that act on the cause of a disease, and to license them "ready for the clinic" to pharmaceutical partners. According to Bruno Tocque, ExonHit's chief executive officer, "[d]rugs affect splicing in a cell-type and drug-specific way. DATAS identifies such drug- and disease-related signatures and can be put to fruition to follow up drug efficacy and patient selection." DATAS technology is therefore being applied to pharmacogenomics—providing a means to identify the best treatment for each patient, while reducing the risk of adverse side effects.

Indeed, ExonHit's first product is a predictive toxicology kit—Safe-Hit. Launched in 1999, Safe-Hit is a DNA array that can detect the splice variants induced by toxic stress on cells, providing a means to determine the relative toxicity of compounds. Another two diagnostic tools are in development: Proof-Hit, a diagnostic tool to determine patients who will respond to standard chemotherapy; and Profile-Hit, a test to screen out patients at risk of severe adverse drug reactions. ExonHit has several products in the pipeline: a research tool for neurodegenerative diseases; three diagnostics including one in clinical trials for cancer therapies, and one for presymptomatic detection of "mad-cow" disease. *ED*

Signature Bioscience

Catching proteins in action.

Proteins have two defining properties: structure and mobility. Although many companies are currently elucidating protein structure using x-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy, few are studying how proteins and their domains move during physical interaction with other molecules. Signature Bioscience has sought to remedy this situation using its technology platform, multipole coupling spectroscopy (MCS).

First conceived by John Hefti, MCS involves probing proteins with microwaves and recording the resulting electromagnetic spectra, creating a unique "signature" for each protein. The protein is then combined with a small molecule, spliceosome, or cell, and a new signature obtained. Changes in the protein's signature may reflect various characteristics of the protein, including domain movements, enzymatic activity, conformational change, or denaturation. MCS can therefore be used to determine whether a drug candidate binds to a protein target, and can detect cellular alterations such as changes in morphology, ion redistribution and flux, and protein redistribution within a cell.

Hefti says that MCS can also determine if two enzymes with similar amino acid sequences have radically different structures and therefore different functions, or whether two enzymes with dissimilar sequence have similar structures and therefore related functions. Such information is valuable when mapping protein–protein interactions, in which a crystallographic approach would be both difficult and time-consuming.

The technology itself is not original; it is identical to methods used by computer chip engineers to determine the purity of semiconductor crystals. However, Signature Bioscience has been able to eliminate what had been the main limitation to the technique: the background noise generated by water in the solutions of proteins. A similar problem arises with the noise created by the cell membranes in which most important drug targets are embedded, but Hefti is confident that the company will eventually overcome this difficulty.

Signature Bioscience is also developing software tools that can translate the raw data into valuable information. Within two years, revenue will be generated by licensing out a "package" of database and software for protein mapping and drug screening of the 100 protein families that are the most popular drug targets. Some revenue with be generated through the marketing of spectroscopes—manufactured with a partner—but Signature Bioscience's main profit generator will be target-validation collaborations. The company currently has three collaborations, including a deal with Sunesis Pharmaceuticals (Redwood City, CA) to determine small-molecule inhibitors of protein–protein interactions within inflammation pathways. By the end of the year, Hefti hopes that Signature Bioscience will be able to carry out 1,000 assays per day per machine, further attracting customers to its unique database. *AB*

Founded: October 1998
Founders: John Hefti (chief technology officer)
CEO: Mark McDade
Employees: 65
Financing to date: $21 million
Location: Hayward, CA
http://www.signaturebio.com

Protein Pathways

Discovering conservation among molecular targets.

Determining the function of the 100,000 or more proteins that underlie all human biochemical processes is a formidable task. Most proteins are assigned a function through studies of their homology with other proteins whose function is known, but this has severe limitations. Protein Pathways is now employing in tandem two approaches—phylogenetic profiling and Rosetta stone analysis—that could take the identification of protein function to a new level.

The tools were developed by David Eisenberg at the University of California at Los Angeles (UCLA), who then licensed them exclusively to Protein Pathways. Phylogenetic profiling is based on the concept that different proteins work together in groups within, for example, a specific

Founded: April 1999
Founders: David Eisenberg, Matteo Pellegrini, Kenneth Goodwill, Michael Thompson, Edward Marcotte, and Todd Yeates
Employees: 14
President: Matteo Pellegrini
Financing to date: $7 million
Location: Los Angeles, CA
http://www.proteinpathways.com