

The biological therapy of cancer

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DR PARKINSON. *The biological therapy of cancer. Can J Infect Dis 1992;3(Suppl B):26B-33B.* The current status of biological approaches to the therapy of malignancy is reviewed. Biological response modifiers have been used in immunobiological therapeutic strategies, as myelorestorative agents during chemotherapy, as modulators of cytotoxic chemotherapeutic actions, and as adjuncts to the differentiation therapy of cancer. Immunobiologically active agents currently under study include recombinant cytokines such as interferons-alpha and -gamma, interleukin (IL)-1 and IL-2, and tumor necrosis factor. A range of hematopoietic growth factors are being studied alone or in combination; these include granulocyte-, granulocyte-macrophage- and macrophage-colony stimulating factors, IL-3 and IL-6, and the recombinant growth factor PIXY-321. Targeting strategies to cytotoxic cancer therapy including immunotoxin and radioimmunoconjugate therapy have used monoclonal antibodies and derivative bio-engineered molecules as targeting modalities. Finally, the recent descriptions of therapeutic successes with retinoid-based differentiation strategies opens new possibilities for biologically-based treatment of malignancy.

Key Words: *Biological therapy, Cancer, Cytokines, Hematopoietic growth factors, Retinoids*

Traitemment biologique du cancer

L'état actuel des approches biologiques au traitement du cancer est passé en revue. Les modificateurs de la réponse biologique ont été utilisés dans le cadre de stratégies thérapeutiques immunobiologiques; que l'on pense aux agents myelorestauratifs durant la chimiothérapie, aux modulateurs des actions chimiothérapeutiques cytotoxiques ou aux traitements d'appoint dans les thérapeutiques de différenciation du cancer. Les agents actifs sur le plan immunobiologique actuellement à l'étude incluent les cytokines recombinantes comme les alpha- et gamma-interférons, l'interleukine IL-1 et IL-2 et le facteur de nécrose tumorale. Une variété de facteurs de croissance hématopoïétique sont présentement à l'étude seuls ou en association; s'y trouvent entre autres les facteurs granulocytes, granulocytes-macrophages, les facteurs de stimulation des colonies de macrophages, l'IL-3, l'IL-6 et le facteur de croissance recombinant PIXY-321. Les stratégies de ciblage dans les thérapeutiques antinéoplasiques cytotoxiques, y compris les immunotoxines et les radioimmunoconjugués ont eu recours aux anticorps monoclonaux et à des molécules obtenues par génie génétique. En dernier lieu, les récentes réussites thérapeutiques obtenues avec les stratégies de différenciation à base de rétinoïdes, ouvrent la porte à de nouvelles possibilités pour le traitement biologique du cancer.

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IMMUNOLOGICALLY BASED CANCER THERAPIES FOUND THEIR origins in the observations of cancer regression following infection, and increasingly today it is apparent that while the elaboration of some cytokines is central to the pathophysiology of many disease states associated with both malignancy and infection, some of these same cytokines may also be useful in the treatment of malignancy. Initial immunotherapeutic strategies in cancer therapy were modelled on the vaccination approaches originating with prophylactic therapy for infectious diseases. The difficulty in defining tumour-specific antigens, and even tumour-associated antigens suitable for immunization, as well as the complexities involved in evaluating the success of such approaches, have slowed progress in this area. Nevertheless, there is still great interest in the promise of immunization strategies against cancer; the focus of this article, however, will be the current state of defined biologicals in cancer treatment. This definition includes the recombinant cytokines and hematopoietic growth factors, monoclonal antibodies whether used alone or conjugated to cytotoxic moieties and differentiation-inducing agents such as the retinoids. It will become clear that old classifications based on the initial biological understanding of these proteins become insufficient as newer understanding of these proteins and their receptors permits new treatment strategies.

