

- Toll-like receptor agonists (TLR agonists)
- Antibodies
- Inhibitors of T regulatory cells (Tregs).

1. Vaccines

Vaccines have the longest history of use of all of the immune modulating drugs (41). Edward Jenner is the scientist most associated with the invention of vaccination. Jenner's vaccination of a boy, James Phipps, involved the removal of fluid from a cowpox lesion on the hand of Sarah Nelmes. The fluid was inserted into two incisions in the skin of Phipps' arm. After 7 days the boy became slightly unwell, but soon recovered (42). Vaccination had a basis in the earlier practice of variolation, which had been practiced in China as early as the Sung Dynasty (960–1280 AD) (43).

2. Cytokines

The “cytokines” encompass three categories of molecules, namely, cytokines, chemokines, and certain growth factors (44). Interferon was the first cytokine to be described, as documented in a paper from 1957 (45). Cytokines function as autocrine signals (secretion and stimulation of the same cell), paracrine and juxtacrine signals (stimulation of nearby cells), or endocrine signals (circulating in the peripheral blood to act on cells remote to the source of production). A small proportion of the cytokines have been used as drugs. For example, interleukin-12 (46) interferon-gamma (47) and interferon-alpha (48) have been tested, or are in actual use, for treating various cancers and immune disorders. The cytokine, granulocyte-macrophage colony-stimulating factor (GM-CSF), has shown promising results for treating melanoma (49) lymphoma (50)

⁴¹ Plotkin SA, ed. *History of Vaccine Development*. New York, NY: Springer, Inc.; 2011.

⁴² Morgan AJ, Parker S. Translational mini-review series on vaccines: the Edward Jenner Museum and the history of vaccination. *Clin Exp Immunol*. 2007;147:389–394.

⁴³ Oldstone MBA. *Viruses, Plagues, and History: Past, Present and Future*. New York, NY: Oxford University Press; 2009;74.

⁴⁴ Tarrant JM. Blood cytokines as biomarkers of in vivo toxicity in preclinical safety assessment: considerations for their use. *Toxicol Sci*. 2010;117:4–16.

⁴⁵ Isaacs A, Lindenmann J. Virus interference. I. The interferon. *Proc R Soc Lond B Biol Sci*. 1957;147:258–267.

⁴⁶ Alatrash G, Hutson TE, Molto L, et al. Clinical and immunologic effects of subcutaneously administered interleukin-12 and interferon alfa-2b: phase I trial of patients with metastatic renal cell carcinoma or malignant melanoma. *J Clin Oncol*. 2004;22:2891–2900.

⁴⁷ Miller CH, Maher SG, Young HA. Clinical use of interferon-gamma. *Ann NY Acad Sci*. 2009;1182:69–79.

⁴⁸ Bottomley A, Coens C, Suci S, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma: a phase III randomized controlled trial of health-related quality of life and symptoms by the European Organisation for Research and Treatment of Cancer Melanoma Group. *J Clin Oncol*. 2009;27:2916–2923.

⁴⁹ Sato T, Eschelman DJ, Gonsalves CF, et al. Immunoembolization of malignant liver tumors, including uveal melanoma, using granulocyte-macrophage colony-stimulating factor. *J Clin Oncol*. 2008;26:5436–5442.

⁵⁰ Cartron G, Zhao-Yang L, Baudard M, et al. Granulocyte-macrophage colony-stimulating factor potentiates rituximab in patients with relapsed follicular lymphoma: results of a phase II study. *J Clin Oncol*. 2008;26:2725–2731.