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Immunotherapy: A Review Article

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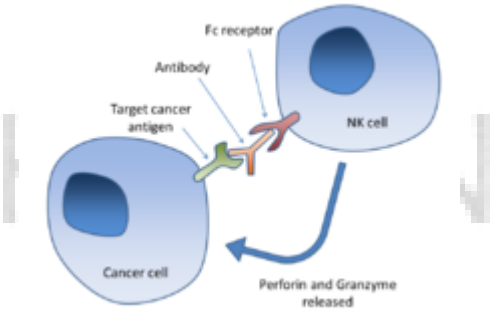
ABSTRACT

The use of monoclonal antibodies (mAb's) for cancer therapy has achieved considerable success in recent years. Antibody-drug conjugates are powerful new treatment options for lymphomas and solid tumors and immunomodulatory antibodies have also recently achieved remarkable clinical success. The development of therapeutic antibodies require a deep understanding of cancer serology, protein engineering techniques, mechanism of action and resistance and the interplay between the immune system and cancer cells. Antibody dependent cellular cytotoxicity (ADCC) mediated by natural killer (NK) cells is presumed to be a key effector function. The use of therapeutic antibodies after allogenic hematopoietic stem cells transplantation is an interesting option. Despite the success of approved second generation antibodies in the treatment of several malignancies, efforts are made to further augment ADCC *in vivo* by antibody engineering. This review outlines the fundamental strategies that are required to develop antibody therapies.

INTRODUCTION

Immunotherapy (also called biologic therapy or biotherapy) is a type of cancer treatment designed to boost the body's natural defenses to fight against the cancer. It uses materials either made by the body or in a laboratory to improve, target, or restore immune system function. Although it is not entirely clear how immunotherapy treats cancer, it may work by stopping or slowing the growth of cancer cells, stopping cancer from spreading to other parts of the body, or helping the immune system to increase its effectiveness on eliminating cancer cells. Naturally occurring cytotoxic cells against tumor cells were first described in humans and mice in 1970's[1]. These cells were recognized eventually as novel lymphocyte population and named natural killer cells after their natural occurrence and spontaneous capacity to kill lymphomas and leukemic cells in non immunized animals[2]. Nowadays, NK cells are recognized as a subset of cytotoxic innate lymphoid cells which are able to directly kill virus infected cells and tumor cells and participate in shaping the adaptive immunity by secretion of cytokines (eg IFN $-\gamma$[3]). Human NK cells are defined by the phenotype $CD3^-$ CD56+; additionally they are CD19 and CD14 negative. The only marker that is specific for NK cells is Nkp46. NK cells comprise 5-15% of all circulating lymphocytes[4].



There are several types of immunotherapy, including monoclonal antibodies, non-specific immunotherapies, and cancer vaccines.

Monoclonal antibodies

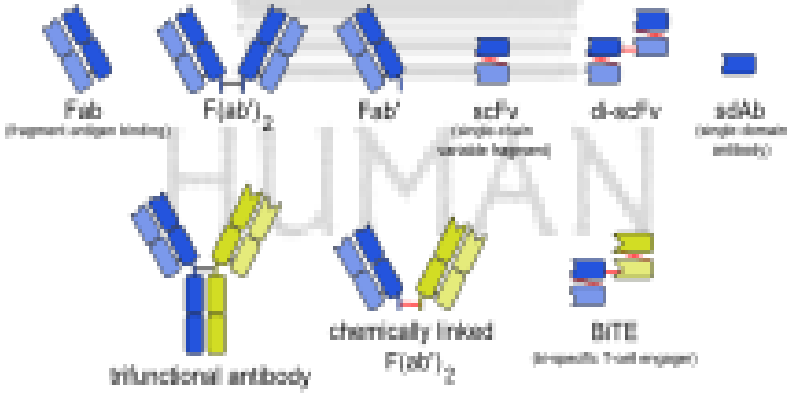
When the body's immune system detects antigens (harmful substances, such as bacteria, viruses, fungi, or parasites), it produces antibodies (proteins that fight infection). Monoclonal antibodies are made in a laboratory, and when they are given to patients, they act like the antibodies and the

body produces naturally. Monoclonal antibodies are given intravenously (through a vein) and work by targeting specific proteins on the surface of cancer cells or cells that support the growth of cancer cells. When monoclonal antibodies attach to a cancer cell, they may accomplish the following goals:

Allow the immune system to destroy the cancer cell. The immune system doesn't always recognize cancer cells as being harmful. To make it easier for the immune system to find and destroy cancer cells, a monoclonal antibody can mark or tag them by attaching to specific parts of cancer cells that are not found on healthy cells.