RECOMBINANT CYTOKINES

Interferon alpha: Studied initially as an antiviral agent, interferon alpha (IFN α) has found an increasing role as anticancer therapy. The initial indication for Food and Drug Administration (FDA) approval for this IFN was for hairy cell leukemia; IFN therapy reproducibly results in the attainment of remission in patients with this disease (1). The next approved cancer indication was in the treatment of Kaposi's sarcoma associated with acquired immune deficiency syndrome (2). Other approved clinical indications include the use of IFN α for condylomata acuminata and hepatitis C (3). Yet there continues to be intense interest in other potential uses for this agent in cancer therapy. While IFN does have some single agent activity in metastatic malignant melanoma, preclinical studies suggest that the combination of IFN and interleukin (IL)-2 should have enhanced activity; a number of clinical trials conducted with this combination of cytokines has confirmed the activity of the combination but no phase III trials have compared the efficacy of the combination with that of the single agents (4). Similarly, in vitro data suggest that IFN α may enhance the therapeutic activity of several anticancer chemotherapeutic agents, through as yet unknown mechanisms (5). Recent clinical results have suggested that the IFN-5-fluorouracil combination in colon cancer (6) and the IFN-dacarbazine combination in melanoma (7) may be of particular interest; randomized clinical trials to investigate this possibility are underway.

Interferon gamma: IFN γ was recently approved by the FDA for the treatment of chronic granulomatous disease; therapy with this cytokine is associated with a decreased incidence of infections in this condition (8). Despite disappointment with its antitumour activity when used as a single agent, the immunological activities of IFN γ have led to continued study of the possible roles for this agent as an adjunct in cancer therapy. This cytokine is a macrophage activator, and is being used in therapeutic trials in conjunction with monoclonal antibodies capable of targeting macrophages to tumour sites. The ability of IFN γ to upregulate class II major histocompatibility complex (MHC) and tumour-associated antigens on tumour cell surfaces (9) has led to its current use both to increase the immunogenicity of tumour cells in vaccination strategies, and to improve the targeting in trials of monoclonal antibodies labelled with therapeutic doses of radioisotope.

Interleukin-1: Two species of IL-1, designated as alpha and beta, have been described in humans. Although products of different genes, both proteins have similar weight, bind to the same receptor and apparently exert similar biological functions. IL-1 represents the prototypic pleiotropic cytokine, exerting a wide range of biological effects. Produced primarily by activated macrophages and endothelial cells, many other cell types are also capable of IL-1 production upon stimulation. While a number of therapeutic strategies to block IL-1 production or biological effect are under development because of the central role of this cytokine in inflammation and the repair process of mesenchymal tissues (10), other biological activities of this cytokine suggest that it may ultimately find a role as an adjunct in cancer treatment. The numerous effects of IL-1 on the proliferation and differentiation of hemopoietic progenitor cells has led to the use of this agent in conjunction with both radiation and cytotoxic chemotherapy (11). IL-1 is both a chemo- and radioprotector, and clinical trials of recombinant human IL-1 used together with myelosuppressive chemotherapy are underway. Other preclinical studies suggest that concomitant IL-1 administration may increase the therapeutic effectiveness of cytotoxic chemotherapy, perhaps through improved drug delivery, suggesting another potential benefit through the combination of this agent with chemotherapy (12).

Interleukin-2: Many of the biological properties of IL-2 suggest that it should be a useful agent in the immunologically-mediated approach to cancer treatment. A lymphokine, or product of activated T lymphocytes, this small protein binds to a specific high affinity receptor expressed on activated T lymphocytes. The binding of IL-2 to its receptor can lead to lymphocyte proliferation, production of a range of cytokines and the development of enhanced antitumour cytotoxicity (13). Due to these characteristics, IL-2 has been extensively studied both in preclinical model systems and in clinical trials

(14). Results from animal experiments suggest that IL-2 is active as a single agent, but this activity can be enhanced greatly by the concomitant administration of other cytokines, including either IFN α or tumour necrosis factor (TNF), or by the administration of ex vivo activated antitumour lymphocytes together with the cytokines (15). Antitumour activity is affected by the dose and schedule of IL-2 used, the bulk of tumour present, the immunogenicity and immune status of the host animal (15). IL-2 has been most extensively studied in patients with renal cell carcinoma and malignant melanoma. Response in the 20 to 30% range has been obtained with high dose IL-2 therapy in patients with metastatic melanoma or metastatic renal cell carcinoma with significant attendant toxicity. Durable complete responses in approximately 5% of patients have led to numerous attempts both to increase the effectiveness and to decrease the toxicity of this therapy. Clinical results to date, however, have not yet confirmed an advantage for the use of combination of cytokines or for the addition of activated lymphocytes, when compared with the results of therapy with IL-2 alone.

