263 Identification of Novel NLRP3 Inflammasome Inhibitors

Asset Overview

Product Type	Target related to NLRP3 inflammasome
Indication	Oncology, Immunology, CNS diseases, etc.
Current Stage	Lead Identification/optimization
Target(MoA)	Inhibition of NLRP3 inflammasome activation
Brief Description	• Identified a novel kinase whose inhibition prevents NLRP3 inflammasome activation by all its known stimuli, and identified its essential catalytic pocket and mechanism of action • Applying for a patent application (US Provisional Application Serial no. 62/690,175) covering the use of IRF1 and/or CMPK2 genetic/chemical inhibitors to treat NLRP3 inflammasome-associated diseases in the process • Business model: collaboration to identify small molecule inhibitors of this kinase would be of interest as well as licensing the technology
Organization	University of California, San Diego

Differentiation

□ **NLRP3 inflammasome as a therapeutic target**

- The NLRP3 inflammasome is a molecular machine that becomes activated during acute and chronic inflammation and leads to production of biologically active IL-1β and IL-18 that initiate inflammatory responses triggered by tissue damage
- NLRP3 inflammasome activation is required for production of IL-1β. Antibodies to IL-1β have been proven useful in a number of inflammatory diseases and can even reduce the likelihood of secondary cardiovascular events for heart attack victims
- IL-1β, however, is also important for protection from infection and IL-1β-blocking drugs can increase infection risk
- NLRP3 inhibition will avoid such a risk because it only blocks IL-1β production that depends on the NLRP3 inflammasome, which is not involved in the response to microbial or viral infections
- Aberrant NLRP3 activation is the key promoter to many chronic diseases. Specific inhibitors to this new kinase identified should be useful to treat cryopyrin-associated periodic syndromes, gouty arthritis, osteoarthritis, Alzheimer's disease, type 2 diabetes, atherosclerosis, lupus, macular degeneration and cancer
- There are no effective ways to inhibit the NLRP3 inflammasome, thus there is a therapeutic need for this class of molecule

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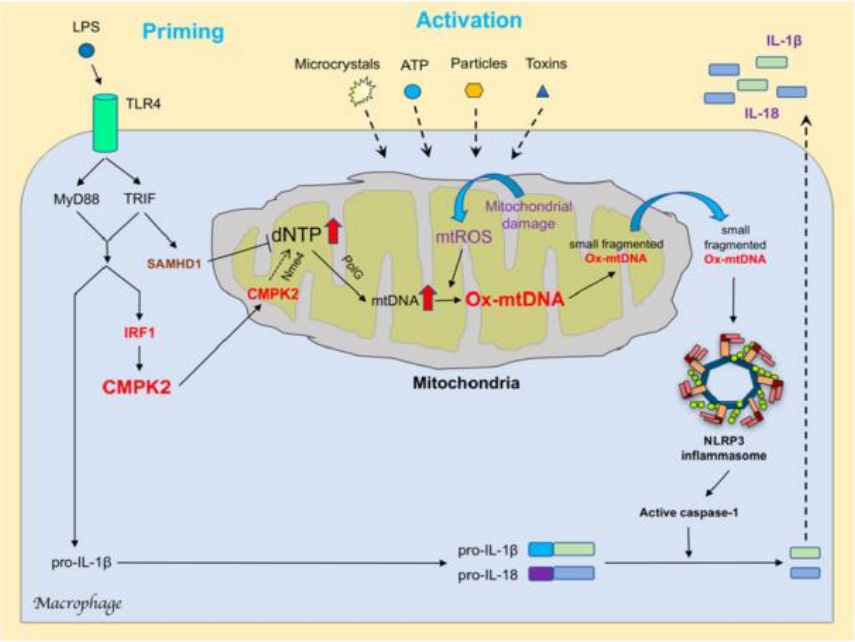
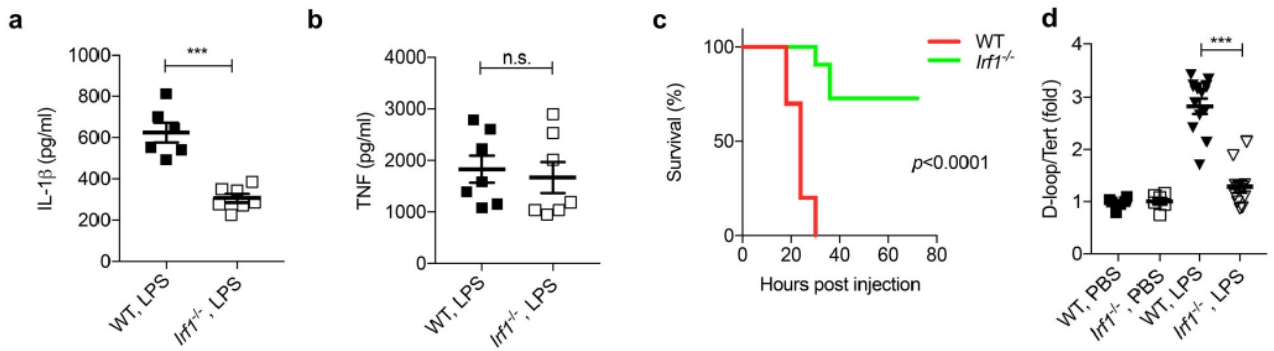
Key Data

