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# Clinical Efficacy of Antibodies in Cancer Patients

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**Abstract**

Antibody-based therapy for cancer has become established over the past 15 years and is now one of the most successful and important strategies for treating patients with haematological malignancies and solid tumours.

**Keywords:** Antigen targets; Bio-informatic database; Gene mutations; Antibody; Therapeutic efficacy; Immune-mediated cell

## Introduction

Evidence from clinical trials of antibodies in cancer patients has revealed the importance of iterative approaches for the selection of antigen targets and optimal antibodies. The killing of tumour cells using monoclonal antibodies can result from direct action of the antibody, immune-mediated cell killing mechanisms, payload delivery, and specific effects of an antibody on the tumour vasculature and stroma [1]. Tumour antigens that have been successfully targeted include epidermal growth factor receptor, ERBB2, vascular endothelial growth factor, cytotoxic T lymphocyte-associated antigen, CD20, CD30 and CD52. Serological, genomic, proteomic and bio-informatic databases have also been used to identify antigens and receptors that are overexpressed in tumour cell populations or that are linked to gene mutations identified as driving cancer cell proliferation, including EGFRvIII, MET, CTLA4 and fibroblast activation protein. The successful development of candidate mAbs for the clinic involves a complex process of scientific and preclinical evaluations that include identification of the physical and chemical properties of the antibody; the detailed specificity analysis of antigen expression; the study of the immune effector functions and signalling pathway effects of the antibody; the analysis of in vivo antibody localization and distribution in transplanted or syngeneic tumour systems; and the observation of the in vivo therapeutic activity of the antibody [2]. A major objective for the clinical evaluation of mAbs has been determining the toxicity and therapeutic efficacy of the antibody alone or as a delivery system for radioisotopes or other toxic agents. It is also crucial to assess its in vivo specificity by determining its bio-distribution in patients and to assess the ratio of antibody uptake in the tumour versus normal tissues. Twelve antibodies have received approval from the US Food and Drug Administration for the treatment of various solid tumours and haematological malignancies, and a large number of additional therapeutic antibodies are currently being tested in early stage and late-stage clinical trials. This cell killing can be summarized as being due to several mechanisms: direct action of the antibody; immune-mediated cell killing mechanisms; and specific effects of an antibody on tumour vasculature and stroma. The Fc function of antibodies is particularly important for mediating tumour cell killing through CDC and ADCC. All of these approaches have been successfully applied in the clinic.

## Discussion

The abrogation of tumour cell signalling, the induction of effector function primarily through ADCC and the immune modulation of T cell function are the approaches that have been most successful and that have led to the approval of antibodies using these mechanisms. Although most of the antibodies that have been successful in the clinic are intact immunoglobulin G molecules, multiple approaches for antibody construction and for the delivery of conjugated cytotoxic drugs have been used [3]. The broad range of antibody engineering approaches that have been used in the clinic has recently been reviewed. The safety and efficacy of therapeutic mAbs in oncology vary depending on the nature of the target antigen. Ideally, the target antigen should be abundant and accessible and should be expressed homogeneously, consistently and exclusively on the surface of cancer cells. Antigen secretion should be minimal, as secreted antigens can bind the antibody in the circulation and could prevent sufficient antibody from binding to the tumour. If the desired mechanism of action is ADCC or CDC, then it is desirable that the antigen mAb complex should not be rapidly internalized so as to maximize the availability of the Fc region to immune effector cells and complement proteins, respectively. By contrast, good internalization is desirable for antibodies or proteins that deliver toxins into the cancer cell and for antibodies the action of which is primarily based on the down regulation of cell surface receptors. Tumour-associated antigens recognized by therapeutic mAbs fall into several different categories. Haematopoietic differentiation antigens are glycoproteins that are usually associated with cluster of differentiation groupings and include CD20, CD30, CD33 and CD52. Cell surface differentiation antigens are a diverse group of glycol-proteins and carbohydrates that are found on the surface of both normal and tumour cells [4]. Antigens that are involved in growth and differentiation signalling are often growth factors and growth factor receptors. Growth factors that are targets for antibodies in cancer patients include CEA2, epidermal growth factor receptor, ERBB2, ERBB3, MET, insulin-like growth factor 1 receptor, ephrin receptor A3, tumour necrosis factor (TNF)-related apoptosis-inducing ligand receptor 1, TRAILR2 and receptor activator of nuclear factor-κB ligand. Antigens involved in angiogenesis are usually proteins or growth factors that support the formation of new microvasculature, including vascular endothelial growth factor, VEGF receptor, integrin αVβ3 and integrin α5β1. Tumour stroma and the extracellular matrix are indispensable support structures for a tumour. Stromal and extracellular matrix antigens that are therapeutic targets include fibroblast activation protein and tenascin. Considerable effort has

