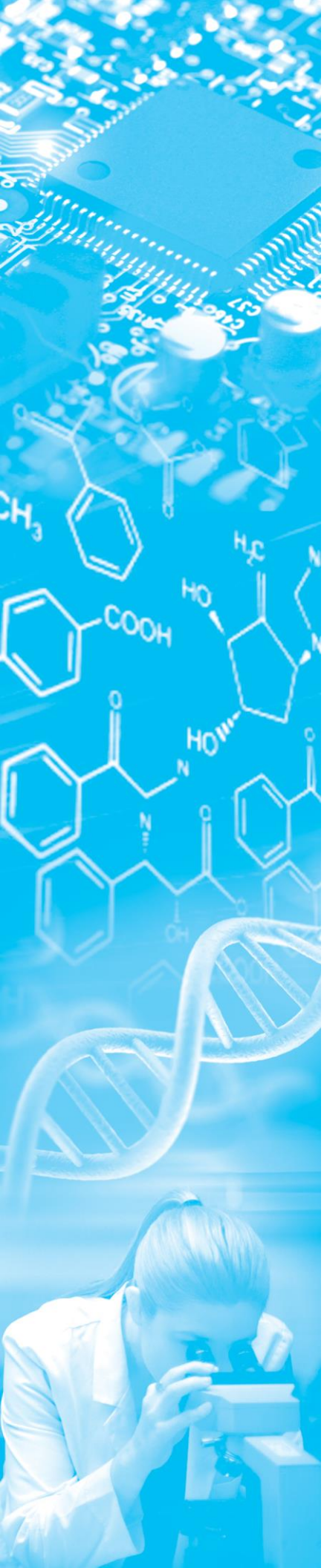

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Method for Treating Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune systemic disease that attacks the synovial tissues within joints and other organs. In the US alone about 1.5 million people are currently living with RA and 71 out of every 100,000 people will be diagnosed with this autoimmune disorder. Although currently there are multiple treatment options for alleviating symptoms, there is no approved cure for RA. Mode of action of currently approved Disease Modifying Anti-Rheumatic Drugs (DMARD) include Janus Kinase (JAK) inhibition, TNF inhibition, T-cell co-stimulation blockade, IL-6 receptor inhibition, B cell depletion, and interleukin 1 inhibition. Some current medications have demonstrated efficacy as per the American College of Rheumatology 70 percent (ACR70) improvement criteria. However, the response rate to treatments has been below 50 percent meaning that more than 50% of patients do not respond to any existing treatments. Therefore, there is an unmet need to develop therapies with better efficacy and improved response rate over currently existing options. Considering this necessity for a more efficient RA therapeutics Dr. Minond focused on developing a RA therapeutic that can inhibit a novel target involved in this disease and produce better outcomes both for responders and non-responders of existing therapies. This effort resulted in screening and identification of a specific inhibitor of A Disintegrin And Metalloprotease 10 (ADAM10). This target, ADAM10, is a cell surface enzyme that sheds various cell surface proteins which play important roles in the progression of cancer, inflammatory diseases, and immune response. As both inflammation and immune response are involved in RA, it makes ADAM10 an ideal target for the treatment of this ailment. This novel technology has the potential to be a first in class therapeutic for RA and possibly a new treatment modality for other diseases whose progression involves immune dysfunction and/or inflammation.

Technology

The lead molecule from this class identified through High Throughput Screening (HTS), has the potential to be ideal selective ADAM10 inhibitor that can address the need for an improved anti-rheumatic drug. The new class of ADAM10 inhibitor described in this invention act through a non-Zn binding mechanism and possibly bind to a location that is outside of an active site (exosite). Owing to its binding to a non-Zn binding site the substrate specificity demonstrated by the lead compound from this class of inhibitors is superior to other currently known ADAM10 inhibitors. This specificity significantly reduces the probability of this inhibitor's off-target effects towards other Zn metalloproteases making it a more desirable candidate as a RA therapeutic. Specific inhibition of ADAM10 by this inhibitor will result in effects such as lowering of multiple inflammatory cytokines and recruitment of inflammatory cells, which is not possible through single-target RA drugs.

Application

This novel technology can be used for treatment of inflammatory and/or autoimmune conditions such as RA. This novel selective ADAM10 inhibitor offers a new treatment modality for RA and possibly other diseases that involves inflammation and/or immune dysfunction.

Advantages/Benefits

- Currently there are no known ADAM10 inhibitors for RA therapy in the market or in clinical trials. Therefore, this will be a unique treatment modality
- This therapeutic molecule will be a conceptually novel class of molecule that will inhibit ADAM10 through a non-zinc binding inhibition mechanism. Targeting a non-zinc binding exosite of ADAM10 will possibly make it a more efficient inhibitor
- This class of molecule will have significantly lower off-target effects, thus resulting in reduction of negative side effects often caused by currently used RA drugs
- This new treatment modality can potentially be combined with the existing therapies to improve outcomes and response rates

Status of Development

- A specific novel inhibitor of ADAM10 was identified by the inventor through HTS and evaluation of multiple compounds
- Evaluation of the lead compound from this class through various cell-based assays demonstrated lack of toxicity and efficient inhibition of inflammatory cytokines and inflammatory cell recruitment and recruitment of pro-inflammatory cells
- The selected inhibitor was further tested in an *in vivo* model (mouse Collagen-induced arthritis). The findings of this rodent model study indicate that this inhibitor produced dose dependent lowering of RA score, paw swelling, and biomarkers of inflammation associated with RA (IL-10 and IL-6) and no clinical signs of distress suggesting low toxicity.

Intellectual Property Status: Provisional patent application submitted on March 8th, 2022.

Information on Inventors

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