CSBC Investigator Highlight

Dr. Juan Fuxman Bass uses systems biology to understand cancer-specific molecular interactions

Juan Fuxman Bass, a CSBC investigator at Boston University, studied biology as an undergraduate and graduate student at the University of Buenos Aires in Argentina. Now, he uses systems approaches to investigate the role of gene regulatory networks in cancer.

In this interview he discusses his career journey, challenges in cancer systems biology, and his CSBC research focused on breast cancer.

- **Can you describe your career journey to systems biology?**

  During my graduate studies, I felt like math and computational work were missing from my research.

  For my postdoc, I wanted to switch from immunology to systems biology, since I knew that the future of research was in integrating high-throughput experimentation with mathematical modeling. However, getting a postdoc interview was challenging because I had no experience in systems biology. I sent out a lot of applications, and eventually had an interview with Dr. Marian Walhout. It was an instant fit and she offered me the position over the phone. I accepted right away, and that was the best decision that I could have made. She was and she still is an excellent mentor. She helped me learn about the field of systems biology and how to develop a scientific career in the U.S.

  Switching fields for my postdoc was hard, because I had to learn everything from scratch. But it was also very rewarding. It gave me the opportunity to learn new experimental approaches and new ways of tackling biological questions.

- **What are current challenges in cancer systems biology?**

  One challenge is identifying the right datasets and modeling approaches which will be informative of the cell state and provide accurate predictions for therapeutics. These datasets may not necessarily be the ones that are easy to obtain, and this is going to require the development of new tools.

  The other challenge is that we need to generate accurate models that consider the tumor microenvironment and immune cells in a patient-specific manner.

  There are many groups that are starting to tackle these challenges. It's also important to remember that every challenge represents an opportunity to develop new tools and mathematical frameworks. Now, a lot of the new technologies that can address these challenges are coming from cutting-edge investigators of the CSBC and the Physical-Sciences – Oncology Network.

- **Can you describe your CSBC project?**

One of the ultimate goals of cancer systems biology is to generate models of tumorigenesis by identifying all the perturbing interactions between molecules in cancer cells. The central hypothesis of our grant is that perturbations emerging from cancer-specific gene isoforms (in other words, different versions or forms of a normal gene) are going to be crucial for cancer development.

Most studies have focused on genome alterations, such as mutations, amplifications, deletions, and large chromosome changes in cancer cells, which are often considered to be the primary event of cancer progression. However, cancer-specific isoforms have also been shown to be important in tumorigenesis. Changes in the isoforms of transcription factors, which are the proteins that are responsible for turning on and off gene expression in different cells and conditions, have been shown to play a major role in cancer progression and metastasis. Yet the extent to which differences in transcription factor isoforms between normal and cancer tissues lead to altered gene expression in cancer remains unclear. Hundreds of transcription factor isoforms have been identified in cancer samples, but the vast majority remain uncharacterized at the functional level. This means that we don't know which gene they will affect, and whether it will be turning gene expression on or off.

In this project, are working on an initial step towards this long-term goal by characterizing the effect of a large number of transcription factor isoforms in breast cancer. We aim to combine mathematical modeling with high-throughput experimental strategies at the level of molecular interactions to predict cancer drivers and suppressors. The lessons learned from these studies will provide a framework to design novel therapeutics.

- **How will your CSBC project ultimately contribute to the development of cancer therapies?**

  Identifying cancer-specific interactions and perturbations provides an opportunity to design therapeutics that can either wire back normal interactions that were rewired in cancer or perturb the system in a way that will bring it into a state like a normal cell. Without having a map of what interacts with what, it's very hard to develop a mathematical model to predict responses. This predictive modeling enables the design of therapeutic interventions that target cancer-specific interactions.