

Cancer Vaccines and Immunotherapy

Cancer immunotherapies, including cancer vaccines, are novel investigational cancer therapies. In contrast to chemotherapy and radiotherapy regimens that are often associated with severe side effects, cancer immunotherapy stimulates the body's immune system and natural resistance to cancer, thus offering a gentler means of cancer treatment that is less damaging to the rest of the body. Surgery is generally (but not always) performed, prior to immunotherapy, to remove most of the tumor (Hanna MG, Jr. et al 2001; Jocham D et al 2004). Vaccination or immunotherapy prompts the immune system to kill residual cancer cells that persist after surgery and could result in the cancer recurring.

The status of the patient's immune system is the key physiological factor affecting the outcome of cancer immunotherapy. However, each individual's immune status is in turn affected by several factors (including age, tumor-induced and surgery-associated immunosuppression, and nutritional status) that need to be assessed, and some require continuous monitoring for the successful application of immunotherapeutic regimens. Immune cells play a central role in mediating the effects of immunotherapy, and specific nutritional supplements that enhance immune cell function can be effective in preparing patients for immunotherapy or vaccination (Malmberg KJ et al 2002).

Therapeutic cancer vaccines developed for melanoma, renal cell carcinoma, and colorectal cancer have shown benefits in phase III trials by extending the disease-free survival period (before relapse) and overall survival. In addition, several immunotherapy clinical trials have been performed for metastatic breast cancer and non-Hodgkin's lymphoma.

THE IMMUNE SYSTEM AND CANCER

Evidence showing the role of the immune system in detecting and killing cancer cells has been available for some time (Richardson MA et al 1999; Wiemann B et al 1994; Hellstrom IE et al 1968; Oliver RT et al 1989; Penn I 1986, 1988; Vose BM et al 1985). This knowledge has been used in developing immunotherapies to bolster the immune system's natural capacity to counteract cancer cells.

How Does the Immune System Detect Cancer Cells?

Cancer cells display abnormal proteins (antigens) on their surface, and the immune system can detect and destroy cancer cells because of these proteins (Knuth A et al 1991; Naftzger C et al 1991). (An antigen is a substance that causes the immune system to make a specific immune response.)

The immune system has an innate ability to resist cancer development; however, in most cases, the immune system fails due to a series of sophisticated strategies that tumor cells use to evade immune detection. These strategies range from methods designed to hide tumor cells, to active incapacitation of immune cells by tumor-produced agents that lower the immune system's responses, which are known as immunosuppressive agents (Cordon-Cardo C et al 1991; Junker U et al 1996; Pantel K et al 1991; Ranges GE et al 1987; Sarris AH et al 1999; Staveley-O'Carroll K et al 1998). Therefore, a prerequisite to successful cancer immunotherapy is the implementation of strategies to boost the immune system's natural resistance to cancer.

T cells and B cells (lymphocytes) are immune system cells responsible for what is known as specific immunity (Brodsky FM et al 1991; Janeway CA, Jr et al. 1994; Levine TP et al 1991). By contrast, other immune cells (for example, eosinophils, natural killer (NK) cells, and macrophages) generate non-specific responses to infections by bacteria and parasites (Klein E et al 1993; Mantovani A et al 1992). T cells and B cells respond only when they detect specific markers that identify infected cells (Brodsky FM et al 1991; Janeway CA, Jr et al. 1994; Levine TP et al 1991).

A Role for the Immune System in Cancer Control

The role of the immune system in counteracting the development of cancer was initially supported by individual clinical case reports. Groundbreaking work in the late 1800s by a New York surgeon, William Coley, noted that some cancer patients who were simultaneously suffering from bacterial infections had regression in their tumors (Richardson MA et al 1999; Wiemann B et al 1994). He concluded that, in trying to fight off the bacterial infection, the patients' immune systems had become highly activated and that this had given them some resistance to the tumor. Coley later concocted a crude vaccine preparation, called "Coley's toxins," that was made up of killed bacteria. While some of Coley's patients enjoyed complete tumor regression, the responses were somewhat varied and his work was initially regarded with skepticism (Richardson MA et al 1999; Wiemann B et al 1994).

However, more recent research has produced a considerable body of scientific evidence documenting the immune system's role in controlling cancer growth. For example, cancer occurs more frequently in individuals with weakened immune systems (Oliver RT et al 1992; Penn I 1986, 1988). In addition, some types of cancer undergo spontaneous regression, again adding weight to the notion that the immune system is naturally able to fight cancer (Oliver RT et al 1989). Furthermore, cancer patients often have specific antibodies (proteins that bind to antigens) circulating in their blood, again demonstrating that the immune system can detect tumor cells and mount a specific response (Hellstrom IE et al 1968) that also involves specific T cells, or T lymphocytes (Itoh K et al 1988; Muul LM et al 1987; Vose BM et al 1985).

Why Do Tumors Escape Immune Detection?

Under normal circumstances, all cells display segments of their proteins on their surface. Upon infection with a viral or bacterial agent, cells display on their surface sample segments from these foreign proteins (Brodsky FM et al 1991; Janeway CA, Jr et al. 1994; Levine TP et al 1991). T cells and B cells patrolling the body for foreign invaders seek and destroy any cells that display these foreign proteins on their surface. These proteins are called antigens, substances that can stimulate a specific immune response or activity.

In cancer, the tumor cell also displays a sample of its abnormal proteins on its surface, which can signal the immune system that it is no longer a normal, healthy cell. These protein segments—either from proteins over-produced in the cancer cell or from viral or bacterial proteins that infected the cell and caused the cancer—act as red flags and attract the attention of T cells and B cells (Wang RF 1999). Tumor cells evade immune detection by failing to display protein segments (antigens) on their surface, thus, in effect, hiding from immune cells (Cordon-Cardo C et al 1991; Pantel K et al 1991).