Prevent cancer cells from growing rapidly. Chemicals in the body called growth factors attach to receptors on the surface of cells and send signals that tell the cells to grow. Some cancer cells make extra copies of the growth factor receptor, which makes the cancer cells grow faster than normal cells. Monoclonal antibodies can block these receptors and prevent the growth signal from getting through.

Monoclonal Antibody Therapy



Cancer immunotherapy: Monoclonal antibodies					
Antibody	**Brand name**	**Type**	**Target**	**Approval date**	**Approved treatment(s)**
Alemtuzumab	Campath	humanized	CD52	2001	B-cell Chronic lymphocytic leukemia (CLL)
Bevacizumab	Avastin	humanized	vascular endothelial growth factor	2004	metastatic colorectal cancer
				2006	non-small cell lung cancer
				2009	renal cell carcinoma
				2009	glioblastoma multiforme
Brentuximab vedotin	Adcetris	chimeric	CD30	2011	relapsed Hodgkin lymphoma
				2011	relapsed Anaplastic large-cell lymphoma
Cetuximab	Erbitux	chimeric	epidermal growth factor receptor	2004	colorectal cancer
				2006	advanced squamous cell carcinoma of the head and neck (SCCHN)
				2011	recurrent locoregional or metastatic squamous cell head and neck cancer
				2012	EGFR-expressing metastatic colorectal cancer
Gemtuzumab	Mylotarg	humanized	CD33	2000	acute myelogenous

ozogamicin					leukemia (with calicheamicin)
Ibritumomab tiuxetan	Zevalin	murine	CD20	2002	non-Hodgkin lymphoma (with yttrium-90)
Ipilimumab	Yervoy	human	CTLA4	2011	metastatic melanoma
Ofatumumab	Arzerra	human	CD20	2009	refractory CLL
Panitumumab	Vectibix	human	epidermal growth factor receptor	2006	metastatic colorectal cancer
Rituximab	Rituxan, Mabthera	chimeric	CD20	1997	non-Hodgkin lymphoma
				2010	CLL
Tositumomab	Bexxar	murine	CD20	2003	Non-Hodgkin lymphoma
Trastuzumab	Herceptin	humanized	ErbB2	1998	breast cancer

Deliver radiation directly to cancer cells. This treatment, called radioimmunotherapy, uses monoclonal antibodies to deliver radiation directly to cancer cells. By attaching radioactive molecules to monoclonal antibodies in a laboratory, they can deliver low doses of radiation specifically to the tumor while leaving healthy cells alone. Examples of these radioactive molecules include ibritumomab, tiuxetan (Zevalin) and tositumomab (Bexxar).

Diagnose cancer. Monoclonal antibodies carrying radioactive particles may also help to diagnose certain cancers, such as colorectal, ovarian, and prostate cancers. Special cameras identify the cancer by showing where the radioactive particles accumulate in the body. In addition, a pathologist (a doctor who specializes in interpreting laboratory tests and evaluating cells, tissues, and organs to diagnose disease) may use monoclonal antibodies to determine the type of cancer a patient may have after tissue has been removed during a biopsy.

Side effects of monoclonal antibody treatment are usually mild and are often similar to an allergic reaction. Possible side effects include rashes, low blood pressure, and flu-like symptoms, such as fever, chills, headache, weakness, extreme tiredness, loss of appetite, upset stomach, or vomiting.

Although monoclonal antibodies are considered a type of immunotherapy, they are also classified as a type of targeted treatment (a treatment that specifically targets faulty genes or proteins that contribute to cancer growth and development).

Non-specific immunotherapies

Like monoclonal antibodies, non-specific immunotherapies also help the immune system destroy cancer cells. Most non-specific immunotherapies are given after or at the same time as another cancer treatment, such as chemotherapy or radiation therapy. However, some non-specific immunotherapies are given as the main cancer treatment.