It seems clear that major advances in IL-2 therapy must await a greater understanding of the mechanisms of the antitumour responses noted and the relationship of these mechanisms to the pathophysiology of the toxicity encountered during IL-2 administration. The nature of the toxicities encountered during high dose IL-2 therapy have been the focus of much attention (16). It is clear that much of this toxicity is due to the cytokines released in association with lymphocyte activation; much of the toxicity of IL-2 therapy can be prevented with the concomitant administration of anti-TNF (17). If the newer approaches to the management of TNF toxicity noted elsewhere in this article do not interfere with the antitumour efficacy of IL-2 therapy, it may be possible to administer high doses of IL-2 with much less toxicity (18).

IL-2 has been approved for some time for the treatment of renal cell carcinoma in several European countries, and has recently been approved in both the United States and Japan for the same indication. It is clear that this agent will form the basis of much of the experimental work involving cellular and vaccine approaches to cancer therapy to be conducted over the next several years.

Tumour necrosis factor: Despite its dramatic effectiveness in several animal tumour models, recombinant human TNF has been both difficult to administer and largely ineffective as a single agent in cancer patients. In clinical trials the cytokine has been toxic at low doses, resulting in severe chills, fever and hypotension. This toxicity may account for the lack of antitumour efficacy, because the amount of TNF necessary for antitumour activity in mice (which are far more tolerant of this agent) is significantly higher than that which can be administered safely to humans. Yet it can be demon-

strated in vitro that many human tumours are very sensitive to this agent. As a result, strategies to deliver high concentrations of TNF locally, at the site of the tumour, have been developed. One approach has been through the introduction of the TNF gene into tumour-infiltrating lymphocytes cultivated from the metastases of patients with advanced malignant melanoma (19). These lymphocytes have been shown to be capable of migrating to the sites of tumour involvement; the hypothesis is that local high concentrations of TNF will be reached and that an increased antitumour effect will be achieved.

An alternative strategy involves blocking some of the dose-limiting side effects of TNF. The severe hypotension seen with TNF (as well as with IL-1) administration appears to be due to the elaboration of nitric oxide from arginine in endothelial cells through the action of the enzyme nitric oxide synthase (18). Inhibitors of this enzyme are capable of reversing the hypotension. While such strategies have the potential for permitting larger (and possibly more effective) doses of cytokines such as TNF, IL-1 and IL-2 to be used, they also have significant implications for the treatment of septic shock, as cytokines elaborated in this process seem to account for much of the morbidity (20).

Recently the interactions of TNF with cytotoxic chemotherapy have attracted interest. For example, animal data suggest that the pulmonary fibrosis associated with bleomycin therapy is due to TNF production within the lung and that this toxicity can be blocked by the use of anti-TNF monoclonal antibody concomitant with bleomycin administration (21). It has also been suggested that TNF has topoisomerase II inhibiting activity (22), and the use of TNF in relatively small doses together with topoisomerase II-inhibiting chemotherapeutic agents such as etoposide is in clinical trial.

Other cytokines entering clinical trial in cancer: Identification, isolation, cloning and production of recombinant cytokines has proceeded apace, challenging understanding of the biology of these proteins and their potential usefulness as therapeutic agents in the treatment of malignancy. IL-4 is currently in clinical trial; this cytokine was originally identified because of its effects on B lymphocyte biology, but has subsequently been demonstrated to interact with IL-2 in the generation of cytotoxic T lymphocytes (23). IL-6, a central cytokine in the modulation of the acute response aspects of inflammation, has been demonstrated to have significant effects on T lymphocytes and to interact with IL-2 in antitumour animal models (24). Clinical trials of recombinant human IL-6 have recently been initiated. Other cytokines, including IL-7 and IL-8, are still in early preclinical study. Beyond any potential direct therapeutic application for these newly produced cytokines, it is clear that the availability of these recombinant cytokines will help to clarify many of the aspects

of the complex interaction of tumour and host, aiding ultimately in the development of more rational biological approaches to therapy (25).

