

15<sup>th</sup> October 2008

## ATL1101 suppresses tumour growth in key mouse models of prostate cancer

- *Significant suppression of human prostate tumour growth in mouse model of prostate cancer*
- *Data highlights unique mechanism of action of ATL1101*
- *Results to be presented Friday 17<sup>th</sup> October 2008 at New York Academy of Sciences Annual Meeting of the Oligonucleotide Therapeutics Society, Harvard Conference Center, Boston*

Antisense Therapeutics (ANP) is pleased to report positive results from its collaborative preclinical research study on the therapeutic potential of ATL1101 in prostate cancer. ATL1101 is a second generation antisense inhibitor of the insulin-like growth factor-I receptor (IGF-IR), which has previously shown potent activity in laboratory studies, including in human cancer cells.

In the study, human prostate tumour cells were grafted into recipient mice. ATL1101 or control drugs were injected into the bloodstream of the mice, and tumour growth was monitored and compared between the treatment groups.

**The key findings were that ATL1101 injections significantly suppressed the growth of the human tumours and slowed down their transition to the most dangerous form of prostate cancer, castration-resistant prostate cancer (CRPC).**

ANP's research collaborator in the study is Prof. Martin Gleave, a leader in prostate cancer treatment and drug development. Martin Gleave is Professor, Department of Urological Sciences, University of British Columbia and Director of The Prostate Centre at Vancouver General Hospital.

"There is a compelling need for new therapeutic options in CRPC. The preclinical anticancer activity of ATL1101 in these mouse models of human prostate cancer is encouraging and justifies further evaluation as a potential treatment", said Prof. Gleave.

"These animal studies mimic two key aspects of this life-threatening disease: the transition of prostate tumours to castrate-independence, and the ability of tumours to grow despite androgen ablation therapy," said ANP's Research Director Dr Christopher Wraight. "Importantly, ATL1101 injection inhibited both aspects of tumour growth."

"To our knowledge, this is the first demonstration of systemic efficacy in a prostate cancer model with an RNA-silencing IGF-I receptor drug. Our study clearly shows that ATL1101 is an effective inhibitor of IGF-IR signalling *in vivo*, and that its pharmacological mechanism is highly relevant in the control of prostate tumour growth."

ANP CEO, Mark Diamond said "This project is a very exciting opportunity for ANP. By our assessment it is the only antisense drug targeting IGF-IR in development as a potential treatment for prostate cancer. We now have positive animal efficacy data on ATL1101 as we have for ATL1103 for sight and growth disorders, which is progressing through pre-clinical toxicology studies prior to the initiation of planned human clinical trials next year. Our ability to successfully develop and commercialise our drugs is validated by our licensing of ATL1102 for multiple sclerosis to Teva Pharmaceuticals, a top 20 global pharmaceutical company, who are now continuing the drug's development."

"The preclinical prostate cancer results from Prof. Gleave's laboratory provide compelling support for the continued development of ATL1101 as a cancer therapeutic."

Drugs targeting IGF-IR are being developed by a number of the major pharmaceutical companies, demonstrating the importance of the IGF-IR target in cancer. ATL1101 provides a different therapeutic mechanism to other IGF-IR drugs: ATL1101 is designed to block IGF-IR production and stop it appearing on the surface of tumour cells. Other drugs bind to the molecule already on the surface of the cells. In this way ATL1101 benefits from the scientific validation of the biological target provided by other IGF-IR drugs in clinical development, but offers a novel mechanism of action and in turn, a potentially different treatment option or approach.

An abstract summary of the study, entitled "Targeting IGF-IR with Antisense Oligonucleotides in Prostate Cancer" is to be released today at the New York Academy of Sciences 4<sup>th</sup> Annual Meeting of the Oligonucleotide Therapeutics Society, Harvard Conference Center, Boston, 15-18 October 2008. A copy of the abstract follows this announcement.

The detailed study data will be presented in Poster Session II at the meeting this Friday 17<sup>th</sup> October 2008.

## Background Information

### ATL1101 prostate cancer study – design and outcomes

Design:

- Human prostate tumour cell lines LNCaP and PC3 were xenografted by subcutaneous injection into recipient athymic nude (nu/nu) mice.
- For LNCaP xenografts, serum PSA values were monitored, and when PSA values exceeded 50 ng/ml, mice were castrated and randomly selected for treatment with ATL1101 or control ODN (15 mg/kg) injected intraperitoneally once daily for 7 days and 3 times per week thereafter.
- For PC-3 xenografts, when tumors reached 100 mm<sup>3</sup>, mice were randomly selected and treated with the same protocol as LNCaP.

The main outcomes of the study are:

