

CSBC Investigator Highlight

Dr. Arjun Raj Uses Single-Cell Systems Approaches to Understand Melanoma

Arjun Raj, Ph.D., a CSBC investigator at the University of Pennsylvania, uses systems biology approaches to study therapeutic resistance in melanoma.

With a background in mathematics and physics, he pursued a Ph.D. focused on mathematical biology at the Courant Institute of New York University. After his first year as a graduate student, Arjun told his advisor, [Charlie Peskin](#), that he wanted to see what it was really like in a molecular biology lab. Charlie introduced him to [Sanjay Tyagi](#) (via [Fred Kramer](#)), who was developing molecular beacons for RNA detection at the Public Health Research Institute. Arjun worked in Sanjay's laboratory every day that summer which ignited his interest in biological research.



His passion for experimental biology and quantitative approaches led him to the field of cancer systems biology. In this interview, he discusses his views on systems approaches and his collaborative CSBC research project investigating cancer treatment responses at the single-cell level.

- **How would you describe systems biology?**

For a long time, mechanism in molecular biology meant drawing a line from genotype and phenotype. In other words, here's this mutation that leads to this phenotype, which causes an organism to have a disease.

I think systems biology is a response to the fact that we are hitting the limitations of one-gene, one-phenotype relationships. It is clear that a lot of biology remains to be explained, and the explanations must come from a quantitative set of interactions between multiple players or multiple biological processes. To me, systems biology is trying to build a mechanistic understanding, or a model, of how those interactions lead to phenotype, biological control, and diseases like cancer.

This is different from statistical approaches that many people have taken, which try and say that A affects B but are not really coming up with a model for how A affects B. To me, systems biology, at its core, should be about how biological things work in a quantitative way.

- **What systems approaches does your lab use for basic cancer research?**

My lab has done a lot of work on single-cell analysis with applications in cancer. This includes single-cell measurements of gene expression, connecting lineage information to cell fate, and developing genetic screens on single-cell phenotypes.

Basically, we're interested in trying to connect cellular states to their ultimate fate. If a cell has a little bit more of this gene or a little bit less of that gene, does that mean it will become drug resistant if I were to add an anticancer drug to it? These are the kinds of questions we ask.

- **Why does your CSBC project focus on melanoma?**

There have been so many breakthroughs in melanoma research over the last decade, including the development of targeted inhibitors and new immunotherapies. It's an exciting area and there's still a lot of big research questions to be asked and answered.

There's also an enormous amount of local expertise in melanoma in the Philadelphia community. Working with these experts allows us to pursue systems ideas while remaining grounded in melanoma biology.

- **How are you investigating therapeutic resistance in melanoma?**

My lab has taken a very conceptual approach. We're trying to understand why individual cancer cells are drug-resistant, since most cancer cells respond to the drug. Only one in many thousands of cells is resistant to the drug. What's different about those cells? We've found that there's a non-genetic fluctuation in the cellular state, which allows the cell to survive. We've been mapping out the factors that can affect the probability that the cell will survive and what cellular states are required for cell survival. We want to know exactly what genes need to fluctuate and by how much for a cell to survive when you add a drug to it.

- **Can you discuss the importance of collaboration for your CSBC research?**

My lab is isolating factors from cell lines that we think might impact drug resistance. For our findings to be translated into clinical applications, they have to be tested in animal models. We don't have expertise with these systems, but we are beyond fortunate to work with [Ashani Weeraratna](#), a world-expert in mouse models and melanoma research in general. We've been collaborating with her to test the factors that we've isolated on the effects of drug resistance in a more translational context.

We have this joint grant for a cooperative CSBC research project that allows us to use our strengths to complement each other's work.

Links

[University of Pennsylvania – Engineering Profile of Arjun Raj](#)

[Raj Lab Website](#)

[Raj Lab Blog](#)