HEMATOPOIETIC GROWTH FACTORS

Progress in toxicity reduction and development of new therapeutic strategies: The effectiveness of hematopoietic growth factors in reducing myelosuppression associated with chemotherapy has been demonstrated (26,27), and both granulocyte and granulocyte-macrophage colony stimulating factors (GM-CSF) have received FDA approval. It is clear that the availability of proteins capable of affecting recovery from cytotoxic chemotherapy or from radiation therapy will have a profound effect on approaches to the development of new clinical strategies using myelosuppressive treatment modalities. The basis for initial FDA approval for G-CSF was the attenuation of the period of neutropenia following cytotoxic drugs; for GM-CSF it was the recovery of neutrophils following bone marrow transplantation. These indications are examples of reduction in toxicity, an important role but only one of several possible which this type of agent can play in cancer therapeutics. For example, it may be possible to increase the dose intensity of chemotherapy delivered over time with the support of growth factors. This may be particularly true with agents such as cyclophosphamide and doxorubicin (28,29) used in combination chemotherapy for common malignancies where the elimination of dose reductions or delays may increase therapeutic success rates. For other drugs, including alkylating agents such as melphalan and thioguanine, and drugs such as carboplatin, it appears that dose intensification cannot be successfully achieved with G-CSF or GM-CSF.

Limitations in the factors available to date include the fact that (for the most part) the neutrophil nadir is not eliminated; rather, the period of severe neutropenia is shortened. For significant dose intensification of chemotherapy to occur, more effective abrogation of neutropenia will be necessary, and hematopoietically active agents capable of attenuating thrombocytopenia will be necessary. It is possible that IL-3, now in early clinical trial, will be more effective than either G-CSF or GM-CSF in abrogating thrombocytopenia. However, primate studies suggest that the sequential use of IL-3, which acts on a very early stem cell, followed by GM-CSF may be a particularly successful clinical strategy (30).

Other strategies to avoid the limitations of currently available growth factors include the harvest of peripheral blood stem cells, perhaps enriched by pretreatment with G-CSF or GM-CSF infusion following completion of drug therapy. Such stem cells may be used in addition to, or potentially instead of, bone marrow harvest. In the future it may be possible to produce these cells by culture techniques in large numbers

outside of the body. The use of myeloprotective agents such as IL-1 may protect from some of the severe effects of cytotoxic agents such as carboplatin on platelets. Ultimately, however, direct platelet-stimulating agents would be most beneficial; although no clear 'Meg-CSF' has been defined. IL-6 has platelet-stimulating properties in primates (31) and is being investigated for such properties in ongoing clinical trials. The recently described 'stem cell factor' (also known as c-kit ligand, steel factor or mast cell factor) will soon be entering clinical trial and may have multilineage stimulatory properties (32).

Beyond possibly permitting more intensive chemotherapy, hematopoietic growth factors may permit transient stimulation of malignant myeloid leukemia cells into cycle, to increase potentially the fraction of cells susceptible to cycle-active chemotherapeutic agents. Such clinical trials have been initiated.

Erythropoietin, approved for use in the anemia of chronic disease, also is being studied for use in anemias associated with malignancy and for its ability to decrease transfusion requirements in patients undergoing bone marrow transplantation, chemotherapy and radiation therapy. Erythropoietin may also find a role with other growth factors in the therapy of primary bone marrow failure disorders, such as myelodysplasia and aplastic anemia.

A particularly important development in the arena of hematopoietic growth factors, however, may be the creation of chimeric growth factors which have properties beyond those of the individual agents used alone. The PIXY molecule, a hybrid molecule incorporating both IL-3 and GM-CSF, is soon to enter clinical trial and represents an example of an engineered growth factor which may encompass both activities of the parent molecules, with greater activity than either alone (33).

M-CSF is a hematopoietic growth factor being studied for its ability to stimulate immune antitumour activity. M-CSF, produced by monocytes, fibroblasts and endothelial cells, both induces proliferation of monocytes and functionally activates these cells (34). M-CSF will therefore enhance antibody-dependent monocyte cytotoxicity, and current clinical strategies include the use of this cytokine together with monoclonal antitumour antibodies. M-CSF therapy also causes a significant decrease in serum cholesterol, through as yet unexplained mechanisms (35).