- Significantly delayed onset of castration-resistant prostate cancer (CRPC) progression of LNCaP xenografts measured as tumor growth and serum PSA levels, and significant inhibition of castration-resistant tumour growth of PC3 xenografts
- In LNCaP mice, mean tumor volume was assessed in each group (ATL1101 & control oligo treatment groups). At 3 weeks' treatment, ATL1101-treated mice had undetectable tumour growth, compared with ~100% increase in tumour volume in control oligo-treated mice. Differences between mean tumour volumes were statistically significant compared with the control oligo-treated group ( $p < 0.05$ , Student's t test,  $n = 10$ ) from 3 weeks of treatment.
- In LNCaP mice, tumour growth inhibition was associated with inhibition of the rate of increase in serum PSA. Differences between mean PSA levels were statistically significant compared with the control oligo-treated group ( $p < 0.05$ , Student's t test,  $n = 10$ ) from 3 weeks of treatment.
- In PC3 mice, mean tumor volume was assessed in each group (ATL1101 & control oligo treatment groups). At 4 weeks, mean PC3 tumour volume in ATL1101-treated animals was approximately half that of the control oligo-treated animals. Differences between mean tumour volumes were statistically significant compared with the control oligo-treated group ( $p < 0.05$ , Student's t test,  $n = 10$ ) from 4 weeks of treatment.
- Decreased proliferation and increased apoptosis of androgen-independent PC3 cells *in vitro*
- Increased apoptosis of androgen-responsive LNCaP cells under androgen-deprived culture conditions
- Dose- and sequence-specific suppression of IGF-I receptor mRNA and protein in the human prostate tumour cell lines LNCaP and PC3
- Suppression of tumor growth *in vivo* correlated with decreased IGF-IR expression

**Prostate cancer** is the second most frequently diagnosed cancer in men after skin cancer. It is estimated there will be 218,890 new cases diagnosed in the U.S. this year. Around 1 in 6 men will develop prostate cancer, a third to a half of whom will recur after local treatment and risk progression to metastatic prostate cancer. Metastatic disease invariably progresses to hormone refractory or castrate-resistant prostate cancer (CRPC) if given enough time. Prostate tumours are initially androgen (male sex hormone) dependent, and can be treated with androgen ablation therapy (the term "castration" can be used to describe removal of the source of androgen), however once the disease progresses to its most dangerous and aggressive form, CRPC, treatment options are limited and prognosis is poor. Treatment options depend on disease severity and include radiation and chemotherapy, which are designed to induce programmed cell death (apoptosis) of tumour cells. There is a pressing need for the development of new treatment options.

**ATL1101** is an antisense inhibitor of IGF-IR, which has shown potent activity in laboratory studies, including in human cancer cells. IGF-IR is one of the best known of a family of cell signaling molecules that are referred to as "anti-apoptotic". These molecules prolong cell survival by inhibiting programmed cell death (apoptosis). The connection between IGF-IR activity and prostate cell tumorigenicity has been studied for many years. Drugs targeting IGF-IR are designed to slow down tumour growth and make tumour cells more susceptible to cell death. Inhibition of IGF-IR is also designed to make tumour cells more susceptible to killing by cytotoxic treatments like radiation therapy and chemotherapy. Such therapeutic approaches are under investigation in several large pharmaceutical companies, lending support to our own antisense-based strategy against the same target.

**Antisense Therapeutics Limited (ASX: ANP)** is an Australian publicly listed biopharmaceutical drug discovery and development company. Its mission is to create, develop and commercialise antisense pharmaceuticals for large unmet markets. ANP has two drugs in development and two drugs in pre-clinical research. ATL/TV1102 (injection) has completed a Phase IIa trial as a potential treatment of multiple sclerosis. ATL1103 is a second-generation antisense drug designed to lower blood IGF-I levels and is entering pre-clinical development as a potential treatment for acromegaly and vision disorders. ATL/TV1102 (inhaled) is at the pre-clinical research stage as a potential treatment for asthma. ATL1101 is a second-generation antisense drug at the pre-clinical research stage being investigated as a potential treatment for prostate cancer. ATL/TV1102 has been licensed to Teva Pharmaceutical Industries Ltd.

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Conference Abstract, New York Academy of Sciences 4<sup>th</sup> Annual Meeting of the Oligonucleotide Therapeutics Society, Harvard Conference Center, Boston, 15-18 October 2008:

## TARGETING IGF-IR WITH ANTISENSE OLIGONUCLEOTIDES IN PROSTATE CANCER

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Initiating as an androgen-dependent adenocarcinoma, prostate cancer (PC) gradually progresses to a metastatic, castrate-resistant (CR) disease following androgen deprivation therapy (ADT) with a propensity to metastasize to bone. Altered expression of insulin-like growth factor (IGF) axis components have been consistently found in PC. The action of IGFs is mediated through IGF-I receptor (IGF-IR) and modulated by IGF binding proteins (IGFBPs). We hypothesize that increased expression and/or responsiveness of IGF-IR may promote establishment of PC metastatic lesions and CRPC progression in patients undergoing ADT. ATL1101 is a 2'-MOE-modified antisense oligonucleotide (ASO) targeting human IGF-IR. Using mismatched and scrambled sequence oligonucleotides as negative controls, we observed dose- and sequence-specific suppression of IGF-IR mRNA and protein expression in ATL1101-treated LNCaP and PC3 PC cell lines *in vitro*. Suppressed IGF-IR expression correlated with decreased proliferation and increased apoptosis of androgen-independent PC3 cells under standard culture conditions and increased apoptosis of androgen-responsive LNCaP cells under androgen-deprived culture conditions. Compared to control oligonucleotides, ATL1101 significantly suppressed PC3 tumor growth as a monotherapy in murine xenografts. Similarly ATL1101 significantly delayed onset of CRPC progression of LNCaP xenografts following castration as measured by tumor growth and serum prostate specific antigen levels. Pharmacodynamic activity *in vivo* was assessed using immunoblot analysis of harvested tumor tissues, and confirmed that suppression of IGF-IR expression correlated with decreased tumor growth *in vivo*. This study reports the first preclinical proof-of-principle data that this novel IGF-IR ASO selectively suppresses IGF-IR expression, suppresses growth of CRPC tumors and delays CRPC progression *in vitro* and *in vivo*.

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