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One Sizeable Step for Immunology, One Giant Leap for Cancer Patients

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Background

Although cynicism and disillusionment with the failed “war against cancer” are widespread, I remain very optimistic that we will triumph over this seemingly invincible killer. Given the disappointing results and many drawbacks of cytotoxic therapies, it seems clear that our best hope for a decisive victory against cancer lies in immuno-augmentive therapies – those that enhance the body’s innate immune response to cancer cells.

As a research immunologist, I have spent 18 years studying immunomodulating substances – natural compounds derived from mushrooms, herbs, fungi, and bacteria, as well as synthetic drugs like Interleukin-2 and interferon. Approximately six years ago, I stumbled across a natural substance that was so promising, so profoundly superior to everything else I had ever evaluated, that I abandoned all other projects, including NIH-funded research, in order to focus entirely on this substance.

The product, MGN-3 (an arabinoxylane compound), is a polysaccharide composed of the hemicellulose- β extract of rice bran, modified by enzymes from

Shiitake mushrooms. As we have detailed in 7 previously published studies, involving a total of 72 *human* subjects, the efficacy of MGN-3 equals or surpasses the very best immune-modulating drugs available but, in stark contrast to these, exhibits a complete lack of toxicity. (Copies of complete research papers and data on MGN-3 can be obtained from Lane Labs at 201-236-9090.)

Much of the data regarding MGN-3 has been previously published in technical journals and presented at international research conferences, but the information remains largely unknown to oncologists and other health professionals dealing directly with the cancer patient. The aim of this article is to bring this research to the attention of the practicing clinician, to summarize what is known about the actions of MGN-3, and explore its present role in the treatment of cancer patients.

Anti-viral activity: In addition to very encouraging results using MGN-3 in the treatment of malignancies, other research suggests a promising role for MGN-3 as a therapy for HIV, Hepatitis C, and other viral

infections. MGN-3 has antiviral activity and also enhances the body’s immune response against virally-infected cells. In vitro research shows that MGN-3 inhibits replication of the HIV virus without cytotoxicity in a dose-dependent manner.¹ Human studies suggest that MGN-3 may also be extremely useful in the treatment of hepatitis C. In these patients liver enzymes return to normal levels within 1-8 weeks of treatment with MGN-3. The results of our ongoing clinical research into the antiviral applications of MGN-3 will be the subject of future reports.

The role of NK cells in the treatment of cancer

Over 150 different types of white blood cells have been identified and, of these, NK cells are one of the most common, representing up to 15% of total white blood cells. They are important because, unlike other white blood cells, they are able to work more or less independently, not requiring special instructions from the immune system in order to recognize or attack a foreign cell. For this reason, they are often considered to be the body’s first line of defense against cancer and viral-infected cells.

Circulating through the body by way of the blood and lymph systems, the majority of NK cells present in the body are in a resting state. NK cells become more active in response to immunoregulatory proteins called cytokines. Once activated, the NK cells become quite rapacious in their search-and-destroy activities. Upon encountering a tumor cell, the activated NK cell attaches to the membrane of the cancer cell and injects cytoplasmic granules that quickly dissolve (lyse) the target cell. In less than five minutes, the cancer cell is dead and the NK moves on to its next victim. A single NK cell can destroy up to 27 cancer cells before it dies. Although quite small in comparison to tumor or virus cells, a single NK cell can often bind to two or more cancer cells at once.

The absolute number of NK cells present in the blood gives little indication of the efficiency of immune function. Instead, it is the activity of the NK cells – the avidity with which they recognize and bind to tumor cells – that is important. Most immunomodulators, including MGN-3, do not increase the number or percentage of NK cells, but instead increase their level of activation. NK cell activity can be tested by means of a 4-hour radioactive-Chromium release assay. NK cells are isolated from a blood sample and are incubated in vitro with a fixed number of chromium-labeled tumor cells. After 4 hours, the percentage of tumor cells that have been killed by the NK cells is determined, and this percentage can be used to describe NK cell activity.

In a healthy immunocompetent individual, when NK cell activity is examined at an effector:target ratio of 100:1, we would expect to see NK cell activity ranging from 60-75%. However, in cancer patients, NK cell activity typically ranges from near 0% to 30%. Although it is not entirely clear whether this is a cause or result of the disease process, there is evidence suggesting that low NK cell activity may be a risk factor for malignancy or metastases, as well as a negative prognostic indicator.² Therefore, agents that stimulate NK cell function are being sought as possible cancer therapeutic agents.

