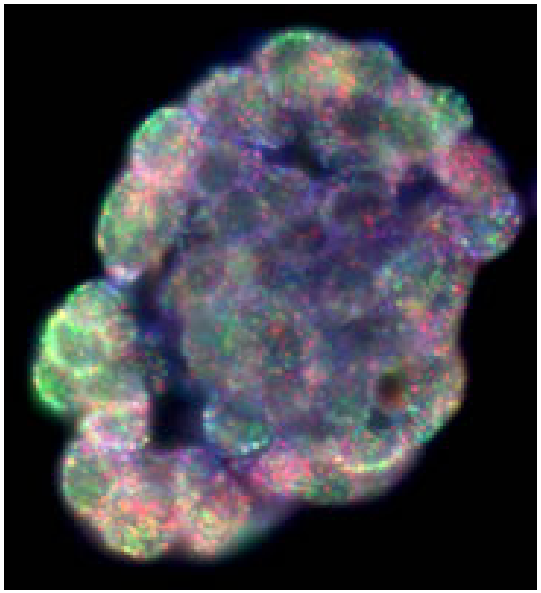
Cell-Signaling Bioanalysis Lab



Changes in cellular behavior underlie development, disease, and tissue homeostasis. The response of cells to external factors depends upon posttranslational signals and changes in gene expression. These biomolecules are wired together in cells to form networks. Intracellular signaling and gene-expression networks are highly interconnected and time dependent, making them difficult to study and even harder to understand at the systems level. Our lab designs new experimental and computational approaches for analyzing such networks. We draw from engineering principles to inspire new techniques that can be applied to network-level questions about signal transduction and gene expression. We are particularly interested in using our methods for problems in cancer biology, where the molecular 'signal processing' has gone awry and cellular responses are inappropriate.

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"Using a systems engineering approach to understand signaling processes within cells."

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Bioanalysis of cell-signaling networks activated by growth factors, cytokines, and viral pathogens

A major component of cellular regulation involves diffusible ligands, which bind to transmembrane receptors and thereby activate signaling pathways inside the target cell. These signaling pathways crosstalk with one another and are further controlled by multiple layers of feedback. Many important classes of signaling proteins are known. However, measurements of their function are usually time-consuming and limited in the number of samples that can be handled simultaneously. Our group approaches the challenge of signaling-network measurements from an engineering perspective. The design goal is to develop bioassays that are sensitive, quantitative, and as high-throughput and multiplex as possible. Current projects are focused on bioassay designs for kinase and phosphatase enzymes, which regulate protein phosphorylation in cells and are important targets for infectious viruses.

Single-cell transcriptional heterogeneities in breast development and breast cancer

One recurring theme in development and cancer is the nonrandom emergence of molecular heterogeneities in a clonal population of cells. Though widely appreciated, the overall role of cellular non-uniformities in tissue function or tumor progression is often unclear. This is because it has not been possible to survey cell-to-cell heterogeneities comprehensively and reliably in tissue specimens. Recently, we have developed and validated a new technique, called 'stochastic profiling', for globally analyzing transcriptional heterogeneities in cell populations. We have applied this approach to 3D cultures of breast-epithelial cells and are currently working to understand the mechanisms of the heterogeneities identified by our approach.

Data-driven modeling of biomolecular networks that become misregulated in cancer

Thousands of molecular signaling measurements mean little without a way to interpret them. In anticipation of the types of datasets stemming from our experimental approaches, we actively use, refine, and develop modeling approaches that are 'data-driven'. These models take complex datasets and build simplified descriptions that capture most of the relevant information and are easier to interpret. We have worked extensively with partial least squares methods in the past and are now investigating complementary alternatives, including multiway decomposition, support vector machines, and Bayesian regression.

RECENT RESEARCH DEVELOPMENTS

- Jensen KJ*, Moyer CB*, **Janes KA.** (2016) Network architecture predisposes an enzyme to pharmacologic or genetic targeting. *Cell Syst*, in press.
- **Janes KA.** (2015) An analysis of critical factors for quantitative immunoblotting. *Sci Signal*, 8, rs2.
- Wang CC, Bajikar SS, Jamal L, Atkins KA, **Janes KA**. (2014) A time- and matrix-dependent TGFBR3–JUND–KRT5 regulatory circuit in single breast epithelial cells and basal-like premalignancies. *Nat Cell Biol*, 16, 345-56.

RECENT GRANTS

- NIH – Stochastic profiling of functional single-cell states within solid tumors
- Packard Foundation – Engineering Approaches for Signal Transduction Networks

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