



Immunology / Immunologie

Principles of the therapeutic use of monoclonal antibodies in oncology

Wolf H. Fridman

*INSERM U255, IFR des Cordeliers, universités Paris-5 & Paris-6 et hôpital européen Georges-Pompidou, AP-HP, Paris,
15, rue de l'École-de-Médecine, 75006 Paris, France*

Received 14 December 2005; accepted after revision 20 December 2005

Available online 30 March 2006

Presented by Roger Monier

Abstract

Monoclonal antibodies have reached the stage of therapeutic agents, mostly in oncology, as illustrated by their wide use in lymphoma, breast cancer or colorectal cancer. The unravelling of their mechanisms of action and their interactions with their cellular receptors allows us to engineer new classes of therapeutic antibodies with increased efficacy. The identification of some of the tumour escape mechanisms may also help to define new approaches for patient selection and immunomonitoring. The present review addresses these various aspects. *To cite this article: W.H. Fridman, C. R. Biologies 329 (2006).*

© 2006 Académie des sciences. Published by Elsevier SAS. All rights reserved.

Résumé

Principes de l'utilisation thérapeutique des anticorps monoclonaux en cancérologie. Les anticorps monoclonaux sont devenus des agents thérapeutiques, en particulier en cancérologie, comme cela est illustré par leur utilisation dans le traitement des lymphomes, des cancers du sein ou des cancers colorectaux. La meilleure compréhension de leurs mécanismes d'action, de leurs interactions avec leurs récepteurs cellulaires et des mécanismes d'échappement des tumeurs ouvre la voie à l'optimisation de leurs utilisations thérapeutiques. Ces différents aspects sont abordés dans la présente revue. *Pour citer cet article : W.H. Fridman, C. R. Biologies 329 (2006).*

© 2006 Académie des sciences. Published by Elsevier SAS. All rights reserved.

Keywords: Monoclonal antibodies; Oncology

Mots-clés : Anticorps monoclonaux ; Cancers

1. Introduction

Thirty years after the discovery of monoclonal antibodies (mAb) by Kohler and Milstein, and a series of pit falls and disillusiones, mAb have now reached the

therapeutic stage and have become the first market in biotechnology, its major application so far being cancer (Table 1).

As reviewed by Teillaud in this issue, technological modifications have been prominent to allow the establishment of mAb as therapeutic tools. For a long time, mAb have been of murine origin, impairing their use in immunocompetent patients due to of the develop-

E-mail address: herve.fridman@u255.bhdc.jussieu.fr
(W.H. Fridman).

Table 1
Clinical trials based on monoclonal antibody therapy

Molecular target	Antibody	Applications	Number of trials (% of MAB trials)
CD20	Rituximab	oncology	71 (24%)
Her2/neu	Trastuzumab	oncology	42 (15%)
	Pertuzumab		
VEGF ^a	Bevacizumab	oncology	32 (11%)
CD52	Alemtuzumab (CAMPATH-1H)	oncology	20 (7%)
IL2R α (CD25)	Daclizumab (17.1A)	oncology/psoriasis/ITP	12 (%)

Source: September 2003; <http://www.clinicaltrials.gov>.

^a VEGF: Vascular endothelial growth factor.

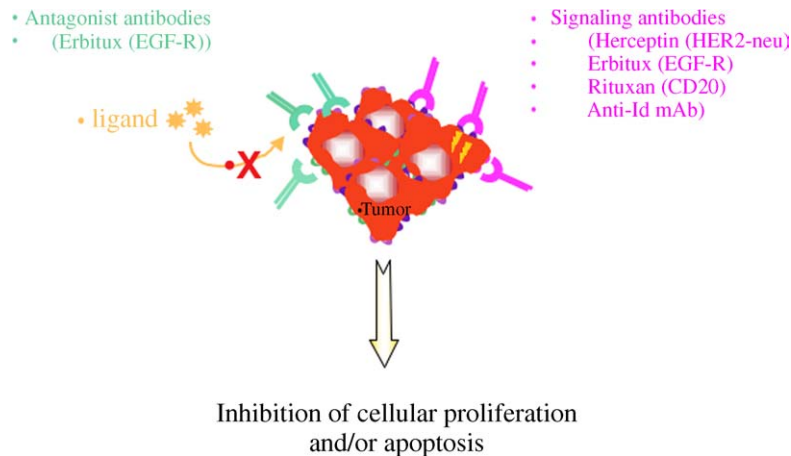


Fig. 1. Mechanisms of action of MoAbs in anti-tumour immunotherapy. (1) Direct mechanisms.

