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Structure-based design of potent tumor-associated mucin-like antigens by O→S/Se replacement at the glycosidic linkage

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Palabras Clave: glycopeptide ● molecular recognition ● antigen ● cancer vaccine

GalNAc-glycopeptides derived from mucin MUC1 are an important class of tumor-associated antigens.[1] α-*O*-glycosylation forces the peptide to adopt an extended conformation, which is far from the structure observed in complexes with a model anti-MUC1 antibody. We propose a new strategy to design potent antigen mimics based on modulating peptide/carbohydrate interactions by means of O→S/Se replacement at the glycosidic linkage. These minimal chemical modifications increase the carbohydrate-peptide distance and change the orientation and dynamics of the glycosidic linkage. As a result, the peptide acquires a preorganized and optimal structure suited for antibody binding. To prove the potential of these glycopeptides as tumor-associated MUC1 antigen mimics, the derivative bearing the *S*-glycosidic linkage was conjugated to gold nanoparticles and tested as an immunogenic formulation in mice without any adjuvant, that resulted in a significant humoral immune response. The mice antisera recognize cancer cells in biopsies of breast-cancer patients with high selectivity. The methodology presented here is of general interest for applications because it may be extended to modulate the affinity of biologically relevant glycopeptides towards their receptors.

Structure-based design of potent MUC1-like antigens
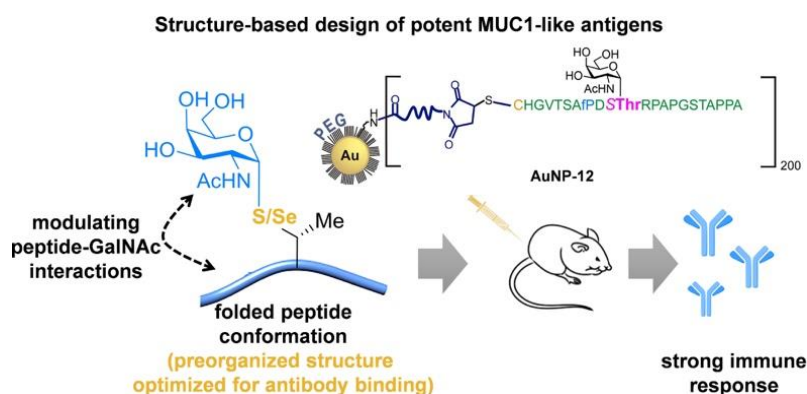
Referencias

[1] Compañón, I.; Guerreiro, A.; Mangini, V.; Castro-López, J.; Escudero-Casao, M.; Avenoza, A.; Busto, J. H.; Castillón, S.; Jiménez-Barbero, J.; Asensio, J. L.; Jiménez-Oses, G.; Boutureira, O.; Peregrina, J. M.; Hurtado-Guerrero, R.; Fiammengo, R.; Bernardes, G. J. L.; Corzana, F. *J. Am. Chem. Soc.* **2019**, DOI: 10.1021/jacs.8b13503.