HistoRx Inc.

Automated digital diagnostics

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Contact: Robert A. Curtis, PharmD, President and CEO
Industry Segment: Molecular Diagnostics
Business: Tissue-based proteomic services, instruments & reagents for R&D and clinical use
Founded: August 2004
Founders: Robert A. Curtis; David Rimm, MD, PhD (Yale University); Yale University
Employees: 7

Financing to Date: $1.5 Million
Investors: Navigator Technology Ventures; Genentech, Inc.; Sachem Ventures; Marnat Investments
Board of Directors: Robert A. Curtis; Alain Hanover (Navigator Technology Ventures); Rana Gupta (Navigator Technology Ventures); E. Jonathan Soderstrom, PhD (Yale University); Gregory Gardiner, PhD (formerly Yale University and Pfizer Central Research)
Scientific Advisory Board: David Rimm; Robert Camp, PhD (Yale University); Gregory Gardiner; Thomas Pollard (Yale University); Meir J. Stampfer, MD, DrPH (Harvard University); David Ward, PhD (Nevada Cancer Institute)

Pathologists eyes have been trained to spot morphological changes in cells to make a diagnosis and to identify diagnostic markers for disease. The molecular revolution in drug discovery and the move toward biomarker-based diagnostic testing, however, have made analysis of cell shape increasingly less relevant while bolstering the need for subcellular molecular study. Development and sales of trastuzumab (*Herceptin*) based on HER2 expression in breast cancer tissue is an example of medicine's molecular diagnostics future. However, pathology remains one of the last bastions among medical disciplines to enter into the molecular age. **Yale University** spinout **HistoRx Inc.** intends to automate protein-biomarker analysis of tissue for drug discovery and development and, eventually, to replace the clinical pathologist's eye for biomarker analysis.

The company, which opened in New Haven incubator space this past summer, draws on proprietary algorithms for automated quantitative analysis of proteins in tissue samples. The need for automation increased greatly with the 1999 development of tissue microarrays by **National Cancer Institute** scientists. Each array can hold as many as 800 half-millimeter tissue cross-sections, enabling large-scale studies across patient populations, organ and cancer types. Analysis of the arrays, though, remains laborious. Automated analysis of isolated cells may now be routine using fluorescent cell sorting and laser scan cytometry, but analyzing histological sections with automated systems has been held back by the complexity of tissue. For instance, tumor tissue sections typically include overlapping cells, organelles and extracellular material. Previously, no direct and rapid method existed to sort out the overlapping layers, leaving pathologist-based analysis as the current standard.

Developed in the Yale laboratory of scientific founder David Rimm, MD, PhD, HistoRx's tissue-analysis algorithms, termed *AQUA* (*Automated Quantitative Analysis*), encompass software that first scans fluorescently tagged tissue sections to separate tumors from stroma and to define subcellular compartments such as membrane, cytoplasm, nuclei and even self-defined virtual compartments. The software then measures levels of a marker protein in the tissue and where it is located in the various subcellular compartments based on the location of the tags.

To discriminate between overlapping subcellular compartments within the tissue section, additional algorithms then subtract information from an out-of-focus image from an in-focus image to sort out spatial locations and quantities of the proteins being studied. *AQUA* can currently score up to five markers simultaneously per tissue dot. "The human eye," says Robert A. Curtis, PharmD, HistoRx's president and CEO, "would never be able to accurately detect the difference."

Unlike other protein expression analysis methods which typically grind up the tissue being studied, *AQUA* maintains and determines spatial relationships among the proteins of interest in the tissue section while quantifying marker expression. This permits far more precise localization of disease than can be achieved with existing pathology instruments and quantification of markers to enable more accurate differentiation among patient populations and cancer types.

"All other automated imaging technologies are fundamentally based on morphological changes and bright-field imaging," says Curtis. "We view that as a significant technical limitation in today's molecular age."

