8th December 2015

ATL1102 Cancer Data Presentation

Antisense Therapeutics Limited ("ANP") wishes to advise that data from the testing of ATL1102 in an animal cancer research study conducted at the Children's Hospital Los Angeles (CHLA) is to be presented today at The American Society of Hematology (ASH) 57th Annual Meeting in Orlando Florida. The data from this pilot animal study shows that ATL1102, an antisense drug targeting CD49d (VLA-4), led to the rapid mobilization of acute myeloid leukemia (AML) cells to the peripheral blood in mice that had been engrafted with human AML cells. Details of the study and results are outlined in the attached poster presentation. A new provisional patent application incorporating this data and covering ATL1102's potential application in AML and other leukemias has been filed by ANP.

The rationale for this study of ATL1102 is based on the bone marrow microenvironment having been shown to promote cell adhesion-mediated drug resistance in leukemia cells. Breaking the adhesive bonds of AML cells with their protective niche to mobilize them from the bone marrow to the peripheral blood may make drug treatment more effective. Studies have suggested the adhesion molecule CD49d is an anchor molecule for AML and certain other leukemia cells in the bone marrow and that drugs like ATL1102 which reduce CD49d expression may cause the release of these cancer cells from their protective environment to make the cancer cells more accessible to chemotherapy. No drug targeting CD49d is currently approved for use in leukemia.

AML is the most common acute leukemia in adults and the seventh most common pediatric malignancy comprising approximately one-fifth of pediatric leukemias. Treatment is dominated by generic chemotherapeutic drugs. In children, relapse following primary chemotherapy approaches 40%, and the 5-year event-free survival rate is only approximately 50%. Novel therapeutic strategies are highly warranted to eradicate residual disease.

Further animal studies are ongoing at the CHLA at their cost to more fully assess ATL1102's therapeutic potential in this disease setting.

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About Antisense Therapeutics Limited
Antisense Therapeutics Limited is an Australian publicly listed biopharmaceutical drug discovery and development company. Its mission is to create, develop and commercialise second generation antisense pharmaceuticals for large unmet markets. Antisense Therapeutics has 4 products in its development pipeline that it has in-licensed from Isis Pharmaceuticals Inc. (ISIS), a world leader in antisense drug development and commercialisation - ATL1102 (injection) which has successfully completed a Phase IIa trial in patients with relapsing-remitting multiple sclerosis (RRMS), ATL1103 drug designed to block GHR production which in a Phase II clinical trial reduced blood IGF-1 levels in patients with the growth disorder acromegaly, ATL1102 (inhaled) which is at the pre-clinical research stage as a potential treatment for asthma and ATL1101 a second-generation antisense drug at the pre-clinical stage being investigated as a potential treatment for cancer.

ATL1102 background Information
ATL1102 is a second generation antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4). In inflammation, white blood cells (leukocytes) move out of the bloodstream into the inflamed tissue, for example, the Central Nervous System (CNS) in MS, and the lung airways in asthma. The inhibition of VLA-4 may prevent white blood cells from entering sites of inflammation, thereby slowing progression of the disease. Antisense inhibition of VLA-4 expression has demonstrated activity in a number of animal models of inflammatory disease including asthma and MS with the MS animal data having been published in a peer reviewed scientific journal. ATL1102 was shown by the Company to reduce MS lesions in a Phase IIa clinical trial in RRMS patients and the data have been published (Limmroth, V. et al Neurology, 2014; 83(20): 1780-1788).
Mobilizing acute myeloid leukemia cells using a novel integrin a4 targeting antisense, ATL1102.

Ducharte Y1, Gang EJ1, Kim HN1, Shishido SN1, Grishin A3, Fabbri M1,2, Parekh C1,2, Abdel-Azim H1,2, Bhojwani D1,2, Wayne AS1,2, Tachas G4 and Kim YM1,2

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Abstract

BACKGROUND: Acute myeloid leukemia (AML) patients have a poor prognosis with a low (30-50%) disease-free survival rate. Novel therapeutic strategies are highly warranted. The bone marrow (BM) niche has been shown to protect cells from chemotherapeutic drug resistance (CAM-DR) in leukemia cells. However, current treatment regimens cannot achieve a cure due to the lack of tools to prevent interactions with BM cells. Breaking adhesion bonds of AML cells with integrin a4b1 allows for drug treatment more efficiently. Studies in our own laboratory have identified a role for CD49d in chemoresistance in AML, which has been shown in the clinic for mobilization purposes. Here, we evaluate a novel integrin a4 antisense (ATL1102) on mobilization of bone marrow AML cells.

MATERIALS & METHODS: We determined integrin a4 expression in human BM cells and compared with an integrin a4 targeting antisense (ATL1102) on mobilization of leukemia cells in a bone marrow niche. We focused on CD49d as it is adhesion molecule expressed in the BM niche. This is due to current treatment methods for AML patients using chemotherapy combined with G-CSF. We used flow cytometry in HL-60 nucleofected with ATL1102 after 24h, 48h and 72h. ATL1102 significantly decreases CD49d expression on mobilized leukemia cells in a pilot experiment. For this reason, we determined CD49d expression on mobilized leukemia cells in an AML cell line model. ATL1102 treatment in vitro induces a rapid and significant decrease of CD49d at the RNA and cell surface protein levels. The loss of integrin expression on mobilized leukemia cells in a pilot experiment. For this reason, we determined CD49d expression on mobilized leukemia cells in an AML cell line model. ATL1102 treatment in vitro induces a rapid and significant decrease of CD49d at the RNA and cell surface protein levels. The loss of integrin expression on mobilized leukemia cells was significant.

RESULTS: We demonstrated here that ATL1102, a novel CD49d antisense, can efficiently decrease CD49d expression on mobilization of bone marrow AML cells in the peripheral blood.

CONCLUSION: We demonstrate that ATL1102 can efficiently decrease CD49d expression in AML cell line in vitro and in vivo, and that ATL1102 mobilizes AML cells to the peripheral blood.

Conclusion / Prospects

We demonstrated here that ATL1102, a novel CD49d antisense, can efficiently decrease CD49d expression in vitro and in vivo in an AML cell line model. ATL1102 treatment in vitro induces a rapid and significant decrease of CD49d on the RNA and cell surface protein levels. The loss of integrin expression does not affect cell viability of HL-60 cells. The combinational treatment with conventional chemotherapy Arac does not show any synergetic effect on cell viability in vitro. Interestingly, in vivo ATL1102 leads to a fast and substantial mobilization of bone marrow HL-60 to the peripheral blood in treated mice compared to control antisense-treated mice. These results could be of great relevance in the treatment of AML and other leukemias where reliance on relapse after treatment can occur potentially because of the chemoprotective effect of the bone marrow stroma. Further animal experiments are required to more fully assess and characterize the ATL1102 mobilization of AML and other leukemic cells to the peripheral blood.