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Acetylon Licenses Powerful Discovery Methodology and Platform from Harvard University and the Dana-Farber Cancer Institute for Development of Further Next-Generation Class II-Selective HDAC Inhibitor Compounds

-- Featured Article by Acetylon Scientific Founders Published in the Current Issue of *Nature Chemical Biology* Validates Discovery Technology and Identifies Need for Novel HDAC Inhibitors with Enhanced Selectivity and Clinical Utility --

BOSTON, Mass., March 8, 2010 – [Acetylon Pharmaceuticals](#) today announced an exclusive therapeutic license for a robust platform technology and chemical methodology to conduct high-throughput screening and lead optimization for HDAC inhibitor compounds, as well as a portfolio of small-molecule selective histone deacetylase (HDAC) enzyme inhibitors including the first-ever selective inhibitor of HDAC6. The license was granted to Acetylon by Harvard University and the Dana-Farber Cancer Institute. Acetylon is currently focused on the development of potential drug candidates based on next generation Class II-selective HDAC inhibitors. Class IIB enzymes such as HDAC6 have emerged as important targets in inflammatory disease, neurologic disease and broadly in cancer. The platform and methodology were discovered by two of Acetylon's scientific founders, [James E. Bradner MD](#) of the Dana-Farber Cancer Institute and [Ralph Mazitschek Ph.D.](#), now of the Massachusetts General Hospital, along with colleagues at Harvard and the Broad Institute of Harvard and MIT. Acetylon Pharmaceuticals believes that its next-generation, selective HDAC inhibitor compounds may accomplish enhanced clinical utility by reducing or eliminating the debilitating and sometimes life-threatening side effects associated with the current first-generation of non-selective HDAC inhibitors.

A March 2010 paper published in the leading scientific journal, *Nature Chemical Biology*, by Drs. Bradner and Mazitschek, in collaboration with other scientists at Harvard University and the Broad Institute of Harvard and MIT, highlights the breakthrough utility of this technology. The article, titled "[Chemical Phylogenetics of Histone Deacetylases](#)", presents a new perspective on HDAC inhibitor selectivity and underscores the need for a new generation of potent, selective inhibitors. Using the novel methodology and platform, the authors profile the spectrum of enzyme selectivity amongst HDAC inhibitor drugs that are either marketed or currently in clinical development, as well as drug-like compounds used broadly by scientific investigators. Their data indicate that current HDAC inhibitor drugs and drug candidates target only a limited subset of the 18 known human histone deacetylases, contrary to the common perception of pan-inhibition of HDACs by such compounds. The authors found that these drugs are active inhibitors of Class I HDAC enzymes including HDACs 1, 2 and 3, which have "epigenetic" activity and cause broad alteration of the expression of human genes. Most were also found to be inhibitors of HDAC6, an important member of the Class II family of HDACs. The high, pan-Class I target redundancy exhibited by these compounds is suggested to account for the overlapping, limited clinical utility and severe, class-

associated toxicities of current HDAC drugs and emphasizes the need for a new generation of potent, Class II-selective HDAC inhibitors.

“Selective inhibition of individual deacetylases provides the potential for specific targeting of gene expression and cellular signaling pathways. We expect to see substantial improvements in the tolerability and efficacy of HDAC inhibitor drugs as a result of these ongoing research efforts,” commented James E. “Jay” Bradner, MD, Assistant Professor of Medicine at Harvard Medical School and Dana-Farber Cancer Institute.

“We believe that highly Class II-selective HDAC inhibitors may accomplish enhanced clinical utility by reducing or eliminating the debilitating and sometimes life-threatening side effects associated with the current first-generation of non-selective epigenetic HDAC inhibitors which predominantly inhibit Class I HDAC enzymes,” commented Walter Ogier, Chief Executive Officer of Acetylon. “The drug discovery and development tools, which are featured on the front cover of the current issue of *Nature Chemical Biology*, open new doors to expand our Class II-selective HDAC inhibitors program.”

The new *Nature Chemical Biology* article also features a “chemical phylogenetic” analysis of human Class I and II HDACs, using a structurally diverse panel of inhibitors as chemical probes – a theme common to other articles appearing in the same issue of the journal. The authors utilized the novel platform technology and chemical methodology to identify a truly non-selective compound, pandacostat, which inhibits all Class I and II HDAC isoforms with equal potency. Pandacostat is expected to be an extremely useful chemical probe and reference compound in the development of new HDAC inhibitor drugs.

“Our finding that the known group of HDAC inhibitor drugs and other compounds have little impact on Class II HDACs, aside from HDAC6 which is inhibited by those compounds albeit non-specifically, was quite a surprise,” commented Ralph Mazitschek, Ph.D., Instructor of Chemical Biology at Harvard Medical School and the Massachusetts General Hospital. “This new ability to measure and discern the activity of putative HDAC inhibitors across each of the Class II HDAC isoforms, along with a new compound which is the first true pan-HDAC inhibitor, provides powerful new methodology for the understanding of this important area of cellular biology and the broad range of diseases which may be favorably impacted by selective HDAC inhibition.”

About HDAC6 Inhibition

Acetylon’s lead HDAC6 inhibitor program is focused on enhancing drug potency and reducing or eliminating side effects common to HDAC inhibition through highly selective targeting of the HDAC6 enzyme. Inhibition of HDAC6 versus other isoforms uniquely preserves normal gene expression in cells, thereby minimizing patient toxicity. At the same time, HDAC6 inhibition severely disrupts diseased cells’ ability a) to produce normal proteins, through disruption of the HSP-90 protein chaperone system, and b) to dispose of damaged misfolded proteins through modification of microtubules and disruption of the aggresome protein disposal pathway. Since metabolically active cancer and autoimmune cells produce large amounts of misfolded proteins, inhibition of HDAC6 results in further increased generation and accumulation of protein “trash”, triggering self-destruction of diseased cells via programmed cell death and leading to regression of disease.



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Acetylon Pharmaceuticals, Inc. is applying its unique capabilities to discover and develop next-generation, highly selective small molecule drugs to realize the therapeutic potential of HDAC inhibition to treat cancer, autoimmune and other diseases, while reducing the side effects common to this class of drugs. The Company is based on technology initially developed at the Dana-Farber Cancer Institute and at Harvard University. Acetylon's technologies were initially discovered and developed by its scientific founders: Kenneth C. Anderson, MD, Kraft Family Professor of Medicine at Harvard Medical School and the Dana-Farber Cancer Institute; James E. Bradner, MD, Assistant Professor of Medicine at Harvard Medical School and the Dana-Farber Cancer Institute; and Ralph Mazitschek, Ph.D., Instructor at Harvard Medical School and the Center for Systems Biology at Massachusetts General Hospital, in conjunction with their academic collaborators.

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Drs. Bradner and Mazitschek and Anderson, are equity shareholders of Acetylon as well as consulting members of its Scientific Advisory Board.

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