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Trends in the development of therapeutic anti-cytokine antibodies

In a recent issue of *Drug Discovery Today*, Zagury and Gallo provided an excellent review [1] that focused on the use of therapeutic anti-cytokine monoclonal antibodies (mAbs). I would like to supply further information about this topic. The Tufts Center for the Study of Drug Development (<http://csdd.tufts.edu/>), founded in 1976, collects clinical development and regulatory review data for a variety of investigational and approved therapeutics, including mAb, recombinant protein and small molecule products. The data are used in our studies of the development of innovative therapeutics by the pharmaceutical and biotechnology industry, and the approval for marketing of these products [2].

As of January 2004, our databases contained records for 311 therapeutic mAbs that entered clinical study sponsored by commercial firms during 1980 through 2003, including 30 anti-cytokine mAbs. These 30 mAbs were designed to target the following cytokines: interferon (IFN)- γ , interleukins 4, 5, 6, 8, 10, 12, 15 and 18, transforming growth factors β 1 and 2, tumor necrosis factor (TNF)- α , and vascular endothelial growth factor

(VEGF). Of the anti-cytokine mAbs, 16 products are treatments for autoimmune diseases (e.g. rheumatoid arthritis, Crohn's disease, psoriasis, systemic lupus erythematosus, multiple sclerosis, allergic rhinitis or asthma). These 16 mAbs target IFN- γ , interleukins 4, 5, 8, 10, 12, 15, 18 and TNF- α . Most (62%) of the products are still in clinical study, although two anti-TNF mAbs, infliximab and adalimumab, are approved in the USA. Therefore, the autoimmune anti-cytokine mAbs have a calculated approval success rate of 33%. In comparison, the cohort of all mAbs studied as treatments for autoimmune diseases (55 products) has an 18% approval success rate, and the cohort of anti-cytokine mAbs studied in any therapeutic category has a 20% approval success rate.

Regarding mAb immunogenicity, humanized and human mAbs (which are designed to elicit little or no immune response from patients) have entered clinical study in increasing numbers over the past decade. For example, nearly 60 humanized mAbs were first administered to humans from 1995–2000, although fewer than 20 human mAbs entered clinical studies in the same period. The number of human mAbs in studies is now beginning to grow – at least 25 human mAbs started human testing between 2001 and 2003. Of the 13 products approved in the USA from

1995–2003, two are murine, three are chimeric, seven are humanized, and one is human. The approved human mAb, adalimumab, is produced in a mammalian cell expression system.

Expansion of the current pipeline to include more studies of both passive and active immunotherapy, especially in light of the role of cytokines in immunological disorders and cancer [3], could benefit patients with chronic and serious diseases in the future. In the near term, patients can benefit from the anti-cytokine mAbs marketed now, and will soon benefit from the launch of the humanized anti-VEGF mAb, bevacizumab, in the USA.

References

- 1 Zagury, D. and Gallo, R.C. (2004) Anti-cytokine Ab immune therapy: present status and perspectives. *Drug Discov. Today* 9, 72–81
- 2 Reichert, J.M. (2003) Trends in development and approval times for new therapeutics in the United States. *Nat. Rev. Drug Discov.* 2, 695–702
- 3 Dranoff, G. (2004) Cytokines in cancer pathogenesis and cancer therapy. *Nat. Rev. Drug Discov.* 3, 11–22

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Target driven chemistry in drug discovery

An increasing number of research groups in industry and academia are exploring target-driven chemistry as a tool to identify new small molecule inhibitors. Complementary to the traditional tools of drug discovery, such as HTS and structure based design, this approach aims to reduce the number of inactive compounds synthesized and screened in the discovery process, as well as to compensate for the lack of precision in the predictive ability of computational chemistry.