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The NIMML Institute and NImmune Biopharma Announce Publication of New Mechanistic Insights on the Immunometabolic Control of Systemic Lupus Erythematosus in the Journal of Immunology

NIM-1324 validated as the first LANCL2 drug with therapeutic efficacy in systemic inflammation in three mouse models of lupus to support immune tolerance

A mechanism of LANCL2 newly discovered in phagocytes that combines with established functions in Tregs reduces nuclear antigen reactivity, autoantibody protection, and kidney histopathological scores in SLE

Immune responses to LANCL2 activation translate to SLE patient peripheral blood mononuclear cells, further de-risking continued clinical development of NIM-1324 in lupus

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BLACKSBURG, Va.--(BUSINESS WIRE)--**The NIMML Institute,** ("NIMML"), a 501 (c)(3) nonprofit research institute dedicated to the discovery of novel precision medicines for infectious and autoimmune diseases, today announced the publication of a seminal article that reports the mechanisms of therapeutic efficacy of NIM-1324, an orally administered LANCL2 agonist, in ameliorating the severity of Systemic Lupus Erythematosus (SLE) and addressing the unmet clinical needs of SLE patients. These novel mechanistic findings were published in the Journal of Immunology.

As part of a precision medicine research collaboration with NIMML, NImmune Biopharma ("NImmune"), a Phase 3 precision inflammation and immunology (I&I) biopharmaceutical company focused on the discovery and development of first-in-class and best-in-class biomarker-driven I&I therapeutics, leveraged NIMML's A.I.-powered TITAN-X precision medicine platform to develop NIM-1324 as a next-generation precision medicine.

"While the effects of LANCL2 on CD4+ T cell differentiation and function have been characterized in other autoimmune diseases such as IBD, this paper describes for the first time an additional LANCL2 mechanism with direct effects on phagocytes," said Dr. Josep Bassaganya-Riera, Founding Director of NIMML and NImmune CEO. "This study provides molecular evidence *in vivo* and validation for the LANCL2 pathway in the context of SLE. The consistent immunological changes observed across three SLE models validate the LANCL2 pathway as a druggable target for therapeutic intervention in inflammatory and autoimmune diseases and demonstrate that NIM-1324 effectively engages the LANCL2 pathway to provide optimal therapeutic efficacy in SLE. Accordingly, NIM-1324 is a prime candidate for a first-in-class oral therapeutic in the treatment of SLE due to its substantial potential for addressing the underlying immunometabolic alterations of SLE and significantly improving patient outcomes at a potentially very distinct cost advantage of a once daily oral over current and in-development SLE therapies."

The study characterized the importance of LANCL2 in SLE by using loss-of-function studies in vivo and evaluated the therapeutic efficacy of NIM-1324 in murine models of SLE, including NZB/W, MRL/lpr, and bm12 adoptive transfer models. The LANCL2 pathway has been implicated in modulating immune responses and inflammation, providing protection from SLE dysregulation of the immune system, particularly aberrant activation of B cells and T cells which contribute to the disease's pathogenesis. Therefore, as a key receptor involved in immunoregulation, LANCL2 is an attractive target for

therapeutic intervention in SLE. The paper's findings provide new mechanistic insights, validate the critical importance of LANCL2 in mouse models of SLE, and underscore the potential of NIM-1324 as a novel therapeutic agent for addressing the unmet clinical needs of SLE patients.

Immunological studies on the role of LANCL2 in IBD elucidated a new immunometabolic mechanism by which pharmacological activation of LANCL2 by omilancor enhances Treg function while decreasing excessive effector immune responses such as Th1 and Th17. LANCL2 activation enhances the anti-inflammatory functions of Treg cells by amplifying IL-2 signaling and promoting T cell metabolic reprogramming resulting in enhanced mitochondrial metabolism. Omilancor is an oral first-in-class, once-daily, gut-restricted LANCL2 therapeutic in late-stage clinical development for ulcerative colitis (UC) and Crohn's disease. In a phase 2, proof-of-concept, double-blind, randomized, placebo-controlled trial, oral omilancor induced clinical remission in 30.4% of patients with active UC (78% with baseline Mayo endoscopic subscore [MES] of 3) relative to 3.7% of the placebo arm ($\Delta = 26.7$, $P = 0.01$). While omilancor acts locally activating LANCL2 in the gastrointestinal tract, NIM-1324 is highly systemically distributed reaching a wide range of inflamed organs and tissues in inflammatory and autoimmune disease patients.

