

BCATS Keynote Speaker

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Biography

Peter Sorger, Ph.D is a Professor of Systems Biology at Harvard Medical School and holds a joint appointment in MIT's Dept. of Biological Engineering. He received his A.B. from Harvard College, Ph.D. from Trinity College Cambridge, U.K. and trained as a postdoctoral fellow with Harold Varmus and Andrew Murray at the University of California, San Francisco. Sorger was co-founder of the MIT systems biology program CSBi, Merrimack Pharmaceuticals and Glencoe Software and serves on the scientific advisory and corporate boards of several other technology companies. He is director of the Center for Cell Decision Processes, an NIGMS-funded Center of Excellence in Systems Biology.

Prof. Sorger's lab of graduate students, postdoctoral fellows and staff scientists is involved in both computational and experimental biology. The mechanisms that maintain genomic integrity are a major area of interest. When healthy cells divide, chromosomes are partitioned among daughter cells with great fidelity. However, in cancer cells, this fidelity is lost and cells exhibit genomic instability. It is thought that genomic instability plays an important role in the accumulation of genetic mutations during the development of cancer. The long term goal of the Sorger lab's research is to identify the molecular lesions that cause genomic instability, to determine their frequency in normal and cancerous cells and to develop improved means to kill selectively diseased cells.

Keynote Address

Modeling a snap action variable relay switch controlling cell death

Caspases, the proteases that dismantle apoptotic cells, normally switch from off to on in an all-or-none process that enforces an unambiguous choice between life and death. To understand the operation of this switch in quantitative terms we have constructed a mass-action mathematical model of receptor-mediated cell death triggered by TNF and TRAIL based on known reaction pathways and trained the model on data from single cells perturbed by protein depletion, over-expression, or inhibition. We find that receptor-mediated cell death is characterized by sudden and efficient cleavage of caspase substrates (over a 10-15 min period), but only after a remarkably long delay (1 to 12 hr), whose duration and variance depend on ligand dose and identity. Thus, caspase regulatory pathways simultaneously achieve snap-action activation, long and variable delay and high efficiency; it is not sufficient that all processes be fast. We hypothesize that variable delay generates a tunable dose-dependent behavior at a population level from a binary decision at a single-cell level.