Treating Cancer with Site Specific Immunotherapy

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There is growing evidence that immune cells within the tumor microenvironment have a substantial impact on prognosis. Tumor associated macrophages (TAMs), prominent cells in the tumor microenvironment, can function either in a ‘pro-cancer’ tissue repair role (M2 macrophages) that suppresses immune function and supports cancer growth, or an ‘anti-cancer’ immunological role (M1 macrophages) that can initiate an anti-cancer immune response. Site Specific Immunotherapy (SSI) provides a simple, novel approach to cancer immunotherapy that shifts macrophage function from M2 (pro-cancer) to M1 (anti-cancer). This article will discuss the science, both animal and clinical research, and its practical application in clinical practice.

It is well known that chronic infection can predispose to cancer development. For example, if someone has chronic H. pylori infection of the stomach, they have an increased risk of developing stomach cancer. Chronic HPV infection in the cervix increases the risk of cervical cancer. What is not as well known, but is well documented, is that acute infection, meaning infection that’s there for a few days or for a week or so, actually has an anticancer effect. There’s an interesting paradox that chronic infection predisposes to cancer but acute infection has an anticancer role.

There have been a dozen studies that have shown that the more acute infections you have, the less your risk of getting cancer. There have been many hundreds of cases very well documented in the literature of people with incurable cancer who have gone into remission following severe acute infection. These remarkable recoveries illustrate the potential of our immune system to clear cancer. Three times in my own clinical practice, I’ve witnessed remissions in patients with advanced cancer following acute infection, once in a patient with Stage III B (late stage) lung cancer, once in a patient with advanced prostate cancer, and once in a patient with advanced pancreatic cancer. All three cases were remarkable and the latter case was published. These cases inspired me to further explore the role of acute infection in stimulating an anticancer immune response.

Acute infections are common in childhood. Prior to the advent of effective treatments for acute childhood leukemia, about 15% of children with acute leukemia would go into temporary remission after an acute infection. Unfortunately the remissions were temporary, but it once again points to potential of acute infection to stimulate an anticancer immune response.

The Role of M1 and M2 Macrophages

So how does that happen? A large proportion of cells within a tumor are immune cells. There is an emerging recognition in the field of cancer immunology of the important role that immune cells have not only in potentially helping the body get rid of cancer but also, paradoxically, in supporting the growth of cancer and suppressing immune function.

The most predominant immune cells in the tumor microenvironment are macrophages. What is emerging in immunology research over the last three years is a recognition that macrophages are either helping the cancer grow or are helping the body get rid of cancer. In four different cancer studies, what macrophages are doing has been found to be the most important factor in determining prognosis (see references later in article). This is an important concept that, when it is fully recognized in clinical oncology, is going to revolutionize the way that we understand cancer treatment. It is fully compatible with the way that integrative medicine has understood cancer treatment, with its focus on immune system function. The goal is to support the immune cells to do the right thing rather than the wrong thing. The genetic expression of the immune cells (i.e., what they are doing) is most highly correlated with prognosis, more highly correlated with prognosis than the gene expression of the cancer cell. This is changing our conception of the important focus of cancer treatment.

I will summarize the science, and then we’ll start to explore why chronic infection has a pro-cancer effect and how acute infection has an anticancer effect and how we might use that mechanism to help to stimulate an anticancer immune response.

There are two basic types of macrophages. There is probably a spectrum of possibilities but these two defined phenotypes provide a simplistic understanding of macrophage function. On the one hand, there are M1 macrophages. Their role is to kill bacteria and cancer cells. On the other hand, there are M2 macrophages, which play an important role in tissue repair of damaged tissue. Both the M1 and M2 roles are very important in the body. However, in cancer, they are opposing roles. Macrophages can function in only one role at once. When they are functioning in their M1 role, they cannot function in their M2 role, and vice-versa. When they are functioning in their M2 role (i.e., tissue repair role) they suppress immune function and support cancer growth. They suppress not only their own immune function, but the immune function of all the other immune cells in the tumor microenvironment.

Both of these types of macrophages are very important in the body. We need M2 macrophages to repair damaged tissue and we need M1 macrophages to help get rid of bacterial infection and cancer. However, an important challenge in cancer is that macrophages within a cancer tumor are doing the wrong thing. Functioning in the M2 role, they perceive cancer as damaged tissue, and they try to support the
healing of the cancer tissue by promoting angiogenesis, by promoting growth factor production, and by suppressing immune function. M2 macrophages play a coordinating role in helping the cancer grow and creating immunosuppression within the tumor. About 7 or 8 years ago, researchers in breast cancer found that the higher the density of macrophages in breast cancer, the poorer the prognosis. Due to M2 macrophage dominance, macrophages drive the growth of cancer. If the problem is that M2 function dominates in tumors, the challenge is to make the M1 function dominant. Acute infection strongly drives macrophage function to the M1 immunological role.

