Abstract
Here, I update the recent advances and current status of Granulocyte macrophage colony-stimulating factor (GM-CSF), since we have reported for the first time that porcine GM-CSF gene in a DNA vaccine formulation exerted immuno-adjuvant and protective effects against Aujeszky’s (Pseudorabies) viral disease to the natural host pigs with a single vaccination. GM-CSF has been broadly used as an adjuvant in preclinical DNA vaccine studies for cancer and viral diseases. Currently, GeoVax Labs, Inc. reported a recombinant HIV vaccine (GEO-D03) that co-expresses the human GM-CSF and non-infectious HIV-1 virus-like particles (VLPs) is being evaluated in HIV infected young adults in several Phase I studies (NCT01571960). In addition, I summarized here the outcomes of the use of GM-CSF in DNA vaccine for other viral diseases. Further, phase 3 clinical studies reported that GM-CSF showed an improvement in patient outcome when applied in combination with suitable anti-tumor vaccines. However, GM-CSF in excessive levels was reported to expand myeloid suppressor cells that were shown to dampen adaptive immune responses.

Keywords: Granulocyte macrophage colony-stimulating factor; GM-CSF; Genetic adjuvant; DNA Vaccine; Viral disease; Cancer; Clinical trial

Abbreviations:
GM-CSF: Granulocyte Macrophage Colony-Stimulating Factor; HIV: Human Immunodeficiency Virus; SIV: Simian Immunodeficiency Virus

Introduction
Here, I update the recent advances and current status of Granulocyte macrophage colony-stimulating factor (GM-CSF), since we have reported for the first time [1,2] that a DNA vaccine formulation with porcine GM-CSF gene exerted immuno-adjuvant effects and protected the natural host pigs against Aujeszky’s (Pseudorabies) viral disease with single vaccination. The hematopoietic cytokine GM-CSF has been shown as an efficient adjuvant in DNA vaccine preclinical studies for cancer and viral diseases. Xiang Z et al. [3] first reported that GM-CSF is a genetic adjuvant for DNA vaccine.

GM-CSF as a genetic adjuvant for HIV DNA vaccine in human clinical trials
A recombinant HIV vaccine (GEO-D03) that co-expresses the human GM-CSF and non-infectious HIV-1 virus-like particles (VLPs) is being currently evaluated in HIV infected young adults in several Phase I studies (NCT01571960) [4,5]. This trial will determine whether this vaccine will provide excellent protection in humans as in macaques by simian immunodeficiency virus (SIV)-prototype [6] (NCT01909414).

Lai et al. [7] reported that the SIV vaccine co-expressing GM-CSF achieved significantly higher reduction in risk of infection and protected more SIV challenged macaques in preclinical studies. In addition, this vaccine elicited both anti-viral T cells and antibody. The vaccine-induced prevention of infection was shown to increase from 25% to 71% in the presence of GM-CSF [7]. The outcomes of the use of GM-CSF as genetic adjuvant in DNA vaccine for other viral diseases is given in Table 1.

Use of GM-CSF in Cancer
GM-CSF was found as the most efficient adjuvant for cancer cell vaccines in early preclinical screens of retroviral-expressed cytokines [27]. Further, the ability of the fused GM-CSF to elicit anti-tumor immune responses and boost vaccine efficiency is found in the first licensed cancer vaccine, Provenge [28].

Despite, a number of studies demonstrating cytokines can act as adjuvants in tumor vaccines, the cost prevent their widespread use, except for the GM-CSF. More recently, GM-CSF has shown improved patient outcome in phase 3 studies when applied in combination with suitable anti-tumor vaccines [29].