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recently been invested in identifying new antigen targets that are suitable for antibody-based therapies in cancer. Serological, genomic, proteomic and bio-informatic databases have been used to identify antigens and receptors that are overexpressed in tumour cell populations or that are linked to gene mutations identified as driving cancer cell proliferation2,5. Examples of antigens that have been identified as suitable targets for antibody therapy with these approaches include EGFRvIII, MET, cytotoxic T lymphocyte-associated antigen. The successful development of candidate antibodies for the clinic involves a complex process of scientific and preclinical evaluations, informed by deep understanding of cancer biology and the properties of antibodies in vivo [5]. Essential preclinical characterization includes identification of the physical and chemical properties of the antibody; detailed specificity analysis of antigen expression using panels of normal and malignant tissues; study of the immune effector functions and signalling pathway effects of the antibody; analysis of in vivo antibody localization and distribution in transplanted or syngeneic tumour systems; antibody chimerization and humanization; and observation of the in vivo therapeutic activity of the antibody either alone or conjugated with radioactive isotopes or other toxic agents. With regard to the clinical phase of antibody analysis, a major objective has been determining the toxicity and therapeutic efficacy of the antibody either alone or as a delivery system for radioisotopes or other toxic agents [6]. However, one of the most essential steps in the clinical evaluation of a potential therapeutic antibody is in vivo specificity determining the bio-distribution of an antibody in patients to assess the ratio of antibody uptake in the tumour versus normal tissue. This information is essential for the rational design of antibody therapy, for which knowledge about the targeting of normal tissues is crucial for predicting toxicity. In addition, the presence of normal tissue uptake of antibodies can assist with defining dose requirements for achieving optimal tumour and plasma concentration of antibodies, as well as in establishing the possible effects of antigen receptor saturation at high protein-loading doses. At the Ludwig Institute for Cancer Research, we developed a model of a clinical trial that incorporates bio-distribution, pharmacokinetics and pharmacodynamics analyses with toxicity assessment [7]. This trial design has been successfully applied to first-in-human clinical trials of more than 15 antibodies in cancer patients. This approach can identify properties of antibodies, including subtle physic-chemical changes that affect bio-distribution, which can significantly affect efficacy. Normal tissue distribution can be quantitated, thus allowing the relationship of the loading dose to tumour concentration to be accurately assessed, rather than relying on plasma concentration and clearance rates to establish an optimal dose. Examples of the successful use of this approach include the early bio-distribution studies of mouse EGFR specific antibodies, which identified the liver antigen sink for systemic antibody and its effect on the concentration of antibody that reached the tumour; and the more recent studies of trastuzumab bio-distribution and in vivo assessment of ERBB2 expression by tumours [8]. In non-Hodgkin's lymphomas, the bio-distribution of a radio-conjugate in the tumour and an assessment of whole-body dosimetry were essential in initial trials exploring patient suitability for treatment and treatment dose for the US Food and Drug Administration (FDA)-approved CD20-specific radio-immuno-conjugates tositumomab and ibritumomab tiuxetan. In conjunction with other pharmaco-dynamic studies, including computerized tomography with magnetic resonance imaging, positron emission tomography, plasma-based protein, cell and genomic analyses, and tumour biopsies, the effect of antibody abrogation of a signalling pathway function can also be determined. Because antibodies by themselves may have limited therapeutic activity, more emphasis is being placed on increasing the biological effector function of antibodies, such as ADCC and cytotoxicity, and on using antibodies as delivery vehicles for toxic agents. Clinical efficacy of antibodies in cancer patients despite the great promise of antibody-based therapies, we are only beginning to see and explore the full potential of antibodies in the control and therapy of cancer. Since 1997, antibodies have received approval from the FDA for the treatment of various solid tumours and haematological malignancies, and a large number of additional therapeutic antibodies are currently being tested in early stage and late-stage clinical trials. Most antibodies that have been approved have different and often milder toxicities compared with conventional chemotherapeutic agents [9]. Approval for the therapeutic use of these antibodies by regulatory bodies such as the FDA usually requires the demonstration of an overall survival benefit with their use compared with standard therapy use in large Phase III trials. However, in some instances, approval has been granted based on surrogate markers. For example, tumour response rate was used for the approval of bevacizumab in glioblastoma and for gemtuzumab ozogamicin in relapsed acute myeloid leukaemia, and progression-free survival was used for the approval of panitumumab in colorectal cancer. Occasionally, regulatory approval can be based on Phase II data when this is considered sufficiently promising in a disease with few therapeutic options, as occurred for bevacizumab therapy in patients with glioblastoma. The use of therapeutic mAbs in patients with solid tumours has been most successful with classes of anti-bodies targeting the ERBB family and VEGF. Recent evidence showing that patients with colorectal cancer treated with EGFR-specific antibodies who have improved responses, disease control and survival have wild type KRAS has resulted in the approved use of these agents being restricted to patients with colorectal cancer in which KRAS is not mutated. The use of trastuzumab has also been restricted to patients with high levels of ERBB2 expression, as studies have shown that this is the group that derives maximum benefit from trastuzumab treatment. These are examples of predictive biomarkers that are pivotal in optimal patient selection and in regulatory and funding approval. As a result of the clinical success of these anti-bodies, and preclinical data demonstrating the improved tumour response of combined signalling blockade with antibodies to different receptors or to different epitopes on the same receptor, numerous clinical trials of antibodies as combination therapies are currently underway. A number of antibodies have also been approved for the treatment of haematological malignancies, both as unconjugated antibodies and for the delivery of isotopes and drugs or toxins to cancer cells [10]. Rituximab has enjoyed considerable success in patients with CD20-positive NHL and chronic lymphocytic leukaemia.

## Conclusion

Nonetheless, even cancers impervious to the new drugs could be treated if those malignancies have the right error-riddled DNA signature. In its refined version, the genome of a common bacteriophage and synthetic strands that were designed to fold up its DNA are encapsulated and do not encode any proteins or do any of the normal DNA functions. Potentially, the technique should work on most any form of drug-resistant cancer.

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### Conflict of Interest

None

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