New study shows multiple inflammasomes combine to cause lupus, macular degeneration and other neuroinflammatory diseases such as Alzheimer's disease and multiple sclerosis

- Research published Friday in *Science Immunology* shows the NLRC4 inflammasome, previously thought to be important only for bacteria recognition, combines with NLRP3 to form a dual inflammasome within the cell, triggering inflammation that causes lupus and macular degeneration.
- Blocking the formation of these inflammasomes is effective in preventing disease in animal models of macular degeneration and reducing the production of disease-causing inflammatory cytokines in the blood of patients with lupus.

Newton, MA (December 6, 2021) – Inflammasome Therapeutics (https://inflam.com), a private company developing therapies for prevalent, degenerative diseases, said today that research published in *Science Immunology* (https://www.science.org/doi/10.1126/sciimmunol.abi4493) "DDX17 is an essential mediator of sterile NLRC4 inflammasome activation by retrotransposon RNAs", uncovers a previously unrecognized mechanism by which NLRC4 combines with NLRP3 to form activated inflammasomes that trigger causes of active disease in macular degeneration and lupus.

The paper, published by a team of scientists led by Dr. Jayakrishna Ambati, Inflammasome Therapeutics' co-founder and the DuPont Guerry, III Professor and Founding Director of the Center for Advanced Vision Science at the University of Virginia, builds upon previously published science and demonstrates that a combination of both NLRP3 and NLRC4 is required to trigger inflammasome-mediated diseases.

"The common belief was that although many inflammasomes were identified, only one of them, NLRP3, was responsible for sterile inflammatory diseases – conditions like Alzheimer's, Multiple Sclerosis and Lupus," said Dr. Paul Ashton, president and CEO of Inflammasome Therapeutics. "Advancing science now shows that things are a little more complicated, and opens up the opportunity to effectively target these diseases."

"Most research in this area has focused on developing selective inhibitors of NLRP3, which have no effect on NLRC4. This work indicates that approach may not be optimal and that inhibition of NLRP3 and NLRC4 may be required for maximal benefit," explained Dr. Ambati.

"This research published Friday, points to the role that the NLRC4 inflammasome plays in lupus and macular degeneration, specifically. We are developing a new class of drugs called Kamuvudines, which effectively inhibit activation of both NLRP3 and NLRC4. We believe that our ability to inhibit both inflammasomes – and the dual inflammasome – is one of the reasons that our preclinical work has been so exciting in this area," said Dr. Ashton.

Kamuvudines have been found to be extremely effective in pre-clinical models of macular degeneration, Parkinson's disease and multiple sclerosis. They are based on nucleoside reverse transcriptase inhibitors, a class of drugs used to treat or prevent HIV and were recently found to be associated with a reduced risk of developing macular degeneration https://www.science.org/doi/10.1126/sciadv.abj3658 & https://www.pnas.org/content/118/6/e2022751118.

“Unfortunately, NRTIs are relatively toxic and can’t be used to treat people with diseases like macular degeneration, multiple sclerosis and lupus. The low toxicity Kamuvudines however can, and we hope to start clinical trials next year.” said Dr Ashton.

Inflammasome Therapeutics (www.inflam.com) was founded by Jayakrishna Ambati, M.D. and Paul Ashton, Ph.D. in 2016 to develop therapies for prevalent, degenerative diseases. The company combines scientific excellence with proven development expertise and works to develop products via a mixture of licensing agreements and internal development. The company currently has collaboration agreements with Boehringer Ingelheim and the Bill & Melinda Gates Foundation.

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