

# Modeling the Effect of Melanoma Tumor Cell Growth in the Presence of Natural Killer Cells

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[https://info.ornl.gov/sites/rams09/a\\_wells/Pages/default.aspx](https://info.ornl.gov/sites/rams09/a_wells/Pages/default.aspx)

## Abstract

Receptors NKp46, NKp44, NKp30 and NKG2D play a critical role in Natural Killer (NK) cell mediated lysis. MICA and various matrix metalloproteinases (MMP) have also been determined to play a role in tumor cell growth. A mathematical model will simulate the interactions between the NK cell receptors, MICA, MMPs and melanoma tumor cells. New immunotherapies can be developed with accurate predictions from this simulation. NK cell behavior can also be studied further in relation to tumor cell lysis.

## Research Objectives

- Predict behavior of NK Cell populations
- Predict behavior of tumor cell populations
- Predict interaction between NK cells and tumor cell populations
- Create a mathematical model that can be used to create immunotherapies for cancer patients

## Methods

- Found experimental data in previous literature
- Created a series of continuous partial differential equations (PDE)s
- Used MATLAB and Systems Biology Workbench to create simulation model

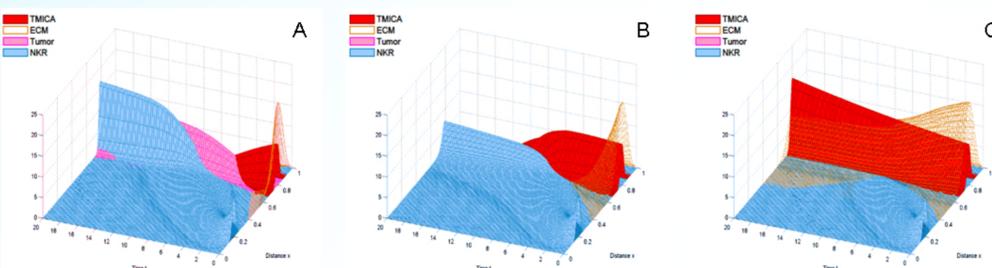


Figure 2. Graphs depicting the effects of MMPs released by NK cells on tumor growth when in the presence of an extracellular matrix.

- A. High MMP levels.  
B. Normal MMP levels.  
C. Low MMP levels.

## Model Assumptions/Theoretical Results

NK cells that express NKG2D can recognize and kill tumor cells. Tumor cells that come in contact with MMPs shed MICA causing them to become invisible to NK cells. Soluble MICA can bind to NKG2D receptor, down-regulating surface density of NKG2D receptors on NK cell surface. NK cells follow a tumor secreted cytokine gradient. The Extracellular matrix (ECM) surrounds tumor cells creating a barrier preventing NK cells from invading the tumor. NK cells can breakdown ECM through the secretion of MMPs.

## NK cell-Tumor Pathway

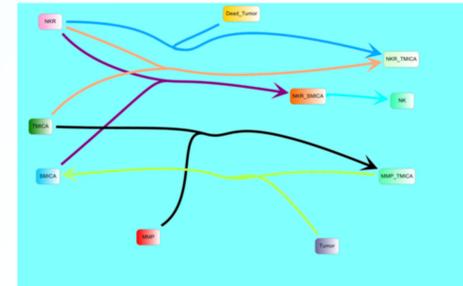


Figure 1. Reversible biochemical reactions during NK cell-Tumor interaction.

## Partial Differential Equations

$$\begin{aligned} \frac{\partial [MMP]}{\partial t} &= -k_3[MMP][TMICA] + k_3[MMP-TMICA] \\ &\quad + p_R[NKR] + p_B[NK] + D_{MMP} \nabla^2 MMP \\ \frac{\partial [Tumor]}{\partial t} &= k_6[MMP-TMICA] + D_T(ECM) \nabla^2 Tumor + G_T Tumor \\ \frac{\partial [NKR]}{\partial t} &= -k_1[NKR][SMICA] + k_1[NKR-SMICA] - k_2[NKR][TMICA] + k_2[NKR-TMICA] \\ &\quad + k_5[NKR-TMICA] + D_{NKR}(ECM) \nabla^2 NKR + \lambda_{NKR}(ECM) \nabla \cdot (NKR \nabla C_T) \\ \frac{\partial [SMICA]}{\partial t} &= -k_1[NKR][SMICA] + k_1[NKR-SMICA] + k_6[MMP-TMICA] + D_{SMICA} \nabla^2 SMICA \\ \frac{\partial [NK]}{\partial t} &= k_4[NKR-SMICA] + D_{NK}(ECM) \nabla^2 NK + \lambda_{NK}(ECM) \nabla \cdot (NK \nabla C_T) \\ \frac{\partial [TMICA]}{\partial t} &= -k_2[NKR][TMICA] + k_2[NKR-TMICA] - k_3[MMP][TMICA] \\ &\quad + k_3[MMP-TMICA] + D_{TMICA}(ECM) \nabla^2 TMICA + G_{TMICA} TMICA \\ \frac{\partial [TumorP]}{\partial t} &= k_5[NKR-TMICA] \\ \frac{\partial [C_T]}{\partial t} &= p_{TB} Tumor + p_{TMICA} TMICA + D_{C_T} \nabla^2 C_T \\ \frac{\partial [ECM]}{\partial t} &= -\delta * MMP * ECM \end{aligned}$$

## Future Research

NK and tumor cell lines will be used to conduct experiments at the University of Tennessee Knoxville to parameterize and confirm model. The mathematical model will be expanded to include a hybrid continuous-discrete model.

## References

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