In aggressive cases, tumor cells can also evade immune detection by producing agents that reduce immune cell activity (Junker U et al 1996; Ranges GE et al 1987; Sarris AH et al 1999; Staveley-O'Carroll K et al 1998). Alternatively, the immune system may not be able to cope with a tumor's rapid growth if the initial immune response to the tumor is not sufficient to reject or control it completely. Despite the immune system's natural ability to detect and kill cancer cells, in most circumstances the immune system fails to control tumor growth. The goal of immunotherapy is to specifically target tumor antigens as a means of killing cancer cells (Knuth A et al 1991; Naftzger C et al 1991). Table 1 shows some tumor antigens (substances that stimulate an immune response) that form the basis of cancer vaccines in clinical studies.

Table 1: Tumor antigens form the basis of vaccines in clinical development

Tumor Antigen	Cancer
Carcinoembryonic antigen (CEA)	Colon, breast, lung, pancreatic
Prostate-specific antigen (PSA)	Prostate
Tyrosinase protein	Melanoma
Human papillomavirus nucleoproteins	Cervical

What You Have Learned So Far

- The immune system has a natural ability to detect and kill cancer cells; however, tumors that develop in the presence of a competent immune system evolve complex immune-evasion strategies to avoid destruction and removal of the tumor.
- Not all tumors are naturally programmed to alert the immune system and mount an immune response, due to loss or coverage of cell surface antigens.
- The goal of immunotherapy is to produce anti-tumor effects through activation of the patient's immune system or through patient supplementation with natural substances, and thus to ultimately destroy the cancer.
- Therapeutic cancer vaccines are used to boost the immune system as a way to control established cancer. Preventive cancer vaccines are used to vaccinate people against infectious agents known to cause cancer.
- Surgery is often performed to remove most of the tumor before cancer immunotherapy or vaccination, which should then eliminate any persisting tumor cells that would grow or spread.
- For each individual, immune system status is the key factor that will affect the success of cancer vaccine therapy.
- Cancer patients preparing to undergo immunotherapy should ensure optimal immune system function through adequate nutrition and the use of nutritional supplements.

TYPES OF IMMUNOTHERAPY

Monoclonal Antibody (mAb). Monoclonal antibodies target specific tumor antigens, such as tumor growth factors, and can enhance the immune response against cancer. Many monoclonal antibodies (for example, Herceptin®) have other anti-cancer activities such as biological response modification and signal transduction inhibition, which slow or prevent cancer growth signals. Monoclonal antibody therapies for various cancers are outlined in Table 1.

Herceptin®. Approximately 25 percent to 30 percent of breast cancer patients exhibit an excess of the protein HER-2/neu (a member of the human epidermal growth factor receptor family), which can be measured in the blood via its extracellular domain (Hayes DF et al 2001). HER2/neu-positive breast cancer cells are associated with aggressive disease and decreased overall survival.

Herceptin® (trastuzumab) is the first monoclonal antibody that "targets" the HER2/neu protein on human cancer cells. This drug is approved for the treatment of metastatic breast cancers that are HER2-positive (Luftner D et al 2005) and provides a median overall response rate of 23 percent (Vogel CL et al 2001). Herceptin® attaches to HER2 present on cancer cells, thus preventing cancer proliferation and inducing cancer cell death (apoptosis). Herceptin® is also a biological response modifier and a mediator of antibody-dependent cell-mediated cytotoxicity via natural killer cells and monocytes (Baselga J et al 2001). Because Herceptin® damages the heart, an echocardiogram and complete blood count are usually monitored.

Drug	Molecular Target	Mechanism of Action	Cancer Type	References
Herceptin® (trastuzumab)	HER2/neu (human epidermal growth factor receptor)	mAb, BRM, STI	Breast (metastatic)	(Baselga J et al 2001)
Erbitux™ (cetuximab)	EGFR (epidermal growth factor receptor)	mAb, BRM, STI	Colorectal (advanced), head and neck, and pancreatic	(Bonner JA et al 2006; Moroni M et al 2005; Xiong HQ et al 2004)
Tarceva® (erlotinib)	EGFR-TKI (epidermal growth factor receptor-tyrosine kinase inhibitor)	mAb, BRM, STI	Non-small cell lung and pancreatic (advanced)	(Johnson JR et al 2005; Moore MJ 2005)
Iressa® (gefitinib)	EGFR-TKI	BRM, STI	Non-small cell lung (restricted access)	(Fukuoka M et al 2003)
Avastin™ (bevacizumab)	Humanized antibody to VEGF (vascular endothelial growth factor)	BRM, anti-angiogenic	Colorectal (metastatic), clear-cell renal carcinoma (metastatic)	(Hainsworth JD et al 2005; Jubb AM et al 2006)
Rituxan® (rituximab) (see chapter on Lymphoma)	Monoclonal antibody to CD20, a B-cell antigen	mAb, BRM	B-cell non-Hodgkin's lymphoma (NHL)	(van Heeckeren WJ et al 2006)
Thalidomide	Anti-TNF- α (tumor necrosis factor- α)	Anti-angiogenic, TNF modifier	Multiple myeloma, renal cell carcinoma (not FDA approved; restricted to clinical trials)	(Rajkumar SV et al 2006; Srinivas S et al 2005)

Table 2. Targeted Therapies (mAb = monoclonal antibody; BRM = biologic response modifiers; STI = signal transduction inhibitors)

Cytokine Therapy

Cytokines such as interleukin-2 and the interferons (alpha, beta, and gamma) have been used clinically in cancer patients.

Interleukin-2 (IL-2). Interleukin-2 (IL-2) is naturally produced in the body by T cells after activation by antigen, but it can also be given as a drug (immunotherapy). Clinical use of IL-2 counteracts the immunodeficiency state caused by the tumor and conventional treatments. IL-2 does not directly affect cancer cells; rather, its effects result from its ability to stimulate immune reactions in the body. Used as immunotherapy for metastatic melanoma (7 percent complete response) and kidney cancer (9 percent complete response), IL-2 can mediate durable regression (that is, prevent cancer recurrence) (Rosenberg SA 2001). However, a significant side effect of IL-2 therapy is vascular leak syndrome (Baluna R et al 1997).

