In silico investigation on the antigenic properties of Dolphin morbillivirus haemagglutinin complexed to sperm whale (*Physeter macrocephalus*) SLAM and nectin-4 receptors

Luca Zinzula[1,2], Sandro Mazzariol[3], Giovanni Di Guardo[4], Massimiliano Orsini[5]

[1]The Max-Planck Institute of Biochemistry, Department of Molecular Structural Biology, Martinsried, Germany. zinzula@biochem.mpg.de
[2]Centro di Recupero Cetacei e Tartarughe marine "Laguna di Nora", Pula, Sardinia, Italy. lzinzula@lagunadinora.it
[3]Department of Comparative Biomedicine and Food Science, University of Padua, Legnaro, Padua, Italy. sandro.mazzariol@unipd.it
[4]University of Teramo, Faculty of Veterinary Medicine, Teramo, Italy. gdiguardo@unite.it
[5]Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise "G. Caporale", Teramo, Italy. m.orsini@izs.it

Introduction

As the most pathogenic virus for marine mammals, Cetacean morbillivirus (CeMV) has caused lethal disease outbreaks worldwide over the last 30 years [1].
A severe threat is posed to isolated populations like those of the Mediterranean basin, where Dolphin morbillivirus (DMV) strain was spreading across several species, including the endangered sperm whale (*Physeter macrocephalus*) [2].
DMV infects immune and polarized epithelial cells through attachment of its haemagglutinin (H) to signaling lymphocyte activation molecule (SLAM) and nectin-4, respectively [1].
So far unsolved, H protein is an attractive and promising antiviral target. We describe homology-modeled DMV H complexed to sperm whale SLAM and nectin-4 putative receptors, and use this scaffold to predict B-cell epitopes as candidates for therapeutics and diagnostics developments.

Results

High quality 3D models of DMV H bound to sperm whale SLAM and nectin-4 were built with reliable Q-mean, RMSD and TM-score values.
Out of 40 overlapping metapredicted peptides, 5 linear and 2 conformational B-cell epitope candidates were found. All locate outside the interface between H and the two receptors, are evolutionarily conserved within CeMV strains and show extremely low (<40%) local sequence similarity to homologs within Morbillivirus genus.