Two common non-specific immunotherapies are:

Interferons

Interferons help the immune system to fight against cancer and may slow the growth of cancer cells. An interferon made in a laboratory, called interferon alpha (Roferon-A [2a], Intron A [2b], Alferon [2a]), is the most common type of interferon used in cancer treatment. Side effects of interferon treatment may include flu-like symptoms, an increased risk of infection, rashes, and thinning hair.

Interleukins

Interleukins help the immune system to produce cells that destroy cancer. An interleukin made in a laboratory, called interleukin-2, IL-2, or aldesleukin (Proleukin), is used to treat kidney cancer and skin cancer, including melanoma. Common side effects of IL-2 treatment include weight gain and low blood pressure, which can be treated with other medications. Some people may also experience flu-like symptoms.

Cancer vaccines

A vaccine is another method used to help the body to fight against disease. A vaccine exposes the immune system to a protein (antigen) that triggers the immune system to recognize and destroy that protein or related materials. There are two types of cancer vaccines: prevention vaccines and treatment vaccines.

Prevention vaccine

A prevention vaccine is given to a person with no symptoms of cancer to prevent the development of a specific type of cancer or another cancer-related disease. For example, Gardasil is a vaccine that prevents a person from being infected with the human papillomavirus (HPV), a virus known to cause cervical cancer and some other types of cancer. It was the first FDA-approved vaccine for cancer. Cervarix is another vaccine that is approved to prevent cervical cancer in girls and women. In addition, the U.S. Centers for Disease Control and Prevention recommends that all children should receive a vaccine that prevents infection with the hepatitis B virus, which may cause liver cancer.

Treatment vaccine

A treatment vaccine helps the body's immune system to fight against cancer by training it to recognize and destroy cancer cells. It may prevent cancer from coming back, eliminate any remaining cancer cells after other types of treatment, or stop cancer cell growth. A treatment vaccine is designed to be specific, which means it should target the cancerous cells without affecting healthy cells. At this time, sipuleucel-T (Provenge) is the only treatment vaccine approved in the United States. It is designed for treating metastatic prostate cancer. Additional cancer treatment vaccines are still in development and only available through clinical trials.

Carry powerful drugs directly to cancer cells. Some monoclonal antibodies carry other cancer drugs directly to cancer cells. Once the monoclonal antibody attaches to the cancer cell, the cancer drug it is carrying enters the cell, causing the cancer cell to die without damaging other healthy cells. Brentuximab vedotin (Adcetris), a treatment for certain types of Hodgkin and non-Hodgkin lymphoma, is an example.

Immunotherapy

Immunotherapy is the "treatment of disease by inducing, enhancing, or suppressing an immune response"[5]. Immunotherapies designed to elicit or amplify an immune response are classified as **activation immunotherapies,** while immunotherapies that reduce or suppress are classified as **suppression immunotherapies.**

Immunomodulators

The active agents of immunotherapy are collectively called immunomodulators. They are a diverse array of recombinant, synthetic and natural preparations, often cytokines. Some of these substances, such as granulocyte colony-stimulating factor (G-CSF), interferons, imiquimod and cellular membrane fractions from bacteria are already licensed for use in patients. Others including IL-2, IL-7, IL-12, various chemokines, synthetic cytosine phosphate-guanosine (CpG) oligodeoxynucleotides and glucans are currently being investigated extensively in clinical and preclinical studies. Immunomodulatory regimens offer an attractive approach as they often have fewer side effects than existing drugs, including less potential for creating resistance in microbial diseases[6].

Agent	Example
Interleukins	IL-2, IL-7, IL-12
Cytokines	Interferons, G-CSF, Imiquimod
Chemokines	CCL3, CCL26, CXCL7
Other	cytosine phosphate-guanosine, oligodeoxynucleotides, glucans

Cell based Immunotherapies are proven to be effective for some cancers. Immune effector cells such as lymphocytes, macrophages, dendritic cells, natural killer cells (NK Cell), cytotoxic T lymphocytes (CTL) etc. work together to defend the body against cancer by targeting abnormal antigens expressed on the surface of the tumor due to mutation.

