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### Immunoprotective Activity of CpG Oligonucleotides

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Synthetic oligonucleotides (ODN) expressing unmethylated CpG motifs stimulate an innate immune response characterized by the production of polyreactive IgM antibodies and immunomodulatory cytokines. This immune response protects normal mice from infection by a variety of pathogens for approximately 2 weeks. Protection can be maintained indefinitely by repeatedly administering CpG ODN. This protection is associated with a significant increase in the number of immune cells that are rapidly activated to secrete IL-6 and IFN $\gamma$  when exposed to pathogens. CpG ODN also facilitate the development of pathogen-specific immunity, and the subsequent generation of antigen-specific memory. Mice treated repeatedly with CpG ODN remain healthy, and do not develop either macroscopic or microscopic evidence of tissue damage or inflammation.

Two distinct types of CpG-based ODN activate PBMC from humans and non-human primates. “K” type ODN stimulate human monocytic dendritic cells and B cells to proliferate and secrete IL-6 and/or IgM while “D” type ODN stimulate NK cells to produce IFN $\gamma$  and induce monocytes to differentiate into dendritic cells. In vivo studies of rhesus monkeys show that “D” type ODN are particularly effective in boosting the immune response to co-administered antigens and improving the innate immune system’s capacity to control infectious pathogens, mimicking their effect in mice. This activity persists in animals with a diminished adaptive immune response.

Although CpG motifs are present in the primate genome, human DNA suppresses (rather than augments) the activity of co-administered CpG ODN. This reflects the presence of “suppressive” motifs in mammalian DNA that prevent endogenous CpG motifs from chronically stimulating the immune system. These suppressive motifs also inhibit the immunoprotective activity of exogenous CpG DNA. Of interest, pathogenic adenovirus utilize “suppressive” motifs to down-regulate the host’s immune response to virus infected cells. Thus, DNA is emerging as an important component in the regulation of the innate immune system, with ODN expressing stimulatory and suppressive motifs providing fertile ground for studying and improving the host response to infectious agents.