In our own research at Qu Biologics, the biotechnology company I founded, we found that if we inject a preparation made from bacterial cell components subcutaneously, the body appears to respond in a site specific way, directing an innate immune response to the organ or tissue in which that bacteria normally causes infection (Figure 1). Chronic inflammation plays an important role in cancer development. Most treatments in integrative medicine reduce chronic inflammation. One of the important reasons why chronic inflammation drives cancer development may be that it drives macrophage function towards the M2 role, thus, promoting cancer growth and progression.

According to our hypothesis, treatments that reduce chronic inflammation should act synergistically with SSI therapy, helping to shift the tumor microenvironment to M1 dominance and immunological competence.

Reviews by Schmid and Varner define this distinction between M1 and M2 macrophages and their roles in the tumor microenvironment.

Monocytes are released by the bone marrow. When they enter tissues, they differentiate (polarize) into M1 macrophages or M2 macrophages. M1 macrophages (anti-cancer) release a whole different cascade of chemokines and cytokines than M2 macrophages (pro-cancer), because the role of M1 macrophages (anti-bacterial/anti-cancer) is completely different from the role of M2 macrophages (tissue repair).

Macrophages function as coordinating cells within that tumor microenvironment. In M2 dominance, M2 macrophages function with T-Reg cells, which are the T cell ‘partner’ of M2 macrophages, to suppress immune function in the tumor microenvironment. M2 macrophages suppress not only their own immune response but they suppress the immune response of all the of SSI derived from Klebsiella pneumoniae, a common cause of lung infection, would initiate an immune response in the lung with a shift from M2 to M1 macrophage dominance. Similarly, an injection of an SSI derived from E. coli, a common cause of colon infection, would initiate an immune response in the colon with a shift from M2 to M1 macrophage dominance.

This site specific nature of the innate immune response had not been recognized previously. Historically, the innate immune system has been considered relatively primitive and the adaptive immune system was considered the sophisticated part of the immune system.

Our research suggests that the innate immune system is more sophisticated than it has been given credit for. In other words, our research suggests that the innate immune system, rather than creating a generalized innate immune response everywhere in the body, focuses its response on the organ or tissue in which a bacteria commonly causes infection (Figure 1).

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other immune cells within the tumor microenvironment.

Chronic infection is the result of a failed immune response, with macrophage function shifting to M2 tissue repair, resulting in immunosuppression and support of cancer growth. As a result, chronic infection increases the risk of cancer development.

At Qu Biologics, we hypothesize that acute infection, or the simulation of acute infection with Site Specific Immunomodulation, is capable of shifting macrophage function from M2 to M1 dominance.

M1 macrophages produce chemokines and cytokines that stimulate an immune response, activating cells of both the innate and adaptive immune system, relieving the immuno-suppression created by the M2 macrophages.

One important aspect of the SSI approach, is that it is intended to be a “whole system” approach. One of the problems with the standard pharmacological approach is that it is targeted to a single molecular target or pathway. However, the body typically has numerous pathways to achieve the same thing. If you block one of those pathways with a drug, the body finds a different parallel pathway, resulting in resistance or tolerance and short-lasting therapeutic benefit. In contrast, Site Specific Immunomodulation is designed to shift the whole system of the tumor microenvironment (and its multiple pathways) from pro-cancer (M2 dominance) to anti-cancer (M1 dominance).

A useful analogy is to think of the immune system as an orchestra. In the context of cancer, that orchestra is playing the wrong song. Pharmaceutical medicine has historically tried to get the orchestra to play the right song by taking away the tubas (i.e., blocking a specific pathway) or by adding another hundred violins (e.g., cytokine therapy). SSI therapy is designed to shift the whole system and, by analogy, to get the orchestra to play a different song using the whole orchestra. I called the company Qu, because it cues the immune system.

