29th International

Carbohydrate Symposium

14th – 19th July 2018

Faculdade de Ciências, Universidade de Lisboa

Book of Abstracts

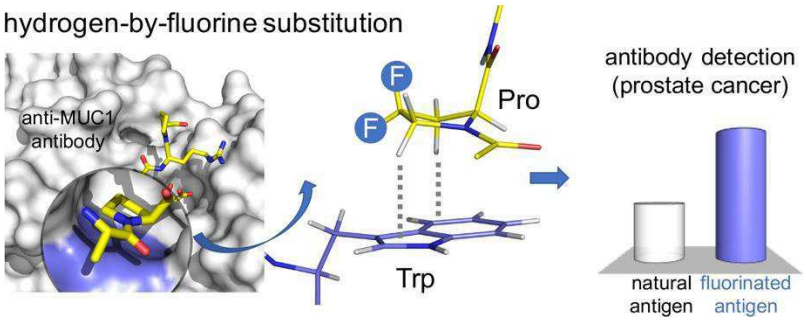
THE USE OF FLUOROPROLINE IN MUC1 ANTIGEN ENABLES EFFICIENT DETECTION OF ANTIBODIES IN PATIENTS WITH CANCER

Víctor J. Somovilla,[a] Iris A. Bermejo,[a] Inês S. Albuquerque,[b] Nuria Martínez-Sáez,[a] Jorge Castro-López,[c] Fayna García-Martín,[d] Ismael Compañón,[a] Shin-Ichiro Nishimura,[d] Jesús Jiménez-Barbero,[e] Juan L. Asensio,[f] A. Avenoza,[a] J. H. Busto,[a] Ramón Hurtado-Guerrero,[c] Jesús M. Peregrina,[a] Gonçalo J. L. Bernardes[b,g] and Francisco Corzana[a]*

[a] Departamento de Química, Universidad de La Rioja, Centro de Investigación en Síntesis Química, 26006 Logroño, Spain.
[b] Instituto de Medicina Molecular, Faculdade de Medicina da, Universidade de Lisboa, 1649-028, Lisboa, Portugal.
[c] Institute of Biocomputation and Physics of Complex Systems (BIFI), University of Zaragoza, BIFI-IQFR (CSIC), Zaragoza, Spain.
[d] Graduate School and Faculty of Advanced Life Science, Field of Drug Discovery Research, Hokkaido University, N21 W11, Sapporo 001-0021, Japan.
[e] CIC bioGUNE, Bizkaia Technology Park, Building 801A, 48170 Derio, Spain; (ii) Ikerbasque, Basque Foundation for Science, Maria Diaz de Haro 13, 48009 Bilbao, Spain.
[f] Instituto de Química Orgánica General, IQOG-CSIC,28006 Madrid, Spain.
[g] Department of Chemistry, University of Cambridge, CB2 1EW, Cambridge, U.K.

MUC1 is a glycoprotein overexpressed in most types of cancer [1]. This overexpression is associated with elevated concentrations of antibodies against MUC1 in the blood of patients [2].

In this talk, a structure-based design of a new generation tumor-associated glycopeptides with improved affinity against two anti-MUC1 antibodies is described [3]. These unique antigens feature a fluorinated proline residue, such as a (*4S*)-4-fluoro-L-proline or 4,4-difluoroproline, at the most immunogenic domain (see Figure). Binding assays using bio-layer interferometry reveal 3-fold to 10-fold affinity improvement with respect to the natural glycopeptides. According to X-ray crystallography and MD simulations, the fluorinated residues stabilize the antigen-antibody complex by enhancing key CH/π interactions. Interestingly, a notable improvement in detection of cancer-associated anti-MUC1 antibodies from serum of patients with prostate cancer is achieved with the non-natural antigens, which proves that these derivatives can be considered better diagnostic tools than the natural antigen for this type of cancer.



References

[1] N. Martínez-Sáez, J. M. Peregrina, F. Corzana, *Chem. Soc. Rev.* **2017**, *46,* 7154-7175.
[2] Z.-M. Tang, Z.-G. Ling, C.-M.Wang, Y.-B. Wu, J.-L. Kong, *PLoS One* **2017**, *12*, e0182117.
[3] V. J. Somovilla, I. A. Bermejo, I. S. Albuquerque, N. Martínez-Sáez, J. Castro-López, F. García-Martín, I. Compañón, H. Hinou, S.-I. Nishimura, J. Jiménez-Barbero, J. L. Asensio, A. Avenoza, J. H. Busto, R. Hurtado-Guerrero, J. M. Peregrina, G. J. L. Bernardes, F. Corzana, *J. Am. Chem. Soc.* **2017**, *139*, 18255–18261.