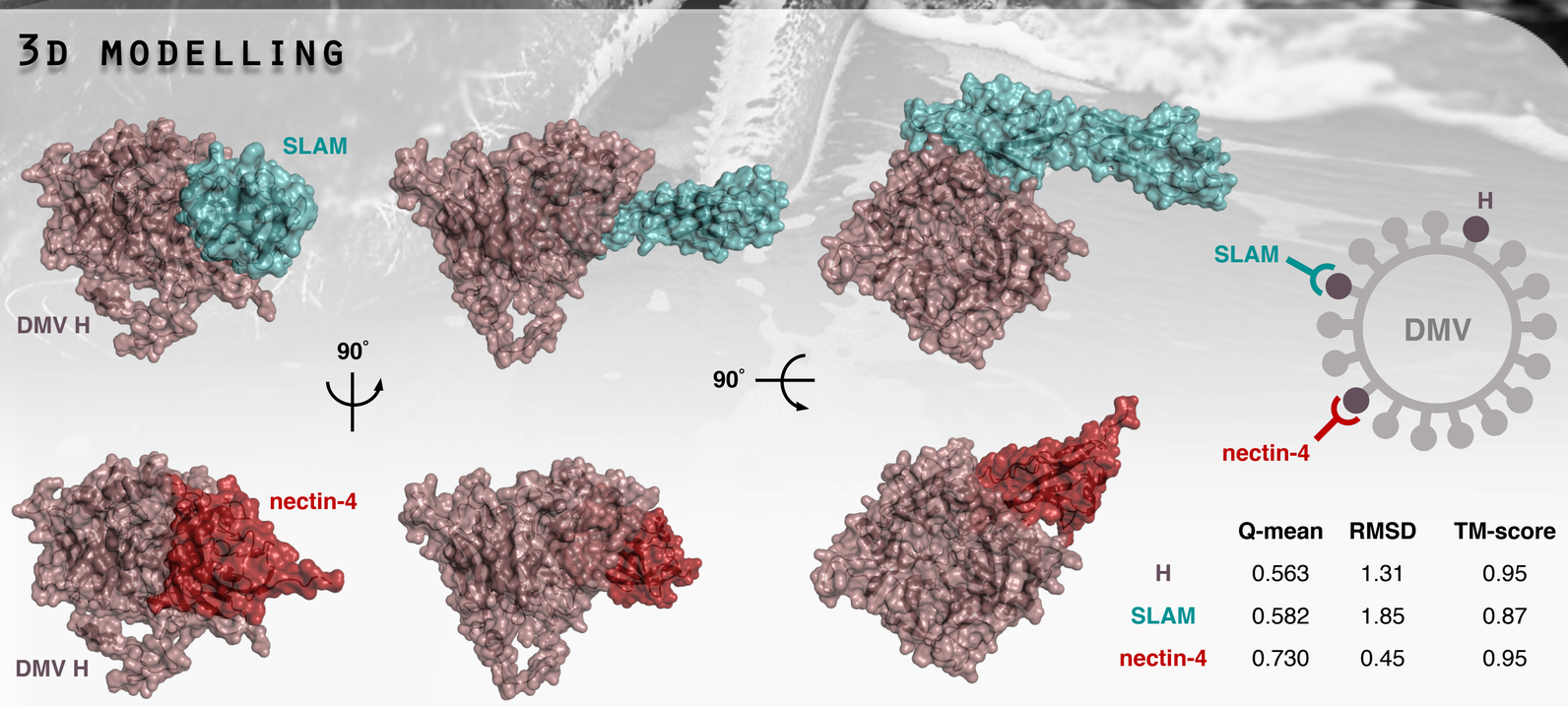
Discussion & conclusions

In the absence of a solved structure, screening of antigenic determinants is the most challenging step in immunodiagnostics pipelines.
Given the high costs and technical difficulties of experimental methods, reliable bioinformatics approaches that reduce efforts and prioritize design are urgently needed [3].
The workflow here shown relies on multiple predictions, consensus filtering and visual mapping on a confident homology-modeled 3D structure, thereby achieving rapid and cost-effective identification of B-cell epitopes as candidates for antibody-based diagnostics.

Material & methods

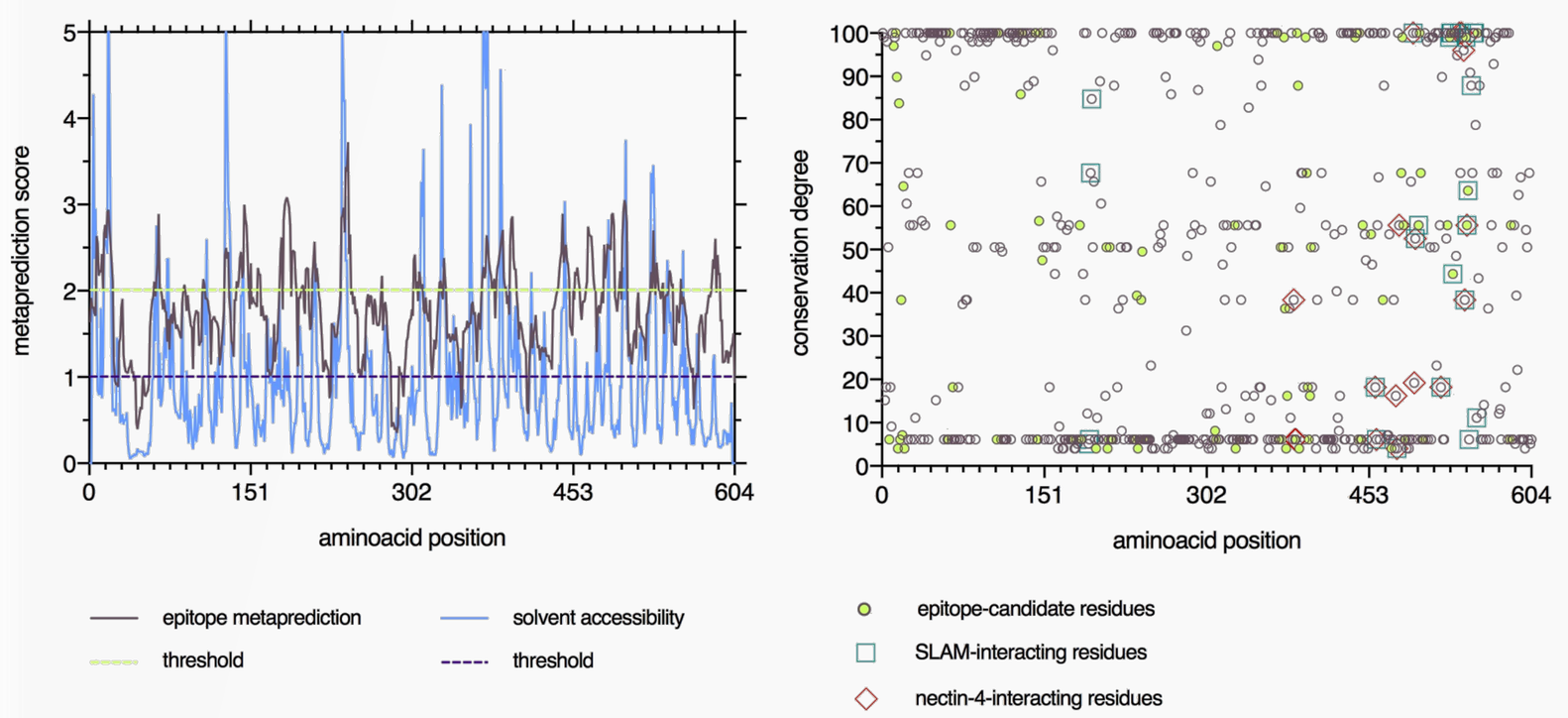
Aminoacid sequences of DMV H, sperm whale SLAM and nectin-4 were downloaded from GenBank (NP_945029, XP_007124119 and XP_007112357).
Hidden Markov model (HMM) was used to query (HHpred) Protein Data Bank for template candidates, which were evaluated by knowledge-based criteria.
Selected templates (PDB codes 2ZB6, 3JZ7 and 4FOM) underwent alignment by MUSCLE and editing by visual inspection according to PSIPRED secondary structure prediction. 3D-models were obtained by MODELLER and refined by energy-minimization in MOLPROBITY.
Docking of SLAM and nectin-4 onto DMV H surface was performed by AutoDock. 3D-models were superimposed by TM-Align and Chimera against Measles virus H bound to marmoset (*Saguinus oedipus*) SLAM (PDB: 3ALZ) and human nectin-4 (PDB: 4GJT). Metaprediction of DMV H antigenicity was performed by BepiPred, ABCpred, LBtope, CBtope and Discotope, then iteratively filtered by consensus degree and solvent accessibility. Evolutionarily conserved best candidates were mapped on DMV H – SLAM – nectin-4 3D model complex.

