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Aptamers for the detection of cytokines and their potential as cytokine inhibitors

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Cytokines are known to play a causative role in the development and progression of many diseases. The use of neutralizing antibodies to specific cytokines has revolutionized the treatment of a broad number of diseases and benefited thousands of patients. However the development and production of these antibodies involves an enormous expense that translates into increased costs for the patients. In addition, some patients develop antibodies to the therapeutic antibodies, thus limiting their effectiveness. DNA aptamers have been identified that bind target proteins with a very high specificity and affinity and thus may represent an alternate approach to neutralizing cytokines. Here we report the development and characterization of DNA aptamers specific for human Interferon-gamma. These DNA aptamers are effective in neutralizing the ability of IFN-γ to rapidly induce STAT1 phosphorylation. Modifying the DNA aptamer, by the addition of a few non-natural hydrophobic bases as a fifth base, greatly increases the affinity to IFN-γ (Kd = 38 pM). The modified aptamers demonstrate increased stability in binding to IFN-γ in the presence of serum and act by directly binding to IFN-γ and preventing the interaction of IFN-γ with its cell surface receptor. Thus DNA aptamers are small molecule inhibitors of cytokine signaling that may offer an alternative approach to the use of neutralizing antibodies.

Biography

Howard A Young obtained his PhD in Microbiology at the University of Washington and carried out Postdoctoral research at the NCI. He was a member of the Laboratory of Molecular Immunoregulation, NCI, from 1983 to 1989 prior to joining the Laboratory of Experimental Immunology in 1989. He was President, International Society for Interferon and Cytokine Research (2004-2005) and served as Chair of the Immunology Division of the American Society for Microbiology. He has also served as Chair of the NIH Cytokine interest Group and co-Chair of the NIH Immunology Interest Group. He is a two time recipient of the NIH Director's Award for Mentoring (2000, 2006) and in 2006 he received the National Public Service Award. In 2007, he was named Deputy Chief, Laboratory of Experimental Immunology.

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