ment of human anti-mouse antibodies (HAMA), which, at least, neutralized the activity of the injected mAb and, at most, were responsible for acute inflammatory syndromes upon repeated treatments with murine mAb. It is therefore not surprising that the only real success of murine therapeutic mAb were anti-lymphocytic antibodies that induced strong immunosuppression needed to help controlling the rejection of renal grafts. Thereafter, the development of mouse-human chimeric, then humanized, mAb and the recent appearance of fully human mAb have solved in great part the HAMA problem and opened the way for the use of repeated injections of mAb in a dosing and a schedule allowing us to reach therapeutic efficacy. Finally, increasing knowledge of the mechanisms of action of therapeutic mAb permits to engineer and to target them in the most appropriate way for the disease and the disease modifications that therapists want to achieve. The present review summarizes these approaches for immunotherapy of cancer, particularly of solid tumours, with special emphasis on the role of Fc Receptors.

2. Antigens targeted by therapeutic mAb in human cancer, and mechanisms of their action

Three types of mAb have been developed and are efficiently used in human cancers. A first type is directed against antigens expressed by tumour cells either specifically, such as Her2-neu on breast cancer and other carcinomas, or shared with normal cells, such as differentiation antigens (CD20, CD52, CD19...). The aim of using the type of antibodies is to induce the death of the tumour either by neutralizing the effect of a growth factor or by inducing apoptosis (Fig. 1) or by activating effector mechanisms of the host, such as complement activation (Fig. 2) or killing by macrophages or NK cells through their interaction with cellular receptors for IgG called Fc γ receptors (Fc γ R) (Fig. 3).

The second type of therapeutic mAb targets the stroma reaction around the tumour. The leader of this type is a mAb that neutralizes V-EGF, a tumour-derived factor that increases neo-angiogenesis that the tumour needs for its high requirements in oxygen and instru-

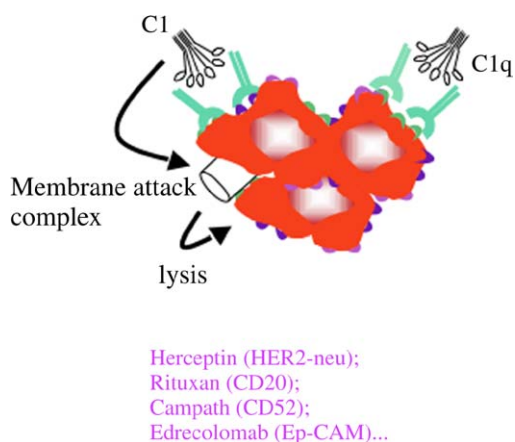


Fig. 2. Mechanisms of action of MoAbs in anti-tumour immunotherapy. (2) Indirect mechanisms: CDC; complement-mediated lysis.

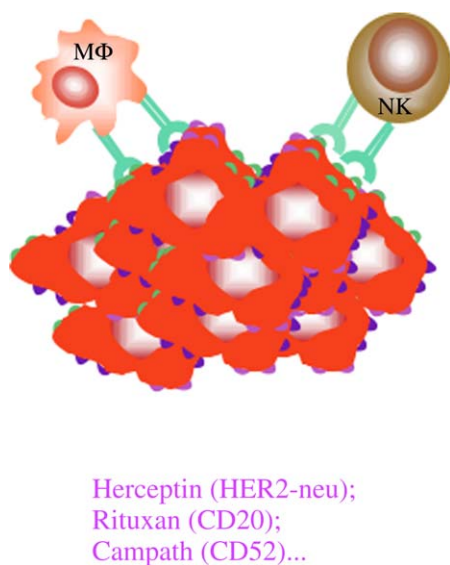


Fig. 3. Mechanisms of action of MoAbs in anti-tumour immunotherapy. (3) Indirect mechanisms: ADCC.

ments. Neutralization of V-EGF blocks angiogenesis and results of hypoxic of the tumour (Fig. 4). Other mAb are being tested, such as those targeting the receptors for V-EGF or neutralizing adhesion molecules or proteases used by the tumour cells to invade its environment.

