Masthead Logo

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# Using Non Stem-Cells to Understand Early Tumor Growth

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# Using Non Stem-Cells To Understand Early Tumor Growth

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## Introduction

Tumors of similar size and shape can exhibit different responses to the same treatment. Targeted therapy aims to better treat these tumors by classifying them according to genotypic traits. A better understanding of how tumor traits such as non-stem cells influence tumor growth could improve targeted therapy. **We hypothesize that the production of non stem-cells may aid tumor growth in avascular tumors (tumors lacking blood vessels).**
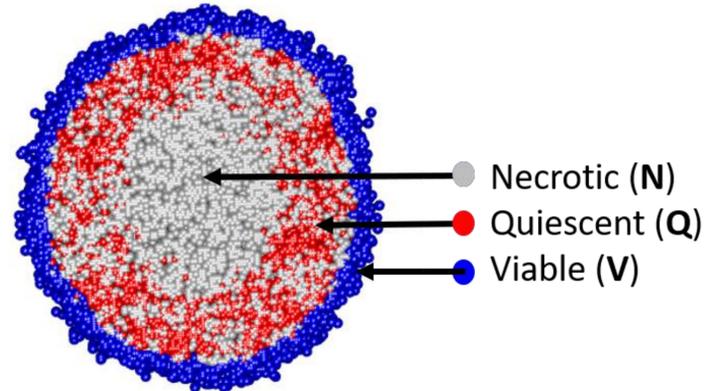
### Patient Tumor Showing Three Distinct Layers[1]
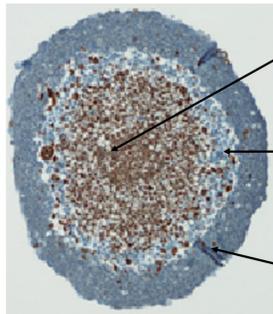
**Necrotic core-** dead cells that release TNF$\alpha$ (Tumor Necrosis Factor Alpha- see key terms)

**Hypoxic layer- quiescent cells-** those that don't move or reproduce due to lack of oxygen

**Viable layer-** active, oxygen-consuming cells

## Methods

### Mathematical Model

We used an **ABM (Agent Based Model):** a mathematical model where cells (or agents) interact according to a set of rules[2]. Cells are represented as points on a 3-dimensional grid.

Cells in the tumor are either **stem** or **non-stem** cells. At each time step, viable cells **(1)** consume oxygen, **(2)** move, **(3)** and reproduce (if there's enough space). They are affected by 2 factors:

1. **Oxygen levels-** Oxygen is diffused from the blood vessels on the edges of the grid. Live cells consume oxygen at a constant rate.

2. **Tumor Necrosis Factor alpha (TNF$\alpha$) levels-** TNF$\alpha$ is released at a constant rate by necrotic cells. High levels of TNF$\alpha$ cause necrosis in surrounding cells.

## Results

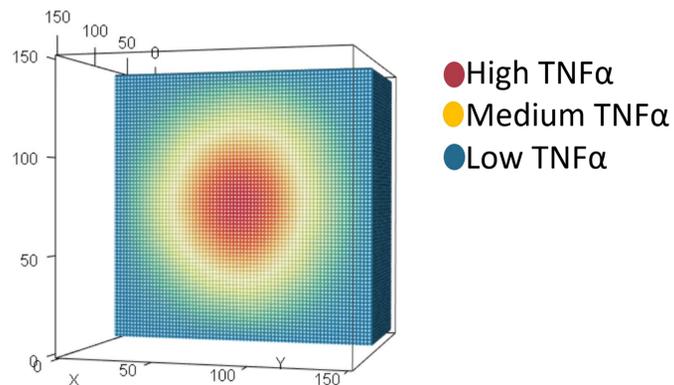### Stem-Cell Tumor Growth Matches Patient Tumors

Necrotic (**N**)
Quiescent (**Q**)
Viable (**V**)

**Figure 1**- The results of this model match the three-layered growth shown in Image 1. Note the radial symmetry and large necrotic core.

### TNF$\alpha$ Causes Increased Cell Death in Stem-cell Tumor

High TNF$\alpha$
Medium TNF$\alpha$
Low TNF$\alpha$

**Figure 2**- This diagram corresponds to Figure 3. The release of TNF$\alpha$ increases the size of the necrotic core in stem-cell tumors.

### Key Terms

**Non-stem cells-** cells that die out after a certain number of replications.

**Stem cells-** cells that can replicate an infinite number of times.

**Tumor Necrosis Factor Alpha (TNF$\alpha$)-** chemical released by necrotic (dead) cells that can induce necrosis in surrounding cells.

## Comparison of Non Stem-Cell and Stem Cell Tumors
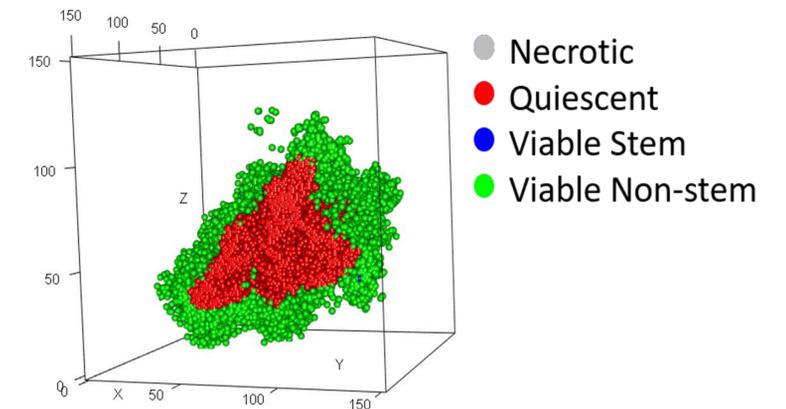
Necrotic
Quiescent
Viable Stem
Viable Non-stem

**Figure 3**- Tumor of mainly non-stem cells showing
- abnormal growth patterns
- lack of a necrotic core

The non-stem cell tumors simulated by the model showed abnormal growth patterns, while the stem cell tumors showed radial symmetry. The abnormal growth of non stem-cell tumors gives them an increased surface area as compared to volume. This factor contributed to the lack of a necrotic core by giving more cells access to consumable oxygen.

## Discussion

The 3-dimensional model supports our hypothesis that non-stem cells could help early growth stage tumors overcome the negative effects of TNF$\alpha$. This is due to the lack of a necrotic core in non-stem cell tumors when compared to stem-cell tumors, which prevents non-stem cell tumors from going dormant due to TNF$\alpha$. However, more simulations exploring different parameters are necessary.

This experiment invites further inquiry about the role of non stem-cells as an evolutionary advantage in larger, heterogeneous tumors as well as early growth stage tumors. Further research in this subject could potentially aid the development of targeted therapy in determining what genotypic traits are likely to cause cancer metastasis.

**References:**
1. Wong C, Vosburgh E, Levine AJ, Cong L, Xu EY. Human Neuroendocrine Tumor Cell Lines as a Three-Dimensional Model for the Study of Human Neuroendocrine Tumor Therapy. J Vis Exp. 2012;(66). doi:10.3791/4218 Poleszczuk
2. J, Macklin P, Enderling H. Agent-Based Modeling of Cancer Stem Cell Driven Solid Tumor Growth. Methods Mol Biol. 2016;1516:335-346. doi:10.1007/7651_2016_344