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Immunotherapy of herpetic recurrence and protective immunity to acute HSV infection by interleukin 2-fused glycoprotein D. *Y. Fujisawa, M. Hazama, A. Mayumi-Aono, S. Hinuma and M. Nakao. Takeda Chemical Industries, Ltd., Research and Development Division, Biology Research Laboratories, Osaka, Japan.*

As an immunotherapeutic approach for herpetic recurrences, co-administration of interleukin 2 (IL-2) and viral antigen was reported. However, dispersion and short half-life of IL-2 in vivo obstruct the lymphokine in exhibiting full activity. We, therefore presumed that co-existence of IL-2 and antigen would circumvent the problems, and constructed fusion protein consisting of truncated glycoprotein D (t-gD) of herpes simplex virus type 1 (HSV-1) and human IL-2. The fusion protein (t-gD-IL-2) was evaluated for the ability to induce protective immunity to acute HSV infection and to treat the herpetic recurrence. The mice immunized subcutaneously with t-gD-IL-2 produced high level of neutralizing antibodies, and protected from HSV infection similarly to the mice immunized with t-gD emulsified with complete Freund's adjuvant. Immunization with t-gD-IL-2 also induced cell-mediated immunity, e.g., DTH response and killer activity against HSV. Interestingly, the nasal instillation of t-gD-IL-2 rendered mice protective state against intraperitoneal HSV infection. In UV-induced herpetic recurrent genitalis model using guinea pigs, advanced administration of t-gD-IL-2 reduced incidence and severity of the disease more significantly than continuous aciclovir administration. These observations indicate that the fusion protein would be a promising immunotherapeutic agent for treatment of HSV recurrent diseases.

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Treatment of Herpes Simplex Virus Type 2 Infections in Mice with Murine and Humanized Monoclonal Antibodies (MABS).

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The purpose of these studies was to compare efficacy of murine and humanized HSV-1 anti-gD and anti-gB MABS in a murine model of neonatal herpes. Neutralizing antibody titers of the murine and humanized preparations were similar against both HSV-1 and HSV-2 strains indicating that humanization did not change the binding or neutralization properties of the MABS. Both anti-gD MABS had greater neutralizing capacity than the anti-gB MABS. In an ADCC assay using human cells, the humanized anti-gD MAB was highly active against both HSV-1 and HSV-2 whereas the anti-gB MABS were inactive. In a brief pharmacokinetic study, mice that received 300 μg of humanized anti-gD or anti-gB had approximately 32 to 84 μg per ml in serum on day 7. In mice infected by the intranasal route with HSV-2, 300 μg of either murine or humanized anti-gD given 24h before infection gave significant protection. Concentrations of 100 to 300 μg of anti-gB were protective. When treatment was delayed until 24h post infection, similar protection was observed. In mice that received 300-600 μg of either murine or humanized MABS, viral replication was prevented in lung, spleen, and kidney and reduced significantly in brain tissue. These data indicate that humanized HSV MABS are protective in an HSV-2 infection of mice and suggest that humanized MABS may have a role in the prevention or treatment of severe HSV infections in humans.