

Oligonucleotide-based Inhibitors of TLR -7, -8 and -9 and their Potential for the Treatment of Systemic Lupus Erythematosus (SLE)

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Increasing evidence links autoimmunity with the overactivation of components of the innate system such as Toll-Like receptors (TLR) and the ability to control TLR activation may thus have great therapeutic potential. Several groups have reported oligonucleotide sequences that can inhibit TLR-9 activation mediated by CpG-containing oligonucleotides in mouse models. We have now developed 3 series of novel oligonucleotide-based inhibitors of TLR signaling. These oligonucleotides include inhibitors of TLR-9, inhibitors of TLR-7 and 8 but not TLR-9 and, most interestingly, sequences that inhibit signals through all 3 receptors. These sequences are active on human B cells and plasmacytoid dendritic cells (PDC) and inhibit cytokine and IFN- λ induction both by appropriate synthetic ligands and by RNA or DNA viruses, respectively. They are active on both mouse and human cells *in vitro* and in mice *in vivo*. The high levels of IFN- λ found in SLE patients which are associated with the severity of the disease appear to be derived from PDC, the dominant source of IFN- λ in the blood. PDC are chronically activated in SLE patients, possibly in response to viral infections or immune complexes (IC) containing nucleic acids. Immune complexes from SLE patients consisting of autoantibodies to dsDNA or to ribonucleoproteins (RNP) have been shown to induce IFN- λ from PDC. We show that inhibitory oligonucleotides block the induction of IFN- λ from PDC by either anti-dsDNA or anti-RNP IC through inhibition of TLR-9 and TLR-7, -8 signaling, respectively. The ability of inhibitory oligonucleotides to block PDC activation by both viruses and nucleic acid-containing IC provides a rationale for their use in the treatment of SLE.

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