The Modeling of Cancer Progression and Immunotherapy

organized by
Lisette de Pillis, Ami Radunskaya, and Charles Wiseman

Workshop Summary

Overview: This unique interdisciplinary workshop was evaluated to be extremely successful. It represented a significant step toward building bridges of cooperation between the mathematical and medical communities. Workshop participants flew in from far distances to participate, including from Israel, New Zealand and Australia, as well as from the East coast, and West coast (eg, UCI and Stanford University). Participating in this meeting were leading names in tumor-immunology research (Theresa Whiteside), a founder of a biotech firm in Israel (Zvia Agur), as well as award winning younger tumor immunologists (Shari Pilon-Thomas from the Moffitt Cancer Center, and Sarah Hook, an immunologist from University of Otago in New Zealand), and many other great minds. During this week, we kick-started new collaborations between mathematicians and clinical cancer researchers. This was a very exciting week, and workshop attendees were so enthused by the experience that they expressed a strong desire to see this meeting become an annual event, with annual conference proceedings.

It was a remarkable seminar: to bring together experts, in some cases world-class experts, from widely divergent fields, to engage in cross- talk about the problem of tumor immune responses, mathematical modeling of tumor growth (and hopefully, regression), and the potential for each field to inspire and to generate insight into physiological mechanisms potentially useful for persons with advanced cancer.

It was the intent of the organizing committee that this be a learning experience that there be synergism, and that this was not to be a forum for any particular expert to do some "grandstanding". We think those goals were amply met.

Personal Reflections: Perhaps the most seminal comment I remember was "Hmmmm, I never thought about it that way. I don't know if there's any data at all about that". The goal of this meeting was precisely that response. One might try to assess the success of the meeting by any number of criteria. But perhaps the least measureable was the effect of persons with quite different perspectives in helping create saliency of some of the "blind spots" inherent in concentrating on the cancer problem from one approach.

Personally, I was very gratified to hear a comment from a mathematics graduate student to the effect that he never quite understood what clinicians deal with, engaged with real patients. The point is not that I received a compliment but that there was some real learning that probably could not have otherwise taken place.

Scientific progress: One focus group, which included Drs. Clemence, Moore, Whiteside and Wiseman, generated a model of differential equations to describe tumor vs immune growth, not unique certainly. But it was unique to include the possibility of autoimmune

responses, a not infrequent finding in immune therapies and one receiving increasing. Some initial motions have been made to create further collaboration between the members of this group.

Another focus group discussed the problem of how to make use of a database of genetic profiles of patients with breast cancer, including treatments administered and the outcomes of these treatments. A neural network decision model was developed that would generate survival probabilities depending on treatment administered, given a new genetic profile. Some discussion between group participants has continued after the workshop, and the preparation of a "methods" paper is underway. (Participants in this ongoing discussion: Drs. Gordon, Hogea, Radunskaya).

A collaboration has evolved between Drs. Hook and Radunskaya who are developing a mathematical model of cancer vaccines that will be calibrated to a murine model. Dr. Hook is currently running laboratory experiments to determine the kinetics of the immune response. A preliminary model consisting of nine delay-differential equations has been developed and calibrated to preliminary lab results, and a manuscript describing the results is in preparation. The plan is to expand this collaboration to include Drs. dePillis and Teboh-Ewungkem, who will apply optimal control techniques to suggest optimal dosing and timing strategies for the specific cancer vaccine being studied by Dr. Hook.

As a result of the workshop, Dr. Radunskaya will meet with Dr. Pilon-Thomas in June at the Moffitt Cancer Center in Florida. The problem that was posed at the AARC workshop was to identify the mechanism that is responsible for the expansion of an antigen-specific T-cell clonotype in response to a tumor. In particular, must there be a pre-existing bias in the T-cell repertoire, or is it a stochastic event, susceptible to timing influences? It is our hope that a collaborative effort linking laboratory studies and mathematical models will illuminate this fundamental question. This collaboration, initiated at the workshop, will begin in earnest in June.