MONOCLONAL ANTIBODIES

Monoclonal antibody conjugates and chimeric toxins: The promise of targeted anticancer therapy with enhanced therapeutic index heralded by the development of monoclonal antibody technology has proven difficult to realize in clinical practice. While initial generations of murine antibodies have been developed which recognize tumour-associated antigens and therefore have

found important roles both in scientific investigation and cancer diagnosis, therapeutic applications have been limited to date. In general, single murine antibodies are ineffective as therapeutic agents, and their repeated administration is limited by immunogenicity, with the development of human antimouse antibodies (HAMA). Despite these problems, the successful use of murine antibodies to target toxins, including the plant toxin ricin (36,37) or the radioisotope ^{131}I odine (38,39), with major objective responses in patients with B cell non-Hodgkin's lymphoma have been described. These successes even in phase I trials have led to the development of a series of phase II clinical trials to explore further this activity in lymphoma. In addition, the Division of Cancer Treatment of the National Cancer Institute has initiated a series of clinical trials to explore the potential therapeutic use of radioisotope therapy in patients with solid tumours. Based on preclinical studies, clinical trials to investigate the pharmacokinetics and toxicities of monoclonal antibodies labelled with radioisotopes are underway in patients with adenocarcinoma. Variables being explored in these trials include the value of using antibodies with higher affinity, and the relative characteristics of whole antibody as opposed to F(ab')² antibody fragments in radiolabelled antibody therapy. The complexities of the therapeutic development of radioimmunotherapy has recently been the subject of extensive review (60).

Limitations of the murine antibodies have led to the development of human monoclonal antibodies and of genetically-engineered mouse-human 'chimeric' antibodies or 'humanized' antibodies. These antibodies are entering clinical trial.

Other strategies use protein ligands to target therapy. In one approach, tile protein is a recombinant DNA product of the cloned gene for the variable regions of murine monoclonal antibody (40). When the heavy and light chain variable regions are linked together, the resultant 'single chain binding protein' combines the properties of the targeting characteristics of the initial antibody with the advantages of a short half-life, lower immunogenicity and production by recombinant rather than cell culture technology.

An alternative family of ligands is the cytokines. Binding to their specific cell surface receptors with high affinity, recombinant cytokine-toxin fusion molecules have numerous possible therapeutic applications. The first of this class of novel genetically engineered agents to be developed for clinical use has been DAB486IL-2 toxin, a hybrid protein derived from the genes for IL-2 and diphtheria toxin (41). This agent targets the high affinity IL-2 receptor, and in vitro has been shown to kill selectively IL-2 receptor positive lymphocytes at low drug concentrations (42). A phase I trial of this drug has been completed, revealing significant antitumour activity and minimal toxicity (43). Other cytokine-toxin therapeutic agents are under development.

LEVAMISOLE

Levamisole represents an anomaly in this list of biological agents with potential in cancer therapy. Despite a great deal of preclinical and clinical study some 10 to 15 years ago, no clear role for this agent in cancer therapy was suggested until two large controlled adjuvant clinical trials in patients with Duke's stage C2 cancer suggested survival benefit in patients receiving the combination of levamisole with 5-fluorouracil (44); no benefit was seen over control in patients receiving levamisole alone, and these trials did not include 5-fluorouracil alone arms. The nature of this apparent benefit from levamisole, whether through some immunological effect or through some biochemical modulation of the fluoropyrimidine, is unknown and is the focus of current clinical study. A recently published study suggested a marginal benefit of levamisole alone in the adjuvant therapy of melanoma (45); this result must be viewed in the context of other negative trials in this disease (46,47).

RETINOIDS IN CANCER THERAPY

Analgeses of vitamin A have been studied extensively preclinically for both their cancer preventative and therapeutic properties (48). Attention focused initially on *cis*-retinoic acid (isotretinoin), a drug already in clinical use for dermatological disorders, because of its favorable toxicity profile based on clinical trials conducted almost 20 years ago. A recently published chemoprevention trial involved head and neck cancer patients who were randomized to receive either isotretinoin or placebo following initial therapy for their malignancy. While retinoid therapy did not affect recurrence rate, the development of second upper respiratory tract malignancies was significantly decreased (49). *Cis*-retinoic acid has also been studied in clinical trials of patients with advanced malignancies; responses have been noted in epidermal malignancies as well as in cutaneous T cell lymphomas (48). Based on the clinical activity demonstrated with both single agents and in vitro data suggesting synergistic interaction, a trial of 13 *cis* retinoic acid and IFN α was recently performed in patients with advanced squamous cell carcinoma of the skin. The regimen was well-tolerated and highly active (73% objective responses) (50); as a result, trials of retinoid/IFN combinations are now underway in other epidermoid malignancies.