Key review references for M1 and M2 Macrophage subsets in cancer may be found in Nature Immunology.6

The important role of macrophage function in cancer emerged a few years ago. One of the first articles that came out about the important role that macrophages can play in the context of cancer was titled “Macrophages: obligate partners for tumor cell migration, invasion and metastasis”, which recognized that cancer cells cannot actually grow without the support of M2 macrophages.7

If we begin to put as much energy and resources towards understanding how we can get the immune system to do the right thing as we have historically in Medicine’s focus on killing cancer cells, I think we will make a substantial amount of progress in cancer treatment.

Research published in 2010 documented the important role of M1 macrophages in determining prognosis in lung cancer. The data was from 100 patients with stage 2 lung cancer whose tumors had been removed and stored in a tumor bank. These hundred patients were divided into two groups, one in which the M1 macrophage density in the tumor islets was above the median for the group and the other in which the M1 macrophage density was below the median. The researchers found a substantial impact on prognosis, with a 7 year longer median survival in the group with high M1 macrophage density (8 year median survival) compared to the group with low M1 macrophage density (1 year median survival). This remarkable difference suggests a potentially important role of M1 macrophages in determining patient prognosis.

M1 and M2 macrophage density and their relation to prognosis have been studied in other cancers, with similar findings suggesting that macrophage function may be the most important factor in determin-
The Journal of Clinical Oncology published a study, “M1 Macrophages in Serum and Tumor Have Prognostic Impact in American Joint Committee on Cancer Stage I/II Melanoma.” These researchers studied early-stage melanoma and found that patients with M1-like macrophage dominance had a very good prognosis, while the prognosis was much poorer in those with M2-like macrophage dominance.

Another study in the same issue of the Journal of Clinical Oncology, found that if there was M2-like macrophage dominance within the pancreatic tumor, the prognosis was very poor but if there was M1-like macrophage dominance the prognosis was improved.

In a study in Haematologica, in patients with Hodgkin’s lymphoma, again the same relationship between M1 dominance and improved prognosis was found.

The studies above point to the therapeutic potential of a treatment that could shift macrophage function from M2 to M1.

Observations into Action

Dr. William Coley, now known as the father of cancer immunotherapy, was one of the first to recognize the link between acute infection and an anticancer immune response. He developed Coley’s Toxins, a killed bacterial preparation, in the 1890’s. Coley often injected his preparation into the tumor or IV. He had well documented success in some cases, but no benefit in others.

When I reviewed the published literature documenting Coley’s cases, a previously unrecognized pattern emerged. Coley found that his therapy was much more likely to be effective if the patient had melanoma (skin), breast cancer, sarcoma or lymphoma. Of the two bacteria from which Coley’s Toxins is derived, Streptococcus pyogenes, causes infection in the skin, breast and soft tissues, suggesting that Coley’s successful cases were examples of Site Specific Immunomodulation. Qu Biologics’ proprietary SSIs are a modern refined version of Coley’s approach.

Upon founding Qu Biologics, we were able to demonstrate in animal models of cancer that that there is a site specific anticancer effect in the targeted organ in response to a bacterial preparation injected underneath the skin. In addition, in a lung cancer animal model, the anti-cancer effect was associated with a shift from M2 to M1 macrophage dominance. These results suggest that SSIs may provide a simple and effective way of stimulating an anti-cancer immune response in a site specific fashion.

There are three standard ways to demonstrate whether a macrophage is functioning in its M1 or M2 role. One is by the cytokines they release. A second way is by their cell surface markers, and a third is by the genes that they express. By all three methods Qu Biologics’ scientists have shown that SSI therapy shifts macrophage function from M2 to M1. In addition, SSI therapy results in a marked increase in the number of macrophages in the targeted organ/tissue, as illustrated in Figure 2.

By relieving the immunosuppression within the tumor microenvironment, SSI therapy may work synergistically with chemotherapy, radiation and other immunotherapies. For example, chemotherapy kills cancer cells, but due to the immunosuppression (as a result of M2 dominance) within the tumor microenvironment, the immune cells within the tumor cannot respond to the released tumor antigens to mount an effective anti-cancer immune response.

