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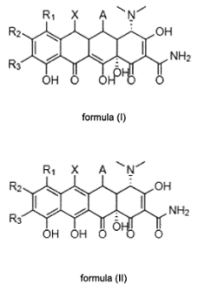
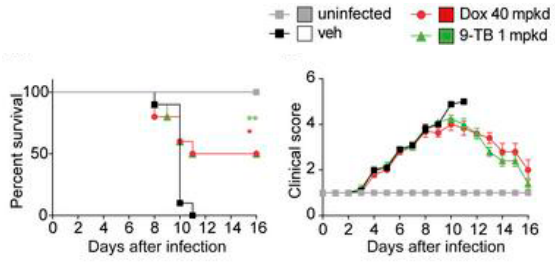
Licensing Opportunity

TTO – Technology Transfer Office

Tetracycline derivative for disease tolerance against viral infections



Structures of tetracycline derivatives



Tetracyclines mediate disease tolerance to IFV in mice

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Keywords

Drug therapy, infectious disease, influenza, SARS-CoV-2, mitochondria

Intellectual Property

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Publications

https://www.jci.org/articles/view/151540

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Description

Mitohormesis defines the increase in fitness mediated by adaptive responses to mild mitochondrial stress. Tetracyclines inhibit not only bacterial but also mitochondrial translation, thus imposing a low level of mitochondrial stress on eukaryotic cells. We demonstrate that tetracyclines induce a mild adaptive mitochondrial stress response (MSR), involving both the ATF4-mediated integrative stress response and type I interferon (IFN) signaling. The present invention relates to tetracycline derivatives of formula (I) or formula (II), where one of the groups R1, R2 and R3 and X is substituted by a linear or branched C3 to C8 alkyl, a cycloalkyl, an alkenyl, a phenylalkenyl (preferably styryl), an aryl, and a heteroaryl while other groups are H, OH or CH3. To overcome the interferences of tetracyclines with the host microbiome, we identify tetracycline derivatives that have minimal antimicrobial activity, yet retain full capacity to induce the MSR, such as the lead compound, 9-tert-butyl doxycycline (9-TB). The MSR induced by doxycycline (Dox) and 9-TB improves survival and disease tolerance against lethal influenza virus (IFV) infection when given preventively. 9-TB, unlike Dox, did not affect the gut microbiome and also showed encouraging results against IFV when given in a therapeutic setting. Tolerance to IFV infection is associated with the induction of genes involved in lung epithelial cell and cilia function, and with downregulation of inflammatory and immune gene sets in lungs, liver, and kidneys.
Mitohormesis induced by non-antimicrobial tetracyclines and the ensuing IFN response may dampen excessive inflammation and tissue damage during viral infections, opening innovative therapeutic avenues.

Advantages

- helping the immune system to defeat viral infection by activating MSR
- compounds significantly triggering the MSR without antibacterial activity

Development stage

Tetracycline derivatives of formula (I) and (II) characterized in primary BMDM, in HEK293T cells and C. elegans. The therapeutic efficacies of the leading compounds have been done in mice models of viral infection.

Applications

Treatment of:

- infections (influenza, COVID)
- neurodegenerative disorders such as Alzheimer's disease
- diseases characterized by schema reperfusion injury (e.g., acute kidney injury and myocardial infarction)