3D modelling

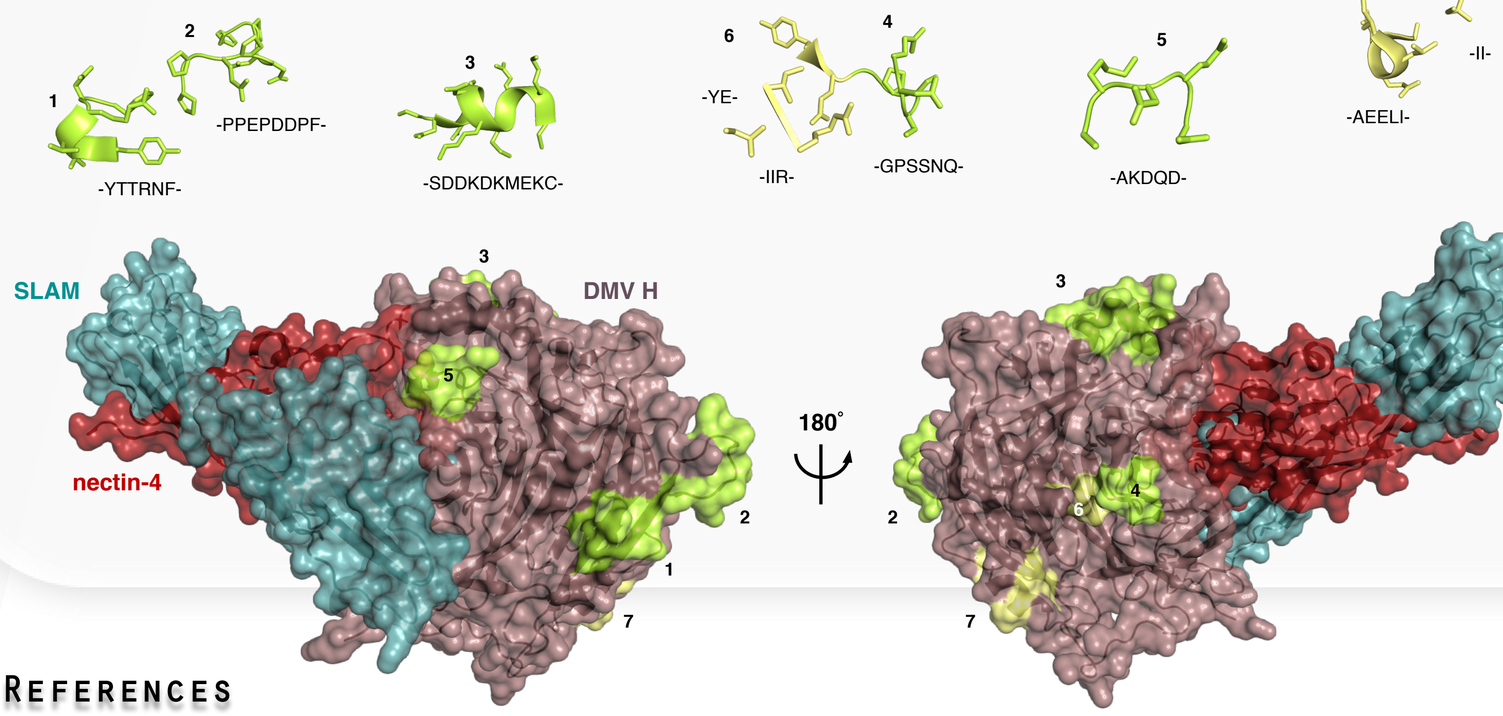


	Q-mean	RMSD	TM-score
H	0.563	1.31	0.95
SLAM	0.582	1.85	0.87
nectin-4	0.730	0.45	0.95

B-cell epitopes metaprediction & analysis



B-cell epitopes mapping



References

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Acknowledgements

Authors want to thank Giuseppe Ollano from Centro di Recupero Cetacei e Tartarughe marine "Laguna di Nora" and Dr. István Nagy from The Max-Planck Institute of Biochemistry for technical support and helpful discussion.

18th WAVLD
June 7th - 10th, 2017
SORRENTO (ITALY)
International Symposium of the World Association of Veterinary Laboratory Diagnosticians