

**P060** The DNA sugar backbone 2-deoxyribose determines Toll-like receptor 9 activation

**Tobias Haas<sup>1</sup>, Jochen Metzger<sup>2</sup>, Frank Schmitz<sup>1</sup>, Antje Heit<sup>1</sup>, Thomas Müller<sup>1</sup>, Eicke Latz<sup>3</sup> and Hermann Wagner<sup>1</sup>**

*<sup>1</sup>Institut für Medizinische Mikrobiologie, Immunologie und Hygiene, Technische Universität München, Trogerstrasse 30, 81675 München, Germany. <sup>2</sup>Institut für Klinische Chemie und Pathobiochemie, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, 81675 München. <sup>3</sup>University of Massachusetts Medical School, Division of Infectious Diseases and Immunology, 364 Plantation St, Worcester, MA 01605.*

TLR9 is believed to represent a pattern recognition receptor specific for pathogen derived DNA, equipped with competence for “foreign-self” discrimination. CpG-dinucleotides are considered important attributes of “foreign”. Based on experiments using phosphorothioate (PS)-modified ODN, TLR9 has been found to require such CpG-motifs to become activated. We show that PD ODN devoid of CpG, unlike PS ODN, activate TLR9 when translocated into TLR9-containing endosomes of immune cells. Determinant of this CpG-motif independent recognition is the PD 2-deoxyribose sugar backbone, which, as base-free homopolymer, binds to and basally activates TLR9. Random bases add to the stimulatory potential. Substitution of the 2-deoxyribose sugar backbone with ribose, however, abrogates TLR9-binding and stimulation. In contrast, homopolymeric, base-free PS 2-deoxyribose is bound by TLR9 with 100fold higher affinity than PD 2-deoxyribose and, surprisingly, has a potent competitive-inhibitory effect on ligand induced TLR9 activation, both *in vitro* and *in vivo*. Adding random bases does not alter this dominant negative effect, whereas adding CpG-motifs reverses it and results in robust TLR9-stimulatory activity. These data show that the sugar backbone 2-deoxyribose determines TLR9-activation vs TLR9-inhibition and explain the current misconception that CpG-motifs are crucial for DNA-recognition by TLR9. We propose that TLR9 is a receptor for natural DNA with no inherent ability to discriminate “foreign” from “self”.