26 June 2017

Antisense Therapeutics to enter clinical development in Duchenne Muscular Dystrophy

- Company to undertake a clinical trial of its drug ATL1102 in new clinical application, Duchenne Muscular Dystrophy
- Clinical trial is planned to be undertaken at the Royal Children's Hospital (RCH), Melbourne
- World class international advisory board established chaired by Mr William Goolsbee ANP's non-executive director and ex-Chairman of Sarepta Therapeutics
- Funding secured for the trial (subject to receipt of approval to commence the trial)
- Australian Ethical Investment to become largest shareholder in the Company

Antisense Therapeutics ("ANP" or the "Company") announced today the Company's advanced planning to undertake a clinical trial of ATL1102, its immunomodulatory therapy initially in development for the treatment of Multiple Sclerosis (MS), in patients with Duchenne Muscular Dystrophy (DMD). The trial is designed to assess the drug's effects on the inflammation associated with this rare and incurable muscle wasting disease of children.

Mark Diamond, CEO of Antisense Therapeutics said: "Our plan to undertake a clinical trial of ATL1102 in DMD patients is facilitated by the extensive pre-clinical and clinical experience that we have established via ATL1102's development in MS. As DMD is a rare disease with a high unmet medical need, ATL1102 is expected to benefit materially from development incentives, including orphan drug designation that are provided to support rare disease drug development".

DMD and ATL1102

DMD is caused by a mutation in the muscle dystrophin gene leading to severe progressive muscle loss and premature death. One of the most common fatal genetic disorders, DMD affects approximately one in every 3,500 to 5,000 males worldwide. A key challenge in the management of DMD patients is to reduce the inflammation that exacerbates the muscle fibre damage. Corticosteroids are the only approved treatments for muscle inflammation, however they do not sufficiently suppress muscle inflammation, are not well tolerated and have serious side effects including adversely affecting growth rate. As a consequence, there is an acknowledged high need for new therapeutic approaches for the treatment of inflammation associated with DMD.

Recently published clinical research on DMD patients has shown that patients who have a greater number of T cells (immune cells) in the blood that express high levels of CD49d (CD49dhiT-cell) are associated with both more severe and rapid disease progression, with an increase in the number of CD49dhi T cells associated with reduced walking capacity[1]. Corticosteroids did not reduce these CD49dhi T cells[1]. ATL1102 has been shown to block CD49d (VLA-4) expression on lymphocytes (including T cells), reduce immune cell numbers (including T cells), and to be highly effective in reducing inflammatory brain lesions in MS patients after only 8 weeks of dosing.

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Clinical Development

The clinical trial of ATL1102 is planned to be undertaken at the Royal Children's Hospital (RCH) in Melbourne, with the clinical development of ATL1102 in boys with DMD to be directed by an Advisory Board of international experts in the field. The Advisory Board is chaired by Mr William Goolsbee, a non-executive director of ANP and ex-Chairman of Sarepta Therapeutics (Sarepta are marketers of the antisense drug, eteplirsen, the first and only drug approved for the restoration of muscle dystrophin). Membership of the Advisory Board includes the Australian inventors of eteplirsen, Professor Steve Wilton and Professor Sue Fletcher (from Perth's Western Australian Neuroscience Research Institute and Murdoch University respectively), and Dr Gillian Butler-Browne, Director, Centre of Research in Myology at Sorbonne University in Paris (whose team observed that circulating high CD49d expressing T-cells lead to poor prognosis in DMD patients).

ANP has clincial supplies available to commence the trial shortly after receipt of relevant approvals to commence the trial. Details on the trial will be provided in future news regarding trial approval.

Capital Raising to fund clinical development of ATL1102 in DMD

Institutional Placement to Australian Ethical Investment.

ANP has agreed to place 24,233,911 shares at $0.032 per share to Australian Ethical Investment to raise $775,485, equal to the maximum number of shares that ANP can issue within the 15% placement capacity limit available under the Listing Rule 7.1. The issue of shares to Australian Ethical Investment is conditional on the Company receiving hospital approval any time before 30 September 2017 to commence the clinical trial for ATL1102 in DMD.

The issue price represents the volume weighted average market price for the Company's shares over the 20 days on which sales were recorded prior to 22 June 2017.

Subject to the approval to commence the trial being given, settlement of the Placement will occur on the second business day after ASX announcement by the Company of the receipt of the hospital's approval.

