Tumor-immune dynamics

organized by
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Workshop Summary

This workshop focused on (1) identifying key questions in cancer immunology and immunotherapy that are suitable and timely for mathematical modeling; (2) assessing modeling approaches that are appropriate to address these biological and medical questions, (3) determining what types of experimental studies and data can inform model development, and (4) facilitating collaboration between experimental and computational scientists in cancer-immunotherapies.

Recent progress in cancer immunology and advances in immunotherapy suggest that the immune system plays a fundamental role in combating tumors, and hence can be used as a vehicle to prevent or cure cancer. Despite the advances in theoretical and experimental studies of tumor-immune system dynamics, fundamental questions concerning complex interactions between the immune system and the growing tumor remain. For example, current research in the field is driven by questions concerning how components of the immune system synergize to limit cancer development, how tumors escape the immune system's recognition and control, and why some immunotherapies inhibit growth of certain tumors while stimulating the growth of others. Indeed, the multidimensional nature of these complex interactions requires cross-disciplinary approaches to capture more realistic dynamics of the essential biology. One such approach combines cancer immunology with mathematics to model these complex interactions.

The workshop brought together twenty-one participants (six leading experts and fifteen junior scientists) in applied and computational mathematics, biology, as well as clinical medicine, spanning both developing and developed countries. The participants came from Australia, Canada, France, Italy, Korea, Mexico, Morocco, South Africa, and the USA. They all gathered with a strong interest in understanding the complex interactions between the immune system and tumors, devising predictive mathematical models, and linking data to models. Some participants were from primarily teaching institutions whereas others from primarily research institutions.

Speakers during the morning sessions of the workshop provided the participants with the background material leading up to specific problems. Chae-Ok Yun, a biologist from Hanyang University in Korea, gave the first talk of the workshop titled *"Immuno Gene Therapy Using Oncolytic Adenovirus."* Heinz Schättler from Washington Univeristy in St. Louis lectured on *"Cancer Chemotherapy and Tumor-Immune Dynamics."* Dominik Wodarz, from the University of California, Irvine talked about *"Mathematical Models of Oncolytic Virus Therapy."* Lisette de Pillis, from Harvey Mudd College, addressed *"Tumor-Immune Modeling."* Dr. Peter Lee, MD, from City of Hope gave a talk on the *"Important Issues in Cancer Immunotherapy."*

The focus of the first day was on the collective understanding of the state of the field of cancer-immunotherapies. There were two parallel ask-the-experts sessions led by Prof. Chae-Ok Yun and Prof. Lisette dePillis in the afternoon of the first day, which generated a lot interesting and timely questions from the participants. Some of the questions included:

- How do patients become resistant to previously effective immunotherapies? Is progression induced by the treatment?
- How might the evolutionary viewpoint explain different emerging behavior, e.g., tumor relapse, immune evasion, etc.?
- How does the interaction between an immune cell and cancer cell alter the biochemistry (intra-cellular signaling) of the cancer cell? How do cancer cells evolve to overcome this and evade the immune system?
- A major hypothesis is that the immune response can be enhanced by chemotherapy by causing immune cells to be stimulated by the death of cancer cells. How does chemotherapy enhance the anti-tumor immune response?
- You said that we do not want to give the virus systemically, because of virus clearance and toxicity, so we want to inject locally in the tumor. Should virus doses all be injected in the same place or should they be injected in multiple spots around the tumor?
- Is there any way of measuring the viral population or infected cell population in the tumor?
- What role, if any, do spatial models (PDEs, agent-based models) have in elucidating tumor-immune interactions?
- How does microenvironment shape the heterogeneity of tumor cells and vice versa?
- Is it possible to measure the diffusion coefficient for viruses in tumors?

These questions fell into three categories: (Co)-evolutionary dynamics, modeling therapies, combined therapies and optimization, and spatial dynamics. Further discussion helped summarize and make these questions more precise and focused, which led to three main problems as follows:

(1) How do components of the immune system synergize to limit cancer progression? What are the impacts of the virus-specific and cancer-specific immune responses?
(2) Can we characterize the dynamics of combination therapies, such as virotherapy combined with chemotherapy, radiotherapy, and/or dendritic cell vaccines? How can we optimize therapy schedules, doses, and combinations to maximize tumor reduction while maintaining toxicity below a threshold?
(3) Can we model viral spread/diffusion throughout a tumor? How does the enzyme relaxin, gel systems, polymer-coating, or multiple injections of viruses affect the spread of virus?