Proven human efficacy. We have previously presented data on 32 cancer patients, with different types of advanced malignancies.³⁻⁵ These patients had received and completed conventional therapy such as surgery, chemotherapy, radiation or hormonal therapy prior to participation in the study. The baseline NK cell activity was found to be low in all patients (10.8-49%). Oral ingestion of MGN-3 at 45 mg/kg/day led to a significant increase in NK cell activity after only 1-2 weeks. The increase in baseline NK cell activity after two weeks of administration ranged from 145%-332% in breast cancer patients, 174%-385% in prostate cancer patients, 100% - 240% in leukemia patients, and 100% - 537% in multiple myeloma patients.

Longevity of response: One of the great and constant frustrations of the immunologist is the phenomenon of hyporesponsiveness. Science has identified many biological

response modifiers (BRMs) that can substantially increase NK cell activity. However, the effect frequently attenuates over time, despite continued administration of the immunomodulator.⁶ One of the most exciting and distinguishing characteristics of MGN-3 is that it appears to maintain its immunomodulatory effect over time. In long-term follow-up of our patients (up to 5 years), we have observed that the enhancing effect of MGN-3 on NK cell activity is maintained indefinitely with continued administration.

Lack of toxicity: Another disappointment regarding synthetic immune boosters such as IL-2 and interferon is that these therapies, while variously effective in boosting the immune response against tumors and viruses, are exceedingly toxic and accompanied by numerous side effects, the most serious of which is kidney failure. By contrast, MGN-3 appears to be exceptionally non-toxic and well-tolerated.

In acute oral toxicity trials in rats, MGN-3 was found to be without toxic effects at dosages up to 36 g/kg. In addition, human trials using up to 45mg/kg/day of MGN-3 for six months have noted no abnormalities in blood chemistry or liver enzymes (SGOT and SGPT).⁷

Moreover, in 4 years of use with hundreds of patients, we have had no reports of side effects or interactions of any kind. In fact, our clinical experience suggests that MGN-3 can be safely and advantageously used in conjunction with conventional treatment, including

chemotherapy and radiation, both to increase the cytotoxic effect of the therapy and to decrease adverse side effects.

Clinical results: Enhanced immune function is, however, only a theoretical victory if it does not lead to clinical improvement. But in fact, the documented increase in NK cell activity in cancer patients taking MGN-3 has been correlated to dramatic reductions in corresponding tumor markers and other pathology indicators, and, most importantly, to long-term stabilization or remission of disease in the large majority of cases (>85%). The complete clinical data for a total of 106 patients treated since 1995, including hematology and pathology reports, as well as incidence of remission and length of survival, are in the process of being collected and analyzed. It can be stated, however, that very few have been lost to follow up and virtually all continue to be in good health.

Discussion

Mechanisms of action: In addition to direct cytotoxic activity against tumor cells, activated NK cells also produce a variety of cytokines, including the interferons, interleukins, tumor necrotic factors and other growth factors. These cytokines, in turn, have direct antiviral and anti-cancer activities, as well as further immunomodulatory effects, such as upregulation of T- and B- cells, and further activation of NK cells. Our research suggests that MGN-3 works by simulating the body's natural production of interferon- γ and tumor-necrosis factor- α .⁸

These chemicals not only have direct anti-tumor activity themselves, but also directly and indirectly activate NK cell, B-cell and T-cells.

Synthetic cytokines interleukin-2 (IL-2), interferon-gamma (IFN- γ) and tumor necrosis factor- α (TNF- α) have all been investigated as possible cancer-therapeutic agents, and have shown varying success. The most success has been seen with interleukin-2; however, the dosages needed to achieve positive results are associated with extreme toxicity.

MGN-3 may offer a novel solution to this dilemma. *In vitro* studies suggest that MGN-3 used in combination with low levels of IL-2 may significantly potentize the effect of IL-2. Figure 1 shows the effect on NK cell activity of MGN-3 and low doses of IL-2, separately and in combination. The combined, synergistic effect of the two substances is significantly greater than either alone. This suggests that the immunomodulatory effect of low concentrations of IL-2 on NK cell activity could be greatly augmented with the adjuvant use of MGN-3.⁹

Clinical applications: Conventional medicine has excellent anti-tumor therapies that can significantly reduce the number of cancer cells. Unfortunately, we have seen that it is difficult to achieve a 100% kill rate without killing the patient in the process. At best, we can hope to kill 95-98% of the cancer cells with these therapies. At this point, a patient may be considered to be "in remission." Therapy is discontinued and the

patient is closely monitored. However, as most oncologists are painfully aware, these remissions are frequently short-lived.