Entitlement Issue

Following the settlement of the placement to Australian Ethical Investment, the Company proposes to undertake a pro-rata Entitlement Issue to shareholders at the same price to raise up to $2,000,000. Subject to approval to commence the trial being granted, Australian Ethical Investment has indicated its intention to take up its pro-rata entitlement and to acquire additional shortfall shares in ANP to increase its holding in the Company to 19.99%.

XEC Partners has been appointed as Lead Manager for the Capital Raising.

Following completion of the Capital Raising, Australian Ethical Investment will emerge as the largest shareholder in the Company.

Mark Diamond, CEO of Antisense Therapeutics said: "We look forward to welcoming as a new shareholder one of the market's most respected ethical investors and a highly regarded fund manager."

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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 Ionis Pharmaceuticals Inc. (formerly Isis Pharmaceuticals Inc.), a world leader in antisense drug development and commercialisation - ATL1102 (injection) which has successfully completed a Phase II efficacy and safety trial, significantly reducing the number of brain lesions in patients with relapsing-remitting multiple sclerosis (RRMS), ATL1103 drug targeting the growth hormone receptor which in a Phase II clinical trial, successfully 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.

About ATL1102 ATL1102 is an antisense inhibitor of CD49d, a subunit of VLA-4 (Very Late Antigen-4). 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 to be highly effective in reducing MS lesions in a Phase IIa clinical trial in RR-MS patients. The ATL1102 Phase IIa clinical data has been published in the medical Journal Neurology (Limmroth, V. et al Neurology, 2014; 83(20): 1780-1788).

About DMD Duchenne Muscular Dystrophy (DMD) is an X-linked disease that affects 1 in 3600 to 6000 live male births (Bushby *et al*, 2010). DMD occurs as a result of mutations in the dystrophin gene which causes a defect in the protein or reduction or absence of the dystrophin protein. Children with DMD have dystrophin deficient muscles and are susceptible to contraction induced injury to muscle which triggers the immune system which exacerbates muscle damage (Pinto Mariz, 2015). Ongoing deterioration in muscle strength affects lower limbs leading to impaired mobility, and also affects upper limbs, leading to further loss of function and self-care ability. The need for wheelchair use can occur in early teenage years, with respiratory, cardiac, cognitive dysfunction also emerging. With no intervention, the mean age of life is approximately 19 years. The management of the inflammation associated with DMD is currently via the use of corticosteroids, which have insufficient efficacy and significant side effects.

1. Pinto-Mariz et al Skeletal Muscle 2015(5:45).

Antisense Therapeutics Ltd

ATL1102 for Duchenne Muscular Dystrophy (DMD)

Scientific Backgrounder

June 2017

Duchenne Muscular Dystrophy and ATL1102

- Duchenne Muscular Dystrophy (DMD) is a genetic muscular disease caused by loss of dystrophin, with progressive muscle wasting and associated muscle injury leading to inflammation and fibrosis
- DMD is X-linked and affects boys with an incidence of ~1 in 3,500 and prevalence of ~44,000 in US & EU
- Corticosteroids are used to treat the muscle inflammation in DMD but have insufficient efficacy and significant side effects
- Dystrophin restoration treatments have recently been approved
  - *Eteplirsen (From Sarepta) for the 13% of DMD children amenable to Exon 51 skipping*
  - *Ataluren to read through stop codon mutations in the dystrophin gene*
- Improved anti-inflammatory therapies with dystrophin restoration treatment strategies are needed to reduce immune-mediated pathology so as to ameliorate DMD severity and delay disease progression
- DMD patients with higher levels of CD49d (α chain of VLA-4) expression on circulating T cells have both more severe and rapid progression of disease in DMD patients[1]
  - *VLA-4 role in immune cell transmigration, maturation, survival, activation & extracellular matrix adhesion*
- ATL1102 is a highly active immunomodulatory antisense drug to human CD49d RNA which has completed a successful Phase IIa trial in Multiple Sclerosis (MS) patients[2]
  - *90% reduction in MS brain lesions vs placebo after only 8 weeks of dosing: generally well tolerated*
  - *Reduced CD49d on T and B cells, and reduced T and B cell numbers by ~25-50% respectively in blood of MS patients*

