



Recent siRNA Research Publications Support Silence Therapeutics Combined Development Approach

Delivery Systems and Specific Molecular Structures Needed for siRNA Therapeutic Success

London, 7th April 2008 – Silence Therapeutics plc (AIM:SLN) Europe's leading RNAi-focused biotechnology company, today comments on two recent journal articles: *Nature*¹ "Sequence-and target-independent angiogenesis suppression by siRNA via TLR3" Mark E. Kleinman, et. al., and *Molecules and Cells*² "Immune Activation by siRNA/Liposome Complexes in Mice is Sequence-Independent: Lack of a Role for Toll-like Receptor 3," Kim et. al. In these two publications, researchers questioned current thinking on the mode of action of siRNA therapeutics suggesting that they work by mechanisms other than via specific gene silencing.

Data published in the *Nature* article (Kleinman et. al.) have been interpreted in recent days in the lay press as a "Setback for Some RNA-Based Drugs" (*New York Times*⁵). Silence Therapeutics views the cited *Nature* paper, and another recent paper in *Molecules and Cells*² as highlighting the need for a functional delivery system to ensure the therapeutic siRNA is able to enter cells and achieve gene silencing.

Both studies further reinforce the importance of chemically modifying siRNA to create molecular structures which do not cause unwanted immune stimulation such as cytokine release and interferon response.

The two new studies support the long-standing development approach of Silence Therapeutics, which has focused its research on developing both a potent RNAi-mediating delivery system (AtuPLEX) and chemically-modified siRNA (AtuRNAi) molecules.

Jeff Vick, CEO of Silence Therapeutics, said, "More than eight years ago, Silence Therapeutics recognized the need for, and pioneered the development of, a functional systemic RNAi delivery system that combines proprietary chemical modification and lipid

technologies to achieve efficient intracellular uptake without triggering an immune system response. This approach has allowed us to successfully demonstrate the inhibition of solid tumor growth and the spread of metastases. Silence continues to develop additional delivery technologies to broaden the clinical applications of our promising new class of siRNA therapeutics.”

Silence Therapeutics has previously reported in 2006, in two peer reviewed publications in *Gene Therapy*^{3, 4}, the functional *in vivo* delivery of different AtuRNAi-lipoplexes (chemically modified siRNA molecules formulated in a proprietary lipid complex). In particular, Silence Therapeutics’ AtuPLEX formulation was shown to both avoid immune responses (published data demonstrates lack of activation of interferon-alpha and IL-12) and induce RNAi-mediated gene silencing as demonstrated by the selective inhibition of endogenous target-specific gene expression *in vivo*. Furthermore, independent publications by Judge⁶ and Kim² also demonstrate that the chemical modification modality utilized in AtuRNAi obviates an immune response.

These *Gene Therapy* papers also show that the target-specific knockdown (gene silencing) resulted in the modulation of a specific biochemical signaling pathway containing the target, thus demonstrating the potential therapeutic benefits in certain oncology indications.

The multi-faceted approach that Silence Therapeutics has taken to realize the enormous potential of siRNA therapeutics was substantiated by Dr. Alan Sachs, Vice President for RNA Therapeutics at Merck Research Laboratories, a unit of Merck, who was quoted in the *New York Times*,⁵ saying that “future versions of RNA drugs could be encapsulated in fat globules and chemically modified. That would help the drugs enter cells and keep them from setting off the immune system.”

Jeff Vick further commented, “That future is now. This is the exact approach pioneered by Silence Therapeutics. Our current pipeline is based on combining our state-of-the-art AtuRNAi molecules and AtuPLEX drug delivery system. We have strong evidence that the siRNA therapeutics we are developing do enter mammalian cells, are appropriately localized intracellularly, and do act by selectively silencing the specifically targeted gene. We believe by continuing to build on this unique expertise we will achieve our goal of becoming a global leader in the RNAi space.”

Footnotes:

Kleinman et. al., *Nature*¹, “Sequence-and target-independent angiogenesis suppression by siRNA via TLR3 | doi:10.1038/nature06765; Received Published online 26 March 2008.”

Kim et. al., *Molecules and Cells*², Vol. 24, 247, 2007: “Immune Activation by siRNA/Liposome Complexes in Mice Is Sequence-independent: Lack of a Role for Toll-like Receptor 3 Signalling.”

Santel et. al., *Gene Therapy*³ 2006 Sep;13(18):1360-70. “RNA interference in the mouse vascular endothelium by systemic administration of siRNA-lipoplexes for cancer therapy.”

Santel et. al., *Gene Therapy*⁴ 2006 Aug;13(16):1222-34. “A novel siRNA-lipoplex technology for RNA interference in the mouse vascular endothelium.”

*New York Times*⁵, April 2, 2008. “Study is a Setback for Some RNA-Based Drugs.”

Adam D. Judge, Gurneet Bola, Amy C.H. Lee, Ian MacLachlan, *Molecular Therapy*⁶ Vol. 13, No. 3, March 2006: “Design of Noninflammatory Synthetic siRNA Mediating Potent Gene Silencing *in Vivo*.”

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Notes to Editors:

About Silence Therapeutics plc (www.silence-therapeutics.com)

Silence Therapeutics plc (AIM:SLN) is a leading RNAi company. RNA interference (RNAi) can selectively 'silence' genes linked to the onset of disease.

Silence Therapeutics has developed novel, proprietary short interfering RNA ('siRNA') molecules, AtuRNAi, which provide a number of advantages over conventional siRNA molecules as they show increased stability against nuclease degradation. In addition, the Company has developed a proprietary systemic delivery system, AtuPLEX. This enables the delivery of siRNA molecules to targeted diseased tissues and cells, whilst increasing their bioavailability and intracellular uptake.

In July 2007, Silence Therapeutics formed a research and development collaboration with AstraZeneca to develop AtuRNAi against five specific targets including those in respiratory indications. The Company's AtuRNAi technology also has been sublicensed to Pfizer through Quark's license to Pfizer of the compound RTP-801i-14 for the treatment of Age-related Macular Degeneration (AMD) and a number of other indications. This compound entered the clinic in early 2007. Silence Therapeutics also has licensed to Quark rights to the AtuRNAi structure for its proprietary compound AKli-5. This compound is in a Phase I human clinical study for treatment of acute kidney injury. In addition, Silence Therapeutics expects to begin the clinical development of its own proprietary AtuRNAi therapeutic molecules for systemic cancer indications in 2008.

Silence Therapeutics is based in London, UK, and Berlin, Germany, and is listed on AIM.