Journal of NeuroVirology, 9(suppl. 1): 1–2, 2003
 ISSN 1355-0284/03 $12.00+.00
DOI: 10.1080/13550280390195414

Taylor & Francis
Taylor & Francis Group

Guest Editorial

Basic, clinical, and epidemiological studies of progressive multifocal leukoencephalopathy: Implications for therapy

Jeymohan Joseph[1] and Eugene O Major[2]

[1]*Neurovirology, Genetics and Molecular Therapeutics Program, Center for Mental Health Research on AIDS, National Institute of Mental Health, Bethesda, Maryland, USA and* [2]*Laboratory of Molecular Medicine and Neuroscience, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, USA*

The Neurologic AIDS Research Consortium (NARC) with support from the National Institute of Neurologic Disorders and Stroke (NINDS) organized the first major meeting on the biology of JC virus and progressive multifocal leukoencephalopthy (PML) in Chicago (February 2001). In recognition of the fact that the incidence of PML has increased in the AIDS (acquired immune deficiency syndrome) era, the key goal of this meeting was the integration of current basic and clinical knowledge to facilitate rapid development of therapeutic options. This meeting proved to be enormously successful in updating the basic and clinical scientists on the major issues and challenges of understanding and treating JC virus–induced demyelinating disease.

The advent of highly active antiretroviral therapy (HAART) has had significant benefits for AIDS patients due to reduced viral load and increased numbers of CD4 T cells. However, successful treatment of human immunodeficiency virus (HIV) infection is not always associated with an improved outcome for PML patients. Therefore, it is widely believed that an urgent need exists to develop and test additional therapeutic modalities that directly target JC virus. It is this realization that led the National Institute of Mental Health (NIMH), the Office of Rare Diseases (ORD), and the NINDS to convene a second meeting in July 2002 in Portland, Maine, to reassess the current state of basic, clinical, and epidemiologic knowledge in the field. Another important goal of the meeting was to define risk factors for PML disease, in order to facilitate early initiation of therapy.

It was evident from the scientific presentations that substantial progress was made in understanding the basic biology of JC virus since the first major PML meeting was held in Chicago (February 2001). There is additional knowledge related to binding and attachment of JC virus to target cells and the subsequent trafficking of virions to the nucleus. There is a better understanding of the complexity of T′ proteins and their potential role in blocking T antigen–induced apoptosis. Further information has emerged on JC virus agnoproteins that has been colocalized with the cellular cytoskeletal protein tubulin, predominantly in the perinuclear region of the cytoplasm. Agnoproteins also exhibit negative regulatory effects on YB-1–mediated activation from JC virus promoters. Additional interesting data were presented on the JC virus minor capsid protein VP2 that was demonstrated to bind to DNA. This finding may be critical to defining the mechanism of virion assembly of the JC virus. Taken together, the improved understanding of the basic biology of JC virus may provide opportunities for preliminary testing of novel therapeutic approaches targeted at the virus cell-receptor interactions or subsequent steps in viral replication and virion assembly.

Substantial progress has also been made in understanding the role of the immune response in regulating PML disease outcome. It is becoming increasingly clear that several parameters have to be taken into account when considering the role of immune response in clinical outcome of PML. These include timing of HAART onset, compliance to treatment, size and location of PML lesions, and JC virus viral load in the cerebrospinal fluid (CSF).

Epidemiological data presented at the meeting demonstrated the high prevalence of JC virus in urine and sewage samples. This suggests that food and

This workshop was made possible by support from the Office of Rare Diseases, National Institute of Mental Health, and National Institute of Neurological Disorders and Stroke. The editors are indebted to them for their recognition of the importance of research in this area. The editors would like to thank the Journal of NeuroVirology Editorial Office and Ms. Ruth Briggs, Editorial Assistant for the *Journal of NeuroVirology* for coordinating the publication of this special issue.

fomites could be a source of infection and may serve as vehicles for JC virus transmission. Additional epidemiologic studies that examine the prevalence of PML in India and Africa have yielded particularly intriguing results. Data are emerging that the number of PML cases reported has been low in spite of increasing infections with HIV. Research on defining the biological basis of this epidemiological finding could yield important clues to the pathogenesis of PML.

The clinical session underscored the disappointing finding that the prevalence of PML in the HAART era has not declined and may actually be increasing because of immune reconstitution. These studies reinforce the urgent need to develop additional therapeutic modalities for PML. Given the relative lack of therapeutic agents that target JC virus it was widely felt that agents such as beta interferon and chlorpromazine should be explored in the clinical trials.

The research reports presented in this special issue highlights the data of the basic, clinical, and epidemiological studies of PML presented at the meeting held in Portland, Maine (July 25–26, 2002). We believe it is important to preserve the scientific advances presented at the meeting and hope that the new knowledge will set the stage for developing new treatment modalities for this devastating disease.

We also wanted to highlight an important outcome of this meeting in the clinical arena. It was felt that a need exists for consistent definition of HIV-associated cases of PML, especially following profound disease changes that have resulted from HAART. A standard patient classification scheme was devised that best reflects the biological events underlying the clinical manifestation of PML. Establishing this standard terminology will facilitate tracking of JC virus–associated central nervous system (CNS) disease in the future following anti-HIV or anti–JC virus treatments. This classification scheme is included in this supplement.