1. Pinto-Mariz et al Skeletal Muscle 2015(5:45).
2. Limmroth V et al Neurology 2014, 83; 1-9

ATL1102 for DMD - Project Status

- ATL1102's extensive pre-clinical and clinical experience to support clinical development in DMD patients
- GMP manufacturing of ATL1102 drug substance (DS) is complete and DS has been formulated into drug product for use in clinical trials
- An international group of experts in myology, paediatric immunology and DMD treatment have been assembled to support clinical development efforts
- Antisense Therapeutics plans to conduct a trial in DMD patients at the Royal Childrens Hospital, Melbourne
- Funding secured for trial subject to approval to conduct the study

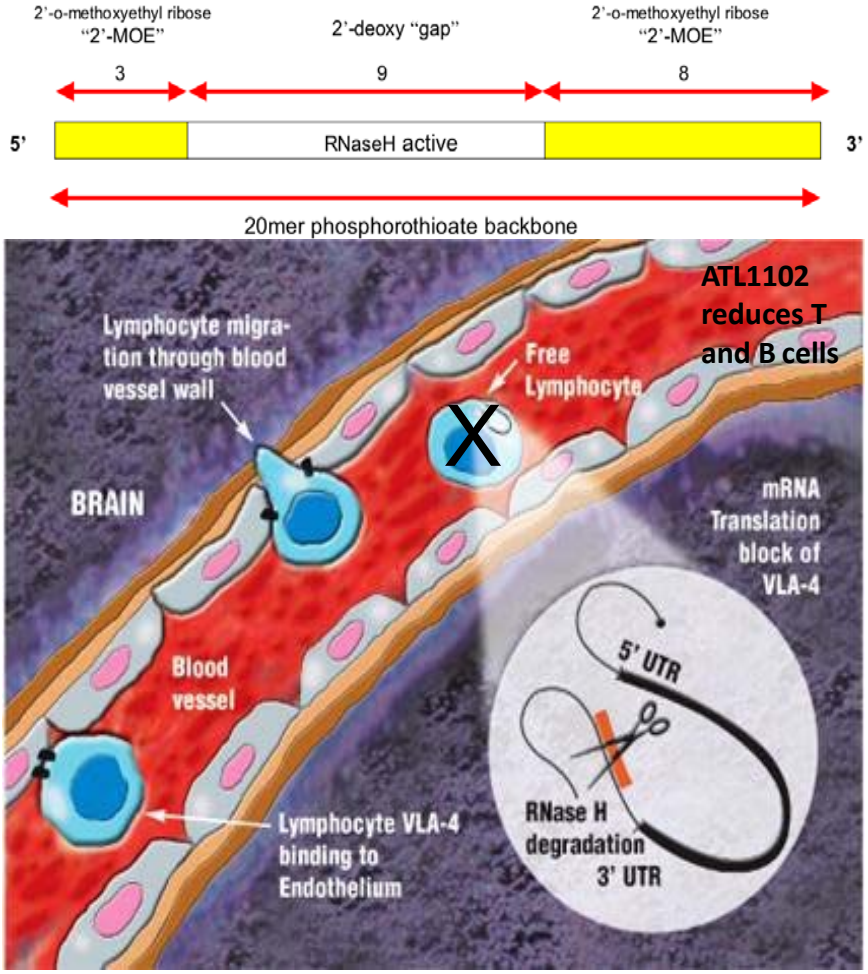
Value Creation Potential

- DMD market is growing at over 160% per annum - one of the fastest growth rates globally
- The market for therapeutic treatments for DMD is forecast to be US$1Billion by 2019, driven by the FDA regulatory approval in September 2016 of Exondys 51 (Eteplirsen) an **antisense drug** for DMD by Sarepta Therapeutics Inc.
  - *Prior to the approval of Exondys 51, Sarepta had a market capitalisation of ~USD$60m (July 2012)*
  - *Following FDA approval of Exondys 51 in September 2016 (based on data from a trial in 12 DMD patients), Sarepta's market capitalisation peaked at US$3.3Billion, representing a 55x increase in value in just over 4 years*
  - *Mr William Goolsbee, ex Chairman of Sarepta, is a non-executive director of ANP*
  - *Exondys 51 inventor, Prof Steve Wilton, a member of the ANP scientific ad board*
- Exondys 51 is the first FDA approved treatment for DMD however is useful in only 13% of boys with exon 51 mutation
- Cost per patient of Exondys 51 is US$300,000/year

All DMD patients experience inflammation and so present as a potential market for ATL1102 treatment