The third type of therapeutic mAb addresses the potentiation of the immune reactions against tumours. It is now established that there are immune reactions in patients against their non-tumours. It has been strongly suggested 35 years ago in acute leukaemia [1], demonstrated in viral-associated tumours, such as Burkitt lymphoma, cervical carcinoma or hepatocarcinoma, and a

recent study of almost 1000 patients have established the case in colorectal cancer [2].

However, in growing cancers, the immune reaction is inefficient and therapeutic vaccines have still low efficacy. Several mechanisms are used by the tumour to escape the immune system. A first way is to induce lymphocytes that will inhibit the immune reactions. These suppressor, also called regulatory, lymphocytes express specific markers (CD25, CTLA-4, PD1) that can be used as targets of mAb that will inhibit or destroy these cells allowing a better immune response to the tumour (Fig. 5). As expected, however, the first therapeutic trials, especially with a human mAb directed against CTLA-4, have shown that therapeutic efficacy in cancer is accompanied by auto-immunity due to the fact that regulatory cells also control anti-self reactivity.

Another way by which tumours escape the immune attack is by either modulating their surface antigens, or by inhibiting complement cytotoxicity or by ectopically expressing Fcγ receptors. The latter major mechanism is discussed thereafter.

3. Roles of Fcγ receptors in antibody-based therapies

There has been a renewed interest since few years in the use of mAbs in the diagnostic and treatment of various tumours. The most impressive clinical results have been obtained with Rituximab, a chimeric anti-CD20 mAb that recognizes the human oncoprotein HER-2/neu over-expressed in some breast cancers and other tumours, induces clinical responses. Other mAbs such as Campath-1H or 17-1A produced encouraging results in the treatment of chronic lymphocytic leukaemia or colorectal carcinoma, respectively. There is increasing evidence that the Fc portion of the anti-tumour mAbs is a major component of their therapeutic activity, through binding to FcγRs expressed by effector cells present in the tumour microenvironment. The polymorphisms of FcγRIIIb (Val/Phe¹⁵⁸) and FcγRIIa (His/Arg¹³¹) that affect binding of IgG-immune complexes predict the response to Rituximab in patients with follicular lymphoma, supporting the hypothesis that ADCC by NK cells and macrophages plays an important role in the clinical effect. As demonstrated in Fcγ receptor-deficient mice, the anti-tumour effects of Rituximab and Herceptin require the presence of the signal transducing γ chain to activate FcγRI and FcγRIII expressed on monocytes/macrophages and NK cells and are down regulated by inhibitory FcγRIIb at the monocyte/macrophage level. The improved ef-