However, since SSI therapy appears to relieve this immunosuppression in the tumor microenvironment, as discussed above, at Qu Biologics we hypothesize that when SSI treatment is administered in conjunction with chemotherapy, it may allow the immune cells to respond to the released tumor antigens. The study shown in Figure 3, in mice, illustrates this synergy.
Promising Clinical Indication of Site Specific Anti-cancer Effects

Figure 4 illustrates a retrospective study in patients with lung cancer treated at InspireHealth, an integrative cancer care center I co-founded, located in Vancouver, Canada. For this study, patients were offered adjunctive treatment with a killed mixed bacterial vaccine which was ‘lung-targeted’, i.e., contained a species of bacteria known to commonly infect the human respiratory tract. The black dotted line is the standard survival curve for Stage 3B lung cancer from the SEER database (Figure 4). Comparison of patients treated with a lung-targeted mixed bacterial vaccine containing a common lung bacterial pathogen (solid blue circles) to patients at the same clinic who received the same care but did not choose to receive treatment with the lung-targeted mixed bacterial vaccine (open blue circles), illustrates a survival advantage associated with site specific immunotherapy. This is a retrospective study, not a randomized controlled trial, so no definitive conclusions can be reached, but it is promising early data in support of the site specific hypothesis.

A second retrospective study, also conducted at InspireHealth (Figure 5), supports the site-specific hypothesis in two ways. This was a study of the survival of patients with stage 4 colon cancer and there are four survival curves. The black dotted line is the standard survival curve for stage 4 colon cancer from the SEER database for the time frame of the study. The blue open squares represent the survival of patients who chose not to receive treatment with a killed mixed bacterial vaccine. The red open squares represent the survival of patients who used the lung-targeted mixed bacterial vaccine described above. And the blue closed squares represent the survival of patients who were treated with a different killed mixed bacterial vaccine, which was ‘colon-targeted’, i.e., contained E. coli, a bacterial species which commonly infects the human digestive tract. As can be seen in the graph, the lung-targeted killed bacterial vaccine, which is targeting the wrong site in this context, was of no benefit. However, the colon-targeted killed bacterial vaccine was associated with substantial benefit, an 18-month median survival advantage. Again, these results represent a retrospective study, not a randomized controlled trial, so no definitive conclusions can be reached, but it is promising early data in support of the site specific hypothesis.

Qu Biologics’ SSIs

Subsequent to the clinical data discussed above, Qu Biologics was founded to develop a new platform of immunotherapeutic treatments called Site Specific Immuno-modulators (SSIs). Qu Biologics has since developed four different SSIs to target different sites within the body, as illustrated in Figure 6.

Compassionate Use of SSIs

From July 2009 through May 2012, over 250 patients with late stage cancer received SSIs through a compassionate ('Named Patient') use program in Austria. An independent research group, Reliable Cancer Therapies (www.reliablecancertherapies.com), was interested in the innovative therapies used at the Austrian clinic and studied the survival of patients with stage 4 breast cancer treated at the various clinic's use program. The independent value of SSI therapy therefore cannot be determined as a contributor to survival from this data set. However, these data provide support for the next appropriate step in drug development, testing the efficacy of SSIs to treat cancer in appropriately designed and conducted randomized clinical trials.

Interestingly, at Qu Biologics we found that SSI therapy potentially has broader applicability than cancer because it’s not designed to target the cancer itself, it’s aimed to activate the body’s innate immune system to reverse the chronic inflammation, which underlies the cancer.

With growing evidence that macrophage dysfunction may underlie a variety of autoimmune diseases, Qu Biologics has begun exploring the potential of using SSIs to treat the chronic inflammation that is at the root of autoimmune disease. The cells of different tissues within our body have a life cycle, measured in days, weeks or months, depending on the tissue. When cells reach the end of their natural life cycle, they undergo a process called apoptosis, signaling to macrophages to engulf them. When macrophages engulf apoptotic cells, they recycle their contents, sending anti-inflammatory ‘tolerance’ signals into the associated tissue to ensure that the adaptive immune system doesn’t react to the antigens of the dying cell.

However, in the context of a defect or deficiency of macrophage function, not all apoptotic cells are phagocytosed by macrophages, in which case these apoptotic cells necrose, releasing their internal contents/antigens, to which the adaptive immune system responds, creating an autoimmune reaction, creating further tissue damage and necrosis, resulting in autoimmune disease.

This process leads to the symptoms that
characterize autoimmune diseases such as Crohn’s disease, ulcerative colitis and rheumatoid arthritis. Qu Biologics’ scientists hypothesize that SSIs could potentially recruit fully functional macrophages to the diseased tissue, where they would remove the antigenic trigger and thus eliminate the underlying source of the inflammation, leading to resolution of symptoms.