ATL1102: Drug, Target and Activity Overview

- ATL1102 is a 2'MOE gapmer antisense oligonucleotide drug to integrin α_4 RNA (CD49d subunit of VLA-4), an adhesion molecule expressed on most human leukocytes
- In MS patients, ATL1102:
  - reduced VLA-4 on T cells in vitro, & ~10% T&B cells in the blood of MS patients
  - interferes with T-cell adhesion in vitro
  - in MS patients blood reduced T&B cell numbers ~25 &50% respectively potentially by reducing VLA-4 dependent leukocyte, activation, maturation and survival
  - Reduced brain lesions in MS patients 90% vs placebo



ATL1102 Phase II trial results in MS published in *Neurology*

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CD49d antisense drug ATL1102 reduces disease activity in patients with relapsing-remitting MS

OPEN

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ABSTRACT

Objective: This study evaluated the efficacy and safety of ATL1102, an antisense oligonucleotide that selectively targets the RNA for human CD49d, the α subunit of very late antigen 4, in patients with relapsing-remitting multiple sclerosis (RRMS).

Methods: In a multicenter, double-blind, placebo-controlled randomized phase II trial, 77 patients with RRMS were treated with 200 mg of ATL1102 subcutaneously injected 3 times in the first week and twice weekly for 7 weeks or placebo and monitored for a further 8 weeks. MRI scans were taken at baseline and weeks 4, 8, 12, and 16. The primary endpoint was the cumulative number of new active lesions (either new gadolinium-enhancing T1 lesions or nonenhancing new or enlarging T2 lesions) at weeks 4, 8, and 12.

Results: A total of 72 patients completed the study and 74 intention-to-treat patients were assessed. ATL1102 significantly reduced the cumulative number of new active lesions by 54.4% compared to placebo (mean 3.0 [SD 6.12] vs 6.2 [9.89], $p = 0.01$). The cumulative number of new gadolinium-enhancing T1 lesions was reduced by 67.9% compared to placebo ($p = 0.002$). Treatment-emergent adverse events included mild to moderate injection site erythema and decrease in platelet counts that returned to within the normal range after dosing.

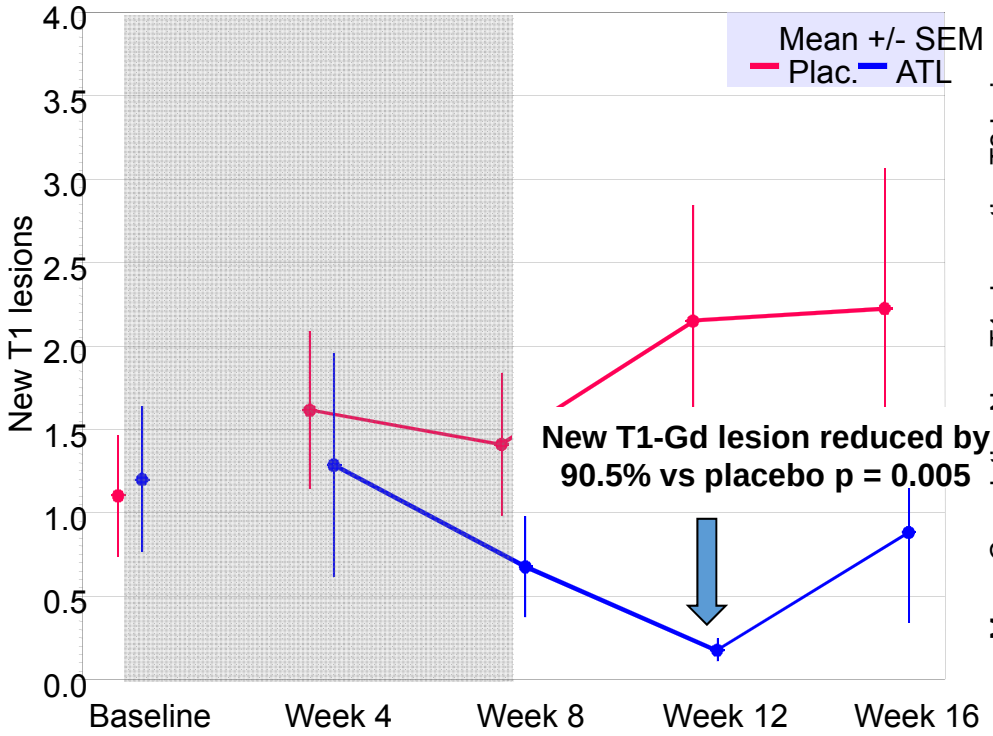
Conclusions: In patients with RRMS, ATL1102 significantly reduced disease activity after 8 weeks of treatment and was generally well-tolerated. This trial provides evidence for the first time that antisense oligonucleotides may be used as a therapeutic approach in neuroimmunologic disorders.

