



# Institutional Repository - Research Portal Dépôt Institutionnel - Portail de la Recherche

researchportal.unamur.be

## RESEARCH OUTPUTS / RÉSULTATS DE RECHERCHE

### Investigation of cyclic ligands inhibiting CD2-CD58 interactions using molecular dynamics and molecular docking approaches

Leherte, Laurence; Petit, Axel; Jacquemin, Denis; Vercauteren, Daniel; Laurent, Adèle

*Publication date:*  
2018

#### [Link to publication](#)

*Citation for published version (HARVARD):*

Leherte, L, Petit, A, Jacquemin, D, Vercauteren, D & Laurent, A 2018, 'Investigation of cyclic ligands inhibiting CD2-CD58 interactions using molecular dynamics and molecular docking approaches', Annual One-Day Meeting on Medicinal Chemistry - MedChem2018, Namur, Belgium, 23/11/18 - 23/11/18.

#### **General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

#### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

# INVESTIGATION OF CYCLIC LIGANDS INHIBITING CD2-CD58 INTERACTIONS USING MOLECULAR DYNAMICS AND MOLECULAR DOCKING APPROACHES

**Laurence Leherte (1), Axel Petit (1), Denis Jacquemin (2,3), Daniel Vercauteren (1), Adèle Laurent (2)**

*1) Unité de Chimie Physique Théorique et Structurale, Department of Chemistry, NAMur MEdicine & Drug Innovation Center (NAMEDIC), Namur Institute of Structured Matter (NISM), University of Namur, Rue de Bruxelles 61, B-5000 Namur (Belgium)*

*2) University of Nantes, CEISAM UMR CNRS 6230 UFR sciences et techniques, 2 Rue de la Houssinière BP 92208, F-44322 Nantes Cedex 03 (France)*

*3) Institut Universitaire de France, 103 Bd St Michael, F-75005 Paris Cedex 5 (France)*

The CD2-CD58 protein-protein interaction is known to favor the recognition of antigen presenting cells by T cells. Molecular Dynamics (MD) and molecular docking calculations are carried out to study the structural, energetics, and dynamical properties of three known cyclic CD58 ligands, named P6 [1-3], P7 [1,4], and RTD-c [3]. Each ligand, connected via turn inducers, mimics the C and F  $\beta$ -strands of protein CD2. The MD analyses focus on the location of the ligands on the surface of CD58 and on the direct and water-mediated hydrogen bonds (Hbonds) they form with that receptor. Ligand P6, with a sequence close to the experimental  $\beta$ -strands of CD2, presents characteristics that explain its higher experimental affinity, e.g., the lower mobility and flexibility at the CD58 surface, and the larger number and occurrence frequency of ligand-CD58 Hbonds. For the two other ligands, the structural modifications lead to changes in the binding pattern with CD58 and its dynamics. In parallel, a large set of molecular docking calculations, carried out with various search spaces and docking algorithms, are compared to provide a consensus view of the preferred ligand binding modes. The analysis of the ligand side chain locations yields results that are consistent with the CD2-CD58 crystal structure and suggest various binding modes of the experimentally identified hot spot of the ligands, i.e., Tyr86. P6 is shown to form a number of contacts that are also present in the experimental CD2-CD58 structure.

This work is supported by the Wallonie-Bruxelles International (WBI) and the Belgian National Foundation for Scientific Research (FNRS), by the French Ministry of Foreign and European Affairs, and by the Ministry of Higher Education and Research, in the framework of the Hubert Curien partnerships (PHC Tournesol “DoIFAD” #40638PL).

## References

- 1) Gokhale A, Weldeghiorghis ThK, Taneja V, Satyanarayanajois D (2011) Conformationally constrained peptides from CD2 to modulate protein-protein interactions between CD2 and CD58. *J Med Chem* 54:5307-5319
- 2) Gokhale A, Kanthala S, Latendresse J, Taneja V, Satyanarayana SD (2013) Immunosuppression by co-stimulatory molecules: Inhibition of CD2-CD48/CD58 interaction by peptides from CD2 to suppress progression of collagen-induced arthritis in mice. *Chem Biol Drug Des* 82:106-118
- 3) Sable R, Durek T, Taneja V, Craik DJ, Pallerla S, Gauthier T, Jois S (2016) Constrained cyclic peptides as immunomodulatory inhibitors of the CD2:CD58 protein-protein interaction. *ACS Chem Biol* 11:2366-2374
- 4) Gokhale AS, Sable R, Walker JD, McLaughlin L, Kousoulas KG, Satyanarayana SD (2015) Inhibition of cell adhesion and immune responses in the mouse model of collagen-induced arthritis with a peptidomimetic that blocks CD2-CD58 interface interactions. *Biopolymers* 104:733-742