POSTER PRESENTATION



Open Access

A novel HSP90 inhibitor, 17-DMAG, induces Tax down-regulation and its oral administration to ATL-model mice intervenes against the infiltration property of the ATL-like lymphocytes and provides extended survival period

Emi Ikebe¹, Akira Kawaguchi^{2,6}, Kenta Tezuka³, Shinya Taguchi¹, Satoshi Hirose¹, Takashi Matsumoto¹, Takahiro Mitsui¹, Kazuyo Senba¹, Akira Nishizono¹, Mitsuo Hori⁴, Hiroo Hasegawa⁵, Yasuaki Yamada⁵, Takaharu Ueno³, Yuetsu Tanaka⁶, Hirofumi Sawa⁷, William Hall⁸, Yasuaki Minami⁹, Kuan-Teh Jeang¹⁰, Masao Ogata¹¹, Kazuhiro Morishita¹², Hideki Hasegawa², Jun-ichi Fujisawa³, Hidekatsu Iha^{1*}

From 16th International Conference on Human Retroviruses: HTLV and Related Viruses Montreal, Canada. 26-30 June 2013

In the peripheral blood leukocytes (PBL) infected with human T-cell leukemia virus type-1 (HTLV-1), which causes HTLV-1 associated diseases including adult T-cell leukemia (ATL), HTLV-1 associated myelopathy (HAM) and HTLV-1 uveitis (HU), NF- κ B-mediated anti-apoptotic signals or inflammatory signals are constitutively activated primarily by the HTLV-1 encoded oncoprotein Tax.

Tax interacts with the I- κ B kinase regulatory subunit, NEMO, to activate NF- κ B, and this interaction is maintained in part by a molecular chaperone, Hsp90, and its co-chaperone Cdc37. The antibiotic geldanamycin (GA) inhibits Hsp90's ATP binding for its proper interaction with client proteins. Administration of a novel water soluble and less toxic GA derivative, 17-dimethylaminoethylamino-17demethoxygeldanamycin hydrochloride (17-DMAG) to Tax-expressing ATL transformed cell lines, C8166 and MT4, induced significant degradation of Tax. 17-DMAG also facilitated growth arrest and cellular apoptosis to C8166 and MT4 and other ATL cell lines while this treatment has no apparent effects on normal PBLs. 17-DMAG also down-regulated Tax-mediated intracellular signals including activation of NF- κ B, AP-1 or HTLV1-LTR in Tax-transfected HEK293 cells.

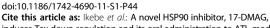
¹Department of Infectious Diseases, Oita University, Faculty of Medicine, Japan Full list of author information is available at the end of the article

Oral administration of 17-DMAG to ATL-model mice xenografted with lymphomatous transgenic Lck-Tax cells or HTLV-1 producing tumor cells dramatically attenuated the aggressive infiltration into multiple organs, viral replication and improved survival periods. These observations identified 17-DMAG as a promising candidate for prevention of ATL progression.

Authors' details

¹Department of Infectious Diseases, Oita University, Faculty of Medicine, Japan.
²Department of Pathology, National Institute of Infectious Diseases, Japan.
³Department of Microbiology, Kansai Medical University, Japan. ⁴Department of Hematology, Ibaragi Pref. Central Hospital, Japan. ⁵Department of Ladotavity Graduate School of Biomedical Sciences, Japan.
⁶Department of Immunology, Graduate School of Medicine University of Ryukyus, Japan. ⁷Department of Molecular Pathobiology, Hokkaido University Research Center Zoonosis Control, Japan. ⁸Department of Medicine and Microbiology, Centre Research Infectious Disease, Conway Institute Biomolecular Biomedical Research University, Coll. Dublin, Ireland. ⁹Department of Biotechnology, Maebashi Institute Technology, Japan. ¹⁰Laboratory and Molecular Microbiology, Oita University, Faculty of Medicine, Japan. ¹¹Department of Medical Sciences, Faculty of Medicine, Japan.

Published: 7 January 2014



induces Tax down-regulation and its oral administration to ATL-model mice intervenes against the infiltration property of the ATL-like lymphocytes and provides extended survival period. *Retrovirology* 2014 11(Suppl 1):P44.



© 2014 Ikebe et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. The Creative Commons Public Domain Dedication waiver (http:// creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.