Presentation at 10th Neurotech Investing and Partnering Conference

Innate Immunotherapeutics Limited (ASX: IIL) CEO Simon Wilkinson presented at the 10th Neurotech Investing and Partnering Conference at Hotel Nikko in San Francisco on the 8th April. Mr Wilkinson presented on the Company’s innovative approach on treating Secondary Progressive Multiple Sclerosis from his presentation entitled “New Strategies in Multiple Sclerosis”.

The Neurotech Investing and Partnering Conference is the premier partnering and investing conference for the neurotechnology industry including pharmaceuticals, medical devices, software and diagnostics for the brain and nervous system. It is a global forum where investors, executives, entrepreneurs, scientists and others involved in the development of new treatments and diagnostics for the brain and nervous system.

The Company is pleased to have received an invitation to speak at this premier event alongside other cutting edge company presentations in neurotechnology.

A copy of the presentation is attached.

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About Multiple Sclerosis (MS)
Multiple Sclerosis (MS) is a chronic disease of the central nervous system, where the body’s immune system attacks the myelin sheath surrounding the nerve fibres. The damaged myelin disrupts the communication mechanism of parts of the central nervous system. This results in a wide range of symptoms, which may include loss of balance and muscle coordination, difficulty walking, slurred speech, tremors, stiffness, cognitive impairment, depression, fatigue and bladder problems.

There are two main forms of MS, an early ‘relapsing-remitting’ stage of disease and, a later, more disabling ‘secondary-progressive’ stage of disease. Worldwide, 30% of all MS sufferers have SPMS and there are currently no approved disease modifying drugs for the safe and effective, ongoing treatment of this highly disabling form of the disease.

About MIS416
The microparticle, MIS416, is a biologically derived novel immune modulator which can uniquely target both the regulatory and defensive functions of the innate immune system. MIS416 targets myeloid cells, a sub-set of innate immune cells not currently targeted by any other drugs in development for the treatment of SPMS.

Myeloid cells have only recently been recognised as a significant potential therapeutic target in SPMS. Myeloid cells have the capacity to remodel the deregulated immune activity which is an important part of the disease process in SPMS. These same cells, remodelled in the correct fashion, can also promote neuro repair pathways critical to slowing or reversing disability in SPMS.

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New Strategies in **Progressive** MS

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Simon Wilkinson, CEO
Multiple Sclerosis: Autoimmune or Neurodegenerative?

- Until recently most market discussions about multiple sclerosis have focused on the early stage relapsing-remitting course of the disease.
- RRMS exacerbations are largely mediated by auto-reactive pro-inflammatory adaptive immune cells crossing the blood brain barrier and attacking the myelin sheath – an autoimmune ‘process’ or ‘disease’.
- In spite of drugs designed to block, or sequester, or divert such autoimmune activity, within 20 years ~70% of RRMS patients transition to a progressive stage of disease where deficits steadily accumulate in the absence of relapses and existing RRMS drugs become ineffective.
- This progressive stage of MS is now largely viewed as a neurodegenerative disorder (some argue RRMS is neurodegenerative with a BIG AI side effect\(^1\))
- The putative role of myeloid derived innate immune cells in neurodegenerative disorders is well described. It is also now recognised that both macrophages and microglia can also play vital roles limiting inflammation & promoting tissue repair in CNS disorders including progressive MS.

Myeloid cells play an important role in CNS disorders

- Such myeloid cell plasticity is essential so that an immune response can adapt according to the stage, severity, location, & type of disease/disorder.

- Peripheral macrophages, and the CNS equivalent microglia, can be activated or polarised towards either a “M1” (‘classically activated’) inflammatory phenotype or a “M2” (‘alternatively activated’) anti-inflammatory phenotype.

- In addition to being anti-inflammatory within the CNS, M2 macrophages and microglia have been shown to:
  - support myelin repair by clearing myelin debris\(^1\).
  - secrete important tropic factors that can directly promote neuronal survival and axon regeneration\(^2,3,4\).