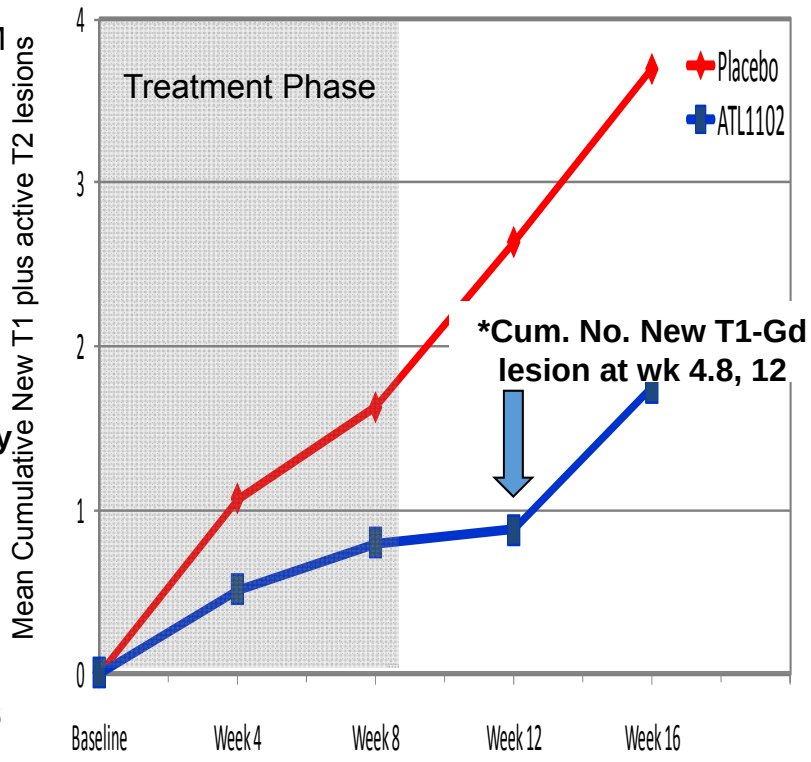
Classification: This study provides Class I evidence that for patients with RRMS, the antisense oligonucleotide ATL1102 reduces the number of new active head MRI lesions. *Neurology*® 2014;83:1–9

ATL1102 outcomes in MS clinically validate and support development of ATL1102 in DMD

ATL1102 Phase II MS trial: New T1-Gd MS lesions reduced by 90% at week 12

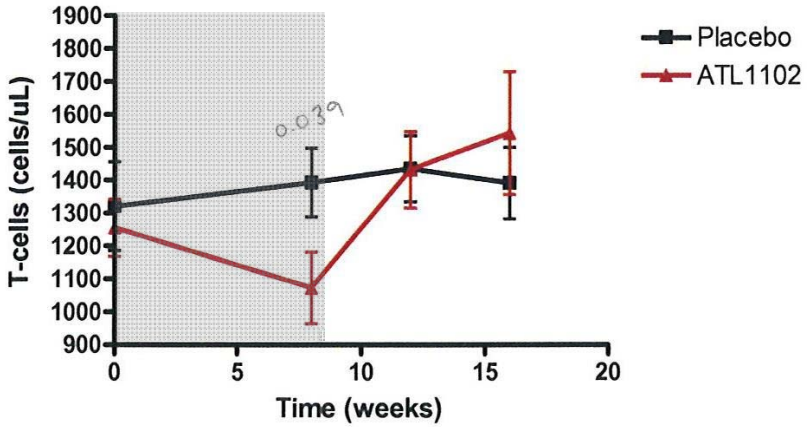
ATL1102 reduced Cum. No. New T1-Gd Lesions at weeks 4,8,12 by 67.9%, p = 0.002 *





