

BioCentury

Emerging Company Profile

Cytokinetics: The cell is a city

By Karen Bernstein
Editor-in-Chief

In the traditional view, the cell was a soup in which proteins and other molecules floated. The new view sees the cell as a city providing a framework on which the interior of the cell is ordered, with highways, molecular motors that move proteins, street cleaning crews and other organizing elements required to keep the cell functioning properly.

Cytokinetics Inc. is focused on the cytoskeleton — which is comprised of the structures of the cell involved in the dynamic “urban design” of cellular function and mechanics, including cell division, intracellular transport, cell motility and the establishment and regulation of cell polarity.

The company estimates that its area of interest includes about 1,000 targets divided into four broad classes. These include the highways or filaments that comprise the primary structural elements of the cell (its skeleton), and the molecular motors that both organize filaments and transport molecules along them.

The other two classes include the construction crews that regulate remodeling of filaments in a wide variety of processes (from wound healing to inflammation to the invasion of cancer cells into tissues), and the street signs or filament binding proteins that organize filaments into functional arrays.

Cytokinetics has licensed patent applications covering genes, compositions of

Cytokinetics Inc.

South San Francisco, Calif.

Technology: Cytoskeletal pharmacology

Disease focus: Cancer, infectious diseases and cardiovascular diseases

Clinical status: NA

Founded: 1998 by Larry Goldstein, James Sabry, James Spudich and Ron Vale

Corporate partners: None

University collaborators: None

Number of employees: 20

Funds raised: \$5 million

Investors: Mayfield Fund, Sevin Rosen Funds, Roy Vagelos and Robert Swanson

CEO: James Sabry

Patents: None issued

matter and assays from the company's academic founders at Stanford University, and the University of California at San Francisco and San Diego, giving the company a platform on which to build a hybrid biotechnology and informatics company.

The company is following a two-pronged business model, doing drug discovery and providing cellular bioinformatics through its Cytometrix database, which it expects to diversify both technical risk and income streams.

In drug discovery, the company plans to provide customers with validated lead compounds in exchange for upfront fees, spon-

sored research money, milestones and royalties. In its cellular bioinformatics business, Cytokinetics expects to earn access fees, subscription fees and royalties.

Certain of Cytokinetics' targets are the molecular motors of the cell, which have only recently become understood. “The advantage of going after the motors rather than the transport proteins, the filaments, or the molecules being transported — which may not be proteins — is that the motors are mechanochemical enzymes with specific functions,” said President and CEO James Sabry.

In cancer, for example, disrupting mitosis is a proven strategy. “It's known,” said Sabry, “that if you disrupt the mitotic spindle you have a very effective agent — this is what Taxol, vincristine and estramustine do.”

He noted that these drugs destroy the cell's highways — the microtubules — by attacking tubulin, the major structural component of the mitotic spindle. As a result they disrupt mitosis and trigger apoptosis. But these drugs have serious side effects resulting from the fact that tubulin is a ubiquitous protein that plays a critical role in diverse processes in every cell type.

“Our goal is to be more specific,” Sabry said.

In contrast to these cancer drugs, Cytokinetics is focusing on molecular motors, which are often upregulated in cancer. Among them are the mitotic kinesins, of which about 15 are known. These proteins

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BioCentury™
THE BERNSTEIN REPORT ON BIOBUSINESS

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are present only during mitosis.

“Our approach is to target the motors which function only in mitosis, disrupting mitosis and triggering apoptosis,” said Sabry.

In cardiovascular disease, Cytokinetics is looking at the direct modulation of the heart’s contractile machinery, a key cytoskeletal function which has applications in heart failure and hypertension.

In the antifungal field, the company is looking at disrupting fungal mitosis and cell division, as well as at disrupting fungal morphogenesis.

To discover and characterize novel compounds, Cytokinetics has developed a high throughput screening system, called PUMA, to screen for the activity of compounds against molecular motors.

The company also has secondary in vitro assays, as well as its Cytometrix cellular bioinformatics system.

Cytometrix is a series of database products that aim to provide high throughput cell-based assays that use high resolution imaging to fingerprint the molecular mechanisms of drug action in both normal and diseased cell lines. The database includes details of the behavior of thousands of drugs with known mechanisms.

According to the company, when the profile of a test compound is compared to the database, predictions about the test compound can be made, such as the molecular mechanism of action, and specificity versus toxicity at various concentrations, as well as correlations between structure and activity.

Unlike the numerous other companies that are looking at gene expression — which is akin to counting the population of a cell, Cytokinetics is adding information on how the cell changes its cytoskeleton — its organization and the relation of cellular components to each other — in response to stimuli.

“The issue,” said Sabry, “is to rapidly measure and quantitate what the cell is doing in real time by leaving the cell structure intact. We’re using the cytoskeleton as a readout system, giving an automated and computational fingerprint of how the cell reacts to a given stimulus.

“We’re linking cell biology to informatics. This provides a middle ground between the slow but information-rich whole organism approach and the speed but information paucity of molecular biology.”