

A precise characterisation of peptide binding stability to HLA-C alleles and correlation with the progression of HIV-1 infection and HIV-1 related neurocognitive impairment

Mauro Voi¹, A. Sangalli¹, E.G. Milano², C. De Martinis¹, E. Orlandi¹, S. Tamburin¹, E. Mantovani¹, A. Federico¹, M. Lanzafame^{3,4}, E. Lattuada³, G. A. Arganaraz⁵, B.C.M. Da Silva⁶, A.J. Duarte Da Silva⁶, J. Casseb⁷, E.R. Arganaraz⁵, A. Ruggiero¹, M.T. Valenti¹, G. Grazioso², D. Zipeto¹

¹Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy

²Department of Pharmaceutical Sciences, University of Milan, Milan, Italy.

³Unit of Infectious Diseases, Santa Chiara Hospital, Azienda Provinciale per i Servizi Sanitari, Trento, Italy

⁴Centre for Medical Sciences (CISMED), University of Trento, Trento, Italy

⁵Lab of Molecular Neurovirology, Faculty of Health Science, University of Brasilia, Brasilia, Brazil

⁶Medical Investigation Laboratory Unit 56 (LIM/56), Faculdade de Medicina FMUSP, University of São Paulo, São Paulo, Brazil

⁷Faculty of Medicine, Institute of Tropical Medicine, University of São Paulo, São Paulo, Brazil

Background. The molecular binding stability of HLA-C to the β 2-microglobulin/peptide complex influences HIV-1 progression and HIV-1 association with neurocognitive impairment. **Materials and Methods.** The NetMHCpan4.1 tool was used to predict the binding affinity of peptides specific to the most common human HLA-C allotypes, expressed as Eluted Ligand score (EL-score). The EL-score was plotted against the peptide ranking percentile, and a stability score was determined by calculating the area under the curve (AUC) for each HLA-C allele.

Naïve, HIV-1 infected subjects showing a different rate of HIV-1 progression and HIV-1 subjects presenting or not neurocognitive impairment were genotyped for HLA-C. Each patient's stability score was calculated and analysed for correlations with HIV-1 progression and neurocognitive impairment.

Results. The peptide binding score curves relative to ranking percentage highlighted differences in HLA-C allele stability. C*05:01 and C*08:02 were the most stable among the considered alleles, while C*07:04, C*07:01, and C*08:01 were the least stable. Individuals with slower progression to AIDS had significantly higher HLA-C stability scores than those with rapid HIV-1 progression ($P = 0.0113$). Furthermore, HIV-infected patients with neurocognitive impairment exhibited significantly lower HLA-C stability scores than those without ($P = 0.0074$).

Conclusion. Peptide binding analysis and AUC calculations provided an effective method for classifying HLA-C stability, overcoming the previous stable-unstable binary classification. The observed correlation between HLA-C stability scores and HIV-1 disease progression revealed that lower stability scores were associated with both accelerated progression to AIDS and the presence of neurocognitive impairment. These findings highlight the potential prognostic value of HLA-C stability in HIV-1 infection and suggest that targeting HLA-C-peptide interactions could be explored as a novel therapeutic approach.