ARSENIC TRIoxide INDUCES GANCIClovIR SUSCEPTIBILITY AND APOPTOSIS IN EPSTEIN-BARR positive cancers

Sides MS*, Block GJ**, Shan B†, Sosulski ML†, Esteves KC†, Lin Z***, Flemington EK***, Lasky JA†
* Department of Medicine, Section of Pulmonary Disease and Critical Care, ** University of
Washington Institute for Stem Cell and Regenerative Medicine. Seattle, WA, USA,
*** Department of Pathology, Tulane University School of Medicine, New Orleans, LA USA

The Epstein-Barr virus (EBV) is a ubiquitous gamma herpesvirus that is considered the
causative agent in anaplastic nasopharyngeal carcinoma (NPC), Burkitt’s lymphoma (BL), B-cell
lymphoproliferative disease, Hodgkin’s disease, T-cell lymphomas, and post transplant
lymphoproliferative disease. The promyelocytic leukemia protein nuclear bodies (PML NBs)
have been implicated in host immune response to viral infection. PML NBs are targeted for
degradation during reactivation of herpes viruses, suggesting that disruption of PML NB function
supports this aspect of the viral life cycle. Our finding that the EBV encoded Latent Membrane
Protein 1 (LMP1) induces PML NB immunofluorescence intensity led to the hypothesis that
LMP1 may upregulate PML NBs as a means of maintaining EBV latency. Increased PML
protein and morphometric changes in PML NBs were observed in EBV infected alveolar
epithelial cells and nasopharyngeal carcinoma cells. Treatment with low dose arsenic trioxide
disrupted PML NBs, reactivated the EBV lytic cycle, and conferred susceptibility to ganciclovir in
EBV positive NPC cells but not in uninfected parental control cells. Additionally, low-dose ATO
induced apoptosis in EBV positive BL cell line Mutu-1 though not in the EBV negative Mutu-1<DNE1>.
This study introduces a possible method of treatment for EBV positive tumors by
combining two FDA approved agents in co-treatment at levels well below those currently used in
the clinical setting. This targeting of EBV positivity rather than the rapid replication of the cancer
cell may provide an additional tool for the treatment of EBV positive tumors when used in
conjunction with current therapies.

This work was supported by the NIH Grant RO1HL083901 to JL and Louisiana Board of
Regents LEQSF(2008-10)-RD-A-26 to BS. MS was supported by Louisiana Board of Regents
RSGS Grant LEQSF (2006-11)GF06