Table S10. The binding free energies (ΔG) in kcal/mol between either MD2 or MD2* monomer and the ligands (either LPS or neoseptin3) at either the MD2/ligand or MD2*/ligand interface computed by both molecular mechanics generalized Born surface area (MM-GBSA) and molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) methods. The free energies in each of the lipopolysaccharide (LPS)-bound (TLR4-MD2)$_2$ tetramer and neoseptin3-bound (TLR4-MD2)$_2$ tetramer complexes are averaged over the 1000 frames of the combined 4 trajectories. A negative value is a favorable free energy, while a positive value is an unfavorable. The values in parenthesis are standard deviation. ΔE_{MM} is molecular mechanics free energy which is divided into ΔE_{ele} and ΔE_{vdw} representing the contributions from the electrostatic and van der Waals interactions, respectively. ΔG_{sol} is solvation free energy expressed by ΔG_{pol} and ΔG_{nonpol}, the polar and non-polar contributions, respectively.

					Generalized Born (GB)			Poisson-Boltzmann (PB)		
Monomer	**Complex**	**#**	ΔE_{MM}		ΔG_{sol}		ΔG	ΔG_{sol}		ΔG
			ΔE_{ele}	ΔE_{vdw}	ΔG_{pol}	ΔG_{nonpol}		ΔG_{pol}	ΔG_{nonpol}	
MD2	(TLR4-MD2-LPS)$_2$	1-4	**-14.50** (17.25)	**-124.26** (8.52)	**47.96** (13.53)	**-17.55** (1.16)	**-108.35** (9.58)	**50.27** (14.60)	**-11.88** (0.58)	**-100.36** (9.40)
MD2	(TLR4-MD2-nst3)$_2$	1-4	**-18.81** (12.94)	**-76.25** (7.61)	**47.81** (11.63)	**-10.48** (1.16)	**-57.72** (8.24)	**50.05** (12.60)	**-8.00** (0.55)	**-53.01** (8.10)
MD2*	(TLR4-MD2-LPS)$_2$	1-4	**-28.93** (22.84)	**-128.43** (10.96)	**59.27** (15.47)	**-18.10** (1.32)	**-116.18** (9.54)	**61.43** (15.78)	**-12.10** (0.54)	**-108.02** (8.76)
MD2*	(TLR4-MD2-nst3)$_2$	1-4	**-11.27** (13.06)	**-65.14** (12.60)	**38.06** (12.75)	**-8.86** (1.63)	**-47.22** (10.72)	**39.89** (14.21)	**-7.07** (1.02)	**-43.59** (9.92)