All-trans-retinoic acid (tRA), because of its unfavorable toxicity profile in the early retinoid trials (largely neurotoxicity), received little clinical attention until the publication of results of tRA therapy in patients with acute promyelocytic leukemia (51). In the study conducted in the People's Republic of China, 23 of 24 patients achieved complete remission with oral tRA therapy, while the final patient achieved remission when tRA was combined with chemotherapy. Sub-

sequent studies in France (52) and the United States (53) have confirmed this activity. Over 80% of both adults and children with this malignancy who have failed initial chemotherapy can successfully be treated with minimal side effects. Many of these patients attain complete clinical remission with this drug.

The Cancer Therapy Evaluation Program of the Division of Cancer Treatment over the past year has rapidly moved to bring the drug into clinical study in the United States, filing for an 'investigational new drug', making it available to patients with relapsing acute promyelocytic leukemia through a compassionate use mechanism developed with the FDA and establishing maximally tolerated doses for the drug through phase I trials. tRA has been made widely available to basic scientific investigators. Further clinical investigations were solicited and letters of intent for over 50 clinical trials of tRA alone or in combination with other differentiation-inducing agents or cytotoxic chemotherapeutic agents have been approved by the Cancer Therapy Education Program. These trials involve a wide range of malignancies and for the most part include detailed biological studies to investigate the biology of retinoid action in the malignant cells. National clinical trials involving the major cooperative groups have been developed for both newly diagnosed and relapsing patients with acute promyelocytic leukemia. The National Cancer Institute has worked actively with Hoffmann-LaRoche Pharmaceutical Co (New Jersey) to gather data supporting licensing approval for tRA for this clinical indication.

This surge in clinical interest in the retinoids as therapeutic agents in malignancy has been paralleled by dramatic breakthroughs in the understanding of retinoid biology. A series of nuclear receptors for the retinoids has been described, the genes cloned and the chromosomal location mapped (54-56). In acute promyelocytic leukemia it has been demonstrated that the characteristic chromosomal translocation associated with this malignancy – the reciprocal movement of material between chromosomes 15 and 17 – directly involves RAR alpha, a major retinoid receptor, at least in some cases; the result is a novel retinoid receptor protein (57). The recent recognition of differential binding of different synthetic retinoids to different retinoid receptors (58), coupled with the developing information that different retinoid receptors are expressed at varying levels in different normal and malignant tissues, provides a rationale for the patterns of toxicity seen with this class of agents and for the possibility that different retinoids may be active in different malignancies. The Division of Cancer Treatment is working actively to introduce a series of new generation retinoids into clinical trial. The parallel developments of recognition of the therapeutic activity of retinoids in established malignancy and the progress in understanding the underlying biology of retinoid effects make a poten-

tially less toxic, differentiation-based strategy of cancer therapy possible for the future (59).

NEW DIRECTIONS IN THE BIOLOGICAL THERAPY OF CANCER

The biological response modifiers listed above represent only the first generations of biological agents which are being used in cancer therapeutics. It is instructive that IFN α was approved for a relatively narrow clinical indication, the therapy of the rare malignancy hairy cell leukemia. In the several years since that introduction of a biological into the general practice of oncology, a great deal has been learned about this agent and the approved clinical uses in both oncology and infectious disease has expanded. Yet the complexities of its biological actions are still not fully defined and potential uses, such as in combination with cytotoxic chemotherapy, are now in development. Although the initial clinical studies of IL-2, the next most intensively studied agent, were focused almost entirely on applications in the treatment of melanoma and renal cell carcinoma (regulatory approval has been requested for these indications), there is now much interest in the potential uses of IL-2 in the therapy of acute myeloid leukemia. The history of the development of these therapeutics includes a period of familiarization with the biology and the exploration of new clinical indications.

The promise of the future certainly includes the introduction of newer cytokines and newer monoclonals. However, what most excites the imagination is the fact that these agents will be useful in a setting of greater biological understanding – the surface features of the tumours which can be exploited for therapeutic targeting, and the immunobiological nature of host recognition of tumours and the blocks to the effective use of this recognition to eliminate tumour cells. Ultimately, of course, delineation of the unique biological nature of each tumour will allow a truly rational 'biological' therapy, capable either of correcting the defect responsible for the malignant state or of selectively eliminating the cells bearing this defect. Strategies to obtain this therapeutic selectivity, including the use of antisense oligonucleotides which have the theoretical capability of regulating the expression of individual genes, are further from clinical use in cancer therapy than the strategies outlined above. Nevertheless, the promise of more successful, less toxic therapies for malignancy seems more possible than even a few years ago and remains a goal of present studies involving biological therapies.

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