Activation Immunotherapies

Cancer

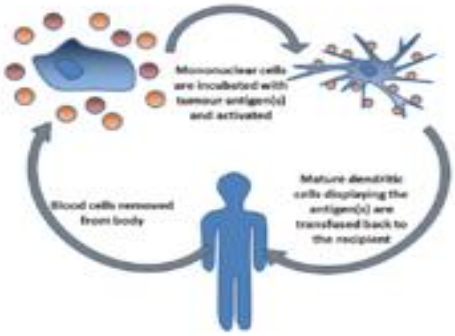
Cancer immunotherapy

Cancer immunotherapy attempts to stimulate the immune system to reject and destroy tumors. Immuno cell therapy for cancer was first introduced by Rosenberg and his colleagues of National Institute of Health USA. In the late 1980s, they published an article in which they reported a low tumor regression rate (2.6–3.3%) in 1205 patients with metastatic cancer who underwent different types of active specific immunotherapy (ASI), and suggested that immuno cell therapy along with specific chemotherapy is the future of cancer immunotherapy[7]. Initially Immunotherapy treatments involved administration of cytokines such as Interleukin[8]. Thereafter the adverse effects of such intravenously administered cytokines[9] lead to the extraction of the lymphocytes from the blood and expanding *in vitro* against tumour antigen before injecting the cells[10] with appropriate stimulatory cytokines. The cells will then specifically target and destroy the tumor expressing antigen against which they have been raised.

The concept of this treatment started in the US in 1980s and fully fledged clinical treatments on a routine basis have been in practice in Japan since 1990. Randomized controlled studies in different cancers resulting in significant increase in survival and disease free period have been reported[11,12,13,14] and its efficacy is enhanced by 20–30% when cell-based immunotherapy is combined with other conventional treatment methods.

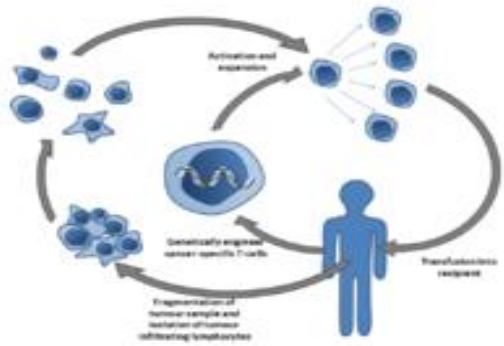
BCG immunotherapy[15] for early stage (non-invasive) bladder cancer utilizes *instillation* of attenuated live bacteria into the bladder, and is effective in preventing recurrence in up to two thirds of cases. Topical immunotherapy utilizes an immune enhancement cream (imiquimod) which is an interferon producer causing the patient's own killer T cells to destroy warts[16], actinic keratoses, basal cell cancer, vaginal intraepithelial neoplasia[17], squamous cell cancer[15,19], cutaneous lymphoma[19] and superficial malignant melanoma[20]. Injection immunotherapy uses mumps, candida the HPV vaccine[21,22] or trichophytin antigen injections to treat warts (HPV induced tumors). Lung cancer has been demonstrated to potentially respond to immunotherapy[23].

Dendritic cell-based immunotherapy



Dendritic cells can be stimulated to activate a cytotoxic response towards an antigen. Dendritic cells, a type of antigen presenting cell, are harvested from a patient. These cells are then either pulsed with an antigen or transfected with a viral vector. Upon transfusion back into the patient these activated cells present tumour antigen to effector lymphocytes (CD4+ T cells, CD8+ T cells, and B cells). This initiates a cytotoxic response to occur against cells expressing tumour antigens (against which the adaptive response has now been primed)[24]. The cancer vaccine Sipuleucel-T is an example of this approach.[25]

T-cell adoptive transfer



Adoptive cell transfer uses T cell-based cytotoxic responses to attack cancer cells. T cells that have a natural or genetically engineered reactivity to a patient's cancer are generated *in vitro* and then transferred back into the cancer patient. One study using autologous tumor-infiltrating lymphocytes was an effective treatment for patients with metastatic melanoma[26]. This can be achieved by taking T cells that are found with the tumor of the patient, which are trained to

attack the cancerous cells. These T cells are referred to as tumor-infiltrating lymphocytes (TIL) are then encouraged to multiply *in vitro* using high concentrations of IL-2, anti-CD3 and allo-reactive feeder cells. These T cells are then transferred back into the patient along with exogenous administration of IL-2 to further boost their anti-cancer activity.

