

INVITED LECTURE T11

Intrinsic Determinants of Protein Immunogenicity

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Proteins are today widely used as vaccines and therapeutic agents. As vaccines, proteins need to be highly immunogenic whereas as therapeutics their natural tendency to trigger an immune response should be minimized or even abolished. In other words, it is highly desirable to control the immunogenicity of proteins. To progress toward that direction, we have searched for determinants that are associated with the humoral immunogenicity of proteins, using two proteins as models. One is a highly structured snake neurotoxin that blocks the nicotinic acetylcholine receptor. Using a set of differentially stable neurotoxin derivatives we demonstrated that antigen stability controls antigen proteolysis, antigen processing in antigen-presenting cells, T cell stimulation, and kinetics of expression of T cell determinants. The other antigen is a natively unfolded viral HIV-1 Tat101 protein, which acts as a transcriptional transactivator. We found that Tat101 possesses an unusual auto-adjuvant property which may be controlled by the N-terminal region, the core region, and/or the cysteine-rich region of the molecule. Based on these observations, we propose efficient strategies to substantially decrease or increase the humoral immune response of proteins.