A working model to illustrate how TLR-mediated priming controls mtDNA replication and NLRP3 inflammasome activation



IRF1 is required for *in vivo* mtDNA replication and NLRP3 inflammasome activation



12-week-old wild-type or Irf1−/− mice were injected intraperitoneally with LPS (50 mg per kg of body weight) and their sera were collected 3 h later and analysed by ELISA for IL-1β (a) and TNF (b). c, Survival of wild-type or Irf1−/− mice that were injected intraperitoneally with LPS d, Relative amounts of total mtDNA in peritoneal infiltrates of wild-type or Irf1−/− mice before and after LPS injecton.

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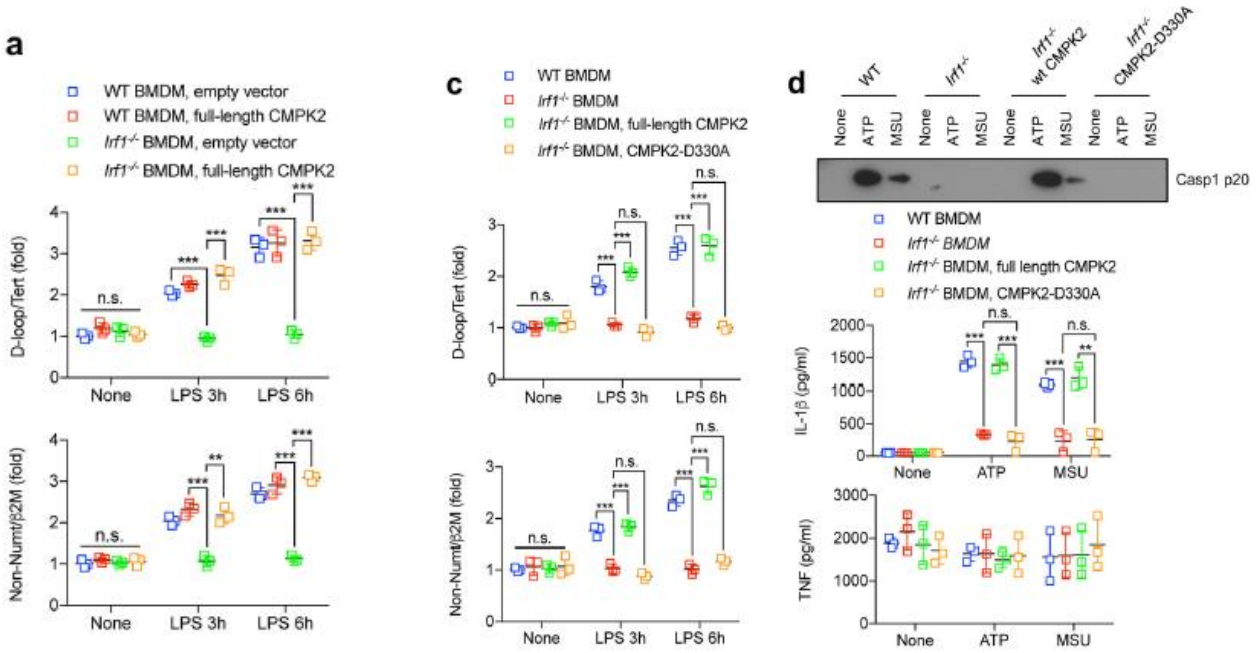
NLRP3 activation depends on CMPK2 catalytic activity



The induction of new mtDNA replication, which depends on CMPK2 catalytic activity, is required for the production of ox-mtDNA by mitochondria that have been damaged by exposure to NLRP3 activators, with ox-mtDNA being responsible for subsequent NLRP3 inflammasome activation.

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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