ATL1102 Phase II: Blood Leukocyte Observations

- Leucocyte reductions were observed in patients treated with ATL1102 versus placebo at the end of treatment (week 8):
  - *CD3+ T-Lymphocytes:*
    - ➢ *CD4+ T cells: 26% (p<0.05)*
    - ➢ *CD8+ T cells: 23% (p<0.05)*
  - *CD19+ B-Lymphocytes: 53% (p<0.0005)*
    - ➢ *HLA-DR+ B-cells: 41%(p<0.05)*
  - Granulocytes: 43% (p<0.0005)

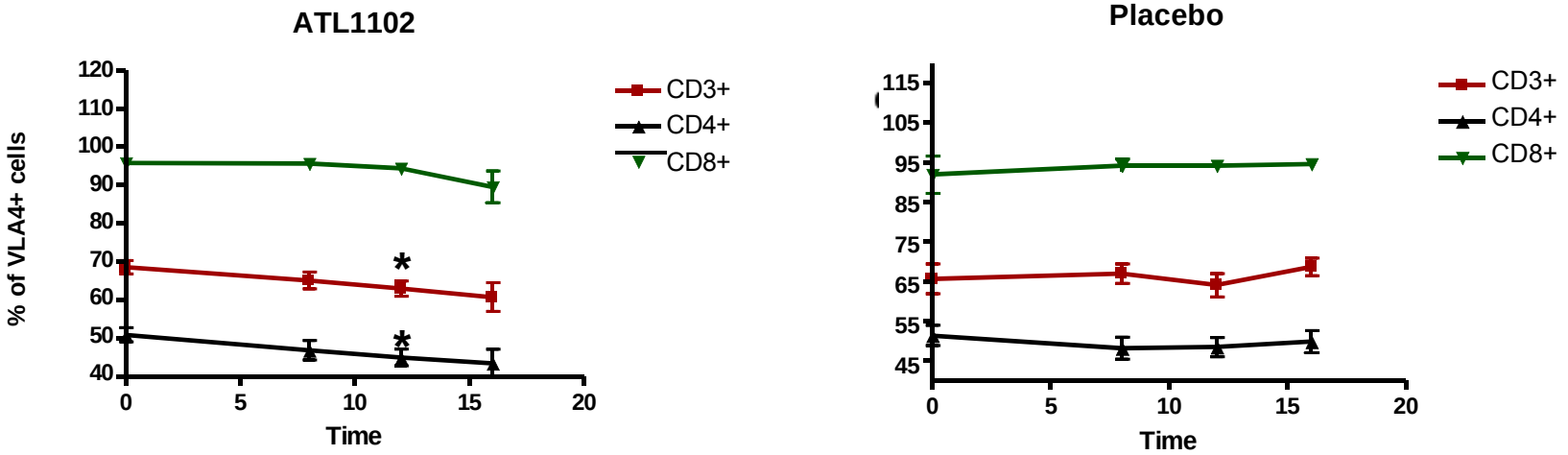


  - Monocyte and NK lymphocyte numbers were not significantly affected at week 8
  - ~25% lymphocyte reductions at 4 and 8 weeks vs baseline were observed by hematology
  - Reduction in cell surface VLA-4 noted in a proportion of the T and B cells in the blood, suggest the drug is potentially reducing VLA-4 dependent T and B cell maturation, survival and/or activation and is a possible mechanism for the reductions in T and B cell numbers[1].
  - Reduction in T and B cell and cytokines they secrete is a possible mechanism for the reduction in granulocytes numbers (tbc).

1. Limmroth V et al Neurology 2014, 83; 1-9 Supplement 2

ATL1102 reduced CD49d on T cells in MS patients

% of VLA4+ cells in populations of CD3+, CD4+ or CD8+ T-cells



* P < 0.05 vs baseline

1. Limmroth V et al Neurology 2014, 83; 1-9 Supplement 2

CD49d DMD progression marker published in *Skeletal Muscle*

Pinto-Mariz *et al. Skeletal Muscle* (2015) 5:45
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Skeletal Muscle

RESEARCH Open Access

CD49d is a disease progression biomarker and a potential target for immunotherapy in Duchenne muscular dystrophy

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Abstract

Background: Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene. The immune inflammatory response also contributes to disease progression in DMD patients. In a previous study, we demonstrated higher levels of circulating CD49dhi and CD49ehi T cells in DMD patients compared to healthy control. DMD patients are clinically heterogeneous and the functional defect cannot be correlated with genotype. Therefore, it is important to be able to define reliable noninvasive biomarkers to better define the disease progression at the beginning of clinical trials.