Various interleukin-2 dosing schedules and combinations with interferon alpha (IFN-alpha) have been tested in patients with advanced melanoma. Response rates reported with IL-2 alone or in combination with IFN-alpha vary from 10 percent to 41 percent, with a small but significant proportion of durable responses (Keilholz U et al 2002a). High-dose interleukin-2 immunotherapy is useful in patients with metastatic renal cell carcinoma, and even in highly selected dialysis patients (Brusky JP et al 2006; McDermott DF et al 2005). IL-2 combined with thalidomide can produce durable, active responses in patients with metastatic renal cell carcinoma (Amato RJ et al 2006).

Treatment of skin and soft-tissue melanoma metastases by injection of IL-2 directly into the tumors resulted in complete response in 62.5 percent of patients (the longest remission lasting 38 months) and partial response in 21 percent of patients (Radny P et al 2003).

Preoperative immunotherapy with interleukin-2 in pancreatic cancer patients achieved a positive effect on postoperative complications and increased two-year survival (33 percent in the treated group compared to 10 percent in the control group) (Angelini C et al 2006).

Interferon. Interferons (IFNs) are produced naturally in the body in response to viral infections, but they can also be given as a drug

(immunotherapy). Interferon alfa has immunomodulatory, anti-angiogenic, anti-proliferative, and anti-tumor properties (Iqbal Ahmed CM et al 2003) against leukemia (CLL, CML, and HCL) (Bonifazi F et al 2001; Guilhot F et al 2004) and lymphoma (Jonasch E et al 2001), and, in combination with other anti-cancer agents, against breast cancer (Nicolini A et al 2005). Adjuvant high-dose interferon alfa-2b is approved for all melanoma patients with intermediate- and high-risk disease, but it benefits only 20 percent to 30 percent of patients and its use is limited due to its toxicity (Tsao H et al 2004). A favorable outcome in patients with high-risk melanoma treated with adjuvant interferon alfa-2b appears to depend on the development of autoimmunity during or after treatment (Gogas H et al 2006). Adverse reactions to interferon therapy include flu-like symptoms of fever, chills, fatigue, and muscle aches.

Gene Therapy. Cancer gene therapy has provided preliminary results through phase I clinical trials. In advanced breast cancer or melanoma patients, gene therapy with MetXia-P450 (a novel recombinant retroviral vector that encodes the human cytochrome P450 type 2B6 gene) was safe, well tolerated, and produced an anti-tumor response, suggesting it merits further clinical assessment (Braybrooke JP et al 2005).

In mesothelioma patients, gene therapy with intrapleural adenoviral (Ad) vector encoding the herpes simplex virus thymidine kinase "suicide gene" (Ad.HSVtk/ganciclovir) was safe, well tolerated, and resulted in long-term durable responses in two patients, which may have been due to induction of anti-tumor immune responses. The researchers hypothesize that approaches aiming to enhance the immune effects of adenoviral gene transfer (that is, with the use of cytokines) may lead to increased numbers of therapeutic responses in otherwise untreatable pleural (lung) cancers (Sterman DH et al 2005).

CANCER VACCINES

In contrast to chemotherapy and radiotherapy, cancer vaccines are not associated with any serious side effects. Cancer vaccines and the immune system have the ability to mount and amplify antigen-specific anti-tumor responses (Sprent J et al 2001, 2002). These activities cannot be produced by chemotherapy or radiotherapy. Once the immune system generates T cells specific for a particular antigen, a group of "memory cells" that remember this antigen will remain in the body, and in the event of a second threat from that antigen, an immune response will be mounted much faster than the first one (Sprent J et al 2001, 2002).

Phase I clinical studies assessing the safety of cancer vaccines have shown them to be associated with no toxicities outside reports of mild flu-like symptoms, irritation at the vaccination site, and fatigue (Carr A et al 2003; Soiffer R et al 2003; Woodson EM et al 2004).

Preventive cancer vaccines are being developed as a means of preventing cancers caused by chronic viral, bacterial, and parasitic infections that are associated with up to 20 percent of all cancer cases, including cervical and liver cancers (Bhopale GM et al 2004; Herrera LA et al 2005).

Therapeutic cancer vaccines. Most cancer vaccines are therapeutic, in that they are intended to treat existing cancer rather than to prevent it (Dalglish AG 2004; Hellstrom KE et al 2003). The cancer patient would initially undergo surgery to remove most of the tumor. Vaccination would then be undertaken to generate a specific immune response capable of clearing any residual cancer, thus preventing relapse (Hellstrom KE et al 2003; Hodge JW 1996; Reinartz S et al 2004) and extending the period of remission or survival in the patient.

The manner in which therapeutic cancer vaccines are used in the clinic is summarized in Table 3.

Stage 1	Cancer diagnosis
Stage 2	Surgery to remove accessible tumor
Stage 3	Vaccination
Stage 4	Patient monitoring

Table 3: The use of therapeutic cancer vaccines in the clinic

How Cancer Vaccines Work

The immune system is capable of both specific and non-specific responses against tumor cells. However, successful cancer vaccines must stimulate the immune system to act largely in a tumor-specific fashion.

A successful cancer vaccine would present tumor antigens to immune cells and activate CD4 (also known as helper T cells) and CD8 T cells (also known as cytotoxic or killer T cells). CD8 T cells become activated and directly kill the tumor cells (Janeway CA, Jr et al. 1994), while CD4 T cells are indirectly activated by dendritic cells and macrophages (Grohmann U et al 1998) to produce messengers (cytokines) that boost CD8 (killer) T-cell activity (Seder RA et al 1994).

B cells are immune cells that produce antibodies to human tumors (Disis ML et al 1994; Sorokine I et al 1991). Cancer immunotherapy that generates a good antibody response produces a better clinical outcome for the patient (Hoover HC, Jr et al. 1993; Mittelman A et al 1994).

The immune system also has a range of non-specific tools that can be stimulated into action by cancer vaccines, including natural killer cells and macrophages (Klein E et al 1993; Mantovani A et al 1992).

Types of Cancer Vaccines

Therapeutic cancer vaccines are classified into two main categories:

- Whole cell vaccines: self (autologous), donor (allogenic), or dendritic cell
- Synthetic protein antigens (soluble vaccines).

