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In Pursuit of a Cure: Searching for Food-Based Cancer Therapies and Preventions at The Hormel Institute

Ann M. Bode

In spite of President Nixon's declaration of the "war on cancer" in 1971, deaths from the most common cancers, including pancreatic, ovarian, colon, lung, breast and prostate, are still rising. Cancer is a dynamic process that involves many complex processes and is therefore not likely to be prevented or cured by a "magic bullet." However, the design and development of chemical or natural agents that act on specific molecular and cellular targets is regarded as a rational approach to control cancer. This strategy for cancer control is based on the presumption that because cancer develops through a multistep long-term process, each step in cancer development can be a possible target for reversing or suppressing the process.

The toxicities associated with standard chemotherapy are as likely to kill the cancer patient as is the cancer itself. Thus, interest in alternative and novel approaches for the prevention and treatment of cancer has increased dramatically, especially in the last few years. The idea of using a chemical agent, drug or food supplement or whole food to stop or reverse the process of cancer development before tumors begin and grow (known as "chemoprevention") has ignited a worldwide revolution in the way scientists, physicians and the general public view cancer.

Research data from epidemiological and scientific experimental studies indisputably indicate that diet is one of the most important links to human cancer. Nutritional or dietary factors have attracted a great deal of interest because of their perceived ability to act as highly effective cancer fighting agents. The general public is clamoring to find the "magic pill" or "health food" that will prevent or cure cancer without unwanted side effects. The use of natural dietary compounds or whole foods for improving health has been around for many years but interest in their use has increased dramatically because of perceived health benefits without unwanted or unpleasant side effects. This is especially true in cancer prevention

and treatment. Nutritional or dietary factors and especially whole foods are professed as being generally safe, which is critical for their success in cancer prevention or treatment. Many individual or combinations of food agents are known to specifically attack *only* cancer cells or cancer-related molecular or cellular targets, which obviously minimizes the potential of undesired side effects often associated with chemotherapy.

On the other hand, one of our greatest challenges is to reduce the enormous amount of misinformation reported in the popular media regarding the health benefits of certain foods or food supplements. Regrettably, to determine whether a nutritional product has *real* health benefits is extremely difficult. The field includes many natural remedies used for centuries such as ginseng, herbal teas and substances like vitamin E, extracted from natural products. Hundreds of compounds are being extracted, concentrated and marketed and are purported to have major health benefits, but many of the claims are based mainly on circumstantial evidence. More and more people are using dietary supplements and herbal remedies without advice from a physician, sometimes with disastrous results. Unfortunately, much of the information regarding the effectiveness and safety of these remedies has been gleaned from anecdotal or historical accounts, which seem to be readily available from a variety of sources. Numerous substances derived from foods have been linked to decreased risk of developing cancer and thus interest in cancer prevention by dietary factors has skyrocketed. However, the available information is often confusing and contradictory due to the complexity of the many interactions that often occur between selected food components and molecular pathways related to development of cancer. Thus a critical need exists to 1) identify individual or combinations of dietary factors that can act as cancer preventive agents and effectively inhibit cancer development; 2) determine the molecular targets within cancer cells that are modulated by specific individual or combinations of dietary factors; 3) move these factors into clinical trials based on solid preclinical data; and 4) develop whole foods that are enhanced with specific individual or combinations of proven anticancer dietary factors.

Identifying natural anticancer agents

The Hormel Institute, a research unit of the University of Minnesota and located in Austin, Minn., is recognized as a world leader in scientific research focusing on the prevention of cancer. In 1942, Jay C. Hormel, son of Hormel Foods founder G.A. Hormel, brought The Hormel Foundation and the University of Minnesota

together to create The Hormel Institute, a medical research center that would become a division of the University of Minnesota Graduate School. The Hormel Institute is one of the oldest research institutes in the United States and during its early history was the nation's leading lipid research center. Among its most noteworthy accomplishments is the development of the first miniature pig, the Swiss Swine, for cardiovascular research and the discovery and naming of omega 3 and omega 6 fatty acids by Dr. Ralph Holman, a former executive director of The Institute. Perhaps The Institute's most infamous contribution was the provision of the pig(s) that played Arnold on the classic television sitcom "Green Acres."

