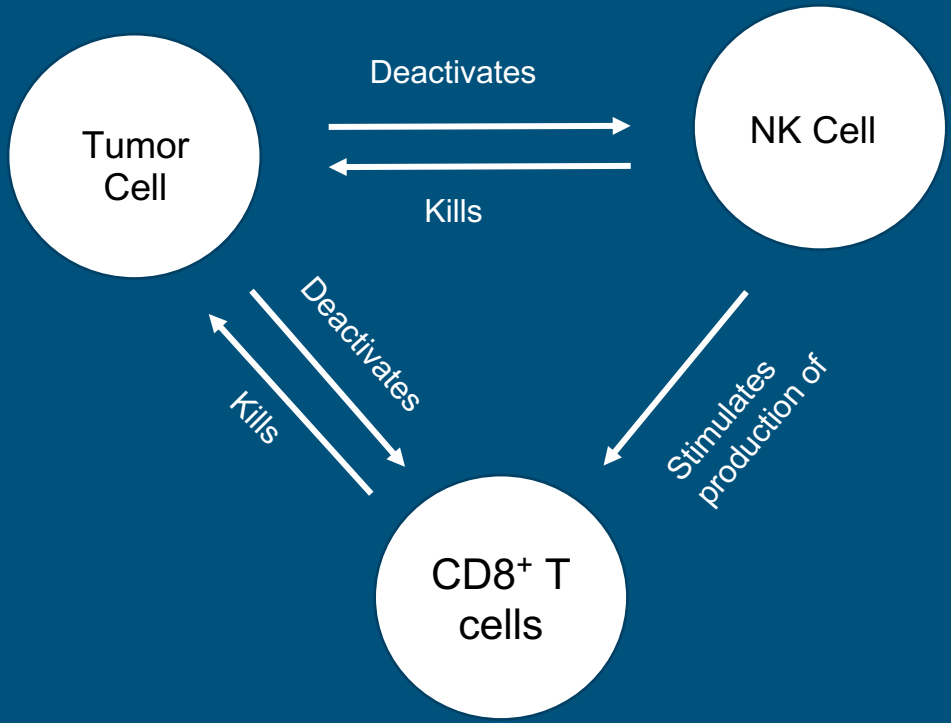
- Hypothesis
  - NK cell and $CD8^+$ T cell have different impact on tumor growth
  - This model is patient specific

Data

- Data Sources
  - Parameter values are borrowed
    - Mouse Data (Diefenbach et al., 2001)
  - Data are provided
    - Human Data (Dudley et al., 2002)
- Data
  - %Lysis of RMA cells for ligand and non-ligand transduced cells
    - Chromium release assay
  - Other parameters
    - MATLAB6 optimization software

Model

- Mechanistic model
  - System of three first order ODEs,
  - Accounts for relationships between cells



Modeling Assumptions

1. Without action from the body, tumor cells grow logistically.
2. NK and $CD8^+$ T cells can kill tumor cells.
3. Tumor cells cause an increase in an effective immune response; the model considers this as an overall, not with regard to its many parts.
4. NK cells are always active and present in the system, regardless of tumor cells.
5. Once tumor cells are present, $CD8^+$ T cells are recruited to fight them.
6. Tumor cells eventually deactivate NK and $CD8^+$ T cells.

Equations

$$\frac{dT}{dt} = aT(1 - bT) - cNT - D$$

- Change in tumor cells
- $aT(1 - bT)$
  - Tumor growth (dependent on tumor carrying capacity)
- cNT
  - Tumor cells killed by NK Cells
  - linear
- D
  - Cells killed by $CD8^+$ T cells

Equations

$$\frac{dN}{dt} = \sigma - fN + \frac{gT^2}{h + T^2}N - pNT$$

- Change in NK cells
- σ
  - New NK cells
- fN
  - Dead NK cells
- $\frac{gT^2}{h+T^2}N$
  - Newly recruited NK cells
  - Michaelis-Menten form
- pNT
  - Inactivated NK cells

Equations

$$\frac{dL}{dt} = -mL + \frac{jD^2}{k + D^2}L - qLT + rNT$$

- Change in CD8⁺ T cells
- $-mL$
  - Dead CD8⁺ T cells
- $\frac{jD^2}{k+D^2}L$
  - Newly recruited CD8⁺ T cells
- qLT
  - Inactivated CD8⁺ T cells
- rNT
  - CD8⁺ T cells stimulated by NK Cells
  - Michaelis-Menten form