Results: We studied 75 DMD patients at different stages of their disease and observed that increased percentages of circulating $CD4^{+}CD49d^{hi}$ and $CD8^{+}CD49d^{hi}$ T lymphocytes were correlated with both severity and a more rapid progression of the disease. Moreover, $T^{+}CD49d^{+}$ cells were also found in muscular inflammatory infiltrates. Functionally, T cells from severely affected patients exhibited higher transendothelial and fibronectin-driven migratory responses and increased adhesion to myotubes, when compared to control individuals. These responses could be blocked with an anti-CD49d monoclonal antibody.

Conclusion: CD49d can be used as a novel biomarker to stratify DMD patients by predicting disease progression for clinical trials. Moreover, anti-CD49d peptides or antibodies can be used as a therapeutic approach to decrease inflammation-mediated tissue damage in DMD.

DMD patients have a greater number of CD4+ and CD8+ T-cells expressing high levels of CD49d vs healthy children

Table 1 Higher relative numbers of circulating $CD4^+$ and $CD8^+$ T cell subsets expressing high densities of CD49d in patients with Duchenne muscular dystrophy

T cell subpopulation	Relative cell number (mean ± SD)[a]		*p* value
	Healthy	DMD	
$CD4^+CD49a^{hi}$	3.66 ± 2.80	4.34 ± 3.18	0.75
$CD8^+CD49a^{hi}$	3.81 ± 3.25	4.02 ± 3.66	0.93
$CD4^+CD49d^{hi}$	23.25 ± 5.86	*29.72 ± 8.66*	*0.007*
$CD8^+CD49d^{hi}$	26.28 ± 5.89	*34.66 ± 12.00*	*0.009*
$CD4^+CD49e^{hi}$	34.95 ± 9.28	34.97 ± 7.70	0.87
$CD8^+CD49e^{hi}$	31.10 ± 8.17	34.04 ± 13.42	0.46
$CD4^+CD49f^{hi}$	30.53 ± 7.60	27.85 ± 9.37	0.36
$CD8^+CD49f^{hi}$	18.73 ± 5.37	18.34 ± 7.75	0.65
$CD4^+CD11a^{hi}$	22.71 ± 14.23	19.30 ± 12.80	0.60
$CD8^+CD11a^{hi}$	38.31 ± 11.39	44.64 ± 11.30	0.33

[a]Data are presented as relative cell numbers of T cell subsets expressing high levels of a given integrin subunit. Numbers in italics illustrate statistically significant differences between normal subjects and Duchenne muscular dystrophy (DMD) patients, with corresponding *p* values

DMD patients have a similar number of CD4+T and CD8+T cells as healthy volunteers

DMD patients had ~22% more CD49dhi CD4+T and ~25% more CD49dhi CD8+T than healthy volunteers

