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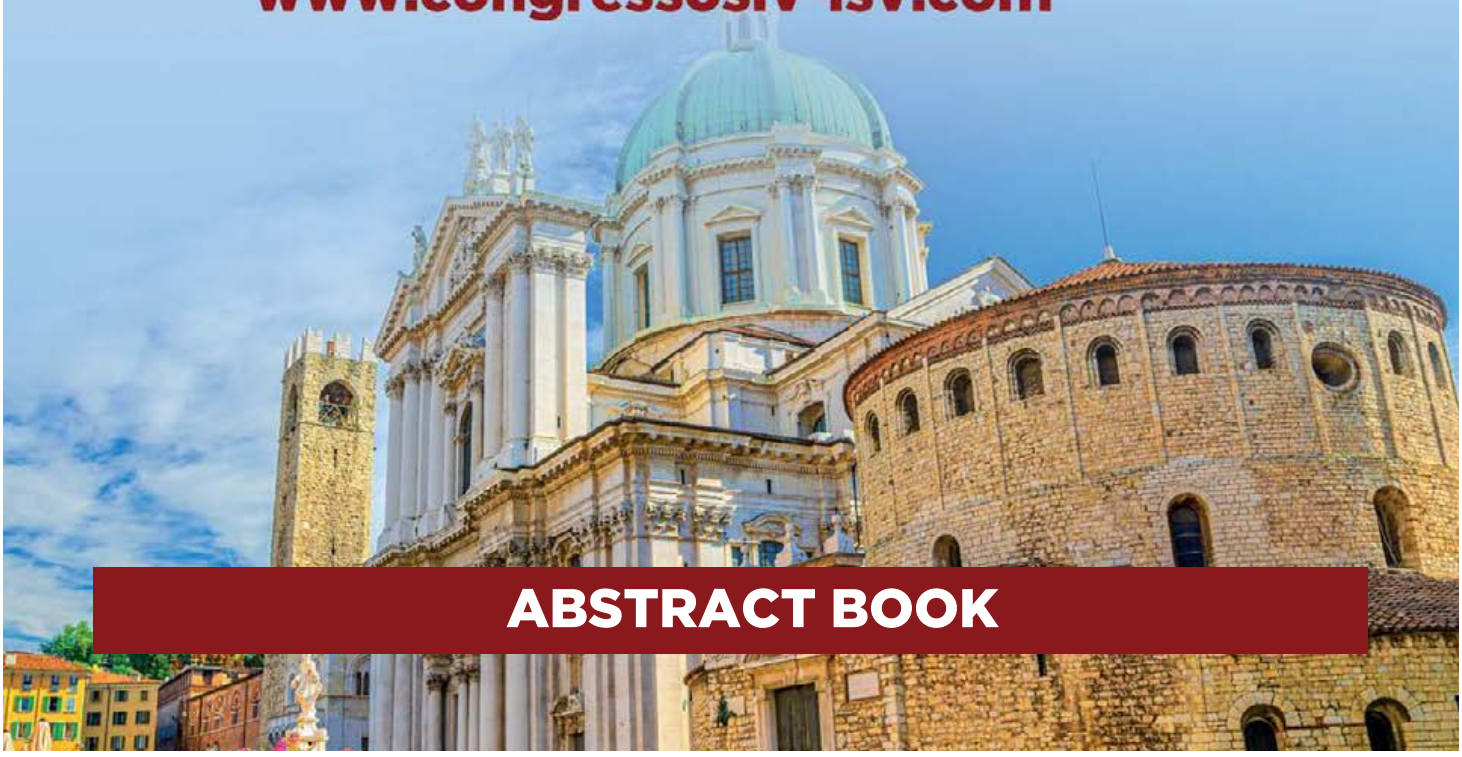

ABSTRACT BOOK

PO 096

EXPLOITING LIPID METABOLISM BY HSV-1: A CHALLENGE TO RETHINK NEW THERAPIES FOR ALZHEIMER'S DISEASE

L. Trifirò[1], C. Albano[1], S. Pasquero[1], F. Gugliesi[1], G. Bajetto[2], W. Hewelt-Belka[3], E. Mina[4], P. Porporato[4], D. Cairns[5], D. Kaplan[5], A. Mullis[5], S. Landolfo[1], M. De Andrea[1,2], V. Dell'Oste[1], M. Biolatti[1]

[1] Department of Public Health and Pediatric Sciences, University of Turin, Italy
[2] CAAD Center for Translational Research on Autoimmune and Allergic Disease, Novara, Italy
[3] Department of Analytical Chemistry, Gdańsk University of Technology, Gdańsk, Poland
[4] Department of Molecular Biotechnology and Health Sciences, University of Turin, Italy
[5] Department of Immunobiology, University of Arizona, Tucson, Arizona, USA

Introduction: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive decline in cognitive functions leading to memory loss and dementia. Only a minority of AD cases have a genetic inheritance and are referred to as familial AD, most (90%) of them are sporadic. Among the environmental risk factors that may promote the development of AD, persistent brain infections, particularly those induced by herpes simplex virus-1 (HSV-1), seem to play a key role in AD pathogenesis although the underlying mechanisms have not been fully elucidated yet. Tightly connected with AD etiopathogenesis is an alteration of lipid metabolism. Recently, CMS121 was shown to protect transgenic AD mice by reducing cognitive loss and inflammation. Interestingly, fatty acid synthase (FAS), a key enzyme in the synthesis of lipids that is increased in AD patients, was identified as a target of CMS121. Considering that cellular lipid metabolism plays a pivotal role in viral infections and that the mechanisms for the metabolic reprogramming by HSV-1 are still poorly understood, we aim at dissecting the host metabolic pathways modulated by HSV-1 in a neuronal-like cell line to identify new targets to prevent AD.

Methods: The experiments were performed in SH-SY5Y neuronal-like cells. The cells were successfully infected with HSV-1, thus representing a suitable *in vitro* model of HSV-1-associated neuronal pathologies. Next, cells were treated with different compounds (*i.e.*, CMS121, C75, SSO) targeting lipid metabolism to test the antiviral activity. Moreover, to understand the link between FAS and HSV-1 infectivity and rule out any off-target effects of the inhibitors, FAS gene expression was silenced by specific short hairpin RNA (shRNA).

Results and Conclusion: We demonstrated the capability of HSV-1 to upregulate the expression of the main lipogenesis enzymes. Accordingly, lipidomic analyses revealed an increase in both *de novo* synthesis and lipid storage following HSV-1 infection, confirming the role of HSV-1 in the deregulation of lipogenesis. In addition, we showed that the virus was still able to replicate upon treatment with compounds, but with reduced infectivity. Thus, we may speculate an antiviral activity of the drugs during virion assembly, leading to a block of virus production.
Overall, our data unveil new aspects of HSV-1-AD interplay and uncover new potential targets to rethink new possible therapies for AD.