Whole cell vaccines use inactivated whole tumor cells as the vaccine given to the cancer patient. These inactivated tumor cells have a range of abnormal tumor proteins to which the patient's immune cells respond by generating an anti-tumor immune response and attacking any cancer cells persisting after surgery. Using the whole tumor cell as a vaccine eliminates the problem of having to identify the various key antigens, most of which remain unknown.

Self Versus Donor (Autologous Versus Allogenic) Vaccines. The tumor cells used in whole cell vaccines can be derived from the patient's own (self or autologous) tumor (Lahn M et al 1997) after it has been removed during surgery. Alternatively, these tumor cells can be obtained from a tumor sample removed from another individual (donor or allogenic) with the same cancer type (Chan AD et al 1998).

Dendritic Cell Vaccines. Dendritic cells are finger-like cells that pick up proteins from tumor cells (antigens) or invading organisms (bacteria, viruses, and parasites), and process and present them to young lymphocytes (Avigan D 1999; Hajek R et al 2000), which then initiate immune responses (Bodey B et al 2004; Vieweg J et al 2005).

Dendritic cell-based cancer vaccines, prepared from blood samples taken from the cancer patient (Hajek R et al 2000; Tjoa BA et al 2000), have been used to treat prostate cancer (Murphy G et al 1996), colorectal cancer (Chen W et al 2000), non-small cell lung cancer (Hirschowitz EA et al 2004), breast cancer (Allan CP et al 2004), and B-cell cancers (Adema GJ et al 2005; Ragde H et al 2004; Reichardt VL et al 2004). Dendritic cells pulsed with tumor cells (lysate) are partially efficient in triggering effective anti-melanoma immunity in stage IV patients (Escobar A et al 2005). Dendritic cell cancer vaccines are safe and well tolerated in humans.

Synthetic protein antigens are mass-produced synthetic versions of abnormal proteins displayed by tumors, and can generate immune responses capable of destroying cells in the body that display these antigens (Schulz M et al 1991). This type of vaccination is given to patients with immune system boosters (adjuvants) or other messengers to further enhance immune system activity (Schulz M et al 1991). Dendritic cells, which coordinate the function of immune cells, are often used as a vehicle to deliver these synthetic proteins to the immune system (Liu KJ et al 2004).

Clinical Studies Using Different Types of Cancer Vaccines

Melanoma. Melanoma is perhaps the cancer that has been the central focus of cancer vaccine research.

Synthetic Proteins. Proteins that have been identified as tumor antigens for melanoma include tyrosinase, MART-1 (also known as Melan A), gp100 (Jager E et al 1996), and products of the MAGE gene family (Gaugler B et al 1994; Van Der BP et al 1991). These proteins are not unique to melanoma cells, but are normal body proteins that are overproduced by melanoma cells and therefore called melanoma-associated antigens (Jager E et al 1996).

Vaccines made up of MART-1, tyrosinase, and gp100 synthetic proteins were successfully used to vaccinate melanoma patients

and induced objective tumor regression in all patients (Jager E et al 1996). Other melanoma cancer vaccines have used synthetic MAGE proteins and have been noted to cause complete tumor regression in some patients (Marchand M et al 1999; Weber JS et al 1999).

Gangliosides (GM2, GM3, GD2, and GD3). Gangliosides are cell surface molecules that are abnormally displayed or overproduced by all tumors. They are linked to an increased ability of tumors to spread, or metastasize (Bitton RJ et al 2002; Fredman P et al 2003), and to poor clinical outcomes (Hakomori S 2001). Therefore, they represent targets for vaccine-generated immune responses. Indeed, vaccination with purified gangliosides, prepared from laboratory-grown melanoma cells, showed that they were capable of generating an immune response in melanoma patients (Tai T et al 1985).

Another clinical study has shown that vaccination of melanoma patients (after surgery to remove skin, lymph node, and other metastases) with a concoction containing GM3, GD3, GM2, and GD2 generated strong immune responses that were associated with increased disease-free survival (Portoukalian J et al 1991). The successful use of ganglioside cancer vaccines is supported by improved survival of stage III melanoma patients who were treated with a GM2 vaccine following surgery to remove most of the tumor (Livingston PO et al 1994).

Heat Shock Proteins (HSPs). Heat shock proteins are abundant cell proteins known as molecular chaperones because they guide the assembly and eventual loading of proteins, prepared within the cell, into the external structures on which they are displayed to immune cells guarding the body (Przepiorka D et al 1998; Ren W et al 2004). Heat shock proteins from tumor cells therefore contain the perfect sample of tumor antigens for that particular tumor type and have proved effective as a basis for cancer vaccines, particularly for melanoma and renal cell carcinoma (Hoos A et al 2003; Huang XF et al 2003; Oki Y et al 2004).

A Phase III trial was performed with 300 patients with stage IV melanoma using heat shock protein (gp96)-peptide complexes derived from the patients' own tumors (given once weekly for the first four weeks and every other week thereafter). The patients with skin and lymph node disease survived an estimated median of 626 days compared to 383 days in the control group (Srivastava PK 2006).

Non-Hodgkin's Lymphoma. Other vaccine approaches (for example, anti-idiotypic) have demonstrated clinical benefit in the treatment of non-Hodgkin's lymphoma (Bendandi M 2004; Caspar CB et al 1997; Rodriguez CM et al 2004) and are being assessed for multiple myeloma treatment (Titzer S et al 2000).

Pancreatic, Lung, Colorectal, Breast, and Ovarian Cancers. Carcinoembryonic antigen (CEA). CEA is a glycoprotein (a protein attached to sugar groups) that is normally produced by cells only during fetal development. However, it is grossly overproduced by almost 50 percent of all human cancers (Huang EH et al 2002; Marshall J 2003; Ullenhag GJ et al 2004), including colon, rectal, breast, ovarian, lung, pancreatic, and gastrointestinal tract cancers (Marshall J 2003; Morse MA et al 1999). Indeed, CEA can be detected in blood samples from cancer patients and is therefore used to monitor cancer therapy and progression (Marshall J 2003).

