

21<sup>st</sup> April, 2010

## **ATL1101 Prostate Cancer Drug Tumour Suppression Data to be Presented at US Cancer Meeting**

Antisense Therapeutics (ANP) advises that a poster outlining the company's latest preclinical research data on ATL1101 will be presented today (US Eastern Standard Time Wednesday 21 April, 2010 8:00 AM - 11:00 AM) at the American Association for Cancer Research (AACR) 101st Annual Meeting 2010 in Washington, DC.

The poster, entitled "Antisense oligonucleotide targeting insulin-like growth factor-1 receptor (IGF-1R) enhances paclitaxel sensitivity in a castrate-resistant and paclitaxel-resistant prostate cancer model", will be presented by Assoc. Prof. Michael Cox, and is co-authored by colleagues Dr Junya Furukawa and Prof. Martin Gleave from the Vancouver Prostate Centre, as well as Dr Brett Monia from Isis Pharmaceuticals and ANP's Research Director, Dr Christopher Wraight.

The Company has previously reported the main points contained in this presentation, notably that:

- ATL1101 potently and specifically inhibits IGF-I receptors in prostate tumour cells
- ATL1101 synergistically enhances prostate tumour sensitivity to chemotherapy induced cell death
- Prostate tumour cells exhibiting multi-drug resistance retain their sensitivity to ATL1101
- ATL1101 treatment of taxane and multi-drug resistant tumour-bearing mice restores taxane sensitivity and suppresses tumour growth

The poster will be presented in the Session "Experimental and Molecular Therapeutics 36" (Poster 5376) and the poster Abstract follows on the next page.

**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 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. IGFIR is one of the best known of a family of cell signalling 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. Designed to block IGF-IR synthesis, ATL1101 offers potential advantages over other therapies targeting IGF-IR due to its highly differentiated pharmacokinetics and unique antisense mode of action. ATL1101 was a product of a discovery collaboration between ANP and Isis Pharmaceuticals (Nasdaq: ISIS) and utilizes second-generation antisense technology, licensed from Isis. Several antisense drugs with the same chemical modifications and design as ATL1101 are advancing in cancer clinical trials, strengthening support for second-generation drugs as targeted cancer therapeutics. For example OGX-011, developed by OncoGenex and Isis, has demonstrated significant clinical benefit when combined with chemotherapy (increased survival time compared to patients receiving chemotherapy alone) in Phase II clinical studies in CRPC and non-small cell lung cancer (NSCLC).

**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. ATL1102 (injection) has successfully completed a Phase II efficacy and safety trial, significantly reducing the number of MRI lesions in patients with multiple sclerosis. ATL1103 is a second-generation antisense drug designed to lower blood IGF-I levels and is entering the clinical stage of development as a potential treatment for growth and vision disorders. ATL1102 (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.

*Contact Information:* Website: [www.antisense.com.au](http://www.antisense.com.au)  
Managing Director: Mark Diamond +61 3 9827 8999  
Investor Relations: Simon Watkin +61 (0) 413 153272

# AACR 101st ANNUAL MEETING 2010

April 17-21, 2010 • Walter E. Washington Convention Center • Washington, DC

## Presentation Abstract

Abstract Number: 5376

Presentation Title: Antisense oligonucleotide targeting insulin-like growth factor-1 receptor (IGF-1R) enhances paclitaxel sensitivity in a castrate-resistant and paclitaxel-resistant prostate cancer model

Presentation Time: Wednesday, Apr 21, 2010, 8:00 AM - 11:00 AM

Location: Exhibit Hall A-C, Poster Section 21

Poster Section: 21

Poster Board Number: 8

Author Block: Junya Furukawa<sup>1</sup>, Christopher J. Wraight<sup>2</sup>, Brett P. Monia<sup>3</sup>, Martin E. Gleave<sup>1</sup>, Michael E. Cox<sup>1</sup>. <sup>1</sup>Univ. of British Columbia, Vancouver, BC, Canada; <sup>2</sup>Antisense Therapeutics Ltd., Toorak, Australia; <sup>3</sup>Isis Pharmaceuticals Inc, Carlsbad, CA

Abstract Body: While prostate cancer (PCa) initially responds to androgen deprivation therapy (ADT), castrate-resistant disease (CRPC) relapse is inevitable. Altered expression of insulin-like growth factor (IGF) axis components have been consistently found in PCa and associated with adaptive growth and survival signaling implicated in CRPC progression. These activities are mediated by activation of the IGF-I receptor (IGF-IR). While CRPC patients treated with taxanes (paclitaxel or docetaxel) alone or in combination with estramustine phosphate or prednisone show a survival benefit, development of chemotherapeutic resistance eventually occurs. Therefore novel strategies targeting the molecular basis of ADT and chemotherapy resistance are required. In this study, we assess the potency and anti-cancer activity of a 2'-MOE-modified antisense oligonucleotide (ASO) targeting human IGF-IR, ATL1101, on the CRPC cell line, PC3 and a paclitaxel-resistant androgen-independent PC3-derived cell line, PtxR PC3, *in vitro* and *in vivo*. PtxR PC3 cells were established by culturing in step-wise increased drug concentrations. IGF-IR mRNA and protein expression in ATL1101- and control oligonucleotides (ODN)-treated PtxR PC3 cells were measured by QT-PCR and immunoblotting. The effect of IGF-IR ASO and paclitaxel combination therapy on parental and PtxR PC3 cell growth and apoptosis *in vitro* was examined by crystal violet assay and flow cytometry. *In vitro* combination index (CI) was calculated by Calcsyn® software. For xenograft studies, parental and PtxR PC-3 cells were inoculated s.c. in the flanks of athymic male nude mice and tumor volume kinetics were compared for mice treated with paclitaxel injected i.v. and either ATL1101 or control ODN injected i.p. *In vitro*, the IC<sub>50</sub> for paclitaxel in PtxR PC3 was 20-fold higher than that in parental cells. PtxR PC3 also show significant cross-resistance to docetaxel and mitoxantrone. We observed equivalent dose- and sequence-specific suppression of IGF-IR mRNA and protein expression, and comparable decreased proliferation and increased apoptosis in ATL1101-treated parental and PtxR PC3 cells *in vitro*. Combination of ATL1101 with paclitaxel showed CI values below 1 at the IC<sub>50</sub>, IC<sub>75</sub>, IC<sub>90</sub>, suggesting the drug interactions resulted in synergy. *In vivo*, ATL1101 significantly increased sensitivity of PtxR PC3 tumors to combination therapy with paclitaxel as compared to control ODN in murine xenografts. This study reports the first preclinical proof-of-principle data that this novel IGF-IR ASO suppresses growth of paclitaxel resistant PC tumors, synergistically enhancing paclitaxel sensitivity *in vitro* and *in vivo*.

American Association for Cancer Research  
615 Chestnut St. 17th Floor  
Philadelphia, PA 19106