

# The 17<sup>th</sup> Global and Local Infectious Diseases Research Seminar



September 26<sup>th</sup> , 2023  
16:00-17:00

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**Presenter : Prof. Tanapat Palaga, PhD**

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## The Roles of a DNA Repair Enzyme O<sup>6</sup>-Methylguanine DNA Methyltransferase in Inflammation, Infection, and Innate Immune Memory in Macrophages

O<sup>6</sup>-methylguanine DNA methyltransferase (MGMT) is an enzyme responsible for DNA repair of lesion induced by alkylating agents. Loss of MGMT predisposes mice to alkylating agent-induced tumorigenesis and aberration in MGMT expression is reported in various tumor types. However, the involvement of MGMT in innate immunity is completely unknown. MGMT was uncovered in our screening to identify enzymes that regulate trained immunity in macrophages. *MGMT* KO macrophages exhibited dampened response to activation by TLR3 agonist, poly I:C, but the response to other TLRs was not altered. Loss of MGMT induced activation of AMP-activated protein kinase (AMPK) and spontaneous autophagy. Colocalization of mitochondria and autophagosome was detected, an indication of mitophagy. When *Salmonella* infection was performed, increased colocalization of bacteria and autophagosomes was found with enhanced bacterial killing. In  $\beta$ -glucan-induced trained immunity, targeted deletion of *MGMT* in macrophages resulted in reduction of the trained responses both *in vitro* and *in vivo* models. The transcriptomic analysis revealed that the dampening trained immunity in *MGMT* KO macrophages is partially mediated by farnesoid X receptor (FXR)/AMPK and mTOR/HIF1 pathways and the reduction in glycolysis function. In a high fat diet-induced obesity model, reduction in liver lipid deposition was observed in *MGMT* KO mice. Taken together, a failure to resolve DNA damage may have consequences for inflammation, infection and innate immune memory.

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### Seminar Contact

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