

(19), and *Listeria monocytogenes* (expressing recombinant tumor antigens) (20,21,22). In the case of bacterial adjuvants, the bacterium as a whole may be called an immune adjuvant. But the bacterium as a whole is not required for stimulating a toll-like receptor. What stimulates the toll-like receptor is the various components of the bacterium, such as flagellin, peptidoglycan, and bacterial DNA.

Immune adjuvants can take the form of a reagent that activates CD4⁺ T cells. Knutson et al. (23) and Disis et al. (24) describe the use of reagents that activate CD4⁺ T cells, in the treatment of breast cancer. Where CD4⁺ T cells are stimulated, either by infecting bacteria or viruses or by an administered drug, the CD4⁺ T cells serve as Mother Nature's immune adjuvant. The activated CD4⁺ T cells are Mother Nature's immune adjuvant because, without them, CD8⁺ T cells are not able to reach their

full potential for mediating an attack against infections.

Manegold et al. (25) provides an excellent diagram showing a DC that is activating a CD8⁺ T cell, and showing the activated CD8⁺ T cell attacking a tumor cell.

After activation by DCs, CD8⁺ T cells leave the lymph nodes and enter the circulatory system, where they may encounter tumors. When the CD8⁺ T cells encounter tumors, they may find that chemotherapy or irradiation has enhanced the ability to kill the tumor cell (by mechanisms in addition to activation of the DC).

For example, chemotherapy or irradiation can enhance immune response against tumors by stimulating the living tumor cells to express Fas-receptor (26). Fas-receptor is targeted by CD8⁺ T cells (which bear Fas-ligand), when the CD8⁺ T cells kill tumor cells. Moreover, chemotherapy (27), radiation (28), or

¹⁹Alexandroff AB, Nicholson S, Patel PM, Jackson AM. Recent advances in bacillus Calmette-Guerin immunotherapy in bladder cancer. *Immunotherapy* 2010;2:551–60.

²⁰Brockstedt DG, Bahjat KS, Giedlin MA, et al. Killed but metabolically active microbes: a new vaccine paradigm for eliciting effector T-cell responses and protective immunity. *Nat. Med.* 2005;11:853–60.

²¹Brockstedt DG, Giedlin MA, Leong ML, et al. *Listeria*-based cancer vaccines that segregate immunogenicity from toxicity. *Proc. Natl Acad. Sci. USA* 2004;101:13832–7.

²²Leong ML, Hampl J, Liu W, et al. Impact of preexisting vector-specific immunity on vaccine potency: characterization of *Listeria monocytogenes*-specific humoral and cellular immunity in humans and modeling studies using recombinant vaccines in mice. *Infect. Immun.* 2009;77:3958–68.

²³Knutson KL, Schiffman K, Disis ML. Immunization with a HER-2/neu helper peptide vaccine generates HER-2/neu CD8 T-cell immunity in cancer patients. *J. Clin. Invest.* 2001;107:477–84.

²⁴Disis ML, Wallace DR, Gooley TA, et al. Concurrent trastuzumab and HER2/neu-specific vaccination in patients with metastatic breast cancer. *J. Clin. Oncol.* 2009;27:4685–92.

²⁵Manegold C, Gravenor D, Woytowicz D, et al. Randomized phase II trial of a toll-like receptor 9 agonist oligodeoxynucleotide, PF-3512676, in combination with first-line taxane plus platinum chemotherapy for advanced-stage non-small-cell lung cancer. *J. Clin. Oncol.* 2008;26:3979–86.

²⁶Chakraborty M, Abrams SI, Camphausen K. Irradiation of tumor cells up-regulates Fas and enhances CTL lytic activity and CTL adoptive immunotherapy. *J. Immunol.* 2003;170:6338–47.

²⁷Alagkiozidis I, Facciabene A, Carpenito C, et al. Increased immunogenicity of surviving tumor cells enables cooperation between liposomal doxorubicin and IL-18. *J. Transl. Med.* 2009;7:104.

²⁸Ciernik IF, Romero P, Berzofsky JA, Carbone DP. Ionizing radiation enhances immunogenicity of cells expressing a tumor-specific T-cell epitope. *Int. J. Radiat. Oncol. Biol. Phys.* 1999;45:735–41.