In addition, GM-CSF is licensed to use as an adjuvant in a fusion protein for a dendritic cell therapy for prostate cancer and for recovery and replacement of white blood cells following bone marrow transplantation and chemotherapy [30]. However, GM-CSF in excessive levels may expand myeloid suppressor cells that were shown to dampen adaptive immune responses [31-33].
Table 1: Efficacy and outcomes of GM-CSF as genetic adjuvant in DNA vaccines for viral diseases.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Efficacy/Outcome of GM-CSF</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Porcine Circovirus Type-2</td>
<td>Pigs immunized with Cap-GM-CSF subunit vaccine showed significantly higher levels of PCV2-specific antibodies and neutralizing antibodies and higher average daily weight gain than pigs receiving immunized with the Cap subunit vaccine and a commercial vaccine (Ingelvac CircoFLEX; P&lt;0.05) after wild-type PCV2 challenge.</td>
<td>[8]</td>
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<td>Flaviviridae Virus</td>
<td>Reported as complex and diverse, ranging from enhancement to suppression, depending on the immunogen of Flaviviridae virus DNA vaccine candidates.</td>
<td>[9]</td>
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<tr>
<td>Simian ImmunoDeficiency Virus</td>
<td>The co-expressed GM-CSF increased vaccine-induced prevention of infection from 25% to 71% in simian immunodeficiency virus in macaques.</td>
<td>[7]</td>
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<tr>
<td>Foot and Mouth Disease</td>
<td>Efficacy of the DNA vaccine with GM-CSF was improved further in reducing the clinical disease and virus excretions by electroporation.</td>
<td>[10]</td>
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<tr>
<td>HIV</td>
<td>Induced long-lived humoral and cell mediated immune memory responses.</td>
<td>[12]</td>
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<tr>
<td>Dengue Virus</td>
<td>DV1 challenged mice showed long-term IgG response, strong cytotoxic T lymphocyte activity, produced high levels of splenocyte-secreted interferon-γ and interleukin-2 and sufficient protection after immunization with pCAG-DV1-GM-CSF immunization than pCAG-DV1/E alone.</td>
<td>[13]</td>
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<tr>
<td>Influenza Virus</td>
<td>GM-CSF gene enhanced systemic and mucosal immunogenicity of the HA DNA vaccine in Rhesus macaque</td>
<td>[14]</td>
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<tr>
<td>Hepatitis B Virus</td>
<td>HBV-S gene fused with GM-CSF strengthened the immune effects of the HBV DNA vaccine in HBV-transgenic mice</td>
<td>[15]</td>
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<tr>
<td>Bronchitis Virus</td>
<td>pVAX-chGM-CSF and pVAX-S1 provided more protection against IBV challenge in chickens than pVAX-S1 vaccination alone.</td>
<td>[16]</td>
</tr>
<tr>
<td>Feline Immuno Deficiency Virus</td>
<td>Preserved global CD4 T lymphocyte function after the challenge.</td>
<td>[18]</td>
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<tr>
<td>Porcine Reproductive and Respiratory Syndrome Virus</td>
<td>Significantly enhanced the humoral and cellular immune responses and protection against PRRSV challenge in pigs.</td>
<td>[19]</td>
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<tr>
<td>Hepatitis C Virus</td>
<td>Reported no change in the Th1/Th2 balance as compared with simultaneous IL-23 administration.</td>
<td>[20]</td>
</tr>
<tr>
<td>Simian-Human Immuno Deficiency Virus</td>
<td>Co-immunization with Flt3-L and GM-CSF showed promise in the development of an effective antiviral HCV vaccine</td>
<td>[21]</td>
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<tr>
<td>HIV-1 Gag</td>
<td>Enhanced IgG response was associated with the best protection, but did not achieve significance.</td>
<td>[22]</td>
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<tr>
<td>Equine Herpes Virus</td>
<td>DNA vaccine with GM-CSF, formulated in DMRIE-DOPE significantly improved virus neutralizing antibody responses to EHV-1.</td>
<td>[23]</td>
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<tr>
<td>HIV-1 Env</td>
<td>The adjuvant treated group showed significantly better control to the challenge than the non-GMCSF group.</td>
<td>[24]</td>
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<tr>
<td>Aujeszky’s (Pseudorabies) Viral Disease</td>
<td>We demonstrated that the Porcine GM-CSF gene in a DNA vaccine formulation exerted immuno-adjuvant and protective effects with single vaccination in the natural host pigs against Aujeszky’s disease.</td>
<td>[1]</td>
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Recent Advances and Current Status of GM-CSF as an Adjuvant in DNA Vaccines for Viral Diseases

References


