Systems approaches to drug discovery and development in oncology

organized by
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Workshop Summary

Cancer is exceedingly common. It is the second leading cause of death in the United States; where over half a million new cases are registered each year. It is an extremely complex, heterogeneous disease involving a large number and variety of elements that interact through complex networks. It is increasingly believed that a systems approach combining empirical, mathematical and computational methodologies to gain an understanding of complex physiological, molecular and biochemical processes that exist in cancer cells, could open up entirely new approaches for cancer treatment. The purpose of the workshop was to bring together a select list of participants working in the field of oncology that range in expertise, from experimental biology to applied mathematics, and to focus on the benefits and challenges of implementing systems approaches in oncology drug discovery and development. We had 27 participants included researchers and graduate students (4) from NC State University, Rensselaer Polytechnic Institute, University of Michigan, Case Western Reserve University, University of Surrey, College of Saint Rose, Harvey Mudd College, Pomona College, Skidmore College, MIT, University of Edinburgh, Tata Institute of Fundamental Research, Merrimack Pharmaceuticals, Novartis, Pfizer, Boeringer Ingelheim Pharmaceuticals, Silver Creek Pharmaceuticals, NIH, and Pacific Northwest National Laboratory. The main goals of the workshop were to (1) outline the current state of the science, (2) identify sources of challenges in systems approaches in oncology, (3) prioritize the challenges based on probable impact, (4) offer potential plans to address the highest priority challenges, and (5) facilitate critical discussions between experimental and computational scientists, and between industrial and academic researchers.

Each morning started with two one-hour presentations, followed in the afternoon by group discussions. The participants were encouraged to use sticky notes for posing additional questions raised by the talks of the morning speakers and for topic suggestions for the afternoons group discussions. The Thursday afternoon was used to collect a list of open problems that are deemed to be crucial for further progress in implementing systems approaches in oncology. This session was moderated by one of the participants. On Friday morning everyone was involved in prioritizing the list of open problems and, in the afternoon, breakout groups were formed to elaborate and suggest proposed solutions to the prioritized list of open problems.

On Monday morning, Michael Zager (Pfizer) mapped out the main themes of the workshop followed by an introduction on the systems approach in oncology drug discovery at Pfizer. Also addressed were the merits as well as challenges in cancer system biology. Matt Onsum (Merrimack) followed with a lecture on some of the success stories in the uses of system biology in recent cancer drug discovery at Merrimack Pharmaceuticals. In the next three

days, the lectures focused more on some specific topics in cancer modeling. The lectures on Tuesday morning dealt with cell signaling pathways. Haluk Resat (Pacific Northwest National Laboratory) began with a lecture on various aspects of computational biology of cell signaling at the Pacific Northwest National Laboratory with the aim of raising questions about the fundamentals of computational biology in oncology. Among results that were presented is the epidermal growth factor receptor signaling pathway, which is very important for physiology and pathology (cancer). In the next lecture Jason Haugh (NC State University) presented the work on signal transduction networks in his laboratory at NC State University. Specifically, he discussed the impact of integrating biochemical and biophysical processes across multiple scales from molecular structure to tissue-level response. A key point from both lectures is that tight integration of experimental studies and computational modeling is a must to advance cancer systems biology. Wednesday morning had Mary Spilker (Pfizer) and Ami Radunskaya (Pomona College) presenting an overview of modeling efforts on tumor growth kinetics from the pharmaceutical industry and academia, respectively. The model complexity ranged from a simple logistic equation to a system of delay differential equations. The focus of Marys lecture was on linking dosing regimen to the tumor growth dynamics to predict the response of tumor growth dynamics at different regimens (Pharmacokinetics-Pharmacodynamics-Tumor Growth Inhibition (PK-PD-TGI)). The emphasis from Amis talk was on the tumor-immune interactions and optimal dosing strategy to maximize immune response. On Thursday morning Lisette de Pillis (Harvey Mudd College) began with a lecture on tumor growth dynamics during immunotherapy and chemotherapy. The lecture also showed how to perform sensitivity analysis to study the response of the system to changes in data and parameters as well as the formulation of an optimal control problem for finding best treatment protocols. Hien Tran (NC State University) then followed with a lecture on modeling techniques for complex biological systems focusing on sensitivity analysis, identifiability, filtering (data-model fusion), and optimal control methodologies including open-loop controls and closed-loop (feedback) controls.

The afternoon sessions were dedicated to group discussions of problems, which are all suggested by participants on sticky notes. These problems included:

(1) Mechanisms for industrial-academic collaboration. Partnerships with academic organizations will be a key to integrate state-of-the-art approaches and tools. However, such partnerships also raise questions about intellectual property, publication rights and timelines;
(2) System approaches to drug resistance. Discussions centered on various mechanisms by which cancers elude treatment. Knowledge of these mechanisms of cancer drug resistance may help in the development of new drugs that are less susceptible to known resistance mechanisms as well as in improving drug delivery and distribution in patients;
(3) Translating pre-clinical models to human. The difficulty in translating preclinical pharmacologic data to patients is the absence of detailed and mechanistic pharmacokinetic and pharmacodynamics models that can predict drug disposition and dynamics in tumors and, consequently, provide a basis to adjust drug schedules in patients;
(4) Model validation. Validation is concerned with building the right model. It is utilized to determine that a model is an accurate representation of (aspects of) the real

biological system. Central to this process is how to obtain biological relevant data and to translate model parameters that were obtained from animal studies to human cases.

On Thursday afternoon we collected a list of problems in oncology for the systems biology modeling community to address, in a session chaired by Matt Onsum. On Friday morning this list was then prioritized to four main problems that were further elaborated and considered for potential solutions by four breakout sessions in the afternoon. The four prioritized main challenges to both academia and pharmaceutical industry are:

(i) Are the animal models used in oncology drug discovery predictive of human diseases, and if so, how should they be used?
(ii) How should we be mechanically linking cell-signaling models to tumor growth?
(iii) How can we apply system approaches to address drug resistance (predicting and/or treatment)?
(iv) How do we address tumor heterogeneity and the role it plays in tumor behavior/characteristics?

The overall enthusiasm and engagement from all participants throughout the workshop was strikingly high, which has led to preliminary plans to continue these efforts through focused groups (possibly sponsored by AIM or other institutes) and collaborations, and to publish the outcomes and conclusions of the workshop. The anticipated manuscript shall offer potential paths forward to address the four issues outlined above, which were discussed during the workshop. A common theme among the potential paths was the need for cooperation among pharmaceutical competitors and focused collaboration with academia. The organizers are extremely grateful to AIM for funding and assisting with this workshop.