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Meeting Report

1st SIV International Workshop on Neurovirology

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The 1st SIV International Workshop on Neurovirology was held on June 23–25, 2002, at the Porto Conte Research Center, Tramariglio (Sassari, Italy), cochaired by A. Dolei (University of Sassari) and G. Palù (University of Padova, Italy). Invited lectures and selected oral communications covered the following topics: virus-related neurological diseases, viral neuropathogenesis, latency and reactivation, viral infections and autoimmune diseases, virus-associated tumors, prion diseases, emerging viral infections, stem cell technology, and gene therapy.

In the session ***Emerging viral infections***, H. Ludwig (Berlin) described the biomolecular and structural features of Borna disease virus (BDV), as well as its pathogenic potential for a wide range of animal species. L. Bode (Berlin) provided evidence of BDV infection of humans, strengthened a clinical role of BDV in human mental disorders, such as acute major depression, and proposed new diagnostic and therapeutic perspectives for this disease. West Nile flavivirus was analyzed by F. Marturana (Cagliari) as a model to envisage chemotherapeutic compounds against RNA-dependent RNA polymerase, helicase-ATPase, and RNA capping. The Toscana bunyavirus (TOSV) has been illustrated with respect to natural history of the infection, as well as to clinical and diagnostic aspects, by P. Verani Borgucci (Rome), P. E. Valensin (Siena) and M. Valassina (Siena), while M. G. Cusi (Siena) analyzed cell-mediated and humoral responses of humans to TOSV, and the potential use of TOSV components for vaccines.

The session ***Viral infections and autoimmune diseases*** was dedicated to multiple sclerosis (MS) whose prevalence is very high in Sardinia, Italy. The epidemiology was described by G. Rosati (Sassari), while S. Sotgiu (Sassari) covered the genetic and environmental (infectious) factors related to MS pathogenesis. H. Perron (Marcy L'Etoile) described the role played in this disease by the multiple sclerosis–associated retrovirus (MSRV), an endogenous retrovirus of the HERV-W family able to produce circulating virus particles, particularly in inflammatory conditions, that can be transactivated by other viruses, such as the HHV-6 herpesvirus. MSRV components possess gliotoxic and superantigen activities that might be the basis of inflammatory and autoimmune reactions in MS, and in other autoimmune diseases. A. Dolei (Sassari) reported on the complete concordance between MSRV positivity in blood and MS disease and progression among Sardinians, as well as the prognostic value of cerebrospinal fluid (CSF) positivity to MSRV, whose production *in vitro* is induced by proinflammatory cytokines. Data on the role of HHV-6 in MS were presented by C. Cermelli (Modena and Bethesda), who detected levels of HHV-6 DNA within MS lesions, by using a Robot-MicroBeam laser microscope to pick up specific brain areas. E. Caselli (Ferrara and Modena) found in MS patients increased prevalence of antibody to HHV-6 U94/REP protein, a unique gene product expressed during HHV-6 latency.

As for ***Viral neuropathogenesis, latency and reactivation***, B. Roizman (Chicago) stressed how many herpes simplex virus (HSV) genes encode for proteins involved in mechanisms subjugating the cell and scavenging it for useful cellular proteins and subverting them for viral use (inhibition of cell protein synthesis by degradation of pre-existing mRNAs, blockage of splicing, and ubiquitination of cellular proteins; blockage of interferon defense pathway and apoptosis; viral antigen presentation; etc.). Each of these systems may differently contribute to virus pathogenicity in various phases of infection and particular host cells. The diagnostic problems of encephalitis by HSV-1 and HSV-2 were highlighted by M. Zavattoni (Pavia) based on a wide experience of clinical and laboratory investigations. The interactions between the nuclear matrix network and Epstein Barr virus (EBV) latent (oriP) and lytic (oriLyt) origins of replication were discussed by E. Mattia (Rome), as possible mechanisms controlling herpesvirus lytic or latent infections. Data on novel neuropathogenetic mechanisms by human immunodeficiency virus-1 (HIV-1) were reported by S. Amini (Philadelphia), who demonstrated that HIV/Tat protein interferes with

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MAPK/ERK1/2 activity, the downstream central component of the nerve growth factor (NGF) neuronal signaling pathway, and binds to the Pur alpha cellular protein. Tat binding to cell surface receptors presynaptically located on cortical cholinergic terminals, eliciting acetylcholine release, was shown by A. Pittaluga (Genoa). This finding might relate to impairments of learning and memory observed during HIV-1 infection and leading to AIDS dementia complex (ADC). P. Cinque (Milan) discussed the central nervous system (CNS) as a target organ of HIV infection, persistence, and virus reservoir. She underlined the role of HIV-1 in ADC and showed differential kinetics of viral response following highly active antiretroviral therapy (HAART) in SNC and plasma. This model of dual CSF infection is important for diagnostic purposes, in order to distinguish true from transient CNS involvement. The JCV human polyomavirus as causative agent of progressive multifocal leukoencephalopathy (PML) was analyzed by P. Ferrante (Milan) with respect to genotype and transcriptional control region rearrangements. JCV detection in CSF and PML response to cidofovir during HAART regimen were discussed by M. Merighi (Verona) and by S. Bossolasco (Milan); both of them concluded that clinical outcome was not correlated to cidofovir administration.

