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For Immediate Release

Nucleonics Receives NIH Grant Supporting Research Partnership Aimed at Developing RNAi Approach to Treatment of Hepatitis B Infections

MALVERN, PA (September 25, 2003): Nucleonics, Inc., a biotechnology company focused on the development of novel RNA interference-based (RNAi) therapeutics for viral and other diseases, today announced the receipt of a research grant from the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). The grant, totaling \$1.6 million over four years, supports collaborative research aimed at developing nucleic acid reagents and methods for silencing Hepatitis B virus (HBV) gene expression and replication *in vivo*. The researchers will also evaluate in clinically relevant animal models the best DNA vector, delivery system and target HBV sequence to advance to clinical trials.

Nucleonics is collaborating on this effort with scientists at Scripps Research Institute, La Jolla, CA in the laboratory of Nucleonics collaborator and scientific advisor Francis Chisari, M.D., as well as in the laboratories of the Hepatitis B Foundation in Doylestown, PA.

“Chronic HBV infection represents an ideal target for potential RNAi-based therapeutics since RNA is an intermediate in both HBV replication and expression, and the reduction of both processes is expected to ameliorate disease,” said Nucleonics Senior Director of Biology, Catherine Pachuk, Ph.D. “Furthermore, a post-transcriptional gene-silencing therapeutic, unlike current nucleoside analogue therapies, could not only decrease viral titers but also decrease viral antigen load, reducing risks of long-term immune-mediated liver damage in those chronically infected. In addition, no significant homology exists between HBV and humans or other mammals, which makes it likely that any gene silencing achieved is exclusive for HBV.”

Post-transcriptional gene silencing, also known as double-stranded RNA (dsRNA) interference or RNAi, is a phenomenon in which genes are silenced in a sequence-dependent manner at the level of mRNA degradation. Researchers believe RNAi may offer potential as a novel way to silence genes involved in disease, including genes encoded by viruses such as Hepatitis B, Hepatitis C and HIV, or genes involved in the establishment of cancer and inflammatory diseases. While some researchers have sought to deliver RNA sequences themselves as therapeutics, such strategies face significant challenges relating to manufacturing, delivery and

the triggering of an interferon-mediated stress response that can limit effectiveness and may cause significant safety issues.

Nucleonics, in contrast, employs an expressed interfering RNA (eiRNA) approach. Scientists insert plasmid DNA coding for dsRNA into cells, letting the cells themselves carry out the dsRNA production and delivery process. Nucleonics researchers have shown the ability of long or short dsRNA strands produced in this way to stably silence target genes, including Hepatitis B and HIV, in relevant human cell lines. Moreover, they have silenced multiple genes in adult mice utilizing the company's proprietary delivery technology without triggering an interferon response. The plasmid DNA approach, which is used by Nucleonics for expression of dsRNA, has demonstrated human safety in over 500 patients to date as part of research in the field of DNA-based vaccines.

“If this research effort is successful in effectively reducing the expression and replication of HBV in mouse models of HBV infection, Nucleonics intends to advance the best-performing gene silencing vectors and formulations into clinical development,” said C. Satishchandran, Ph.D., vice president, research & development at Nucleonics. “Using RNAi therapy to reduce viral load, either on its own or in combination with other antiviral drugs, could reduce the severity of disease in patients chronically infected with HBV. Moreover, an effective RNAi therapy could potentially be used for healthy carriers of HBV, a patient population for whom no current therapy exists and in whom a reduction in viral antigen expression could lead to a reduction in immune-related liver injury with its long-term consequences of cirrhosis of the liver and liver cancer.”

About Nucleonics, Inc.

Nucleonics, founded in January 2001, is an emerging biotechnology company focused on the development of novel RNA interference-based therapeutics for viral and other diseases. The company believes its proprietary technology and delivery systems for expressed interference RNA offers advantages over other RNAi approaches in terms of safety and efficacy that will enable Nucleonics to become a leader in this emerging field. The company is headquartered in Malvern, Pennsylvania and is privately owned.

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