Study Validating MoA of Intranasal Foralumab in Alzheimer's Disease Published in the Prestigious Journal PNAS, Following FDA IND Clearance

- **The authors conclude that "nasal anti-CD3 has the potential to be a non-toxic novel immunotherapeutic approach for the treatment of Alzheimer's disease (AD)"**
- **FDA has cleared the IND for intranasal foralumab, a fully human anti-CD3 monoclonal antibody, for human study in mild to moderate Alzheimer's Disease**
- **The publication shows anti-CD3 monoclonal antibody (mAb) administered intranasally, ameliorates disease in a 3xTg model of Alzheimer's disease by targeting microglial activation in the brain, while expanding regulatory T cells in the periphery**
- **Remarkably, this reduced microglial activation and improved cognition occurs independent of amyloid beta disposition.**

NEW YORK, September 6, 2023 -- Tiziana Life Sciences Ltd. (Nasdaq: TLSA) ("Tiziana" or the "Company"), a biotechnology company developing breakthrough immunomodulation therapies via novel routes of drug delivery, today announced acceptance of a publication, "Nasal Administration of anti-CD3 monoclonal antibody (mAb) ameliorates disease in a mouse model of Alzheimer's disease", in the preeminent[1] journal, *Proceedings of the National Academy of Sciences* (PNAS), that supports foralumab's mechanism as a potential treatment for Alzheimer's disease (AD), a difficult-to-treat neuroinflammatory disease.[2] This is the second publication pertaining to intranasal administration of anti-CD3 monoclonal antibody this year to be published in PNAS.[3]

This study shows that intranasal anti-CD3 ameliorates disease in a rodent model of AD by targeting microglial activation in the brain and brain gene expression independent of affecting amyloid beta deposition. These studies identify a novel approach to treat Alzheimer's disease.

[1] https://www.pnas.org/about/article-journal-metrics
[2] https://www.pnas.org/doi/10.1073/pnas.2309221120
[3] https://www.pnas.org/doi/10.1073/pnas.2220272120

The publication can be found at : https://www.pnas.org/doi/10.1073/pnas.2309221120

Howard L. Weiner, M.D., a Robert L. Kroc Professor of Neurology at the Harvard Medical School, Director and Founder of the Partners Multiple Sclerosis Center and Co-Director of the Center for Neurologic Diseases at Brigham and Women's Hospital, a founding member of Mass General Brigham Healthcare System and Chairman of Tiziana's Scientific Advisory Board, stated, "I am proud to be the senior author on this seminal publication showing that anti-CD3 mAb mitigates Alzheimer's disease in a rodent model. Remarkably, we found this benefit occurred independent of reduction of amyloid beta plaque in the brain. This finding demonstrates a unique mechanism of action that can now be tested in humans using foralumab, a fully human anti-CD3 mAb, foralumab, in which we modulate microglia by inducing T cells in the periphery that migrate to the brain. This represents a unique approach to treating Alzheimer's disease that could also potentially be employed in combination with anti-amyloid therapy. The neuromodulation of the T cell inflammatory response we observed in the brains of Alzheimer's mice is consistent with multiple sclerosis research we have conducted at the Ann Romney Center and validates our scientific rationale for testing foralumab in Alzheimer's patients after the recent IND clearance by the United States Food and Drug Administration."

"We've now have had two seminal publications in the esteemed journal *PNAS* related to novel and significant research on intranasal anti-CD3. It has been established through both publications that intranasal anti-CD3 positively modulates the immune system allowing Tiziana to explore foralumab in multiple neuro-inflammatory disease indications in addition to our ongoing research in non-active secondary progressive multiple sclerosis. We believe this scientific publication, along with the groundbreaking research continuously being conducted by our partners at Brigham and Women's Hospital led by Dr. Weiner, greatly increases the utilization potential of our foralumab portfolio," commented Gabriele Cerrone, Executive Chairman, founder and acting Chief Executive Officer of Tiziana.

Study Rationale

Alzheimer's disease is a neurodegenerative disease characterized by amyloid beta (Aβ) plaques, neurofibrillary tangles, and microglial activation. Neuroinflammation is a major component of AD. Microglia are the primary immune cells of the brain that help both maintain homeostasis and react to injury. Studies showing activated microglia and astrocytes surrounding Aβ plaques suggest significant involvement of inflammatory pathways in Alzheimer's disease. Therapies targeting Aβ have shown positive effects in subjects with AD. Nasal anti-CD3 has been shown to treat animals with a progressive form of experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis, by inducing regulatory T cells that dampen microglial inflammation in the brain.

Study Design

In this study, mice were treated three times a week with intranasal anti-CD3 for five months and compared against isotype control or saline. In the treated mice, the study found modulation of the activated microglia phenotype, changes in gene expression patterns in the brain and improved cognition, which all occurred independent of affecting amyloid beta deposition. Modulation of activated microglia was measured in treated mice by sorting the microglia using microglia-specific markers and performing a gene expression analysis using the Nanostring mouse myeloid panel and comparing treated mice versus control. Changes in gene expression were measured in the cortex and hippocampus. Cognition was measured including spatial learning and long- and short-term memories as assessed by the Morris water maze and the novel arm Y-maze behavioral test. Amyloid beta accumulation was measured by immunofluorescence in the hippocampus and prefrontal cortex areas of the brain.

About Foralumab

Activated T cells play an important role in the inflammatory process. Foralumab, the only fully human anti-CD3 monoclonal antibody (mAb), binds to the T cell receptor and dampens inflammation by modulating T cell function, thereby suppressing effector features in multiple immune cell subsets, an effect demonstrated in patients with COVID and with multiple sclerosis, as well as in healthy normal subjects. Intranasal foralumab Phase 2 trials are expected to start in Q3 2023 in patients with non-active SPMS immunomodulation by nasal anti-CD3 mAb represents a novel avenue for treatment of inflammatory human diseases that affects the brain and other organs.[2,3]

About Tiziana Life Sciences

Tiziana Life Sciences is a clinical-stage biopharmaceutical company developing breakthrough therapies using transformational drug delivery technologies to enable alternative routes of immunotherapy. Tiziana's innovative nasal, oral and inhalation approaches in development have the potential to provide an improvement in efficacy as well as safety and tolerability compared to intravenous (IV) delivery. Tiziana's lead candidate, intranasal foralumab, the only fully human anti-CD3 mAb, has demonstrated a favorable safety profile and clinical response in patients in studies to date. Tiziana's technology for alternative routes of immunotherapy has been patented with several applications pending and is expected to allow for broad pipeline applications.

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