CEA loaded into dendritic cells and used as a cancer vaccine generated (CD4 and CD8) anti-tumor responses that were associated with disease stabilization (Berinstein NL 2002; Liu KJ et al 2004; Ueda Y et al 2004). CEA delivered to the cancer patient's immune system (by a poxvirus) brought about disease stabilization in up to 37 percent of treated patients (Berinstein NL 2002). A CEA-based vaccine (ALVAC-CEA) developed using vaccinia virus has also been shown to be safe in humans and capable of generating specific anti-tumor immune responses (Marshall J 2003).

Breast and Ovarian Cancer. Sialyl-Tn (STn). Sialyl-Tn is a carbohydrate that is overproduced by several types of cancer cells, including breast, ovarian, colorectal, gastric, and pancreatic cancer cells (Holmberg LA et al 2004). As a result, this tumor-associated antigen is a good candidate for a therapeutic vaccine for these cancers.

A sialyl-Tn-based cancer vaccine called Theratope®, developed by a Canadian company (Biomira Inc.), is effective in the treatment of breast and ovarian cancer patients (Holmberg LA et al 2000, 2001). In a clinical setting, this vaccine was safe and was associated with reduced risk of relapse (longer remission period) or death (Holmberg LA et al 2000, 2001).

ENHANCING IMMUNOTHERAPY RESPONSES

Boosters for the Immune System. Tumor cells used as vaccine are often manipulated to produce and secrete messengers such as interleukin-2 and granulocyte macrophage colony stimulating factor (GM-CSF), which directly activate immune cells (Dranoff G et al 1997; Osanto S et al 2000; Sallusto F et al 1994). In the clinical setting, vaccines are often administered with immune system boosters (adjuvants), such as bacillus Calmette-Guerin (BCG) and DETOX, to make the immune system more responsive to the presented antigens (Harris JE et al 2000; Knutson KL 2002; Sondak VK et al 2003).

Cancer Vaccines in Clinical Trials (Phase III)

A variety of cancer vaccines showed promise in early (phase I and II) clinical studies (Murphy G et al 1996; Weber JS et al 1999). However, most failed to translate this success to the larger phase III studies that examine the impact of the vaccine-induced immune response on the period of remission (or disease stabilization) enjoyed by the patient, and on overall survival. The former is also referred to as disease-free survival or progression-free survival (Kaufman HL 2005). Consequently, when making a balanced assessment of cancer vaccines as a treatment option, it is important to focus on vaccines that have reached phase III studies. With the exception of lung cancer, therapeutic cancer vaccines have progressed to phase III clinical studies for all the major cancer types.

Renal Cell Carcinoma. A cancer vaccine for renal cell carcinoma has recently been tested in a phase III setting using autologous (self-donated) cancer cells and lysates (prepared by breaking down cancer cells) (Doehn C et al 2003; Jocham D et al 2004). This study involved 558 renal cell carcinoma patients who were vaccinated (six injections in the skin once a month) with the autologous tumor cell vaccine after surgery (Jocham D et al 2004). After 70 months of follow-up, the progression-free survival of vaccinated patients was 67.8 percent compared to 59.3 percent in non-vaccinated patients (Jocham D et al 2004). These results support the use of this renal cell carcinoma vaccine following surgery (removal of a kidney) in renal cell carcinoma cases not larger than 2.5 cm (Jocham D et al 2004).

Melanoma. Several types of cancer vaccines for melanoma have progressed to phase III clinical assessment, including ganglioside and whole cell (allogenic and autologous)-based vaccines (Hsueh EC et al 1998; Knutson KL 2002; Sondak VK et al 2003).

A whole cell melanoma vaccine (CancerVax/Canvaxin) has been tested in a phase III clinical trial by comparing the outcomes of 935 vaccinated patients (after surgery) and 667 non-vaccinated patients (Hsueh EC et al 1998; Morton DL et al 2002). The five-year overall survival of vaccinated patients was 49 percent compared to 37 percent in the non-vaccinated group of patients (Morton DL et al 2002).

Melacine, a melanoma cancer vaccine prepared from allogenic (donor) tumor cells, has also progressed to phase III clinical evaluation (Sondak VK et al 2003; Sosman JA et al 2003). This vaccine is given to patients with an immunological booster and has been shown to confer vaccinated patients with survival benefits (Sondak VK et al 2003).

A ganglioside-based vaccine, developed for melanoma treatment and administered with an adjuvant, was initially shown to induce antibodies that could clear melanoma cells (Knutson KL 2002). However, evaluation of this vaccine in phase III studies produced somewhat disappointing results, as a standard treatment of high-dose interferon therapy generated better results in relation to relapse-free survival and overall survival (Kirkwood JM et al 2001).

Colon Cancer. Cancer vaccines for colorectal cancer that have progressed to phase III clinical studies have focused on the use of CEA proteins and whole cell autologous (self) tumor cells (Hanna MG, Jr. et al 2001; Harris JE et al 2000; von MM 2005). An autologous tumor cell vaccine used in combination with BCG as an adjuvant (immune booster) has been tested in a study of 412 stage II and III colorectal cancer patients who had undergone surgery to remove most of the tumor (Harris JE et al 2000). Vaccinations were given four weeks after surgery and patients who received this treatment showed benefits in disease-free survival and overall survival (Harris JE et al 2000).

Breast Cancer. The vaccine Theratope® (manufactured by Biomira Inc.), based on the tumor-associated antigen sialyl-Tn, is currently being evaluated in a large phase III study of 1000 metastatic breast cancer patients (Holmberg LA et al 2004; Ibrahim NK et al 2003). Findings from this study have yet to be published.

Note: Biomira Inc., a pharmaceutical company, does not treat patients. However, Biomira provides vaccines to physicians at various cancer clinics in North America and Europe where government-approved clinical trials are ongoing. The vaccines are provided only to physicians who are currently involved in vaccine exploration and who have extensive experience with these agents. To speak to Biomira's Medical Information Assistant, call 1-877-234-0444, ext. 500.

