Formulation of therapeutic cocktails

HYPOTHESIS:

We hypothesize that quantitation of the nonuniform uptake of targeted radionuclide cancer therapy agents can be exploited to create cocktails of these agents that will more uniformly target micrometastatic disease, thereby reducing its progression compared to when a single agent is used.

PROJECT DESCRIPTION (Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)

Prediction of tumor response in therapeutic nuclear medicine largely relies on calculation of the radiation absorbed dose. The radiation absorbed dose delivered to individual cells in a population of malignant cells may differ markedly, and therefore the cells may respond very differently. By the same token, the cellular uptake of chemotherapy agents also differs markedly among a population of cells. Based on our studies, a lognormal distribution of therapeutic agents can be expected among cells that have been treated with radiopharmaceuticals and chemotherapy agents. This type of distribution differs from a normal distribution in that it is skewed, relative to the population mean, in favor of lower agent incorporation. Therefore, regardless of the concentration of therapeutic agent, a significant proportion of cells take up very little or no agent, leading to minimal or no toxic effects on such subpopulations. The significance of this finding to the field of nuclear medicine merited the appearance of our article on the cover of the Journal of Nuclear Medicine (1). Recently, we have published additional studies that show how changes in the lognormal distribution of radiopharmaceuticals and chemotherapy can be used to guide the design of therapeutic cocktails (2). The significance of these findings was highlighted by the Editor through an Invited Perspective in the Journal of Nuclear Medicine (3). The research proposed in the present application builds on our collective findings to test our hypothesis that knowledge of lognormal distributions of agents can be used to design therapeutic cocktails.

A cell culture model of human breast cancer will be used to measure lognormal distributions of monoclonal antibodies relevant to radioimmunotherapy (antibody armed with therapeutic radionuclide such as $^{131}$I) targeted to the breast cancer cells. These data will be used in conjunction with our published methods to calculate the response of the cells to single radiolabeled antibodies and to cocktails of radiolabeled antibodies. To achieve this, MDA-MB-231/RFP or MCF-7 cells will be treated with fluorochrome labeled monoclonal antibodies. Treatments will be conducted with graded concentrations of each agent and histograms of the distribution of targeting among the cell population will be obtained using flow cytometry. Once the cellular uptake of the drugs has been acquired, the fluorescence data for each agent within each cell will be exported from the FlowJo cytometry analysis software to SigmaPlot. We will then simulate arming the antibodies with a therapeutic beta particle emitting radionuclide, $^{131}$I, and use our Monte Carlo simulation model (patent pending at US Patent & Trademarks Office) to calculate the fraction of tumor cells that will be killed by each agent (4). We will also treat the cells with a cocktail of all three antibodies – the concentration of each antibody will be based on the results obtained for the single agents. This will provide us with the amount of each antibody on each cell in the entire population. These data will be used to calculate survival curves for all possible combinations of the agents. The more complex calculations that are required for multiple agents is presently being published (5). We anticipate that this coupling of experimental data and modeling will demonstrate that a cocktail of radiolabeled agents is more effective than any single agent at reducing or sterilizing the breast cancer cell population.
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IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS?

Yes ☐ or No ☒

*(IF YES, PLEASE SUPPLY THE GRANTING AGENCY’S NAME)*

THIS PROJECT IS: ☐Clinical ☒Laboratory ☐Behavioral ☒ Other

THIS PROJECT EMPLOYS RADIOISOTOPES ☐

THIS PROJECT INVOLVES THE USE OF ANIMALS ☐

Pending ☐ Approved ☐ IACUC PROTOCOL #

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS ☐

Pending ☐ Approved ☐ IRB PROTOCOL # M

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

*Culture of human cancer cells. Fluorescence probes and flow cytometry. Monte Carlo modeling.*