FOREWORD

Therapeutic antibodies: past, present and future

Abstract | Over the past 10 years, the market for monoclonal antibodies has grown exponentially. This focus issue brings together articles on the basic biology of antibodies and their therapeutic use, providing an overview of the latest prospects and continued challenges for the development of safe, efficient and affordable therapeutic antibodies.

In 1986, the CD3-specific monoclonal antibody muromonab (Orthoclone OKT3; Janssen-Cilag) was approved by the US Food and Drug Administration for use in the treatment of acute transplant rejection, making it the first therapeutic antibody to be used as a drug in humans. Since then, the field of therapeutic antibody development has flourished, providing new therapies for the treatment of cancer, autoimmunity and inflammatory diseases.

The therapeutic antibody industry has been propelled by the success of the 'big 5': the tumour necrosis factor (TNF)-specific antibodies infliximab (Remicade; Centocor/Merck) and adalimumab (Humira; Trudexa/Abbott), which are routinely used to treat rheumatoid arthritis, as well as Crohn's disease and plaque psoriasis; the human epidermal growth factor receptor 2 (HER2)-specific antibody trastuzumab (Herceptin; Genentech/Roche) and the vascular endothelial growth factor A (VEGFA)-specific antibody bevacizumab (Avastin; Genentech), both of which are used in the treatment of several types of cancer; and the CD20-specific antibody rituximab (Rituxan/Mabthera; Genentech/Roche/Biogen Idec), which is used to treat both rheumatoid arthritis and non-Hodgkin's lymphoma. In 2008, monoclonal antibodies generated revenues of over US$15 billion, the highest earning category of all biological drugs[1]. Cancer and autoimmune diseases are the main indications for monoclonal antibodies, collectively constituting ~78% of the total antibody sales in the US.

Although these and other first-generation monoclonal antibodies have benefited numerous patients, advances in antibody design technology and a deeper understanding of the action of therapeutic antibodies have paved the way for a new and improved generation of therapeutic antibodies, the details of which are discussed in this focus issue of *Nature Reviews Immunology*.

In their Timeline article, Alain Beck, Thierry Wurch, Christian Bailly and Nathalie Corvaia provide an overview of the strategies for therapeutic antibody development. But what are the key challenges for the development of more specific, safer and cheaper antibody-based drugs?

The mechanisms of action of the monoclonal antibodies for the treatment of autoimmune and inflammatory diseases are reviewed by Andrew Chan and Paul Carter. They detail how current therapeutic antibodies can be modified to increase their specificity and decrease potential adverse reactions, for example by modulating their immune effector functions, extending their half-life and optimizing their antigen-binding domains to generate bispecific antibodies.

Louis Weiner, Rishi Surana and Shangzi Wang focus on monoclonal antibodies for cancer therapy. By targeting immune cells and the immunosuppressive tumour microenvironment, as well as by harnessing antibody-dependent cell-mediated cytotoxicity, monoclonal antibodies can be used to modulate the immune response to tumours.

In addition to enhancing the pharmacological properties of monoclonal antibodies, a detailed understanding of the function of their Fc receptors in health and disease has important implications for the optimal use of therapeutic antibodies. Kenneth Smith and Menna Clatworthy describe the role of the only inhibitory Fc receptor for IgG (FcγRIIB) in autoimmunity and infection, and they discuss how this information can influence current and future antibody-based therapies.

Despite great progress in improving the safety of monoclonal antibodies, adverse effects can still occur. László Maródi and Jean-Laurent Casanova propose that the immunodeficiency created by targeting an immune mediator may be viewed as being similar to inherited primary immunodeficiencies and that a deeper understanding of such 'experiments of nature' may help to identify the infectious agents that should be monitored in patients that are treated with monoclonal antibodies.

By examining the successes and failures of the first generation of therapeutic antibodies, we can gain insights into the strategies needed for the development of more specific and safer therapies for the treatment of autoimmunity, cancer and infectious diseases.

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1. Aggarwal, S. *Nature Biotech.* **11**, 987–993 (2009).