Thus far, a 51% objective response rate has been observed; and in some patients, tumors shrank to undetectable size[27,28].

The initial studies of adoptive cell transfer using TIL, however, revealed that persistence of the transferred cells *in vivo* was too short[29]. Before reinfusion, lymphodepletion of the recipient is required to eliminate regulatory T cells as well as normal endogenous lymphocytes that compete with the transferred cells for homeostatic cytokines[30,31,32]. Lymphodepletion was made by total body irradiation prior to transfer of the expanded TIL[33]. The trend for increasing survival as a function of increasing lymphodepletion was highly significant (P=0.007) [33]. Transferred cells expanded *in vivo* and persisted in the peripheral blood in many patients, sometimes achieving levels of 75% of all $CD8^+$ T cells at 6–12 months after infusion[34]. Clinical trials based on adoptive cell transfer of TILs for patients with metastatic melanoma are currently ongoing at the National Cancer Institute (Bethesda, MD, USA), Moffitt Cancer Center (Tampa, FL, USA)[35], MD Anderson Cancer Center (Houston, TX, USA), Sheba Medical Center (Tel Hashomer, Israel), Herlev University Hospital (Herlev, Denmark) and NKI Antonie van Leeuwenhoek (Amsterdam, Netherlands).

Autologous immune enhancement therapy

The Autologous immune enhancement therapy (AIET) is an autologous immune cell based therapy wherein the patient's own peripheral blood-derived NK cells. Cytotoxic T Lymphocytes and other relevant immune cells are expanded *in vitro* and then reinfused to tackle cancer[36]. There are studies also proving their efficacy against Hepatitis C Viral infection[33][34][35] . Chronic fatigue Syndrome[40,41] and HHV6 infection[42].

Genetically engineered T cells

Genetically engineered T cells are created by infecting patient's cells with a virus that contain a copy of a T cell receptor (TCR) gene that is specialised to recognise tumour antigens. The virus is not able to reproduce within the cell however integrates into the human genome. This is beneficial as new TCR gene remains stable in the T-cell. A patient's own T cells are exposed to these viruses and then expanded non-specifically or stimulated using the genetically engineered TCR. The cells are then transferred back into the patient and ready to have an immune response against the tumour. Morgan *et al.* (2006)[43] demonstrated that the adoptive cell transfer of lymphocytes transduced with retrovirus encoding TCRs that recognize a cancer antigen are able to mediate anti-tumour responses in patients with metastatic melanomas. This therapy has been demonstrated to result in objective clinical responses in patients with refractory stage IV cancer. The Surgery Branch of the National Cancer Institute (Bethesda, Maryland) is actively investigating this form of cancer treatment for patients suffering aggressive melanomas. The use of adoptive cell transfer with genetically engineered T cells is a promising new approach to the treatment of a variety of cancers[26].

In one case study, United States doctors from the Clinical Research Division, led by Dr. Cassian Yee at Fred Hutchinson Cancer Research Center in Seattle had successfully treated a patient with advanced skin cancer by injecting the patient with immune cells cloned from his own immune system[44]. The patient was free from tumours within eight weeks of treatment. Dr. Cassian Yee described the research findings at The Cancer Research Institute International 2008 Symposia Series[45]. Responses, however, were not seen in other patients in this clinical trial. Larger trials are now under way[46].

Immune recovery

The potential use of immunotherapy is to restore the immune system of patients with immune deficiencies as result of infection or chemotherapy. For example, cytokines have been tested in clinical trials. Interleukin-7 has been in clinical trials for HIV and cancer patients. Interleukin-2 has also been tested in HIV patients.

Vaccination

Anti-microbial immunotherapy, which includes vaccination, involves activating the immune system to respond to an infectious agent.

Suppression immunotherapies

Immune suppression dampens an abnormal immune response in autoimmune diseases or reduces a normal immune response to prevent rejection of transplanted organs or cells.

Immunosuppressive drugs

Immunosuppressive drugs are important tools in the management of organ transplantation and autoimmune disease. Immune responses depend on lymphocyte proliferation, and cytostatic drugs are immunosuppressive. Glucocorticoids are somewhat more specific inhibitors of lymphocyte activation, whereas inhibitors of immunophilins more specifically target T lymphocyte activation. Immunosuppressive antibodies target an increasingly-broad array of steps in the immune response, and there are still other drugs that modulate immune responses.