Prostate Cancer. Provenge®, a dendritic cell-based vaccine for prostate cancer, is being evaluated in phase III clinical studies by the US company Dendreon (Rini BI 2002). This vaccine involves loading synthetic prostate cancer cell proteins (recombinant protein antigens) into the patient's dendritic cells (grown in the laboratory) and administering them as vaccine. Clinical studies have shown that this vaccine has activity in patients with hormone-independent prostate cancer (Schellhammer PF et al 2005). More recent media reports (NewsRX.com) have indicated that this vaccine improved survival in men with advanced prostate cancer in phase III studies; however, these results have not yet been published in the scientific literature.

Blood (Hematological) Cancers. The National Cancer Institute is currently overseeing a large phase III clinical study using an idiotype-based vaccine given to patients with follicular lymphoma after they have undergone chemotherapy (Kwak LW 2003).

FACTORS AFFECTING IMMUNE SYSTEM STATUS

Age. While cancer is more common in the elderly (Holmes FF et al 1991), immune strength gradually declines with age and can

pose a problem for the successful use of immunotherapy in the elderly (Ginaldi L et al 1999; Pawelec G et al 2002). Although age-related decline in immune status is a natural feature of the immune system, it is also aggravated by lifestyle factors such as diet (Lesourd B et al 1999). Therefore, nutritional supplements to boost immune function may have even more significance in elderly cancer patients than in young adults.

Tumor-Induced and Surgery-Associated Immunosuppression. Two types of immunosuppression affect the successful outcome of immunotherapy: immunosuppression from the tumor and that associated with surgery to remove the tumor. Tumor-induced immunosuppression, due to the production of immunosuppressive factors by cancer cells, is overcome by surgical removal of the tumor mass (Morton DL 1978) and thus creates an environment in which immune cells can better respond to immunotherapy. However, the process of surgery and the associated use of particular anesthetic and analgesic drugs also dampens immune cell function, again reducing the effectiveness of any immunotherapy used (Vallejo R et al 2003). It is recommended that anesthetic and analgesic drugs be carefully selected to minimize immunosuppression, and that patients prepare for surgery by optimizing nutritional and immune status (Vallejo A et al 2002).

Nutritional Status. The production of immune-suppressing (immunosuppressive) agents by cancer cells presents a significant obstacle to cancer immunotherapy (Junker U et al 1996; Sarris AH et al 1999). Excessive production of pro-inflammatory cytokines and reactive oxygen species may damage the immune system, resulting in adverse immunotherapy outcome and cancer progression.

Therefore, nutritional supplements that improve the function of key immune cells will affect the efficacy of immunotherapy and could also be used to prepare patients for immunotherapy (Malmberg KJ et al 2002).

The impact of nutrition on the function of immune cells that play a key role in the efficacy of cancer immunotherapy is well established (Calder PC et al 2002b; Chandra RK 1999). Studies of cancer patients demonstrate that nutritional supplements can play a role in restoring immune status depleted by cancer and surgery to normal levels that would be more responsive to immunotherapy treatment (Malmberg KJ et al 2002).

NUTRITIONAL THERAPY

Although the direct effect of nutritional supplements on the effectiveness of cancer immunotherapy has yet to be clinically evaluated, the impact of nutrition, particularly micronutrients, on immune cell function (that is, immunonutrition) is central to the success of any cancer treatment (Calder PC et al 2002b; Chandra RK 1999). Several nutrients are able to modulate immune response and counteract inflammatory processes. Zinc, omega-3 fatty acids, and glutamine all act differently to modulate immune response, but all appear to have the potential to protect against cancer progression (Grimble RF 2001).

Immunonutrition has gained recognition as an adjuvant cancer therapy and should be an integral part of cancer immunotherapy, particularly against cancers associated with chronic inflammation (Philpott M et al 2004), as it has beneficial effects on patient outcomes, enhances the immune response, and improves the prognosis of cancer patients (Chermesh I et al 2004).

Cells of the immune system that are essential for the success of cancer vaccines include:

- Dendritic cells
- CD4 T cells (lymphocytes)
- CD8 T cells (lymphocytes)
- B cells (lymphocytes)
- Natural killer (NK) cells
- Macrophages
- Neutrophils.

Micronutrients that have been established as being essential to the optimal function of these immune cells include zinc, vitamins C and E, folic acid, and glutamine (Calder PC et al 1999; Calder PC et al 2002b).

Zinc. Zinc supplements improve immune cell function (Ibs KH et al 2003; Prasad AS et al 2002). Indeed, diets lacking in zinc are linked to reduced CD4 and CD8 T-cell function (Chandra RK 1999). While deficiencies in zinc also compromise the function of natural killer cells, macrophages, and neutrophils (Ibs KH et al 2003), this impairment of the immune system can be reversed by dietary zinc supplements (Chandra RK 1999; Ibs KH et al 2003). Zinc supplements should, however, be carefully monitored, as excessive intake (over 100 mg per day) is counterproductive and reverses any benefits seen with the suggested doses of 20 to 50 mg per day (Calder PC et al 2002b; Hercberg S et al 1998; Kohn S et al 2000).

Zinc supplements of 50 mg a day improve the structure of Langerhans' cells (a type of dendritic cell found in the skin epidermis) by endowing them with a more dendritic (or finger-like) structure that improves their mobility and thus their ability to pick up antigens

and transport them to lymphocytes (Kohn S et al 2000).

Antioxidants (Vitamins C and E). Supplementing the diet of colorectal cancer patients with high doses of vitamin E (750 mg per day) for two weeks increased lymphocyte numbers and improved the lymphocytes' ability to produce messengers (interleukin-2 and interferon gamma) that are associated with the type of immune response required to destroy cancer cells (Malmberg KJ et al 2002). Therefore, high-dose vitamin E supplements may be considered to support the use of cancer vaccines and immunotherapy. Long-term supplementation at lower doses of 100 to 200 mg a day has improved immune function (Calder PC et al 2002b; Pallast EG et al 1999).

Vitamin C supplements also improve immune function and protect lymphocytes against damage (Lenton KJ et al 2003; Schneider M et al 2001).

