# Development of Methods to Inhibit IL-1β and IL-18 Production

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## BACKGROUND

Macrophages respond to pathogens and tissue damage via pattern recognition receptors (PRR) that sense pathogen (PAMP) or damage (DAMP) associated molecular patterns. NLRP3, a member of the Nod-like receptor (NLR) family that is induced upon macrophage activation, senses cytosolic oxidized mitochondrial DNA (ox-mtDNA) that is generated when activated macrophages are exposed to NLRP3- activating DAMPs, such as ATP, uric acid, or amyloid β, triggers IL-1β and IL-18 production and release.

IL-1β and IL-18 are members of the IL-1 family of cytokines representing two of eleven members. As a whole, the IL-1 group of cytokines can induce strong inflammatory signals. Moreover, IL-1β and IL-18 are unique members because they are inactive until undergoing proteasomal cleavage by caspase-1 leading to the formation of active biological forms. Recent work has shown that NLRP3 inflammasome dependent production of IL-1β and IL-18 is involved in the pathogenesis of many devastating diseases, including cancer, Alzheimer's disease, rheumatoid diseases and cryopyrin-associated periodic syndromes. and autoimmune diseases such as lupus or Still's diseases. Thus, there exists a need to modulate the production of both IL-1β and IL-18.

## TECHNOLOGY DESCRIPTION

Researchers at UC San Diego have developed a method of treating macrophage-mediated inflammatory and/or degenerative diseases. This is based upon the observation that activated macrophages exhibit increased lipid remodeling and metabolism at inflammatory sites. The inhibition of a kinase involved in lipid metabolism or restriction of its substrate impair NLRP3 inflammasome activation and lead to the inhibition of IL-1β and IL-18 production. Thus, the method of either administering an effective amount of small molecule inhibitor of such kinase or reducing its expression, or inhibiting the uptake of the substrate or reducing the expression of substrate's transporter, would lead to a reduction of the kinase activity or expression, thereby inhibiting NLRP3 inflammasome activation, IL-1β and IL-18 production.

## APPLICATIONS

Blocking the activity of a specific kinase involved in lipid metabolism or the availability of its substrate to activated macrophages can block the activation of NLRP3 inflammasome and therefore the production of biologically active IL-1β and IL-18.

## STATE OF DEVELOPMENT

Although we find specific kinase inhibitors to be effective inhibitors of IL-1β and IL-18 dependent acute and chronic inflammation, full evaluation of the side effects of such inhibitors is needed before embarking on the use of such inhibitors in the clinic.

## INTELLECTUAL PROPERTY INFO

This technology is patent pending and available for licensing and/or research sponsorship.

## PATENT STATUS

Patent Pending

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## OTHER INFORMATION

**KEYWORDS**

anti-inflammatory, Interleukin-1ß, IL-1ß, interleukin-18, IL-18, NLRP3 inflammasome, cytokine antagonists, cytokine inhibitors, NLRP3-dependent cytokines, metabolism, macrophages

**CATEGORIZED AS**

- **Medical**
  - Disease: Autoimmune and Inflammation

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