Functional Form

$$D = d\frac{\left(\frac{L}{T}\right)^{\lambda}}{s + \left(\frac{L}{T}\right)^{\lambda}}T$$

- The fractional cell kill term for $CD8^+$ T cells is not proportional to its population
- Rational form

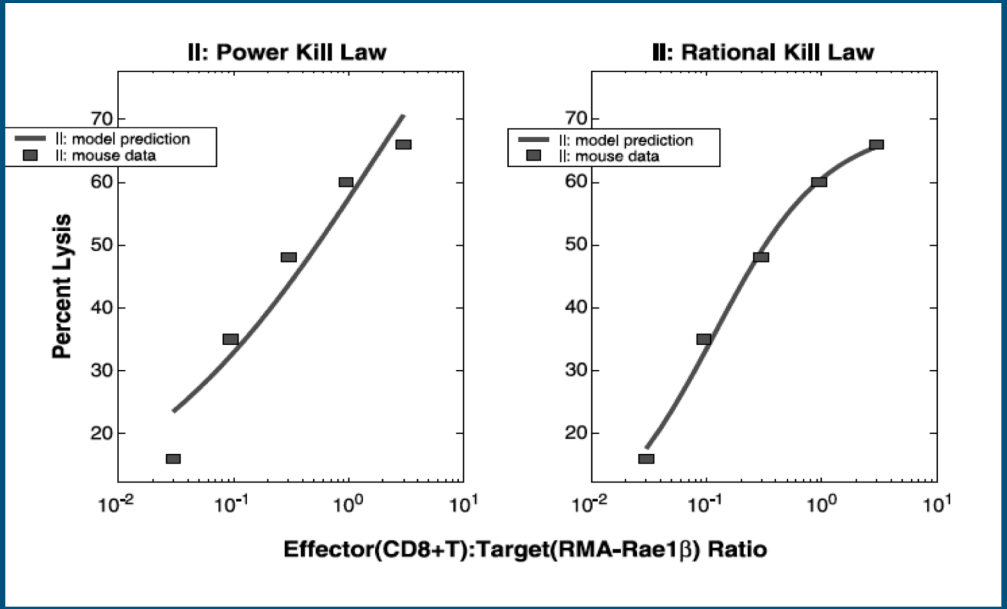
Variable	Meaning
d	• Maximum lysis rate
λ	• Lysis rate is dependent on the effector/target ratio

Results and Discussion

- Solution
  - a least-squares method and numerical differential equations solver
- Efficacy of $CD8^+$ T cell model
  - Determine the parameter by fitting to data
    - Power kill law and rational kill law (D)