Folic Acid. Deficiencies in folic acid impair the immune system by reducing the ability of CD8 T cells to divide and increase in number (Courtemanche C et al 2004). In addition, low levels of folic acid lead to genetic instability in lymphocytes and increased cell death, or apoptosis (Courtemanche C et al 2004; Duthie SJ et al 1998). However, the impairment of lymphocyte function can be restored by folic acid supplements (Courtemanche C et al 2004).

Vitamin B12. Vitamin B12 plays a key role in immune function, as B12 deficiencies in humans lead to low numbers of CD8 T cells and impair the activity of natural killer cells (Tamura J et al 1999). These cells are essential for the cytotoxic arm of the immune system, which in turn is essential for destroying cancer cells. Supplementing with B12 restores CD8 T-cell numbers and natural killer cell activity (Tamura J et al 1999).

Vitamin B6. Deficiencies in vitamin B6 impair the immune system and are associated with a reduced ability of lymphocytes to produce messengers (cytokines) required for sustained immune activation (Doke S et al 1998).

Selenium. Selenium supplements (100 mcg a day) improve immune cell function by increasing the cells' ability to produce messengers (cytokines) associated with the type of immune responses required to clear tumor cells (Broome CS et al 2004).

Glutamine. Glutamine supplements (30 grams a day) sustain immune cell function (Yoshida S et al 1998). Clinical studies have shown glutamine supplements to be particularly effective in counteracting immunosuppression associated with surgery (Calder PC et al 1999; O'Riordain MG et al 1996), and thus to be of benefit to patients undergoing an immunotherapy/vaccination regimen after surgical removal of the tumor.

Ginseng. The medicinal herb ginseng improves immune cell function (Larsen MW et al 2004). Of particular importance to the successful use of cancer vaccines is the recently reported ability of ginseng products to drive the development of dendritic cells that are essential for successful cancer vaccination (Takei M et al 2004).

Melatonin. Melatonin hormone supplements (20 mg a day, at bedtime) improve lymphocyte function and have been tested in clinical studies of blood cancers (El-Sokkary GH et al 2003; Lissoni P et al 2000).

Garlic. Garlic extracts boost the activity of natural killer cells against tumor cells (Hassan ZM et al 2003).

Mushroom Extracts (AHCC). Extracts from various mushrooms boost immune cell function (Kidd PM 2000). In particular, active hexose correlated compound (AHCC) improves the function of natural killer cells and confers benefits to liver cancer patients after surgical removal of the tumor (Matsui Y et al 2002).

Omega-3 Fatty Acids. The ratio of omega-3 and omega-6 polyunsaturated fatty acids (PUFA) modulates the inflammatory response. Inflammatory cells typically contain high levels of arachidonic acid and low levels of omega-3 PUFA (Calder PC 2002, 2002a). Increasing omega-3 fatty acid intake antagonizes arachidonic acid levels in inflammatory cell membranes, and decreases the amount of arachidonic acid that is available for production of pro-inflammatory arachidonic acid-derived mediators (Calder PC 2003).

Omega-3 PUFA may have indirect immunomodulatory activity mediated through tumor necrosis factor-alpha (TNF- α) and nuclear factor-kappa beta (NF- κ B) production (Babcock TA et al 2002). Administration of omega-3 fatty acids before and after surgery (prior to immunotherapy) may have a favorable effect on outcome by lowering the magnitude of inflammatory response and preventing immune suppression (Weiss G et al 2002). Fatty fish such as salmon, mackerel, tuna, and herring are good sources of long-chain omega-3 PUFA.

TRACKING YOUR PROGRESS

Monthly Blood Tests. A range of blood tests and other diagnostic procedures can be used to monitor the effectiveness of cancer

immunotherapy. Results from these tests provide information required to assess the effectiveness of this new treatment modality.

The following tests are essential for monitoring the effectiveness of immunotherapy.

- **Tumor antigen profile:** determining the antigens (abnormal proteins) produced by each tumor is important in assessing the use of cancer vaccines or other forms of immunotherapy as a treatment choice. Tumor antigen profile should also be monitored during immunotherapy, as the tumor can develop variations that stop the display of these antigens as a means of escaping detection.
- **Immune cell function:** the function of lymphocytes is monitored during cancer immunotherapy by a variety of techniques. These include proliferation assays to assess their ability to expand in response to activation, and cell-kill (cytotoxic) assays to assess the ability of CD8 lymphocytes to kill tumor cells (Clay TM et al 2001; Keilholz U et al 2002b; Lyerly HK 2003).
- **PSA:** prostate-specific antigen can be detected in blood samples from prostate cancer patients and has been established as a reliable marker for disease progression or patient response to therapy (Coetzee LJ et al 1996; Kiper A et al 2005). Prostate cancer patients treated with cancer vaccines in clinical studies showed reductions in their PSA levels (Noguchi M et al 2004b; Noguchi M et al 2004a).
- **CEA:** monitoring of serum levels of carcinoembryonic antigen is recommended for colorectal cancer patients as a marker for disease progression or response to treatment (Sunga AY et al 2005).
- **Angiogenesis markers:** angiogenesis is the process of forming new blood vessels, which is essential for tumors to spread to other parts of the body. Increased levels of the angiogenic factor vascular endothelial growth factor (VEGF) in the blood of cancer patients serves as a robust indicator of disease progression and can be used to monitor response to treatment with cancer immunotherapy (Bonfanti A et al 2000; Brostjan C et al 2003; Poon RT et al 2001). Circulating endothelial cells, detectable in the blood of cancer patients, are increased and have also been established as another indicator of disease progression (Beerepoot LV et al 2004; Mancuso P et al 2003).
- **Growth factors:** serum levels of the growth factors pleiotrophin (PTN) and fibroblast growth factor-2 (FGF-2) are increased in prostate cancer patients and can be used as a marker for disease progression or response to therapy (Aigner A et al 2003).
- **Immunosuppressive agents:** levels of tumor-produced immunosuppressive agents (for example, interleukin-10 (IL-10) (Sarris AH et al 1999) and transforming growth factor-beta (TGF- β) (Junker U et al 1996)) can be detected in patients' serum and used to check for disease progression or response to treatment.
- **X-rays and scans:** can be used to monitor the response or progression of disease during cancer immunotherapy.
- **Physical examination:** regular physical examinations can detect changes in body mass and enlarged lymph nodes that may be signs of disease progression (Sunga AY et al 2005).