Today, its reputation is growing rapidly as a center for developing and testing natural, dietary anticancer agents that are nontoxic and highly effective. Its strength is its ability to systematically identify and test hundreds of dietary factors purified from natural agricultural sources locally, regionally, nationally and internationally.

With the rapid development of knowledge and techniques in biology, especially molecular and cellular biology, substantial progress has been made in the study of cancer chemoprevention. A major focus of the work at The Hormel Institute is the discovery of mechanism(s) explaining the anticancer actions attributed to many chemopreventive compounds, especially natural dietary compounds that are considered safe because they are present in what we commonly eat or drink. Of particular interest are selected food factors that influence cell signaling events coinciding with promotion of various types of cancer.

Cancer has now surpassed heart disease as the number 1 killer of Americans under the age of 80. In order to facilitate the development of chemopreventive and chemotherapeutic agents that specifically target molecules important in cancer development, we must know the enemy — we must understand carcinogenesis or how cancer develops. The prevailing thought today is that cancer may be prevented or treated by targeting specific cancer genes, signaling proteins and transcription factors. Cancer is a multistage process, consisting of initiation, promotion and progression stages. The stage of initiation is short and irreversible and entails DNA or gene damage caused by a carcinogen such as cigarette smoke or sunlight. The promotion stage can occur over 5 to 50 years or more and is the period of time during which "initiated" cells multiply and divide to form cancers. The progression stage is the period during which the tumor presents itself. Although each stage could be a possible target for chemopreventive agents, the promotion stage, because

of its extensive length, has the most potential to be reversed and is especially susceptible to lifestyle changes.

By focusing on the molecular mechanisms explaining how normal cells can be transformed into cancer cells induced by tumor promoters (e.g., sunlight, diet, obesity, environmental factors, asbestos exposure, smoking, etc.), we have discovered that several specific cellular components, known as transcription factors and protein kinases, are critical factors in cancer development and significant targets for cancer prevention and treatment. A strength of The Hormel Institute's research is that it has shown that cellular proteins and genes are crucial targets for anticancer agents. Most notably, The Institute scientists have shown that anticancer agents can be developed that exclusively target cancer cells with no harm to normal cells. Specific dietary or natural compounds found in whole foods such as green and black tea, coffee, ginger root, chocolate (cocoa), honey bee propolis, rice, flax and flax seed, cabbage, broccoli, potatoes, tomatoes, berries, onions, and grapes (to name a few) have all been shown to exhibit potent anticancer activities.

Determining molecular targets of natural anticancer agents

The human body is composed of billions of biological components that make up complex and interconnected communication networks and intricate pathways designed to work together to promote optimal health. Understanding the integration of these pathways and how disturbances in their function might lead to diseases such as cancer is critical in determining how these pathways might be restored to normal operation to prevent or cure disease. Crucial players in these pathways are tiny molecules known as proteins, which are manufactured from genes that contain our DNA. Proteins are the miniature machines that allow us to live healthy, productive lives. Each protein has a unique 3-D shape that is specific for that protein's normal function, and if that shape is damaged, diseases such as cancer can occur. Furthermore, specific dietary factors or other small molecules are extremely important to researchers to investigate the proteins comprising biological pathways. These types of small molecules or dietary factors are also extremely valuable for treating and preventing disease. A fundamental challenge has been the ability to successfully identify food factors or other small molecules that are effective at modulating a particular biological process or disease state.

International Center of Research Technology

Over the last two years, The Hormel Institute has been working to create an International Center of Research Technology (ICRT).

The long-term goal of the ICRT is to provide the most advanced tools of technology available today to researchers working at biobusinesses, medical centers, colleges and universities throughout Minnesota and regionally. Working with its collaborative partners, including IBM, the Mayo Clinic, and the University of Minnesota Rochester, the ICRT is developing new technologies to accelerate discovery and facilitate comprehensive study of human disease by combining analyses of protein structure/function with advanced methods of data management and drug screening. The net result will be a greater understanding of biological systems for improving the quality of life in Minnesota, the nation, and the world and a dramatic, positive impact on economic development in bioscience and biotechnology statewide and regionally.