On the afternoon of the second day, the participants broke into three teams according to their common interest in these topics. Through a series of informal presentations and elaborate discussions, these three interactive parallel working teams focused on developing mathematical models to answer the three problems proposed by the participants. There was plenty of time devoted to the parallel breakout sessions every day for the remainder of the week-long workshop. All participants actively engaged in cross-disciplinary discussions on various aspects of cancer-immunotherapies. In addition, each team consisted of entirely new collaborations for all members involved.

Given the level of enthusiasm of each team, the organizers expect that they each will produce a journal article that is suitable for publications in well-ranked and widely accessible journals that focus on mathematical modeling in biology and medicine. Below is the summary from each team so far.

1 Searching for Immune Synergy

This group set out to develop a model to address the following question: What are the separate impacts of the anti-virus and anti-cancer immune responses that are elicited by cancer virotherapy?

To proceed in this direction, this team is working on developing an ordinary differential equation (ODE) model that considers uninfected and infected cancer cells, free virus particles, and anti-virus and anti-cancer T-cell responses. For the T-cell responses, we considered both effector and memory T-cells. The idea is that infected cells, and hence viruses, are eventually cleared from the system by the host's immune response, which could lead to the formation of anti-virus T-cell memory. This could lead to diminishing effectiveness of oncolytic viruses.

On the other hand, some goals of the therapy intended in this model are to (1) reduce tumor burden, and (2) generate anti-cancer T-cell memory. By using this model, the team plans to fit solutions to data to obtain parameter estimates and then try to find certain effective (maybe optimal) treatment strategies to most effectively reduce tumor size and generate immune memory against cancer cells.

2 Physiologically Based Models for Chemo- and Immunotherapy Impacts onto The Immune Response in Cancer

This team set out to propose problems in mathematical modeling to represent the effects, beneficial or detrimental, of cancer chemotherapies on the immune response and to use this insight to understand to possible effects of combining chemotherapy with various types of immunotherapy. The question of a trade-off between these positive and negative effects, that is known to be dependent on the chemotherapeutic drug under study, and likely of the doses used, opens questions of optimal therapeutic control in cancer treatments.

The team first asked the biologists among them to sketch a simple description of the immune response, innate/adaptive/memory. Then, everyone worked together to design a preliminary toy model in which spatial locations of pathophysiological phenomena and time scales were combined.

Following this investigation, the team decided to develop a physiologically based map of the immune response involving two distinct sites: a tumor cell population site (primary or metastatic, functionally merged) and an ensemble of lymph nodes in the vicinity of these tumor cell aggregates, and different time steps: a) antigen recognition from tumor cell lysates by dendritic cells, b) antigen presentation by mature dendritic cells in lymph nodes resulting in CD8 T cells activation and proliferation, and c) migration back to the tumor sites and attack of the tumor cells by immunocompetent CD8 T cells.

Sticking to this physiological scenario, the team began to establish a two-compartment model consisting of ODEs, taking into account these time steps. The guiding principles were as follows: representing evolution of cell population densities using law of mass action

or enzymatic-like reactions with a quasi-steady state approximation; fast communication of cells between the two sites using blood and lymphatic vessels; inclusion of targets for the effects of (blood-mediated) chemotherapies and of chimeric antigen receptor (CAR) T cells on cell populations at both sites. As a future step, the team plans to model the production of memory and regulatory T cells, responsible for immunosurveillance and immunotolerance and the impact of related drugs, such as ipilimumab.

3 Model of Viral Diffusion Through Tumor Tissue

Based on the discussion about the therapy to annihilate cancer cells employing genetically-engineered oncolytic adenoviruses, this team set out to address the question on viral spread/diffusion through a tumor tissue i.e how does the enzyme relaxin, gel systems, polymer-coating, or multiple injections of viruses improve the spread of the virus (or not)? The team proposed a PDE model that describes the dynamics of three major components (or state variables) of this therapy: the concentration of population of cancer cells in tumor, the concentration of population of viruses, and the concentration of molecules of extra-cellular matrix. All variables are described in terms of spatial variations, $x \in \mathbb{R}^n$, with $n = 2$ or 3, and temporal evolution t, on a closed and confined space, $\Omega \subset \mathbb{R}^n$. The model is a system of nonlinear and coupled partial differential equations (PDEs) - reaction-diffusion system.