For More Information

Cancer immunotherapy patients may wish to read the following chapters and design a program that addresses the full range of their cancer problems:

- Complementary Adjuvant Cancer Therapies
- Cancer Surgery
- Immune System Enhancement
- Blood Disorders
- Medical Testing.

The National Cancer Institute Clinical Trials Database lists and describes ongoing clinical trials at different locations throughout the US. This can be accessed at the website <http://cancertrials.nci.nih.gov/> or by calling the Cancer Information Service at 1-800-4-CANCER.

The American Cancer Society, 1-800-ACS-2345.

LIFE EXTENSION FOUNDATION RECOMMENDATIONS

Patients should ask their physicians for assistance in obtaining information on ongoing cancer vaccine and other immunotherapy clinical studies, and the criteria for subject enrollment and participation. Immunotherapy patients should consult their physicians before starting to use any nutritional supplements while receiving treatment. In addition, if using nutritional supplements, they should ask their physicians for assistance in ensuring the implementation of blood tests and diagnostic procedures that are essential in monitoring the effectiveness of any adjuvant therapy for cancer.

Some guidelines for using nutritional supplements with immune-boosting cancer therapies include:

- **Zinc**—20 to 50 milligrams (mg) daily (Hercberg S et al 1998; Kohn S et al 2000)

- **Vitamin C**—120 mg daily (Herberg S et al 1998)
- **Vitamin E**—800 international units (IU) of d-alpha tocopheryl succinate daily for two weeks (Malmberg KJ et al 2002); 400 IU daily for long-term use (Calder PC et al 2002b; Pallast EG et al 1999)
- **Folic acid**—800 micrograms (mcg) daily (Fenech M 2001)
- **Vitamin B12**—7 mcg daily (Fenech M 2001)
- **Vitamin B6**—2.1 to 2.7 mg (one B-complex capsule) daily (Kwak HK et al 2002)
- **Selenium**—100 mcg daily (Broome CS et al 2004)
- **Glutamine**—30 grams (g) daily (Yoshida S et al 1998)
- **Ginseng, panax**—100 mg daily (Anderson GD et al 2003)
- **Melatonin**—20 mg daily, at bedtime (Lissoni P et al 2000)
- **Garlic**—250 mg daily (Dhawan V et al 2004)
- **Mushroom extract**—active hexose correlated compound: 3 g daily (Matsui Y et al 2002)
- **Fish oil**—containing EPA: 4.7 g daily (Kew S et al 2004).

Note that most cancer patients take higher doses of vitamin C (2000 to 20,000 mg/day), selenium (200 to 400 mcg/day), vitamin B6 (100 to 750 mg/day), and vitamin B12 (100 to 300 mcg/day). These doses are considerably higher than the doses used in the studies cited above.

BLOOD TEST AVAILABILITY

Tests for PSA, CEA, selenium, vitamin B12, and folate serum levels are available via Life Extension/National Diagnostics, Inc., and may be ordered by calling 1-800-544-4440 or by ordering online at <http://www.lef.org/bloodtest/>.

Tumor antigen profile can be determined via Genzyme Genetics (<http://www.genzyme genetics.com>) and may be ordered by a physician by calling 1-800-966-4440.

Tests for immune cell function, serum growth factor levels, and immunosuppressive agents (IL-10) are available at UCLA's Jonsson Comprehensive Cancer Center (<http://www.cancer.mednet.ucla.edu/>).

X-rays, scans, and physical examinations can be arranged through your physician.

CANCER VACCINES AND IMMUNOTHERAPIES SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

EPA/DHA

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

Folic acid

- Consult your doctor before taking folic acid if you have a vitamin B12 deficiency.
- Daily doses of more than 1 milligram of folic acid can precipitate or exacerbate the neurological damage caused by a vitamin B12 deficiency.

Garlic

- Garlic has blood-thinning, anticlotting properties.
- Discontinue using garlic before any surgical procedure.
- Garlic can cause headache, muscle pain, fatigue, vertigo, watery eyes, asthma, and gastrointestinal symptoms such as nausea and diarrhea.
- Ingesting large amounts of garlic can cause bad breath and body odor.

Ginseng

- Consult your doctor before taking ginseng if you have high blood pressure. Overuse of ginseng can increase blood pressure.
- Consult your doctor before taking ginseng if you take nonsteroidal anti-inflammatory drugs (NSAIDs) and/or warfarin (Coumadin). Taking NSAIDs or warfarin with ginseng can increase the risk of bleeding.
- Consult your doctor before taking ginseng if you have diabetes. Taking ginseng can cause an extreme drop in your blood glucose level. Ginseng can cause breast pain, vaginal bleeding after menopause, insomnia, headaches, and nosebleeds.

L-Glutamine

- Consult your doctor before taking L-glutamine if you have kidney failure or liver failure.
- L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea.

Melatonin

- Do not take melatonin if you are depressed.
- Do not take high doses of melatonin if you are trying to conceive. High doses of melatonin have been shown to inhibit ovulation.
- Melatonin can cause morning grogginess, a feeling of having a hangover or a “heavy head,” or gastrointestinal symptoms such as nausea and diarrhea.

Selenium

- High doses of selenium (1000 micrograms or more daily) for prolonged periods may cause adverse reactions.
- High doses of selenium taken for prolonged periods may cause chronic selenium poisoning. Symptoms include loss of hair and nails or brittle hair and nails.
- Selenium can cause rash, breath that smells like garlic, fatigue, irritability, and nausea and vomiting.

Vitamin B6

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

Vitamin B12 (cyanocobalamin)

- Do not take cyanocobalamin if you have Leber's optic atrophy.

Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

Vitamin E

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.