Drug discovery is increasingly dependent upon biotechnological advances that require massive amounts of computing power but are limited by inadequate access to high-end supercomputers. For successful drug development, researchers must systematically screen millions of small molecules to find a successful match between a chemical and its protein target, a process that can take years and requires a picture of the 3-D structure of the protein, many of which are not available. In collaboration with IBM, the ICRT houses an onsite BlueGene/L supercomputer that offers researchers access to the large-scale screening capacity necessary to identify small molecules, including dietary components, to be used to study the functions of biological pathways in health and disease. The ICRT already houses a state-of-the-art protein crystallography facility, which will be used in parallel with chemical screening to create a 3-D pictorial library of proteins with functions in diseases like cancer. These tools for studying proteins and pathways lay the foundation for even more complex future projects that will drive biobusiness and bioscience, creating hundreds of new jobs and facilitating opportunities for tech spin-off businesses in Minnesota and the region.

A number of research groups are accommodated in The Hormel Institute–all dedicated to studying and understanding the mechanisms that control the development of cancer cells. Several of the research studies have direct links to agriculture and thus have potential for collaboration with the agriculture industry. These research groups include:

The **Cellular and Molecular Biology** group, which is The Institute's largest research group and is led by Drs. Zigang Dong and Ann M. Bode. A major goal is to identify anticancer

agents that have low toxicity with fewer adverse side effects and might be used alone or in combination with traditional chemotherapeutic agents to prevent or treat cancer. Many dietary factors have potent anticancer activities that work through, as yet, unknown mechanisms. Over the years, this group has been working to identify those mechanisms through their work with cellular signal transduction pathways. Signal transduction is the process by which information from a stimulus outside the cell is transmitted from the cell membrane (e.g., through its receptor) into the cell and along an intracellular chain of signaling molecules to stimulate a response. Various dietary factors, including many isolated from green and black tea, potatoes, broccoli, peanuts, ginger root, or rice, can have effects on key signaling molecules critical in cancer development and prevention.

The **Cancer Biology** group, led by Dr. Johnny Lü, studies the cellular and molecular mechanisms by which the trace element nutrient, selenium, affects prostate cancer chemoprevention and treatment. This group also focuses on the identification and development of new cancer preventive and therapeutic agents based on Chinese and Oriental medicinal herbs. In particular, they investigate the feasibility for drug discovery from complex herbal mixtures expanding their efforts into additional Oriental medicinal herbs for prostate and breast cancer prevention.

The **Nutrition and Metabolism** research section is headed by Dr. Margot P. Cleary and focuses on the relationship between breast cancer or prostate cancer with the number of daily calories consumed and changes in body weight. Their work has shown that intermittent (i.e., ~every other day) caloric restriction is more protective against breast cancer or prostate cancer than is the same degree of caloric intake imposed by chronic (evenly spaced) restriction. They also focus on the study of the effects of obesity on breast or prostate cancer.

Moving natural anticancer agents into clinical trials

The Mayo Clinic and The Hormel Institute have formed a unique collaborative partnership, which includes an Office of Translational Research located within The Hormel Institute. The purpose of this office is to facilitate the development of dietary factors as chemopreventive agents to be tested in human clinical trials. One of the most promising agents at this time is an anticancer

agent formulated with a compound from ginger root. Investigators at The Hormel Institute and Mayo Clinic are also working together to identify and develop small molecules or dietary factors that will directly target specific cancer genes or proteins to stop the development and growth of a variety of cancers.

Developing whole foods enhanced with anticancer agents or the convergence of health-related research and agriculture

Globalization has changed and will continue to change local, regional and national economies. Minnesota is clearly an elite athlete in the global economic race and is poised to win because of our unique ability to join forces and unselfishly share our strengths as a state. To seize critical opportunities and develop the maximum potential, we must continue to establish and nurture firm relationships with one another so that we become increasingly knowledgeable about existing and future assets and continue to support each other through collaborative work and partnerships. This idea is clearly illustrated by the potential convergence of health-related research and agriculture in Minnesota. This cooperative effort could be one of the most crucial opportunities we have seen in years and will require the collaboration of a very diverse group of participants — medical research scientists and those directly involved in agriculture, our Minnesota farmers. The researchers have the capacity to identify the components of food that might have anticancer activity and the farmers have the ability to grow those components at an enhanced concentration in whole foods.

