## CSBC Investigator Highlight

### *Dr. Vito Quaranta Uses Computational Models to Study the Complexities of Tumor Heterogeneity*

Vito Quaranta, M.D., a CSBC Investigator at Vanderbilt University, uses systems approaches to study heterogeneity and treatment responses in cancer.

As a young investigator, he created antibodies that could target tumor-specific antigens in pancreatic tumors. One of these antigens turned out to be a cell adhesion protein and led him into the field of cell adhesion and migration. In the early 2000s, he started using systems biology approaches in his cell adhesion research and built cellular-level models integrating cancer cell interactions with the extracellular matrix. Now, he is investigating how lung cancer cells adapt to different microenvironments and cancer treatments.

In this interview he shares advice for trainees in cancer systems biology, gives his views on strengths and challenges of systems biology, and describes computational models that he uses in his CSBC research.

- **What advice do you give to trainees in cancer systems biology?**

  I think that the most important thing is to start developing an instinct for understanding complexity and the behavior of complex biological systems. In biological systems, you need to become deeply aware of complex behavior that emerges from very simple rules. It's like a game of chess where there are a set of rules but very strange outcomes.

  Once you start looking at biology as a complex system, then you have to develop tools to study complexity. I tell trainees to try to match the available tools to their talents. Some people are good at image processing, while others are good at statistics. It takes a combination of tools and personal talents to attack problems in cancer.

- **What is a current strength and challenge of cancer systems biology?**

  A fundamental strength is that it is quantitative. Even qualitative data are translated into quantitative assessments that can be communicated to a machine. It's hypothesis-driven science using hypotheses that are translated in the language of math, which is a tremendous strength.

  A challenge is that we don't know how to train systems biologists yet. Systems biologists need a breadth of training that spans from math to experimentation. Usually we think of training scientists to know everything about one thing. However, in systems biology, we need to train scientists who know a little bit about many things. A great thing about the CSBC is that we get to see how other people in the consortium practice systems biology and their ideas on how to train students and postdocs.

- **Can you describe some of the computational models that you use for your CSBC research of small cell lung cancer (SCLC)?**

My lab is currently working to define SCLC subtypes in terms of transcription factors. Instead of looking at the role of a single transcription factor in heterogeneity, one of our collaborators in mathematics advised us to look at a transcription factor network. This can be modeled as a network that obeys Boolean logic, since a transcription factor is either on or off. Boolean models are easier to build, simulate, and then test experimentally than other types of models. We think that we can get to the root of SCLC heterogeneity and responses to treatment from these mathematical models.

In a recent preprint on *bioRxiv*, we combined Boolean rules and Bayesian inference into an approach that we called BooleaBayes. This method helps us understand some of the rules that allow transcription factors to be either on or off. Using this approach, we were able to identify gene expression signatures for certain transcription factors that are expressed in SCLC subtypes. We also performed experiments using single-cell RNA sequencing to validate the subtypes that were computationally identified. This approach reveals master regulators and destabilizers of transcription factor networks that contribute to tumor heterogeneity and drug responses.

The biochemistry of the transcription factor networks involved in SCLC needs to be further studied using kinetic models. For this work, my lab uses a framework called PySB that was developed by Carlos Lopez. PySB is a python-based modeling technique that allows us to write kinetic models in terms that are understandable to experimentalists. You can write biological rules, like receptor binding to a ligand or site phosphorylation of a protein, in plain English. The PySB user interface then writes equations for you. We can use PySB to build models at the cell level and interactions with the tumor microenvironment.

Understanding the complex interactions of different SCLC subtypes is key to learning how these tumors progress and respond to treatment.

**Links**

Vito Quaranta Vanderbilt University School of Medicine Profile

Vito Quaranta Lab at Vanderbilt University LabNodes