Myeloid cells are now an important target in progressive MS

Gandhi, Laroni, and Weiner conclude in their 2010 paper that:

“Until now, there are no specific therapies to target innate immune cells in MS. As the role of the innate immune system in MS becomes better defined, it will be possible to design therapy to transform immuno-pathogenic innate immune cells to a more immuno-regulatory innate immune cells.”
Introducing MIS416 – a MYELOID directed immune modulator

- Derived from gram positive (LPS negative) *P. acnes* bacteria
- Retains naturally occurring bacterial ligands for TLR9 and NOD2 pathogen recognition receptors
  - peptidoglycan-associated muramyl dipeptide is a natural NOD-2 ligand
  - bacterial nucleic acid is a natural TLR9 ligand
- Unwanted pro-inflammatory ligands that target cell surface TLRs and antigens are removed
- Microparticle size means that only myeloid cells take up MIS416 by phagocytosis
- MIS416 is functionally inert until biodegraded inside the target cell
- Formulated to 0.2 mg/mL suspension in saline for i.v. dosing at 500 mcg with potential for oral formulation for ‘maintenance’ dosing
MIS416 effect on cellular and soluble anti-inflammatory pathways

- **Pro-inflammatory mechanisms**
  - IL-12p70
  - IL-1b
  - TNFa
  - MHC I/II
  - CD80/86
  - NO

- **Anti-inflammatory/tolerance mechanisms**
  - IL-10
  - TGFb
  - IL-27
  - sTNFR
  - sIL-1R
  - PDL-1
  - ? Arginase
  - ? IDO

- **Bone marrow-derived monocyte**
- **Alternate/non classical/M2 macrophage**
- **Tolerogenic DC**

Upregulation following MIS416 treatment:
- ↑ in Mouse
- ↑ in Human
- ? under investigation
A selection of phase 1B and 2A patient plasma samples were analysed to screen for the induction of factors associated with neuroprotection.

Data are shown from examples that showed a clear response for a given factor. Samples are assigned arbitrary sample numbers.
Peripheral leucocytes (CD45\textsuperscript{Hi}) are naturally present in the CNS. MIS416 treatment enhances the proportion of monocytic myeloid cells (CD11b\textsuperscript{+}F4/80\textsuperscript{+}) associated with regulatory activities (Gr-1\textsuperscript{-}).
MIS416 clinical development programme

- Completed open-label Phase 1B and Phase 2A demonstrated acceptable safety and tolerability profile. Most common AEs were fever, chills, headaches, muscle weakness – all transient and self limiting.

- On completion of 2A study, **80% of subjects showed at least 30% improvement** in at least 1 measure of MS clinical status
  - Both studies conducted with financial support from the US National MS Society (US$550k) and the NZ Government (NZ$600k).

- Phase 2B 12 month double blinded placebo controlled efficacy study currently enrolling up to 90 patients in Australia & New Zealand.
  - Endpoints include clinical measures of neuromuscular function & disability, fatigue, cognition, visual acuity, MRI (whole brain atrophy and MTR), and patient reported outcomes.
  - Target completion mid 2016 and reporting late 2016. Data sharing with MS Outcome Assessment Consortium (MSOAC).
NZ based compassionate use programme

- Under an ongoing New Zealand based ‘Compassionate Use” programme, 19 patient with SPMS have received an average of 76 doses [10-152] over a median treatment period of 30 months [4-77]
- Long term ongoing treatment with MIS416 has shown no evidence of haematologic, hepatic, or renal toxicity in treated patients
- 82% of these patients have reported significant and sustained improvement in their MS related disabilities and/or health related quality of life

“MIS416 certainly appears beneficial to MS patients, although it remains to be seen if it is curative. However, I would certainly recommend MIS416 as I have seen significant improvement in the motor skills and general wellbeing of my current MS patients.”

(Christchurch physician currently treating ten SPMS patients as part of the NZ compassionate use programme)
Acknowledgements

- **Phase 2B Trial Advisory Board:** Dr Jeffrey Cohen and Deborah Miller, PhD (Cleveland Clinic); Dr Doug Arnold (McGill University); Gary Cutter, PhD (UAB School of Public Health); Kristy Rose, PhD (Westmead, Sydney)

- **Principal Medical Consultant:** Dr Michael Silverman (Biostrategies, Boston)

- **Academic Collaborators including:** Dr Larry Steinman (Stanford); Dr Amit Bar-Or (McGill University); Anne La Flamme, PhD (Victoria University, Wellington, NZ); Dr David Brown, (St Vincent’s, Sydney); David Booth, PhD, (Westmead, Sydney)


- **Chief Scientific Officer:** Gill Webster, PhD (Auckland, NZ)
Thank you

Two clinical trial patients talk about their ongoing experience with MIS416: http://youtube/YsH579wcqd0

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Australian Securities Exchange (ASX) ticker - IIL