



Press Release

Instituto de Medicina Molecular, Cenix BioScience, and Alnylam Pharmaceuticals discover new pathway for malaria infection

- New research using RNAi technologies published on the first molecular link between malaria and the host cholesterol uptake pathway -

Lisbon, Portugal, Dresden, Germany and Cambridge, USA, September 11, 2008 – Cenix BioScience GmbH, a leading specialist in advanced RNA interference (RNAi)-based research services, Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, and the Lisbon-based biomedical research centre Instituto de Medicina Molecular (IMM), today announced the publication of their collaborative study in *Cell Host & Microbe*, describing the discovery and *in vivo* validation of scavenger receptor BI (SR-BI), a major regulator of cholesterol uptake by the liver, as a critical host factor for malaria infection. The new research findings are the first to describe a molecular link between cholesterol metabolism and malaria infection, and the new data could lead to new approaches for the treatment of malaria including use of RNAi therapeutics.

“Malaria represents a major global health concern accounting for approximately two million deaths per year. Nevertheless, the molecular mechanisms for the parasite’s pathophysiology have remained poorly understood,” said Maria Mota, Ph.D., Director of the Malaria research Unit at the IMM. “Our current studies advance the potential for new therapies as we have discovered an important molecular link between the earliest stages of infection and a critical host gene.”

The published report by Rodrigues, Hannus and Prudêncio *et al.* (*Cell Host & Microbe* 4, 271-282; 2008) describes the results of studies to investigate a decade-old hypothesis that lipoprotein clearance pathways in the human host may somehow impact the infection of liver cells by malaria-causing *Plasmodium* parasites. In the study, the liver-expressed gene, SR-BI, was identified as a critical host factor for the liver infection stage of malaria using a systematic RNAi screen of known lipoprotein pathway components in a cultured human cell-based infection assay. These findings were then confirmed in animal models of malaria infection using small interfering RNAs (siRNAs), the molecules that mediate RNAi, specific for SR-BI silencing. SR-BI is well-known as the major liver receptor for high density lipoproteins (HDL), where it plays a key role in the transfer of cholesterol from the bloodstream to hepatocytes. In addition to studies using RNAi-mediated gene silencing, the pathophysiological relevance of SR-BI’s requirement for malaria infection was confirmed by a comprehensive series of experiments using synthetic small molecule inhibitor compounds, blocking monoclonal antibodies, SR-BI over-expression with transgenic mice, and SR-BI loss of function with knock-out mice. As such, this study establishes the first clear molecular link between malaria infection and cholesterol uptake pathways, thus describing a new therapeutic strategy in the fight against this devastating parasitic disease.

“All of these studies not only demonstrate the power of our RNAi-based discovery platform, but most importantly, they open brand new interventional routes for developing novel treatments for malaria and other major parasitic diseases now devastating some of the world’s most vulnerable populations,” said Dr. Christophe Echeverri, CEO/CSO of Cenix. “The

various SR-BI-inhibitor molecules demonstrated in this study as having anti-malarial activity, including siRNAs, small synthetic molecules, and antibodies, all represent interesting candidates for the development of novel prophylactic options. Importantly, their equally novel host factor-based mechanism of action promises an inherently more powerful interventional strategy against the emergence of resistant strains of malarial parasites, as compared to existing parasite-targeted therapies.”

“We’re very pleased to participate in the research efforts initiated at the IMM with Cenix,” said Victor Kotelianski, Senior Vice-President and Distinguished Alnylam Fellow. “We feel particularly gratified that our core technology for systemic therapeutic gene silencing with RNAi therapeutics has played an important role in advancing the characterization of novel targets to confront this killer disease, and we look forward to further supporting ongoing efforts to tackle malaria and other major threats to global health.”

The current work results from an ongoing malaria research program started by the IMM group and their longstanding collaboration with Cenix, announced in 2005 to apply high-throughput RNAi technologies for discovery of host factor genes involved in malaria infection. This work was extended to include Alnylam’s technologies for *in vivo* delivery of siRNAs. Together, the collaborators have established a major new platform to drive the systematic, genomics-driven discovery and validation of novel human host genes offering clear therapeutic or prophylactic potential for halting malaria infection at its earliest liver stage, before onset of the disease’s symptomatic blood stage. Driven by Dr. Mota’s ongoing malaria research and the efforts at Cenix and Alnylam, the partners are also seeking opportunities to further scale-up the use of this platform to extend the present screen over the rest of the human genome, and to broaden the reach of these capabilities beyond malaria, tackling other parasitic diseases of major relevance to global health, including so-called neglected diseases of the developing world.

