Stimulation and/or Maintenance of Immune Response with Low Doses of IL-2 & Related Agents

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Technology description

Interleukin-2 (IL2) was the first T cell Growth Factor to be discovered, and has been used in the clinic for ~20 years, primarily for the treatment of cancer. The FDA has approved the use of IL2 for the treatment of renal cell carcinoma and malignant melanoma. However, IL-2 is administered at very high doses that cause severe inflammatory side-effects, thus limiting its usefulness as a front-line therapeutic and precluding its development as a vaccine adjuvant, a role it is well-positioned to play as the primoridal T cell growth factor.

Innumerable experiments in animals have demonstrated the efficacy of IL2 as an adjuvant for vaccines. As a result, attempts have been made to ameliorate the toxicity of IL2 by creating altered IL2 molecules (e.g. IL2-Ig chimeras) and by engineering viral vectors that deliver the IL2 gene together with antigens. Although these approaches have shown promise, at present none of these alternative IL2 products are approved by the FDA for use in humans as adjuvants.

One of his clinical key insights is based on two understandings from his basic science work: that the IL2 receptor on T cells and B cells has a much higher affinity for IL-2 than does the slightly different IL2R on natural killer (NK) cells, and that activation of T and B cells is the goal of IL2 therapy, while activation of NK cells is the most likely source of the severe toxicity of current IL2 regimens. There is a low concentration range of [IL2] at which T- and B-cell IL2Rs are saturated, but NK IL2Rs are not. Thus, Dr. Smith tested much lower doses of IL2 and found that doses 100-fold lower than those currently used in cancer therapy could be given daily without toxicity.

This is the dosage range in which Dr. Smith has sought to demonstrate clinical benefit of IL2 as a therapeutic.

Another insight of Dr. Smith's has been that continuous dosing will be more beneficial than intermittent dosing, as has been used in cancer therapy. If IL2 is withdrawn from cells expressing IL2Rs, gene expression stimulated by the IL2R is extinguished and the cells undergo programmed cell death (apoptosis). Thus, intermittent dosing is counter-productive, causing the death of the very cells one is seeking to activate and expand.

Current phase II clinical trials at Weill Cornell are exploring the use of IL2 as an adjuvant for therapeutic HIV vaccines, to boost immune reactivity to HIV to allow the discontinuation of antiretroviral drugs, which are associated with serious metabolic toxicities. In addition, using a similar rationale, clinical trials are ongoing, testing the use of daily low dose IL2 as an adjunct to antiviral therapy for the treatment of

chronic infection with the Hepatitis C Virus. The aim here is to improve the efficacy of the standard antiviral therapy and to abbreviate the time required for treatment, which is now one year.

Institution

Cornell University

Inventors

Kendall Smith