About NIM-1324

NIM-1324 is an oral, systemically distributed, small-molecule therapeutic candidate which activates LANCL2, a surface membrane-associated receptor that is responsible for modulating key cellular and molecular changes tied to autoimmune diseases. By activating the LANCL2 pathway, NIM-1324 increases the anti-inflammatory capacity and stability of regulatory CD4+ T cells while also supporting the metabolic demands of autophagy in phagocytes. To date, treatment with NIM-1324 has reduced the production of interferon alpha in human peripheral blood mononuclear cells (PBMCs) from systemic lupus erythematosus (SLE) patients and provided protection from clinical disease and tissue pathology in mouse models of lupus, rheumatoid arthritis, and multiple sclerosis. Phase 2-ready NIM-1324 completed Phase 1 clinical testing where it met all endpoints and demonstrated a dose proportional change in plasma exposure within the therapeutic range with no accumulation.

About Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune disorder that causes systemic inflammation and organ damage. SLE can affect the skin, joints, blood vessels, kidneys, lungs, brain, and heart, resulting in fatigue, skin rashes or lesions, fevers, arthritis, lung, heart and kidney damage, seizures, and psychosis. SLE symptomatology often results in low quality of life, and 17% of SLE patients will need a kidney transplant. SLE affects over 1.5 million patients in the United States and over 5 million patients worldwide. With more than half of patients experiencing at least one flare per year or presenting persistently active disease, there is an unmet medical need in SLE for the development of safer and more effective therapeutics.

About the TITAN-X Platform

The TITAN-X Precision Medicine Platform combines A.I. methodologies, bioinformatics, and advanced computational modeling to accelerate the development of precision medicines to address the unmet clinical needs of patients with autoimmune diseases. Building upon NIMML's expertise in engineering large-scale computational models to study immunity as a massively and dynamically interacting system, the TITAN-X Platform integrates each step from new target discovery to enabling biomarker-driven precision clinical drug development. Following bioinformatic analysis of differentially expressed genes from patient biopsy specimens, the TITAN-X Platform can identify transcriptional predictive signatures by using its advanced A.I. algorithms. By analyzing gene expression patterns and integrating clinical data, the TITAN-X Platform can identify responder patterns, facilitating precision medicine approaches for drug development. This ensures that patients receive therapies that are most likely to benefit them according to their unique genetic signatures and clinical profiles, and that are tailored to maximize efficacy, safety, tolerability and minimize adverse side effects. The TITAN-X platform has shaped the development of omilancor, NX-13 (acquired by Abbvie in March 2024 and now called ABBV-113), NIM-1324 and multiple additional novel MoA targets for I&I indications.

About NIMML

The NIMML Institute is a 501 (c) (3) non-profit foundation focused on applying transdisciplinary, team-science approaches to precision medicine. The NIMML Institute applies its TITAN-X advanced A.I.-powered platform to large-scale transdisciplinary projects aimed at solving important public health problems through precision medicine. NIMML combines

the expertise of immunologists, computational biologists, toxicologists, computational modelers, translational and clinical researchers, and molecular biologists to translate novel scientific discoveries into medicines for human diseases. The Institute is headquartered in Blacksburg, VA. For more information, please visit www.nimml.org or contact pio@nimml.org.

About NImmune Biopharma

NImmune is a late-stage precision inflammation and immunology (I&I) biopharmaceutical company that develops novel best-in-class biomarker-driven immunoregulatory therapeutics. Underpinned by a discovery platform that utilizes advanced computational modeling, A.I. and bioinformatics coupled with biomedical research capabilities to pioneer innovation in immunoregulatory drug development, NImmune's business model enables the rapid and capital-efficient clinical development of high conviction drug candidates into New Drug Application (NDA) filing and commercialization. The lead product candidate from NImmune's discovery platform is omilancor, a wholly-owned oral, once-daily, gut-restricted, first-in-class therapeutic currently in Phase 3 development, which targets LANCL2 for Ulcerative Colitis and Crohn's disease. Phase 2 proof-of-concept data for omilancor show potential best in class efficacy and safety. For more information, please visit www.NIMMUNEBIO.COM or contact media@nimmunebio.com.

Contacts

Media:
Alex Jeffrey/Iain Hughes
Gasthalter & Co.
nimml@gasthalter.com
212.257.4170