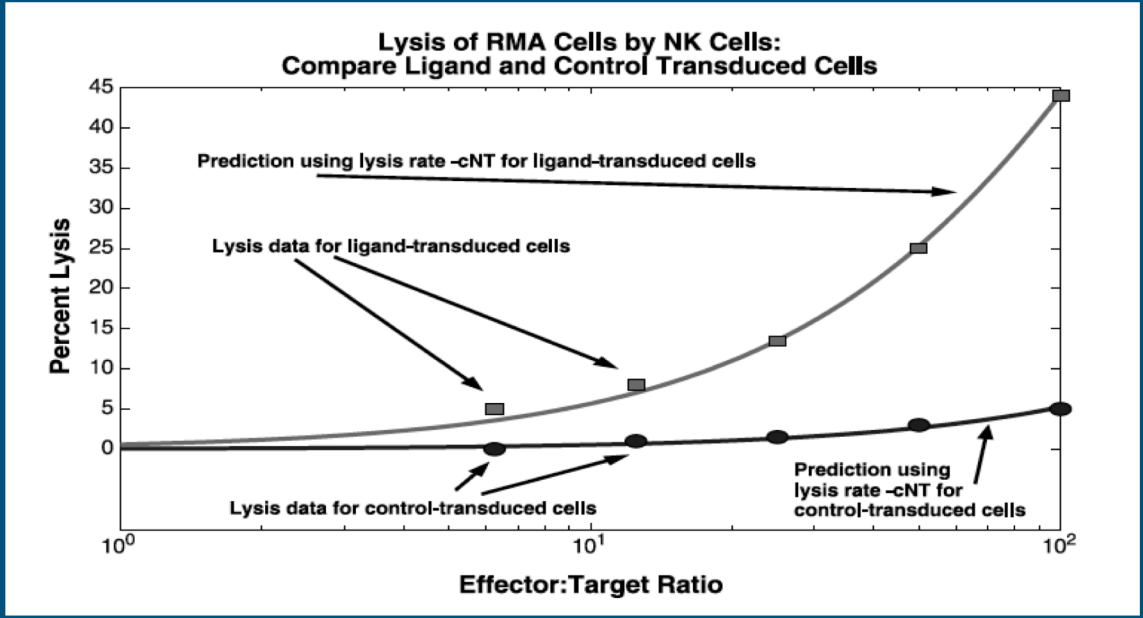
Power Form

Rational Form



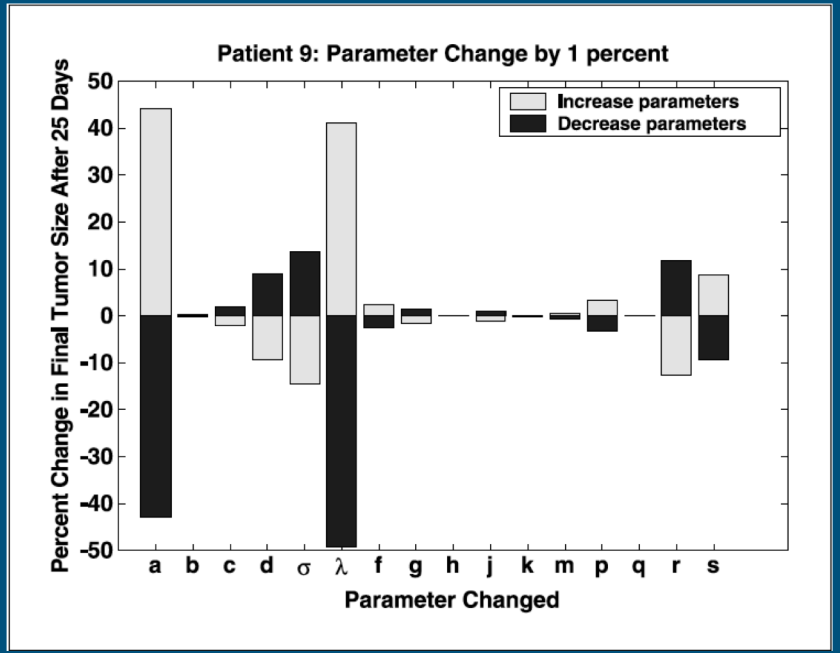
Results and Discussion

- Efficacy of NK model
  - The ligand transduced tumor cells are lysed at a higher rate by NK cells



Results and Discussion

- Model Sensitivity
  - Conducted sensitivity analysis
  - Changed variables in small increase
  - Analyzed effects on final tumor size
- Most significant parameter
  - a: tumor growth rate
  - λ: exponent of fractional cell kill of tumor by $CD8^+$ T cells



Results and Discussion

- Self-criticism of model

Strengths	Weaknesses
● Fits experimental data well ● Agrees with previous models ● Highlights importance of researching NK cell and CD8+ T cell-tumor interactions	● Does not consider immune system self-regulation ● Does not account for down-regulation of immune responses

- Suggestions for future research
  - Laboratory tests to research different cell dynamics between NK and CD8+ T cells
  - Developing cancer treatment methods based on ligand-transduced CD8+ T cells

Impact of article

Citation Count: 314 (Web of Science)

Year	Article	Accomplishment
2021	Dehingia, Kaushik, et al. "Mathematical analysis of a cancer model with time-delay in tumor-immune interaction and stimulation processes." Advances in Difference Equations 2021.1 (2021): 1-27.	• Model the delayed effect on anti-tumor immune response
2021	Trobia, José, et al. "Mathematical model of brain tumour growth with drug resistance." Communications in Nonlinear Science and Numerical Simulation 103 (2021): 106013.	• Model drug sensitive brain tumor growth with chemotherapy
2021	Ghanizadeh, Mojtaba, et al. "Mathematical modeling approach of cancer immunoediting reveals new insights in targeted-therapy and timing plan of cancer treatment." Chaos, Solitons & Fractals 152 (2021): 111349.	• Model the tumor growth with immune response in different phase of treatment

What question do you have?