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## Advanced Drug Delivery Reviews

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## Preface

CpG oligonucleotides as immunotherapeutic adjuvants: innovative applications and delivery strategies<sup>☆</sup>

Cytosine–phosphorothioate–guanine oligodeoxynucleotides (CpG ODN) have shown significant potential for treatment of a wide variety of diseases including cancer. CpG ODN can be used either as a stand-alone molecule or as an adjuvant to other therapies. CpG ODN with sequence patterns like those found in bacterial DNA activate potent cell-mediated immune responses [1,2]. The specific sequence motif present in bacterial DNA that is responsible for triggering these immune responses is the unmethylated CpG dinucleotide flanked by two 5' purines and two 3' pyrimidines [1–4]. CpG ODN are taken up by cells via adsorptive endocytosis and bind to the toll-like receptor 9 (TLR9) present within the endosomes in the intracellular compartment of B cells and plasmacytoid dendritic cells [5–7]. The binding triggers an immunostimulatory cascade inducing the maturation, differentiation and proliferation of multiple immune cells including B and T lymphocytes, macrophages, natural killer cells and monocytes/macrophages that produce interleukin 1, 6, 12 and 18, interferon- $\gamma$  and tumor necrosis factor- $\alpha$  [8–10].

In contrast to anti-sense therapeutics which requires continuous and prolonged exposure to the therapeutic nucleotide, the effects of CpG ODN can last for long periods of time even after a brief exposure. On the other hand, the duration, location, and formulation of CpG ODN therapy can have a profound effect on the immune response, and on the resulting therapeutic effects. This variability in immunologic and therapeutic response is not surprising given that CpG ODN can enhance antigen presentation, improve cellular killing mediated by T cells or NK cells, increase phagocytosis, increase production of cytokines that have anti-tumor effects or initiate proapoptotic effects on malignant cells that express TLR9. Which of these mechanisms is most important therapeutically depends on many factors including the underlying condition being treated, the state of the immune system, the selection of other agents used in combination with CpG ODN, the route of administration and the formulation of the therapy.

It is therefore to be expected that the efficacy of CpG ODN can be substantially improved using a range of drug delivery systems. This theme issue of *Advanced Drug Delivery Reviews* is to provide a comprehensive summary of the therapeutic potential of CpG ODN in a range of diseases and cancer models and the drug delivery systems that are being developed to further enhance CpG ODN adjuvant efficacy. Vollmer and Krieg provide a strong current overview of CpG ODN as a TLR9 agonist and its therapeutic potential [1,11–13].

Krishnamachari and Salem discuss several drug delivery strategies for ensuring that both CpG ODN and antigen are co-delivered to the same antigen-presenting cells. These approaches include the use of biodegradable microparticles [14], CpG-antigen conjugates [15], liposomes [16], metallic nanorods [17], pulsatile releasing chips [18], and cell-microparticle hybrids [19]. Malyala, O'Hagan and Singh provide a more in-depth review of the use of biodegradable microparticles for delivering CpG ODN whilst Tam offers an analysis of the use of liposomes for enhancing CpG ODN adjuvant efficacy in a variety of infectious diseases [20–22]. Mutwiri and colleagues discuss the use of polyphosphazenes, depot-forming formulations and simultaneous activation with other TLR agonists as methods through which CpG ODNs efficacy as an adjuvant can be improved [23]. Wagner's review provides an in-depth analysis of CpG ODN-antigen conjugates and their comparison to biodegradable microparticles [24]. The theme issue then covers some of the recent developments on the therapeutic application of CpG ODN. Klinman and colleagues discuss the use of CpG ODN as an adjuvant for treatment of infectious diseases [21,25]. Fonseca and Kline provide an overview of the use of CpG ODN in treating asthma, including its use in preventing development of airway remodelling and inhibition of atopic responses [26,27]. Weiner provides an overview of the use of CpG ODN-based therapy of lymphoid malignancies [28]. Lubaroff and Karan discuss the development of CpG ODN as an adjuvant to a vaccine for treating prostate cancer that is based on an adenovirus transduced to express a prostate specific antigen [29]. Finally Miles and Sandler discuss the use of CpG ODN for treating neuroblastoma either as a standalone molecule or as an adjuvant to alternative vaccine strategies [30].

This theme issue on the applications and delivery strategies of CpG ODN brings together a diverse and highly inter-disciplinary set of investigators that range from clinicians to basic scientists. The clinical application of CpG ODN as therapeutic agents is just beginning. This issue provides an up to date comprehensive reference guide of the therapeutic potential and complexities of CpG ODN as an immunotherapeutic adjuvant and the advanced drug delivery methods that can be used to enhance its efficacy.

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