PRESS RELEASE

NOXXON PHARMA AG

Nature Communications Publications on the First X-ray Crystal Structures of Spiegelmers Bound to Protein Targets

Anti-CCL2 and anti-C5a Spiegelmers Revealed in Complex with Their Targets

Berlin, Germany and Boston, USA - April 23, 2015 - NOXXON Pharma announced today the publication of two new studies in *Nature Communications*, entitled:

- *Crystal structure of a mirror-image L-RNA aptamer (Spiegelmer) in complex with the natural L-protein target CCL2* (link to the article on nature.com)
- *Structural basis for the targeting of complement anaphylatoxin C5a using a mixed L-RNA/L-DNA aptamer* (link to the article on nature.com)

Scientists from the University of Hamburg, Germany, and Aarhus University, Denmark, have solved the crystal structures of two Spiegelmers (NOX-E36 and NOX-D20) bound to their respective biological targets: the pro-inflammatory chemokine CCL2 (also known as monocyte chemoattractant protein 1, MCP-1) and the complement component C5a. Built on a backbone of mirror-image RNA or DNA, Spiegelmers belong to a class of drugs known as aptamers which can bind to molecular targets with high affinity and specificity in order to modulate the biological function of that target. These are the first crystal structures ever published of Spiegelmers bound to targets.

Sven Klussmann, founder and CSO of NOXXON Pharma, and also co-author on both articles commented: “I am delighted to finally have a high resolution visualization of the remarkable shapes of two Spiegelmer® product candidates. The structural data not only provide the first look at the unusual interaction of a mirror-image oligonucleotide with a natural protein but also deepens our understanding of the two molecules’ mode of action.”

Dr. Dominik Oberthür from the University of Hamburg and colleagues describe the structure of the Spiegelmer® NOX-E36 bound to the pro-inflammatory chemokine CCL2. CCL2 is upregulated under diabetic conditions and implicated in inflammation, such as that present in many tissues and organs in diabetic patients, including the kidney. CCL2, like other chemokines has two types of binding sites: one that binds specifically with receptors to trigger signaling within cells, and a second that binds non-specifically to cell surfaces to allow for the formation of a concentration gradient that migrating cells with the appropriate receptors can follow. The authors revealed that NOX-E36 covers both sites on CCL2 when it binds, suggesting a dual mechanism of action on this chemokine.

Dr. Laure Yatime from Aarhus University and colleagues describe the structure of the Spiegelmer® NOX-D20, a precursor Spiegelmer® to current development candidate NOX-D21, in complex with C5a. C5a is a chemoattractant for immune cells, stimulates the expression of pro-inflammatory cytokines and chemokines, and triggers edema. C5a

is believed to lead to organ damage in life-threatening conditions such as severe pneumonia and sepsis. The Spiegelmer® NOX-D20 was found to cover epitopes that are important for C5a receptor binding, providing an explanation for its inhibition of this target.

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Notes for Editors:

About NOXXON Pharma

NOXXON Pharma is a clinical-stage biopharmaceutical company developing Spiegelmers, a novel class of proprietary nucleic acid-based therapeutic agents built on a backbone of mirror-image nucleotides. Spiegelmers are chemically synthesized L-stereoisomer oligonucleotide aptamers, an immunologically passive alternative to antibodies. NOXXON has a diversified portfolio of clinical-stage Spiegelmer® therapeutics:

- NOX-H94 (lexaptepid pegol) is a Spiegelmer® that binds and neutralizes the human peptide hormone hepcidin. Hepcidin regulates iron metabolism and is a key mediator of iron restriction in anemia of chronic disease. Hepcidin blocks iron inside cellular stores via its interaction with ferroportin, the iron-exporting protein expressed on the surface of iron storage cells, such as macrophages and liver cells. Phase 1 trials demonstrated that NOX-H94 is capable of inhibiting hepcidin in humans, resulting in higher serum iron concentrations relative to subjects receiving placebo and have also shown clinical proof-of concept in patients with cancer-related anemia. A Phase 2a trial studying the effects of NOX-H94 in a ESA-hyporesponsive population is currently underway.

- NOX-A12 (olaptesed pegol) binds and inhibits the human Chemokine CXCL12 also named SDF-1, inhibiting signaling via its two receptors (CXCR4 and CXCR7). Two 28-patient Phase 2a studies of NOX-A12 in combination with chemotherapy have completed the on-treatment phase in patients with relapsed/refractory Multiple Myeloma (MM) and Chronic Lymphocytic Leukemia (CLL). Data from both studies suggest improved efficacy versus relevant historical studies. NOXXON also plans to investigate the use of NOX-A12 in glioblastoma and has received orphan drug designation for glioblastoma in the United States and glioma in Europe.

- NOX-E36 (emapticap pegol) binds and inhibits the human Chemokine CCL2 also referred to as MCP-1 (C-C Chemokine Ligand 2 / Monocyte Chemoattractant Protein 1), which is being developed for the treatment of complications arising from diabetes and specifically diabetic nephropathy. One preclinical study has shown that inhibition of this chemokine led to reduced infiltration of inflammatory cells into the kidney. NOX-E36 has completed a Phase 2a exploratory study, which included 76 patients presenting with Type 2 diabetes with proteinuria on top of standard of care. Promising results were obtained on two key parameters: protein in the urine, or proteinuria, as measured by the albumin to creatinine ratio (ACR), and glycated hemoglobin (HbA1c) in blood. Importantly, the effect on ACR was not accompanied by relevant hemodynamic changes which is consistent with

a novel mechanism of action. Further, the maintenance of the effects even after cessation of treatment suggests that CCL2 blockade interferes with the underlying pathophysiology. These results suggest that NOX-E36 may be the first therapeutic agent with disease-modifying potential in this indication.

The Spiegelmer® platform provides the company with powerful and unique discovery capabilities, which have generated a number of additional candidates in discovery stage research. Located in Berlin, Germany, and Boston, USA, NOXXON has currently 53 employees.

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