# Molecular Modelling of the Complex hIFNI-$\gamma$–hIFN$\gamma$R–Heparin-Derived Oligosaccharides

Elena Lilkova[1], Peicho Petkov[1], Nevena Ilieva[2], Leandar Litov[1]
[1] University of Sofia "St. Kliment Ohridski", Faculty of Physics
[2] Institute of Information and Communication Technologies - BAS, Sofia
elilkova@phys.uni-sofia.bg

*Keywords: Interferon gamma, Heparin-derived oligosaccharides, Force field parameters development, Molecular dynamics simulations*

Human interferon gamma (hIFN-$\gamma$) is an important antiviral and immunomodulating signaling molecule, which is also related to several autoimmune deceases. The cytokine expresses its activity through a specific extracellular receptor, the Interferon gamma receptor (hIFN$\gamma$R). Understanding the process of hIFN-$\gamma$ – hIFN$\gamma$R complex formation is crucial for finding a mechanism for suppressing IFN-$\gamma$ biological activity.

We performed multiple molecular dynamics simulations to study the formation of the complex between interferon gamma and its receptors. It was found that the highly positively charged flexible C-terminal tails of the cytokine interact with negatively charged domains in the receptor molecules. This interaction prevents the proper orientation of the hIFN-$\gamma$ molecule relative to the receptors, so that the binding sites remain separated in space. It became evident that another participant is necessary for the cytokine-receptor binding to occur.

It is known that interferon gamma binds to heparin-derived oligosaccharides. These are linear highly negatively charged carbohydrates, occurring as an integral component of the basement membrane of all mammalian cells. In order to simulate the interaction between hIFN-$\gamma$, hIFN$\gamma$R and heparin-derived oligosaccharides with various degree of polimerisation, we first developed force field parameters for the monosaccharide N-sulfated glucosamine. The CHARMM compatible parameters were developed using the Force Field Toolkit of the molecular visualization and manipulation program VMD.

**Acknowledgements:** Financial support is acknowledged from Grant BG051 PO001-3.3.06-0057 of the Operational Programme Human Resources Development co-financed by the European Social Fund of the EU.