CSBC Investigator Highlight

Dr. Joe Gray: A Nuclear Physicist Who Studies Tumor Heterogeneity

Joe Gray, Ph.D., a CSBC Investigator at Oregon Health and Science University (OHSU), views systems biology as the application of experimental and computational tools to understand and predict the behavior of biological systems.

His lab is developing tools, including molecular profiling and multiscale imaging technologies, to explore the components and multiscale organization of cancer systems. Using these approaches, he wants to find better ways to control and treat cancer.

In this interview, he describes his career journey from physics to cancer research, current challenges in cancer systems biology, and his CSBC-supported studies examining heterogeneity in breast cancer.

- **Why did you pursue training in physics and what made you transition to cancer biology?**

  I was a child of the Sputnik era when there was a huge amount of interest in rocket science. Growing up at this time, I was naturally drawn to the fields of physics and engineering. I wanted to play a role in the national effort to travel into space.

  I ended up getting interested in nuclear physics. In this research area, you do experiments and use fundamental principles to explain the results. However, I didn't find it as relevant to the real world as I wanted it to be. It was very elegant but abstract.

  Around the end of my graduate school studies, my father developed lung cancer. This made me realize that little was understood about the biology of human diseases.

  At the time, I was sharing an office with yeast geneticists who were exploring new facets of biology. I found that I could help them investigate biological mechanisms using tools that I developed and learned from physics.

- **Who were important mentors during your career?**

  Jim Legg at Kansas State University trained me in systems physics. He taught me how to develop experimental and computational tools to measure and then predict the behavior of a system.

  Mort Mendelsohn, Marv Van Dilla, and Brian Mayall at Lawrence Livermore National Laboratory showed me that insights in biomedicine derive from new analytical tools.

  Helen Smith at California Pacific Medical Center, Laura Esserman, Mina Bissell, and Brian Druker taught me about cancer and the power of multidisciplinary team science.

- **What do you think are current challenges in cancer systems biology?**

First, we need better rules to figure out how to reduce the dimensionality of a complex system to its essential components. To determine biological behavior, we need to use the essential components as the basis for computational models. This might require the development of statistical rules based on biological principles, similar to the use of statistical mechanics in physics.

Second, researchers need to learn how to work across spatial and temporal scales. We tend to focus on one aspect, but it's really a multi-dimensional and multi-temporal problem. The behavior of a system is determined by interactions that vary in spatial dimension and occur across multiple time scales. We currently lack tools to enable such multiscale, multitemporal studies.

Third, we need better tools to link regulatory networks inferred from "omic" studies to the spatial structures they represent.

Fourth, we need to develop better strategies to understand how cancers evolve under perturbations. They adapt and evolve biologically, structurally, epigenomically, and genomically. Developing the systems biology of evolution in cancer is going to be important.

- **Why is your CSBC research focused on** triple negative breast cancer**?**

  Triple negative breast cancer is the most heterogeneous subtype of breast cancer and is critically lacking in effective therapeutic strategies. My lab focuses on this type of cancer because we are interested in understanding and controlling tumor heterogeneity, which is fundamental to developing more durable treatments of cancer.

- **Can you discuss your recent** study **involving microenvironmental microarrays?**

  It was based on the development of a platform to assess the effects of thousands of microenvironments on different types of breast cancer cells.

  We identified different sets of environmental signals that changed therapeutic responses in specific subtypes of breast cancer cells. For example, luminal-like breast cancer cells grown in the presence of neuroregulin-1β became stimulated instead of inhibited by breast cancer drugs. Similarly, basal-like breast cancer cells grown in the presence of hepatocyte growth factor were largely resistant to cancer drugs. Guided by these finding, we elucidated underlying mechanisms and developed therapeutic strategies to counter the negative effects of these microenvironment factors.

  The findings set the stage for us to better understand how breast tumor microenvironments may play a role in cancer progression and illustrated the importance of developing cancer therapies that target the resistance-promoting effects of the microenvironment.

Links

OHSU Biomedical Engineering Profile about Joe Gray

OHSU Joe Gray Lab Website