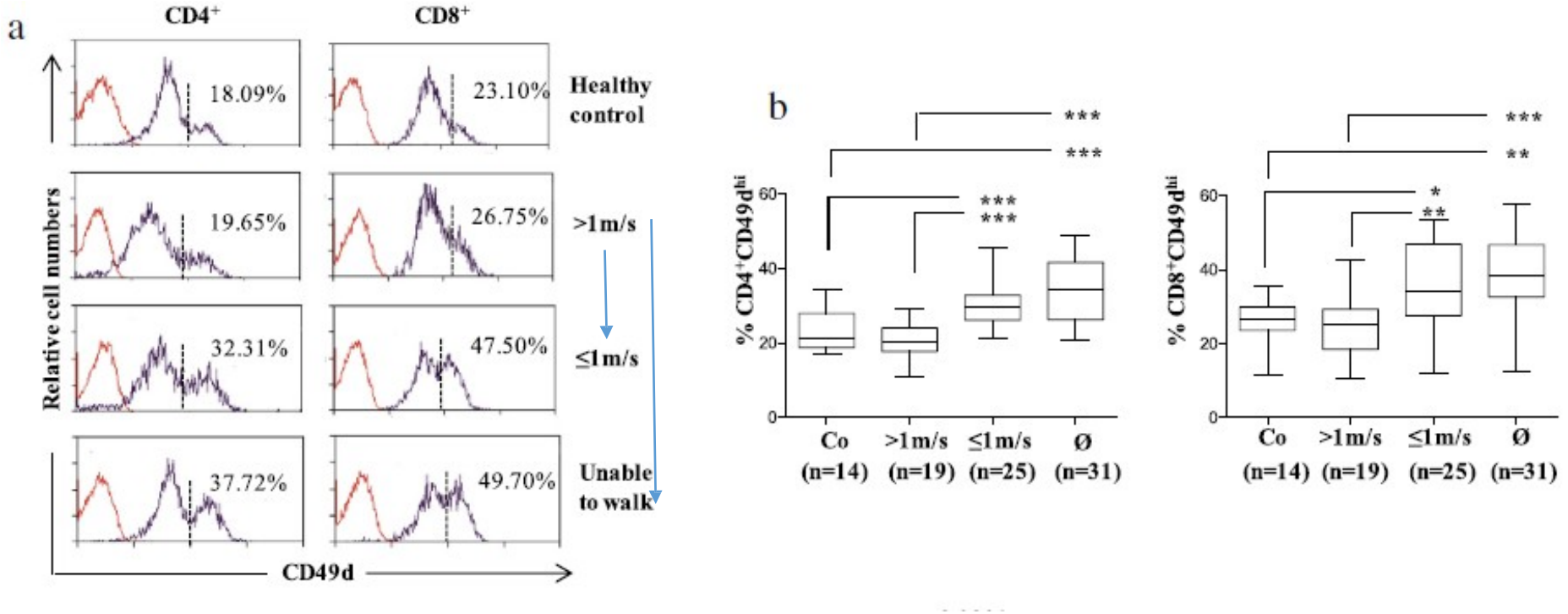
DMD patient population in this study comprised both ambulant and non ambulant

- *N=31 unable to walk*
- *N=25 walking <10m/10s*
- *N=19 walking >10m/10s*

Pinto-Mariz et al Skeletal Muscle 2015(5:45).

Slower walking (and non ambulant) DMD patients have more CD49dhi expressing T-cells vs faster walking patients

- DMD patients who walked slower than <1m/s (and non ambulant patients) have ~40% and ~43% greater number of CD4 and CD8 T-cells expressing high levels of CD49d vs faster ambulant patients walking >1m/s



Dashed bar defines high vs low CD49d expression, and red curves are negative control antibodies

Pinto-Mariz et al Skeletal Muscle 2015(5:45). Fig 1a and b

Corticosteroid therapy does not affect the number of hi CD49d+ expressing T cells

- Corticosteroid (CS) treatment is the current standard of care for DMD patients
  - *Includes Prednisolone, and Deflazacort*
  - *Improves muscle strength and function*
  - *Slows the progression of muscle weakness*
  - *Prolongs ambulation*
  - *Delays the onset of cardiac and respiratory problems,* ***<u>however,</u>***
  - *Has adverse effects e.g. weight gain, reduced bone density, and reduce growth and thus treatments that are CS sparing are required*
- CS treatment did not modulate CD49d expression on T cells in MS[1]
- **Ambulant DMD patients were on CS[1] suggesting CS do not reduce the CD49dhi expressing T cell**

1. Pinto-Mariz et al Skeletal Muscle 2015(5:45).

DMD and hiCD49d T cell: Overview

- DMD is an X linked muscular-inflammatory disease characterized by rapidly progressive muscle wasting from loss of dystrophin, associated muscle injury and inflammation which leads to fibrosis, muscle weakness with respiratory and cardiac complications, and loss of ambulation
- DMD patients with high levels of CD49d expression on a greater number of circulating T cells have poor prognosis with more severe and quicker disability progression with loss of ambulation
- In the Pinto-Mariz 2015 publication, 57% of 44 patients who were ambulant had hiCD49d T cells
- DMD patients have 22-25% more high expressing T cells than healthy children and patients who cant walk or have slower ambulation walking <1m/sec have 40-47% more high expressing CD49d+ CD4+ and CD8+ T cells, compared to patients with better ambulation walking >1m/sec
- 100% of DMD sufferers with > ~ one third CD4+ and > ~half CD8+ T cells with high CD49d lost ambulation by the age of 10 compared to average loss of ambulation at ~12yrs of age
- DMD patients unable to walk by 10 years of age had 14-33% more high expressing CD49d+ CD4+ and CD8+T cells vs boys who lose their ambulation after 10 years of age (data not shown)
- Ambulant patients treated with steroids were included in the studies, suggesting steroids do not reduce the CD49d high expressing T cells sufficiently

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