

Systems biology is...

Two scientists founded BioSeek to do their version of systems work. Is it a stretch?

Brendan Borrell

In 2000, two pathologists decided to try a different kind of systems biology. Ellen Berg and Eugene Butcher were feeling frustrated with the slow progress of in silico approaches, so they developed a series of in vitro cell-based assays they say can recreate some of the complexity of in vivo interactions. They describe their platform, known as BioMAP, as systems biology, even though it lacks a hallmark of the field: computer modeling.¹

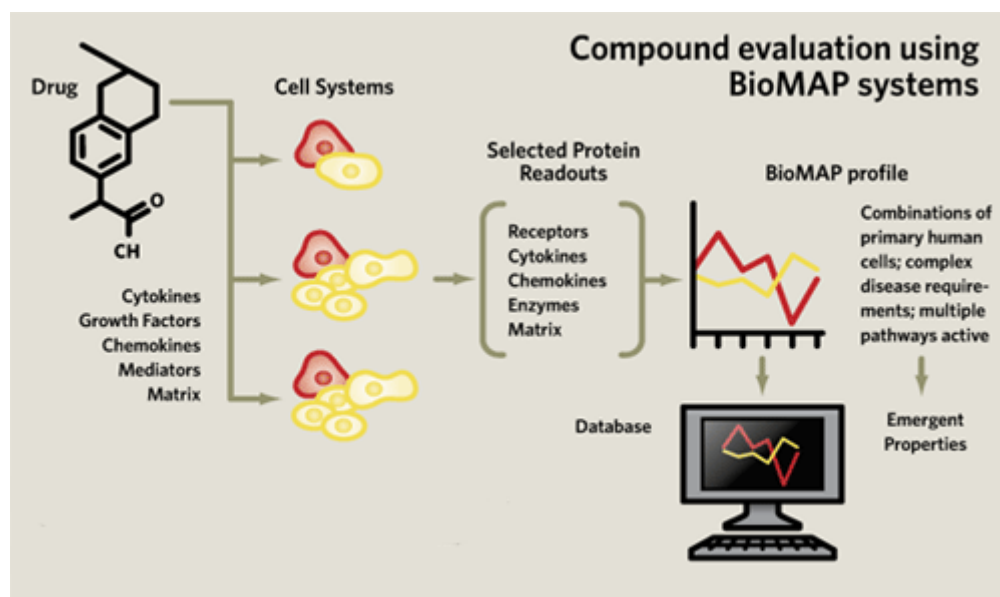
"I really didn't like the early descriptions of systems biology from Hiroaki Kitano and Lee Hood, where their definition of systems biology was, 'We have to measure all of the components over time and then we're going to build a model of the system,'" says Berg, who (with Butcher) founded BioSeek in Burlingame, Calif. To her, the definition should be less exhaustive: "Systems biology has to take advantage of the interactions and complexity of biology." Butcher and Berg argue that cell systems can mark the beginning of a rational drug discovery process.²

So far, the stakeholders in the field have not agreed on a set definition of systems biology. "When you talk about systems biology, it means a lot of things to a lot of people." says Lionel Carnot of Bay City Investors, a venture capital firm that has been with BioSeek for several years. "Every company you go to has a different definition."

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Selling systems biology

Table: Systems biology at biotechnology and pharmaceutical companies



BioSeek uses cell-based systems biology to screen potential therapeutics. Test compounds are added to one of twenty disease models, and a readout of 8-10 proteins provides the BioMAP, which is then compared to reference profiles of known compounds.

So far, BioSeek has forged collaborations with companies including GlaxoSmithKline and Dynavax, and it recently announced a \$10 million collaboration with Amylin Pharmaceuticals to identify novel peptide therapeutics. Since 2000, the company has received an additional \$19 million from traditional venture capital sources.