**SSIs and Autoimmune Disease**

With growing evidence that macrophage dysfunction may underlie a variety of autoimmune conditions, the compassionate use program was expanded to include patients with autoimmune disease. Eighteen patients with Crohn’s disease (N=10), ulcerative colitis (N=2), a non-autoimmune bowel condition (N=1), arthritis (N=5), note: one patient with Crohn’s disease-associated arthritis was treated for both the gastrointestinal and the arthritic symptoms of Crohn’s disease) and an inflammatory skin condition (N=1) were enrolled in the program. All patients had active disease that was uncontrolled by standard treatment at time of enrollment. SSI treatment was generally found to have an acceptable safety profile and be well tolerated; there were no treatment-related serious adverse events reported or systemic allergic reactions observed. Patients were treated with SSIs as follows:

**Crohn’s Disease**

Ten of ten patients had a therapeutic response to treatment, based on patient-reported improvement in symptoms. The majority of patients achieved therapeutic response within one to three weeks of starting treatment. Seven of the ten patients (70%) with Crohn’s disease had full resolution of clinical symptoms after completing a course of QBECO treatment of three months duration or more. Four of these patients have had sustained clinical remission after discontinuing all medications including SSI treatment. The longest clinical remission is ongoing, after more than 2.5 years. Three of ten patients (30%) have had follow-up colonoscopies or CT scan with confirmation of full remission.

**Ulcerative Colitis**

Both patients began to notice improvement in symptoms (i.e., reduced bowel movement frequency, reduced urgency, and reduction of blood in stool) two to three weeks after initiation of treatment. One patient is in full clinical remission; the other has improved with only occasional mild symptoms. Both patients have discontinued all other medications.

**Arthritis**

All five patients have had a therapeutic response to SSI. Patients noticed an initial reduction in morning stiffness after two to three weeks of treatment, with a subsequent reduction in joint pain and swelling. All patients have reduced their concomitant medications and have maintained benefit.

The clinical outcomes observed through the compassionate use experience in autoimmune diseases are preliminary and are not evidence of efficacy or safety at this stage of development. Further, the observations of clinical benefit described above cannot be attributed to the independent value of SSI therapy given the uncontrolled and unblinded nature of the compassionate use program. Based on these preliminary observations, Qu Biologics is planning methodologically rigorous clinical trials to establish the independent contribution of SSI treatment to improved clinical outcomes for patients with autoimmune diseases.

Qu Biologics has received regulatory approval and is actively recruiting for a randomized double-blind placebo-controlled trial in Crohn’s disease, in Vancouver, Canada (for more information, please visit www.qucrohnstrial.com.) Qu Biologics is planning to start additional randomized controlled trials (RCTs) in arthritis, chronic obstructive pulmonary disease (COPD) and cancer.

We are looking forward to making further progress in this promising, potentially broadly applicable approach to stimulating the body’s own immune system. If safety and efficacy are demonstrated, Qu Biologics’ SSIs have the potential to improve the survival and quality of life of millions of patients fighting cancer and the quality of life of patients living with debilitating autoimmune diseases such as Crohn’s disease, ulcerative colitis and rheumatoid arthritis.

**References**


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**Hal Gunn, MD**

Hal Gunn, MD is Co-Founder & CEO of InspireHealth (Vancouver), Canada’s first and foremost integrated cancer care center. As co-founder and CEO, Dr. Gunn has led the organization to become a national model for integrated cancer care. Dr. Gunn is respected nationally, by both his conventional and integrative medicine colleagues, for his interest in bridging the worlds of complementary and conventional medicine. He has had a lifelong interest in wellness and healing and a great respect for the healing potential of the human body. Gunn is actively working with other organizations to integrate the concepts of health and healing into mainstream medicine. As Clinical Assistant Professor with University of British Columbia’s Department of Family Medicine and as head of InspireHealth’s Research Department, Gunn recognizes the value of applying the principles of rigorous scientific research to the field of integrative medicine. Gunn has a special interest in mind-body medicine and psychoneuroimmunology (the study of the effects of the mind and spirituality on the body’s ability to heal). In 2009, Dr. Gunn was awarded the $250,000 Dr. Roger’s Prize for vision, leadership and integrity in the field of Integrative Medicine.

Dr. Gunn is also co-founder and CEO of Qu Biologics Inc. (www.qubiologics.com), a Vancouver, Canada-based clinical stage biopharmaceutical company founded in September 2007. Qu Biologics is working to develop a new platform of immunotherapeutic treatments called Site Specific Immunomodulators (SSIs). SSIs are being designed with the goal of activating the body’s immune system to reverse the chronic inflammation underlying many conditions including cancer and autoimmune disease.