HistoRx combines its *AQUA* software and instrumentation with Yale's unparalleled cancer-patient database to provide a basis for correlating disease with protein expression. The Yale tissue archive holds more than three million tissue blocks representing one million unique patients, 70 percent with cancer. More than 500,000 of the patients have greater than 20 years of clinical follow-up information. One million have at least five years of follow-up data. The company holds exclusive license to

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eight annotated datasets developed by Rimm covering breast, colon, melanoma, bladder, ovarian and testicular cancers and lymphoma. Says Curtis: "The high data content and tissue samples we can generate along with access to the reference database would be hard for any competitor to reproduce." He also believes that in the area of solid-tumor cancers, HistoRx technology offers more information than genomics studies: "Genomics studies don't correlate as well as tissue protein analysis, or what we call *in situ* diagnostics," he says. "Tissue is where you want to be."

As a first step in developing its business, Curtis intends to offer research services such as target identification and validation studies, patient population selection and segmentation for clinical trials and validation of animal models to confirm protein expression patterns similar to humans. The company also sells its own instrument platform and licenses the software to noncommercial research centers. **Brigham & Women's Hospital** in Boston and **Georgetown University** have already obtained the technology.

For commercial clients, the company provides in-house, contract services. HistoRx is presently undertaking feasibility studies for three large pharmaceutical and biotechnology firms and is negotiations with others. According to Curtis, two of the companies have told him if their feasibility studies succeed, the HistoRx diagnostic test kit will become part of their cancer drugs Phase I/II clinical trials.

Unlike most other companies offering R&D services, HistoRx does not want to participate in downstream royalties for the drugs it may help develop. Instead, the company expects to retain rights to all reagents developed as part of these studies. Curtis believes those reagents will eventually form the core of the company's business as high-margin diagnostic test kits that pharmaceutical companies will need to couple with their emerging drugs.

HistoRx will eventually move into the clinical setting where its reagents and *in situ* diagnostic instrumentation and software will automate pathologist's work.

Launching the company required relatively little financing compared to most biotech ventures, just $1.5 million to date. Navigator Technology Venture, the venture arm of Draper Laboratory, took the lead in the first round of funding with **Genentech Inc.** and other smaller investors also participating. "Navigator understood the value right away," says Curtis, "and Genentech is very supportive of the technology and offered to take an ROI investment without any sort of collaboration."

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Early profitability and a quick exit strategy seem likely. Curtis plans to raise an additional $1 million in venture financing. With an anticipated $1.5 million in revenues in the company's first year of operation and a seven-person staff growing only to ten this year, HistoRx expects to go into the black within a couple years. That early revenue comes primarily from providing contract services to pharmaceutical and biotechnology companies as well as limited sales and licensing of the technology platform. However, Curtis says, "The endgame is the molecular diagnostics or reagent business," which he expects to generate high returns. "We may only be a $100-150 million company, but if you only put in a couple million dollars, that's not too bad." He expects that HistoRx will quickly make an attractive target for purchase by a larger instrument or services company.

Curtis describes himself as a "serial entrepreneur." However, he has deep pharmaceutical industry roots. He left Pfizer Inc. after eight years in 1990 as worldwide director of licensing and development and as an associate director of clinical research. "It was getting too cushy," he recalls. He took the dive into biotech as VP of business development at Cambridge Neuroscience; then he became the first business person at Pharmacopeia Inc., and eventually co-founded CombiChem Inc., where he was president and CEO. He took that company through two rounds of financing and rapid growth before leaving to launch a company to capitalize on biomedical discoveries coming out of a consortium of leading research universities. He also helped found MetaMorphix Inc., a joint venture between the Genetics Institute and Johns Hopkins University. Subsequently he founded a now defunct aquaculture biotechnology company. "I've had a couple winners," he says, "but you need the losers too to really understand the business." Three years ago, Yale's Office of Cooperative Research, its technology transfer arm, invited him to put HistoRx together based on its technology and tissue archives. "It took longer than I expected to raise the funds," he says. "But you get a gut feel in starting a company. I know when I've got a winner on my hands."—**Marc Wortman**

