

Japan Academy Prize to:

Hiroaki MITSUYA
 Professor, Faculty of Life Sciences,
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 Executive Director, National Center for
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 and
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for “Discovery and Development of Antiviral Therapeutics for
 HIV Infection and AIDS”

Outline of the work:

In 1981, a new deadly disease with immunodeficiency causing opportunistic infections and malignancies was reported to be spreading in men having sex with men in the United States. In 1983, a new retrovirus, later designated as human immunodeficiency virus type 1 or HIV-1, was isolated from AIDS patients. However, the modality of transmission was yet largely unknown and the disease terrified even researchers since the disease was contagious, ~80% of those with frank AIDS were dead within 2 years, and no natural recovery was seen. Prof. Hiroaki Mitsuya thought that he had obtained knowledge and skills as to how to possibly combat HIV-1 infection and AIDS (HIV-1/AIDS) through his own study on hematological disorders, especially adult T-cell leukemia that is caused by the first known human pathogenic retrovirus (human T-cell leukemia virus type 1) and steered his efforts to research and development of therapeutics for HIV-1/AIDS. Prof. Mitsuya quickly established the first assay system to evaluate possible antiviral activity against HIV-1 of given test agents and found that azidothymidine (AZT), a member of dideoxynucleoside analogs (ddNs), was highly active against HIV-1 in test tubes. Based on the seminal work done by Prof. Mitsuya, clinical trials of AZT were begun in the National Cancer Institute (NCI). AZT was found to be efficacious in treating patients with HIV-1/AIDS, was eventually approved by the Food and Drug Administration of the United States (FDA), and became the first drug for treating HIV-1/AIDS. Prof. Mitsuya subsequently discovered didanosine (ddI) and zalcitabine (ddC), members of the ddN family, which became the second and third FDA-approved drugs for HIV-1/AIDS treatment. Prof. Mitsuya’s work triggered worldwide efforts to develop therapeutics of HIV-1/AIDS.

Prof. Mitsuya also studied the mechanism of the action of anti-HIV-1 drugs (such as AZT, ddI, and ddC) and the emergence of HIV-1 variants resistant to such drugs. In the meantime, Prof. Mitsuya continued his discovery efforts and succeeded to develop a new protease inhibitor called darunavir (DRV) in collaboration with a renowned organic chemist in the US (FDA-approved in 2007). DRV tightly binds to the backbone of the catalytic center amino acids of HIV-1 protease. The structural configurations of the backbone of amino acids do not change much even with amino acid substitutions that otherwise confer drug resistance on HIV-1 through the decrease or loss of drug binding to the catalytic site of HIV-1 protease. DRV, with its highly

favorable anti-HIV-1 potency and the feature of significantly delaying the emergence of DRV-resistant variants, has presently been used as a first-line drug worldwide. In September 2010, DRV was licensed royalty-free to the Medicines Patent Pool, a United Nations-backed organization: an important step toward making affordable and appropriate HIV-1 medicines available to patients in the low-income countries.

The immense advance to date in the therapy of HIV-1/AIDS has converted HIV-1/AIDS from the “deadly disease” to “controllable chronic infectious disease”. Antiviral therapy has now been proven to be practically capable of blocking HIV-1 transmission from infected mothers to infants and from infected adults to his/her sexual partners.

Prof. Mitsuya’s research not only generated significant impact onto the society, leading to extensive progress in the therapy of HIV-1/AIDS, but also showed for the first time that certain retroviral diseases are treatable with chemotherapy. It is noteworthy that Prof. Mitsuya also became the first to show that certain ddNs such as ddC were active against the reverse transcriptase of hepatitis B virus (HBV) and were capable of blocking HBV replication, which led to later successful development of anti-HBV therapeutics such as lamivudine and entecavir.

List of Publication

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9. Mitsuya, H., Jarrett, R. F., Cossman, J., Cohen, O. J., Whang-Peng, J., Guo, H. G., Reitz, M. S., Jr., and Broder, S.: Infection of human T-lymphotropic virus-I (HTLV-I)-specific immune T-cell clones by HTLV-

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