INTRODUCTION

• An effective way to cure disease is to prevent the development of it all together.
• One modality to combat disease is cancer vaccines that would “program” an individual’s immune system to recognize foreign antigens by stimulating cytotoxic T lymphocytes (CTL) to attack cancer cells expressing a certain tumor antigen [1-5].
• Current vaccine strategies to combat cancer include vaccines consisting of lymphocytes, which include: helper T lymphocytes (Th), dendritic cells (DC), macrophages, or reprogrammed oncolytic viruses [1,2].
• We developed a mathematical model of tumor dynamics in response to a vaccine injection composed of lung cancer epitopes (Survivin, Kita-Kyushu lung cancer antigen 1 (KKLC1), and epidermal growth factor receptor (EGFR)) of different fragment sizes (8-12 amino acids (aa) long) with the goal of determining which epitopes produce a strong immune response.

METHODS

• The dynamics of the mathematical model, as well as parameter values, are borrowed from assertions, prior mathematical models, as well as through parameter estimation through numerical simulations.
• Our model is based on a previous model published by de Pillis et al. [9], but expanded to include simplified T cell development and more cell populations to better depict the immune response to cancer.
• No patient data was integrated into this model yet as this model is in its infancy; a literature review shows no prior model with an integrated MonteCarlo simulator.
• This model has been modified further to introduce the addition of lung cancer “vaccines” using MonteCarlo processes to simulate an antigen stimulation response to different HLA epitopes [9,13,19]. The model is as follows:

FIGURES

• Equation 1 describes the change in population of a cancerous pathology in which the state variable is C. Cancer populations propagate (r) at a fixed rate and die off due to cell-to-cell interactions between NK cells (k), CTLs (v), and macrophages (w).
• Equation 2 describes the change of NK cell populations in which the state variable is a cell population (N). Activated NK cells are born at a fixed rate (R) and die off (D) in proportion to population levels. In addition, NK cells are recruited in response to cancer antigen presentation at a fixed rate (Rn) and Me as well as die off due to cell-cell interactions with cancer (L).
• Equation 3 describes the change of naive CD4 populations in which the state variable is a cell population (N). Naive CD4 populations are born at a fixed rate (L) and die off (D) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M) by antigen presenting cells at a fixed rate (M), which then present the processed cancer antigen to naive populations.
• Equation 4 describes the change of primed CD4 populations in which the state variable is a cell population (N). Naive CD4 regulatory populations are born at a fixed rate (R) and die off (D) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M) by antigen presenting cells at a fixed rate (M), which then present the processed cancer antigen to naive populations.
• Equation 5 describes the change of naive CD4 populations in which the state variable is a cell population (N). Naive CD4 populations are born at a fixed rate (L) and die off (D) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M) by antigen presenting cells at a fixed rate (M), which then present the processed cancer antigen to naive populations.
• Equation 6 describes the change of primed CD4 populations in which the state variable is a cell population (N). Naive CD4 populations are born at a fixed rate (L) and die off (D) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M) by antigen presenting cells at a fixed rate (M), which then present the processed cancer antigen to naive populations.
• Equation 7 describes the change of the interleukin-2 concentration in which the state variable is a cell population (N). IL-2 is produced at a constant rate (c) by lymphoid cells, mainly of H1L lineage, and is consumed in varying proportions (R, R, and R) to recruit circulating memory cells to combat cancer. In addition, IL-2 concentrations (D) are inhibited (D) by regulatory cells.
• Equation 8 describes the change of antigen presenting cells in which the state variable is a cell population (N). APC populations are primed (R) in direct proportion to cancer antigen and die off (D) in proportion to population levels.
• Equation 9 describes the change of naive CD4 regulatory populations in which the state variable is a cell population (N). Naive CD4 regulatory populations are born at a fixed rate (L) and die off (D) in proportion to population levels. Such cells then transition from the naive to primed states due to cancer antigen acquisition (M) by antigen presenting cells at a fixed rate (M), which then present the processed cancer antigen to naive populations.
• Equation 10 describes the change of primed CD4 regulatory populations in which the state variable is a cell population (N). Naive CD4 regulatory populations are born at a fixed rate (L) and die off (D) in proportion to population levels. Primed CTLs, populations are then influenced due to memory cell recruitment by interleukin-2 (D).
• Equation 11 describes the change of macrophage populations in which the state variable is a cell population (M). NK cells are primed at a rate (R), in proportion to cancer antigen and die off (D) in proportion to population levels. Primed CTL, populations are then influenced due to memory cell recruitment by interleukin-2 (D).
• Equations 12 and 13 act as placeholder equations for two variables (R, and M) that act as the MonteCarlo simulator via a pseudo-number generator that affects the output of the other eleven equations.

RESULTS AND DISCUSSION

• MHC class I molecules are designed to recognize peptide fragments of about eight to ten aa along with the maximum being 11.
• With the involvement of intracellular antigens for cancer, the selection of the right HLA gene complex depends on the sequence involved to activate the system.
• Our results illustrate that amino acid epitopes between 8-11 aa long will produce a robust immune response, while anything not in this estimated range will produce a non-robust immune response.
• This model, although useful in predicting the long-term status of a patient, cannot effectively predict which antigen epitopes and HLA combinations will produce a strong immune response due to the current nature of the model.

CONCLUSION

• In our model, three antigens Survivin, KKLC1, and EGFR [24] were utilized from the TANTIGEN database to predict an immune response once cancer was detected within an individual following utilization of a synthetic vaccine.
• We applied mathematical modeling as a tool to depict the strength of a host’s immune response after it has been subjected to a lung tumor vaccine.
• Here, we showed and can infer that if a synthetic epitope is not between 8-11 aa long, a host will produce an immune response, but that is not ideal to the elimination of cancer [26,27].

References