BioSeek's BioMAP System is designed to replicate cell and pathway interactions in human disease. The company has a library of 25-30 primary human cell types, from which they construct "systems" that represent specific disease models such as cancer and autoimmune diseases. The asthma model, for instance, uses a combination of endothelial cells and mast cells; one of the inflammation models uses endothelial cells, lymphocytes, and monocytes. Once the system is selected, BioSeek adds a drug or agent to modulate the cells and then measures a set of 8-10 readouts, which tend to be biomarkers, including cytokines, chemokines, lipid mediators, and other molecules involved in cell-cell communication.

With the BioMAP inflammation models, Berg has been able to distinguish between multiple kinase inhibitor mechanisms using only a handful of readout parameters. ¹ "For cell-based assays, there's no platform that can detect as many kinases as we can."

Other companies, including Novartis and Pfizer, have similar technologies in-house, but these are largely much more simplified single cell-based assays for high-throughput applications. In some cases, Berg says, companies have developed one or two more complex models for a single project, but nothing that rivals the diversity at BioSeek. Richard Nelson, director of biomolecular screens at Boehringer Ingelheim, says he has been impressed by BioSeek's technology, particularly in a landscape dominated by in silico approaches. "It's a fairly straightforward system out of which they are able to get very rich data." He says it's "quite remarkable" that they can distinguish between kinase inhibitor mechanisms.



Ellen Berg and Eugene Butcher of BioSeek

Not everyone working with systems biology agrees. "They're basically a screening company that set up a few assays," says Keith Elliston, president and CEO of Genstruct. "Calling that systems biology is a stretch." Though Elliston says he is impressed by the way BioSeek can read out multiple targets at once, at the end of the day, he's not sure what those data mean.

Bruce Gomes, head of mathematical modeling in the systems biology group at Pfizer Research and Technology Center, says he doesn't believe computer modeling is the hallmark of systems work. "There's nothing magical about computational methods," he says. "They're only successful if they deliver something that's useful to the drug discovery company."

References

1. E.L. Berg et al., "Characterization of compound mechanisms and secondary activities by BioMAP analysis," *J Pharmacol Toxicol Methods* , 53:67-74, 2006. [\[PUBMED\]](#)
2. E.C. Butcher, "Can cell systems biology rescue drug discovery?" *Nat Rev Drug Disc* , 4:461-7, 2005. [\[PUBMED\]](#)

Systems biology at biotechnology and pharmaceutical companies

In an effort to restock the dwindling pipeline of new treatments, systems biology is increasingly becoming a part of drug discovery efforts.

Company	Approach	Location
Bioseek	Screen novel compounds with combinations of human primary cells to measure activity and understand their mechanism of action	Burlingame, California
Gene Network Sciences	Use models to improve quality of pre-clinical compounds and guide the design of clinical trials.? Evaluate cardiovascular safety with Visual Heart.?	Ithaca, New York
Genstruct	Apply causal-inference models to identify biomarkers for drug toxicity, drug resistance, and cardiovascular drug mechanisms.	Cambridge, Massachusetts
Rosetta Inpharmatics (subsidiary of Merck)	Identify targets in gene networks regulating obesity, diabetes, and other phenotypic traits, using microarray techniques.	Seattle, Washington
Optimata	Use a human physiological model designed for understanding disease dynamics and optimizing drug and treatment schedules	Ramat Gan, Israel
Entelos	Use virtual patients, recently modeling skin sensitivity for the cosmetics industry.	Foster City, California
BG Medicine	Find biomarkers for diseases, treatment responses and compound safety, including liver toxicity, via pathway databases and statistical analysis of wet lab findings.	Waltham, Massachusetts
GeneGo	License pathway database, MetaCore, for analyzing functional genomics data.	St. Joseph, Michigan
Novartis	Link data from signaling pathways to bone cellular physiology and bone disease, and build models of cardiac	Cambridge, Massachusetts

	safety.	
Pfizer Research and Technology Center	Model small molecule and biological therapies with small networks that incorporate higher-level physiological elements, like kidney function.?	Cambridge, Massachusetts
AstraZeneca	Use both cell-based assays and biosimulation to support small molecule projects and biological therapies.	Cheshire, England