INVITED LECTURE

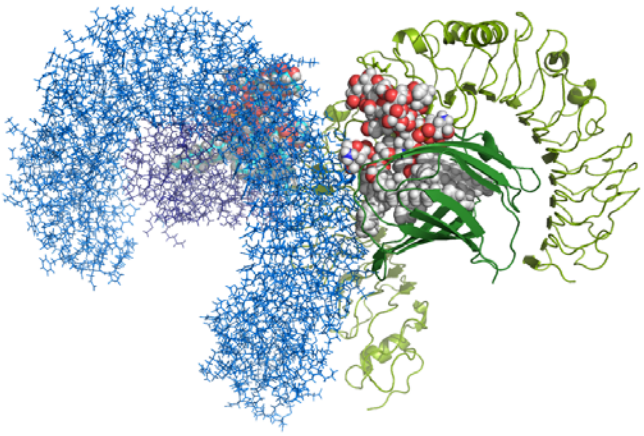
TLR4/MD-2 and galectins recognition by modulators. Molecular modelling approaches

Sonsoles Martín-Santamaría

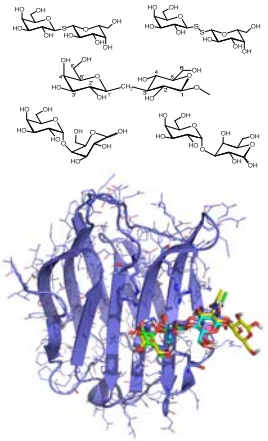
Department of Chemistry and Biochemistry, Faculty of Pharmacy, Universidad CEU San Pablo. Urbanización Montepríncipe, 28668-Boadilla del Monte, Madrid, Spain. E-mail: smsantamaria@ceu.es

Toll-like receptors (TLRs) recognize specific molecular patterns that are present in microbial components (as lipopolysaccharides, LPS). Several new compounds modulating TLRs are now undergoing preclinical and clinical evaluation, for the treatment of sepsis and inflammatory diseases, cancer, and rheumatoid arthritis.[1] TLR4, along with its accessory protein myeloid differentiation factor 2 (MD2), forms a heterodimeric complex (Figure, A), which specifically recognizes LPS, and confers an intracellular signaling cascade that results in the inflammatory and immune response. Our group has applied molecular modelling techniques to the study of TLR4 interactions with novel and reported agonists and antagonists such as taxanes, opioids, natural LPSs, and synthetic small molecules.[2] Our studies can be very valuable for the understanding of the interaction mechanism of these compounds, with high potential to design new molecules able to modulate TLR4 immune response.

On the other hand, we focused on human galectins, biomedically relevant lectins which can act as a proinflammatory and protumoral effectors. In this context, the elucidation of the mechanisms that govern how oligosaccharides are bound can afford a perspective for galectin modulation and rational drug design (Figure, B).[3] Binding studies of several glycomimetics to galectins 1 and 3, by means of molecular modeling techniques, will be presented.[4]



A)



B)

[1] E. J. Hennessy, A. E. Parker, A. J. O'Neill. *Nat. Rev. Drug Discov.*, **2010**, *9*, 293.
[2] Cighetti, R.; Ciaramelli, C.; Sestito, S. E.; Zanoni, I.; Kubik, Ł.; Ardá-Freire, A.; Calabrese, V.; Granucci, F.; Jerala, R.; Martín-Santamaría, S.; Jiménez-Barbero, J.; Peri, F. *ChemBioChem*. **2014**, *15*, 250.
[3] Martín-Santamaría, S.; Gabius, H.-J.; Jiménez-Barbero, J. *Pure Appl. Chem.* **2012**, *84*, 49.
[4] Vidal, P.; Roldós, V.; Fernández-Alonso, M. C.; Vauzeilles, B.; Bleriot, Y.; Cañada, F. J.; André, S.; Gabius, H-.J.; Jiménez-Barbero, J.; Espinosa, J. F.; Martín-Santamaría, S. *Chem. Eur. J.* **2013**, *19*, 14581.