In the session ***Polyomaviruses and brain tumors***, M. Tognon (Ferrara) proposed SV40 as a virus entered in the human species, because his group detected SV40 footprints in human specimens from brain tumors and other tumors (osteosarcomas, mesotheliomas, lymphomas), whereas normal tissues were negative. SV40 sequences were also detected, at low frequency, in blood cells. Possible transmission routes might be blood and sexual intercourse. According to Barbanti-Brodano (Ferrara), the oncogenic mechanism common to the three human polyomaviruses (SV40, JCV, and BKV) would reside on the transforming properties of T-antigen (binding to p53 and Rb oncosuppressor proteins) and on the mutagenic activity of the viral genome. These would induce chromosomal aberrations early after infection, generating a "hit and run" mechanism, where genomic alterations of the host cell remain fixed even after subsequent loss of viral sequences. Recent data on human mesothelioma (with few cells expressing T-antigen) demonstrate that SV40 is able to activate the c-met/HGF signaling with an autocrine-paracrine mechanism, suggesting the existence of a new oncogenic mechanism. K. Khalili (Philadelphia) presented data on JCV agnoprotein, a late protein expressed in human medulloblastoma able to activate Wnt signaling pathway, and suggested a potential role for agnoprotein in pathways involved in development of JCV-associated medulloblastomas. This new oncogenic mechanism may be active even in the absence of T-antigen expression and of p53 alterations. It seems reasonable, therefore, to recognize human polyomaviruses as new oncogenic agents and convey the oncogenic mechanisms of these viruses towards the main pathways of human carcinogenesis.

In the ***Prion disease*** session, A. Aguzzi (Zurich) described the mechanism of neuroinvasion by the prion protein (PrPsc). From the first portal of entry in the gut, represented by M-cells, the lymphoreticular system is diffusely colonized by the agent, accumulating in follicular dendritic cells (FDC) that would capture PrPsc via complement receptors. There is an absolute requirement for B-lymphocytes, probably for presentation of lymphotoxin-β to FDC. From lymphoreticular organs, PrPsc progresses to the CNS, probably via sympathetic nerves. New insights on the comprehension of prion disease pathogenesis and the role, still hypothetical, of PrPsc as unique infectious agent were provided by J. Manson (Edinburgh), who evaluated the effect of specific mutations of the *Prnp* gene in transgenic mice on the onset of transmissible spongiform encephalopathy (TSE). The gene-targeting system used (substitution of the wild-type gene with a mutated one in embryonal stem cells) can avoid interference linked to gene dosage, to barrier to infection between species, and to the original and real infectivity of prion strains. Two presentations by F. Cardone (Rome) and M. Pocchiari (Rome and Bethesda) presented data on the inactivation of prion infectivity (which is unusually resistant to common procedures) by the chemical compound phthalocyanine tetrasulfonate, and by physical methods, such as temperature under very high pressure. These systems might be extremely useful in the food-processing industry and in TSE therapy.

The ***Stem cell technology and gene therapy*** section included data of L. Magrassi (Pavia) on neural stem cells, documenting the poor plasticity and transdifferentiation of neural stem cells (particularly of cerebellar precursors), despite recent data from the literature, because these cells do not regulate their differentiative pathway according to their site of integration after heterotopic/heterochronic grafting; higher plasticity is presented by neural precursors from the olfactory mucosa and striatum. These data must be taken into account in view of possible use of stem cells in therapy. A pilot study of gene therapy in patients with recurrent, end-stage glioblastoma multiforme involving the use of retroviral and herpetic vectors was presented by G. Palù (Padua and Vicenza). Twelve patients have been treated for the first time with a combination of two genes (IL-2 and HSV/TK) without toxic effects and with encouraging results. Finally, P. Marconi (Ferrara) constructed a variety of replication-defective HSV vectors expressing multiple neurotrofic factors, and tested them singly or in combination on animal models of neurodegenerative diseases, providing evidence of increased cell proliferation and neuronal survival.

The final program can be found at the web site http://www.siv-virologia.it/Congressi1.htm.