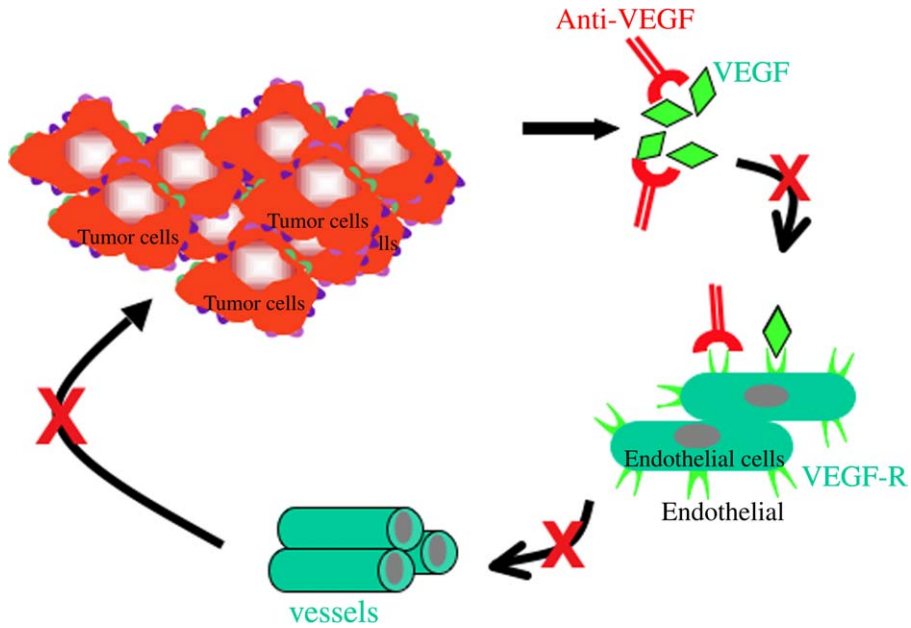


Fig. 4. Mechanisms of action of MoAbs in anti-tumour immunotherapy. (4) Indirect mechanisms.

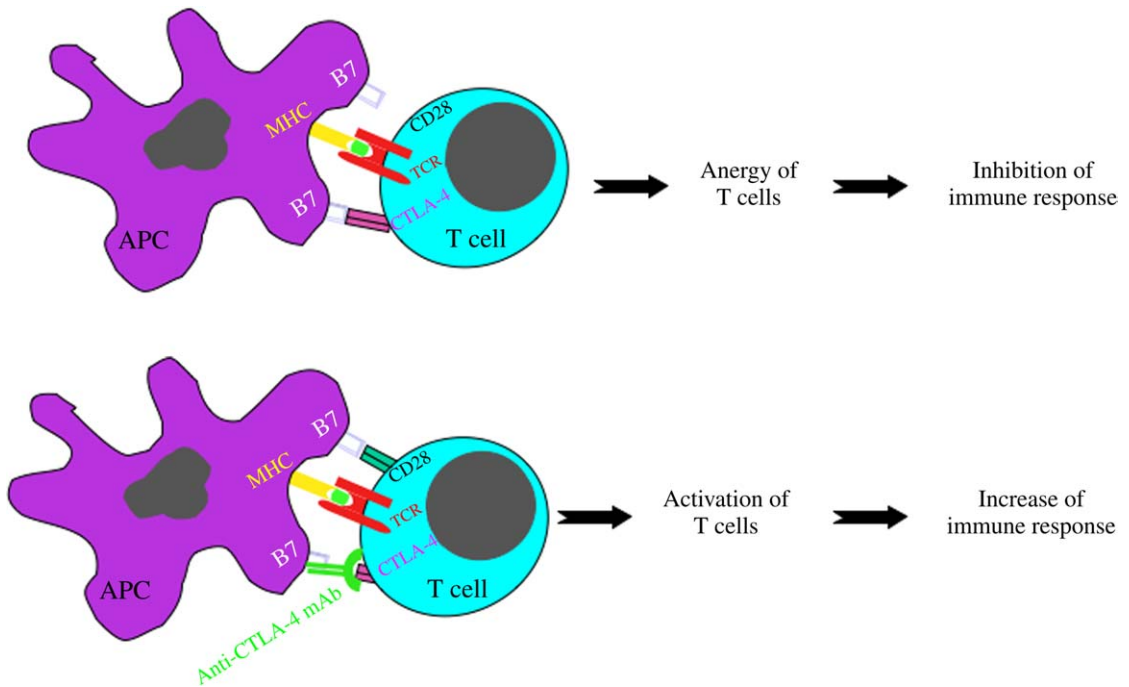


Fig. 5. Mechanisms of action of MoAbs in anti-tumour immunotherapy. (5) Indirect mechanisms: immunostimulatory mAb.

ficacy in tumour eradication of bispecific molecules that have one arm specific for tumour cells and the other specific for Fc γ Rs on immune effector cells, further illustrates the major role of Fc γ Rs in immunotherapy.

