



*VABILO NA PREDAVANJE
V OKVIRU DOKTORSKEGA ŠTUDIJA
KEMIJSKE ZNANOSTI*

prof. Boštjan Kobe

*School of Chemistry and Molecular Biosciences Research
Committee, University of Queensland, Australia*

z naslovom:

**Signalling by cooperative assembly formation
(SCAF) by TIR domains in innate immunity
and cell death pathways**

v sredo, 21. marca 2018 ob 15:00 uri
v predavalnici 1 v 1. nadstropju Fakultete
za kemijo in kemijsko tehnologijo, Večna pot 113

Vljudno vabljeni!

Abstract:

TIR (Toll/interleukin-1 receptor, resistance protein) domains are key components of innate immunity signaling pathways. They are found in animals, plants and bacteria, for example in TLRs (Toll-like receptors) and TLR adaptors in animals, NLRs (nucleotide binding, leucine-rich repeat receptors) in plants, and virulence factors interfering with immune responses in bacteria. Signaling depends on self-association and homotypic association of TIR domains, but the molecular basis of this association has remained elusive [1,2]. We have been able to reconstitute large assemblies of the TLR adaptors MAL and MyD88, and determined the structure of the filamentous assembly of MAL by cryo-electron microscopy [3]. As an unexpected twist, we (unpublished) and others [4] have shown that the TIR domain of the TLR adaptor SARM possesses self-association-dependent NAD⁺ cleavage activity. Jointly, these studies suggest a general mechanism of function of TIR domains, which involves "signaling by cooperative assembly formation (SCAF)" with prion-like features that leads to the activation of effector enzymes. Some TIR domains can themselves function as effector enzymes.

References

- [1] Ve T, Williams SJ and Kobe B, "Structure and function of Toll/interleukin-1 receptor/resistance protein (TIR) domains", *Apoptosis*, 20 (2015), 250-61
- [2] Nimma S, Ve T, Williams SJ and Kobe B, "Towards the structure of the TIR-domain signalosome", *Curr Opin Struct Biol* 43 (2017), 122-130
- [3] Ve T, Vajjhala PR, Hedger A, Croll T, DiMaio F, Horsefield S, Yu X, Lavrencic P, Hassan Z, Morgan GP, Mansell A, Mobli M, O'Carroll A, Chauvin B, Gambin Y, Siercecki E, Landsberg MJ, Stacey KJ, Egelman EH and Kobe B, "Structural basis of TIR-domain assembly formation in MyD88/MAL-dependent TLR4 signaling", *Nat Struct Mol Biol* (2017)
- [4] Essuman KD, Summers W, Sasaki Y, Mao X, DiAntonio A and Milbrandt J (2017). "The SARM1 Toll/interleukin-1 receptor domain possesses intrinsic NAD⁺ cleavage activity that promotes pathological axonal degeneration", *Neuron*, 93 (2017), 1334-1343