About Malaria

Malaria remains the most devastating parasitic disease worldwide. Approximately 40% of the world population lives in areas with the risk of malaria. In any year, approximately 10% of the global population will suffer from malaria – 500 millions clinical cases – and more than two million die as a result. In Africa, malaria kills one child in 20 before five years of age. In addition to causing enormous human suffering, malaria impedes the economic development and stability of many developing countries. Malaria is caused by the infection of the protozoan parasite *Plasmodium* and it is transmitted by female *Anopheles* mosquitoes. Attempts to eradicate malaria have so far been unsuccessful. Their failure is attributed to increasing resistance to insecticides in the mosquito vector and to anti-malarial drugs in the parasite. Due to the continuous emergence of drug resistance there are now fewer tools to control malaria. Liver infection by *Plasmodium* is the first obligatory step of infection and it lasts a week in the human infection. These characteristics make of the liver stage an ideal target for the development of novel intervention strategies against the infection. Understanding the intricate interactions occurring between *Plasmodium* and the host cells not only offers a new perspective into mammalian cell biology but also contributes to the design of rational approaches to combat malaria infections.

About the Instituto de Medicina Molecular

The Instituto de Medicina Molecular (IMM), located on the campus of the University of Lisbon School Of Medicine, has been recognized as a leading research institute in Portugal and thus has acquired the special status of Associate Laboratory of the National Ministry of Science and Higher Education. The mission of the Institute is to foster basic, clinical and translational biomedical Research with the aim of contributing to a better understanding of disease mechanisms, developing novel predictive tests, improving diagnostics tools and developing new therapeutic approaches. IMM is a non-profit, private, research Institute mainly supported by national public funds, European Union funds, and private Foundations. Though still a very young institution, IMM has been able to attract international collaborations, foreign researchers and international funds. Dr. Maria Mota is Director of the Malaria Unit at IMM, where she leads a team of 12 researchers whose main objective is to elucidate the molecular and cellular mechanisms underlying host-parasite interaction in malaria infection. Dr. Maria

Mota is also Associate Professor at the Lisbon School of Medicine and a Howard Hughes International Scholar. For more information, please visit the IMM's website: www.imm.ul.pt

About Cenix BioScience GmbH

Founded in 1999, Cenix BioScience is the first contract research organization specialized in combining advanced applications of RNA interference (RNAi) gene silencing with high content phenotypic analyses to enhance and accelerate the discovery and pre-clinical development of novel therapeutics. Now in its 9th year, Cenix has built-up a solid track record, successfully advancing therapeutic programs for numerous major industry and academic partners by addressing the specific needs of each through fully-customized, cutting-edge research offerings covering a wide range of disease fields. The well-established core capabilities in high throughput RNAi and multi-parametric microscopy assays have yielded optimized protocols in a broad and ever-growing collection of cultured mammalian cells, and are now complemented by microRNA-focused experimentation and in vivo applications of synthetic siRNAs. As such, Cenix is a mature and fully-proven industrial research partner, applying the highest of scientific best practices and offering a breadth and depth of expertise second to none world wide. Please contact Cenix or visit the company's web site www.cenix-bioscience.com for more information.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including *Nature*, *Nature Medicine*, and *Cell*. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection. In addition, the company is developing RNAi therapeutics for the treatment of a wide range of disease areas, including liver cancers, hypercholesterolemia, and Huntington's disease. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Medtronic, Novartis, Biogen Idec, Roche, Takeda, and Kyowa Hakko Kogyo. To reflect its outlook for key scientific, clinical, and business initiatives, Alnylam has established "*RNAi 2010*" which includes the company's plan to significantly expand the scope of delivery solutions for RNAi therapeutics, have four or more programs in clinical development, and to form four or more new major business collaborations, all by the end of 2010. Alnylam is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development, and commercialization of microRNA therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, visit www.alnylam.com.

Alnylam Forward-Looking Statement

Various statements in this release concerning Alnylam's future expectations, plans and prospects, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks related to: Alnylam's approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; obtaining, maintaining and protecting intellectual property; Alnylam's ability to enforce its patents against infringers and to defend its patent portfolio against challenges from third parties; Alnylam's ability to obtain additional funding to support its business activities; Alnylam's ability to realize future milestones and royalties as well as co-development and co-commercialization opportunities; Alnylam's dependence on third parties for development, manufacture, marketing, sales and distribution of products; obtaining regulatory approval for products; competition from others using technology similar to Alnylam's and others developing products for similar uses; Alnylam's dependence on collaborators; and Alnylam's

short operating history; as well as those risks more fully discussed in the “Risk Factors” section of its most recent quarterly report on Form 10-Q on file with the Securities and Exchange Commission. In addition, any forward-looking statements represent Alnylam’s views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam does not assume any obligation to update any forward-looking statements.

Contacts:

Cenix:

Dr. Birte Sönnichsen

Chief Operating Officer

T: +49-351-4173-0

E: info@cenix-bioscience.com

IMM:

Dr. Marta Agostinho

Communication Officer

T: +351-21-7999411

E: marta-elisa@fm.ul.pt

Alnylam:

Cynthia Clayton

Investors

T: +1-617-551-8207

Kathryn Morris

Media, Yates Public Relations

T: +1-845-635-9828

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