Most cytotoxic therapies are themselves immunosuppressive, lowering the activity of anti-cancer effector cells. Following chemotherapy or radiation, the few hardy cancer cells that survive the therapy are left to replicate largely unchallenged by a damaged immune system. When the cancer eventually resurfaces, it does so with increased ferocity and often with increased drug resistance.

In my opinion, the practice of watchful waiting wastes a golden opportunity to administer the *coup de grâce*. At the very early stages of detection, or, in more advanced stages, when the tumor load has been reduced as far as possible by surgery and/or conservative cytotoxic therapies, boosting the immune system with biological response modifiers allows the body to eradicate the remaining cells that have escaped the chemicals, radiation, or surgeon.

However, MGN-3 cannot and should not replace debulking therapy, especially in the case of advanced malignancies. In these cases, even an extremely active immune response is easily overwhelmed by the huge numbers of cancer cells present. Instead, we recommend that cancer patients with solid tumors begin MGN-3 immunotherapy concurrent with or immediately following debulking therapies. With this strategy we have the best chance of winning what essentially becomes a war of numbers.

In addition, we have found that cancers of the blood, such as leukemia and multiple myeloma, have been particularly responsive to MGN-3 therapy, presumably because the activated natural killer cells have even better access to these cancer cells than to those forming solid tumors.

MGN-3 can also be used to advantage as a preventive in high-risk populations. Unfortunately, the realities of our high-stress modern lifestyle, which include increasing exposure to mutagenic environmental toxins, the numbers of people who might be considered 'high-risk' are increasing. In one particularly disturbing study, researchers found persistently depressed NK cell activity in 14% of 'healthy' young adults.¹⁰

Dosage considerations: As figure 2 illustrates, MGN-3 at 30 mg/kg/day caused a steep (310%) increase in NK cell activity after only one week. NK cell activity continued to increase at a slower rate, to a peak activity of 500% over baseline by week 8 of this particular study, which involved 24 healthy subjects.¹¹ This study also illustrates the interesting dose-dependent nature of MGN-3. Lower doses (15 mg/kg/day) yield a much slower initial

increase, however all dosage levels achieve maximum activity by week 8. Within one month of cessation of treatment, NK cell activity returned to baseline. Clinical experience indicates that once maximum levels of NK cell activity have been attained, they can in most cases be maintained indefinitely at the lower dosage level of 15 mg/kg/day.

In the fight against cancer, time is of the essence. At the very early stages or immediately following debulking therapy, the numbers of cancer cells are relatively low and more susceptible to eradication by an aggressive immune system. Therefore, it is important to increase NK cell activity as quickly as possible in these patients. For these reasons, we recommend a loading dose of 30-45 mg/kg/day for cancer patients. After two to three months, the dosage may be reduced to 15 mg/kg/day. In some individuals, the higher dose needs to be continued for a longer period of time. Sustained clinical improvement (for example, normal tumor markers and negative imaging) is an indication that dosages can safely be reduced to a maintenance level. For general prevention, 15mg/kg/day is appropriate. The product is typically administered

in 2-3 divided doses, accompanied by a meal.

Conclusion

Those involved with alternative and holistic medicine may be tempted to dismiss the introduction of yet another natural "immune booster" as hype. Many products are promoted to cancer patients on the strength of "scientific proof" of enhanced immune function. In most cases, however, the only research has been conducted in test tubes, or at most, in animals. But as many have noted, most recently *apropos* the work of Dr. Judah Folkman, if curing cancer in mice were equivalent to curing cancer in humans, this dread disease would already be a relic of a bygone era, rather than accompanying us into the new millennium.

Unlike most natural preparations, MGN-3 offers solid data collected from *human* clinical trials. This data offers compelling evidence that MGN-3 is a powerful biological response modifier that is free of toxicity or side effects. As such, it has enormous promise as an immunotherapy in the treatment of cancer and other diseases.

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