In view of their pivotal role in the activation and in the regulation of IgG-dependent effector responses, Fc γ R provide new tools, not only to predict response to antibody-based therapies, but also to manipulate patient's response to treatment [3].

4. Ectopic expression of Fc γ R on non-haematopoietic tumour cells

The first studies indicating that non-haematopoietic tumours may express FcRs that were performed on a variety of experimental tumours and of human cancers. However, the ectopic expression of Fc γ R by non-haematopoietic tumour cells was a controversy because of the presence of Fc γ R positive inflammatory cells at the tumour site and because Fc γ R expression was lost during short-term culture of tumour cells *in vitro*. We reinvestigated the expression of Fc γ R on human tumour cells of non-haematopoietic origin. We found that tumour cells from about 40% of human metastatic melanoma tested express inhibitory Fc γ RIIb1 *in vivo* and *ex vivo* [4].

In earlier studies using Polyoma virus-induced mouse tumours expressing Fc γ RIIb1, it was shown that this receptor confers an *in vivo* growth advantage to tumour cells and increases their malignancy. It was hypothesized that increased tumorigenicity mediated by Fc γ RIIb1 could involve immunological mechanisms. For example, Fc γ RIIb1 expressed by tumour cells could block complement-dependent lysis of tumour cells or could protect tumour cells from ADCC by binding the Fc portion of Abs covering tumour cells. In nude mice, we have shown that Fc γ RIIb1 expression by human metastatic melanomas has a profound down regulatory impact on tumour growth and uptake in nude mice. This effect is under the control of T-independent IgG anti-tumour antibodies. Conversely, in immunocompetent mice, expression of Fc γ R on murine melanoma cells inhibits ADCC and favours tumour growth in the presence of anti-melanoma antibodies [5].

5. Conclusions

The use of therapeutic mAb in oncology is an exploding field, since in its infancy, which will grow not only by the identification of novel targets on tumour cells, their stroma and the immune host response, but also by engineering the mAb to increase their binding to Fc γ R and producing mAb to inhibit the molecules involved in the tumour resistance to the immune attack, such as complement inhibition of FcR. After a quarter of century of scepticism and doubts, the therapeutic mAb have entered for a long time in our modern therapeutic arsenal in all fields of human medicine.

References

- [1] W.H. Fridman, F.M. Kourilsky, Stimulation of lymphocytes by autologous leukaemic cells in acute leukaemia, *Nature* 224 (1969) 277–279.
- [2] F. Pages, A. Berger, M. Camus, F. Sanchez-Cabo, A. Coste, R. Molitor, B. Mlecnik, A. Kirilovsky, M. Nilsson, D. Damotte, T. Meatchi, P. Bruneval, P.-H. Cugnenc, Z. Trajanoski, W.H. Fridman, J. Galon, Effector memory T cells, early metastasis, and survival in colorectal cancer, *N. Engl. J. Med.* 353 (2005) 2654–2666.
- [3] J. Cohen-Solal, L. Cassard, W.H. Fridman, C. Sautès-Fridman, Fc γ receptors, *Immunol. Lett.* 92 (2004) 199–205.
- [4] L. Cassard, J. Cohen-Solal, A. Galinha, X. Sastre-Garau, C. Mathiot, J. Galon, T. Dorval, A. Bernheim, W.H. Fridman, C. Sautès-Fridman, Modulation of tumour growth by inhibitory Fc gamma receptor expressed by human melanoma cells, *J. Clin. Invest.* 110 (2002) 1549–1557.
- [5] L. Cassard, J. Cohen-Solal, S. Camilleri-Broët, A. Spatz, E. Fournier, S. Chouaib, C. Badoual, A. Varin, S. Fisson, P. Duvillard, C. Boix, X. Sastre-Garau, A.N. Houghton, M.-F. Avril, I. Gresser, W.H. Fridman, C. Sautès-Fridman, Selective expression of inhibitory Fc receptor by human metastatic melanoma: a new mechanism of immune escape (submitted).