Immune tolerance

Immune tolerance is the process by which the body naturally does not launch an immune system attack on its own tissues. Immune tolerance therapies seek to reset the immune system so that the body stops mistakenly attacking its own organs or cells in autoimmune disease or accepts foreign tissue in organ transplantation[47]. A brief treatment should then reduce or eliminate the need for lifelong immunosuppression and the chances of attendant side effects, in the case of transplantation, or preserve the body's own function, at least in part, in cases of type 1 diabetes or other autoimmune disorders.

Allergies

Immunotherapy is also used to treat allergies. While other allergy treatments (such as antihistamines or corticosteroids) treat only the symptoms of allergic disease, immunotherapy is

the only available treatment that can modify the natural course of the allergic disease, by reducing sensitivity to allergens.

A one-to-five-year individually tailored regimen of injections may result in long-term benefits. Recent research suggests that patients who complete immunotherapy may continue to see benefits for years to come[48]. Immunotherapy does not work for everyone and is only partly effective in some people, but it offers allergy sufferers the chance to eventually reduce or stop symptomatic/rescue medication.

The therapy is indicated for people who are extremely allergic or who cannot avoid specific allergens. For example, they may not be able to live a normal life and completely avoid pollen, dust mites, mold spores, pet dander, insect venom, and certain other common triggers of allergic reactions. Immunotherapy is generally not indicated for food or medicinal allergies. Immunotherapy is typically individually tailored and administered by an allergist (allergologist) or through specialized physician offices. Injection schedules are available in some healthcare systems and can be prescribed by family physicians. This therapy is particularly useful for people with allergic rhinitis or asthma.

The therapy is particularly likely to be successful if it begins early in life or soon after the allergy develops for the first time. Immunotherapy involves a series of injections (shots) given regularly for several years by a specialist in a hospital clinic. In the past, this was called a serum, but this is an incorrect name. Most allergists now call this mixture an allergy extract. The first shots contain very tiny amounts of the allergen or antigen to which one is allergic. With progressively increasing dosages over time, one's body adjusts to the allergen and becomes less sensitive to it, in a process known as desensitization. A recently approved sublingual tablet (Grazax), containing a grass pollen extract, is similarly effective with few side effects, and can be self-administered at home, including by those patients who also suffer from allergic asthma, a condition which precludes the use of injection-based desensitization. To read more about this topic, see: Allergy and Allergen immunotherapy.

Other approaches

Helminthic therapies

Recent research into the clinical effectiveness of Whipworm ova (*Trichuris suis*) and Hookworm (*Necator americanus*) for the treatment of certain immunological diseases and allergies means that these organisms must be classified as immuno-therapeutic agents. Helminthic therapy is being investigated as a potentially highly effective treatment for the symptoms and or disease process in disorders such as relapsing remitting multiple sclerosis[49], Crohn's[50,51,52] allergies and asthma[53]. The precise mechanism of how the helminths modulate the immune response, ensuring their survival in the host and incidentally effectively modulating autoimmune disease processes, is currently unknown. However, several broad mechanisms have been postulated, such as a re-polarisation of the Th1 / Th2 response[54] and modulation of dendritic cell function[55,56]. The helminths down regulate the pro-inflammatory Th1 cytokines, Interleukin-12 (IL-12), Interferon-Gamma (IFN-γ) and Tumour Necrosis Factor-Alpha (TNF-ά), while promoting the production of regulatory Th2 cytokines such as IL-10, IL-4, IL-5 and IL-13[54,57].

That helminths modulate host immune response is proven, as the core assertion of the hygiene hypothesis appears to have been, with the recent publication of a study demonstrating that co-evolution with helminths has shaped at least some of the genes associated with Interleukin expression and immunological disorders like Crohn's, ulcerative colitis and Celiac Disease. Much of the research that has been published now indicates a key role, for what have been traditionally regarded as disease causing organisms, so that their relationship to humans as hosts should not be classified as parasitic, rather as mutualistic, symbionts.

CONCLUSION

The use of monoclonal antibodies for the therapy of cancer is one of the great success stories of the past decade. This success builds on a long history of scientific investigations aimed to understand the complexities of antibody serology, target selection, antibody receptor function and immune regulation of tumor growth.

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