Over the last few years, researchers have begun to suspect that isolating a single compound from complex foods may not be effective cancer prevention even at high, relatively toxic doses, whereas combinations of lower, less-toxic doses of each compound might be most effective. This has been illustrated in various research studies showing that many food components seem to require a reaction with or dependence on other components in the whole food source to be effective. Epidemiologic studies suggest that eating diets rich in fruits and vegetables decreases the risk of developing cancer. No scientific evidence exists to support the idea that eating specific compounds isolated from foods prevents cancer. In fact, general clinical findings indicate that individual dietary components have not been very successful in preventing cancer. Examples of these studies include a large clinical study in which vitamin E alone had no effect on lung cancer, and unexpectedly, the risk of lung cancer in smokers was actually increased in men taking beta-carotene. Other studies with folic acid or selenium alone also had

no effect on colon or prostate cancer, respectively. In contrast, a combination of sulindac (a nonsteroidal anti-inflammatory drug) and difluoromethylornithine (DFMO) prevented colon polyp recurrence by 70% overall and by 92% for the highest-risk, advanced adenomas. In addition, green tea extract containing EGCG and other green tea components also appears to be more effective than EGCG alone. These types of results support the idea that isolating single compounds such as selenium, vitamin E, or beta-carotene may cause them to lose their potential anticancer and other beneficial effects, possibly even causing them to exhibit undesired cancer promotion effects, as in the case of beta-carotene. Likewise, to be active anticancer agents, EGCG or other polyphenol chemicals may require their complex, natural-combination forms because they depend on interactions with other whole-food components for efficacy.

Thus the idea of enhancing certain components in the whole food and producing those foods becomes very attractive and creates a union of health-related research and agriculture. Adding crops, grown specifically to improve human health, to Minnesota agriculture creates a landscape conducive to enhancing rural vitality. This strategy could eventually lead to industrially relevant and effective use of specifically grown whole foods to treat or prevent chronic diseases, especially cancer, in humans.

Functional foods and natural plant extracts for treating or reducing the risk of developing cancer have been rapidly gaining national and international recognition and acceptance. Preclinical testing of purified food compounds on cancer growth and development has and will continue to identify those compounds that are safe and highly effective. Those identified compounds might then be moved to the farm for enhancement in whole food production. Besides the humanitarian implications, the knowledge generated from the discovery and validation of effective anticancer dietary components and the enhancement in whole food could be applied to both agriculture and medicine and become a highly profitable industry for rural Minnesota. An example of this strategy has been ongoing with the University of Minnesota's Southern Research Outreach Center (SROC) in Waseca, Minn. In this collaboration, SROC has been working to develop a Minnesota-grown variety of ginger, which is enhanced in the major active compound, [6]-gingerol. Discussions and interactions have also begun to develop between The Hormel Institute and Minnesota "Farma" groups as a part of the Southern Minnesota Regional Competitiveness Project. To seriously pursue a potentially successful collaborative effort, substantial financial resources will be required.

American consumers appear to simultaneously eat in less healthy ways but are becoming more conscious of their health and the influence of food in their life. Thus, a growing demand for foods with specific characteristics has become very popular. Interest in organic foods, fortified and functional foods, foods considered "naturally healthy" or "better for you" has escalated. The market is driven by the science discovering the "health" benefits and documenting their effectiveness. Theoretically, foods could be developed that target genetic predispositions of individuals, creating the possibility of designing diets to address hidden deficiencies or to address individuals with specific health issues including diabetics, transplant patients, or cancer patients on chemotherapy. A real, working partnership between medical and health researchers and agriculture could provide Minnesota with a huge opportunity to develop and patent new health and medical foods and thus create an international market niche. Over the next five years, estimates are that these dietary components and their derivatives will generate a multibillion-dollar business. Drug discovery and natural food products comprise a huge market and the development of this bioscience and biobusiness could have tremendous impact on Minnesota agriculture and the rural economy.