



Aileron Therapeutics Collaborators Publish *In Vivo* Research in *Nature* Showing Stapled Peptides Achieve the First Direct Inhibition of the Notch1 Transcription Factor Oncogene

– *New Data Substantiates Potential for Stapled Peptides as Therapeutics for Key Intracellular Targets Not Addressable by Current Drug Modalities* –

– *Aileron Developing Stapled Peptides that Target Transcription Factors Across Multiple Diseases* –

CAMBRIDGE, MA – November 11, 2009 – Aileron Therapeutics, a biopharmaceutical company leading the development of a new class of drugs called Stapled Peptides, announced today that its collaborators, James E. Bradner, MD of the Dana-Farber Cancer Institute and the Broad Institute of Harvard and MIT, and Gregory L. Verdine, PhD, Professor of Chemistry at Harvard University, published research in *Nature* entitled, “Direct Inhibition of the Notch Transcription Factor Complex.” Results presented in the paper showed that Stapled Peptides can potently and directly inhibit the transcription factor Notch, an oncogene implicated in cancer cell proliferation and survival. This research validates the potential for Stapled Peptides to modulate key intracellular biological targets, such as transcription factors, that have not been addressable with current small molecule or biologic drug modalities. There are estimated to be more than 1,500 transcription factors in the human genome, regulating key biological processes important in diseases such as arthritis, asthma, diabetes, infectious diseases, and cancerⁱ.

In their research published in *Nature*, Drs. Bradner and Verdine showed in multiple models, including T-cell acute lymphoblastic leukemia (T-ALL), that Stapled Peptides achieved tight direct binding to the Notch transcription factor complex, preventing the assembly of a functional transcription complex by the Notch1 oncogene. Further *in vivo* data show that direct and specific antagonism of the Notch multi-protein complex in the nucleus of cancer cells suppressed the transcription of many growth stimulating proteins such as Myc, thereby leading to cancer cell death. Potent, specific pathway inhibition was determined using genome-wide transcriptional signatures, first *in vitro* and later validated as biomarker studies *in vivo*. The direct inhibition achieved did not result in gastrointestinal toxicity, suggesting a viable therapeutic window for Stapled Peptides, without the limitations previously observed with upstream inhibitors of Notch.

“Transcription factors are among the most desirable and validated therapeutic targets in cancer, yet they are among the most elusive targets in cancer drug discovery,” said James Bradner, MD, Division Of Hematologic Neoplasia, Dana-Farber Cancer Institute. “Our research shows, for the first time, how assembly of the Notch multi-protein transcription factor complex can be inhibited in the nucleus of a cancer cell with a stapled peptide, leading to cancer cell death. Using stapled peptides to target transcription factors opens a potential new path for discovering novel and effective therapies for patients.”

A growing body of research describes the critical role that transcription factors play in biological pathways implicated in a broad array of human diseases. In the past 25 years, for example, the 20 most-cited transcription factors have been referenced in the scientific literature an estimated 100,000 timesⁱ. In cancer biology, it has been shown that more than 50% of T-cell acute lymphoblastic leukemias (T-ALL) have activating mutations in Notchⁱⁱ. However, the vast majority

of transcription factors lack an appropriate binding pocket for targeting by small molecules. Moreover, most transcription factors reside within cells and so are not suitable for antibody-based therapies. Stapled Peptides have now been shown to inhibit a previously-undruggable transcription factor at a therapeutically meaningful level.

“These results are tantamount to a declaration of open season on transcription factors,” said Gregory L. Verdine, PhD, Erving Professor of Chemistry, Harvard University and co-chair of Aileron Therapeutics’ scientific advisory board. “While the vast majority of transcription factors are not druggable with current small molecule or biologic modalities, many features of the protein-protein interaction represented by Notch are similar to other transcription factor assemblies, giving us good reason to expect that this technology will be useful for other currently undruggable targets across diseases such as cancer, inflammation, obesity, and infection.”

“The publication of a second major research article in *Nature* within a year demonstrates the momentum and potential for development of Stapled Peptides as a new drug modality,” said Joseph Yanchik, III, Chief Executive Officer of Aileron Therapeutics. “Stapled Peptides designed to target therapeutically important but previously undruggable transcription factors, such as Notch, is a major focus of Aileron’s R&D effort and is of significant interest as one of our potential early clinical development programs.”

In a study published in *Nature* in October 2008 titled “BAX Activation is Initiated at a Novel Interaction Site,” Aileron Therapeutics collaborators at the Dana Farber Cancer Institute demonstrated that a Stapled Peptide was able to uniquely target a new and fundamental activation mechanism of the programmed cell death or “apoptotic” pathway.

Aileron has developed Stapled Peptides designed to target specific transcription factors across multiple therapeutic areas, and is advancing these compounds in its preclinical programs.

Online copies of the article can be obtained at <http://www.nature.com/>.

About Stapled Peptides

AILERON's Stapled Peptides are synthetically locked, or 'stapled', into an alpha-helical shape with an optimized cross-linking chemistry to mimic the structure found at the interface of many protein-protein interactions. To achieve this, Aileron has deployed a comprehensive cross-linking tool-kit to install single staples, multiple staples and contiguous staples to achieve desired efficacy and pharmacokinetic profiles. The resulting Stapled Peptide drugs are endowed with unique properties, including efficient cell penetration, high affinity binding to large target protein surfaces, and excellent stability and pharmacokinetic properties within the body.

About Aileron Therapeutics

Aileron Therapeutics is a biopharmaceutical company leading the development of a new therapeutic modality and class of drugs called Stapled Peptides. Published research on Stapled Peptides has demonstrated their unique ability to modulate intracellular protein-protein interactions, critical control points for most human diseases that have been largely undruggable with existing drug modalities. To address the potentially thousands of currently undruggable targets, Aileron is building a robust pipeline of therapeutics for the treatment of cancer, infectious disease, metabolic disease and immune/inflammatory diseases. Aileron Therapeutics was founded in 2005 and is based in Cambridge, Massachusetts. For additional information, please visit <http://www.aileronrx.com>.

ⁱ Vaquerizas J. *et al.* A census of human transcription factors: function, expression and evolution. *Nature Reviews Genetics* **10**, 252-263 (2009).

ⁱⁱ Weng, Andrew P. *et al.* Activating Mutations of NOTCH1 in Human T Cell Acute Lymphoblastic Leukemia. *Science* **306**: 269-271 (2004). [DOI: 10.1126/science.1102160]