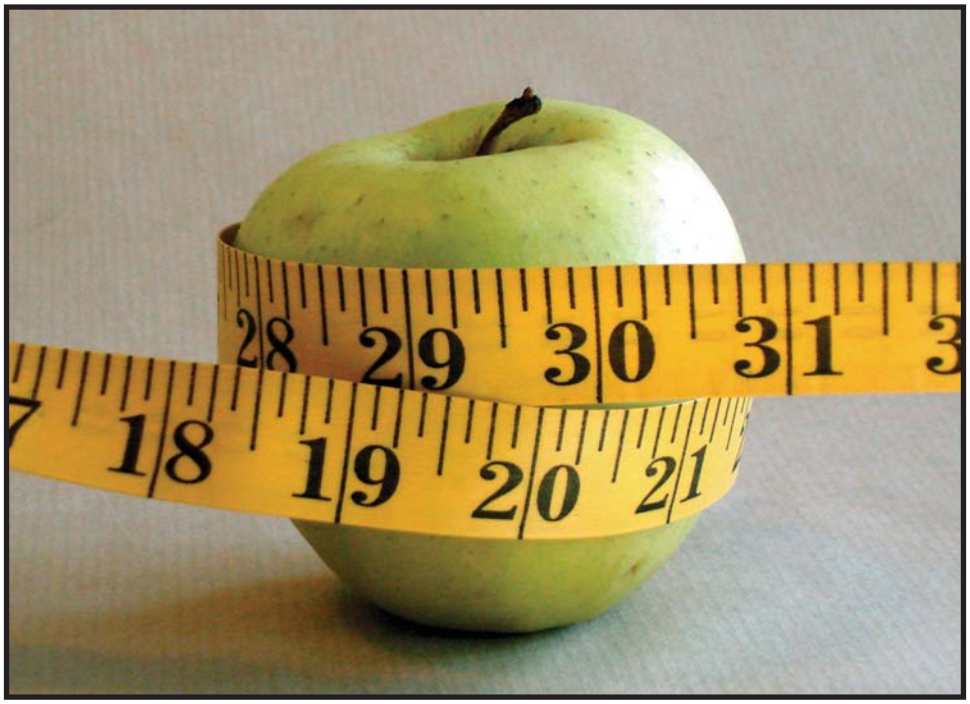
Food and Agricultural Research: Innovation to Transform Human Health



- The role that food plays in human health is historic and broad. “Let your food be your remedy,” attributed to Hippocrates 24 centuries ago, and “an apple a day keeps the doctor away” both encapsulate the food-health relationship.
- A 21st-century plan to make food and agriculture a full partner in human health is proposed. It builds on multiple seminal contributions to key treatment advances from research in food and agriculture, and expands low-cost approaches and quality-of-life benefits by mitigating diet-related diseases.
- A 10% reduction in healthcare costs would save over $200 billion every year.

National Agricultural Biotechnology Council

National Agricultural Biotechnology Council
B 15 Boyce Thompson Institute
Tower Road
Ithaca, NY 14853
607-254-4856 Fax-254-8680
http://nabc.cals.cornell.edu/ nabc@cornell.edu

Providing an open forum for exploring issues in agricultural biotechnology

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The National Agricultural Biotechnology Council (NABC), a consortium of over thirty major research and educational institutions in the United States and Canada, has developed *Food and Agricultural Research: Innovation to Transform Human Health*. This document proposes a 21st-century plan to make food and agriculture a full partner in improved human health. The proposal builds on multiple seminal contributions to key treatment advances from research in food and agriculture, including veterinary medicine and nutrition, and expands low economic-cost and quality-of-life benefits through mitigation of diet-related disease.

We are excited by this opportunity for food and agricultural research to expand its contributions to our human-health challenge. The track record and potential are succinctly stated and a plan of action outlined. A 10% reduction in healthcare costs would be equivalent to over $200 billion annually.

Bruce A. McPheron
Associate Dean for Research &
Director of the Agricultural
Experiment Station
College of Agricultural Sciences
The Pennsylvania State University
University Park, PA

Ralph W.F. Hardy
President
NABC
Boyce Thompson Institute for
Plant Research, Inc.
Ithaca, NY

Food and Agricultural Research: Innovation to Transform Human Health

Executive Summary

Delivery of healthcare is one of the most pressing social, economic, technical and political challenges of our time. Of the expenditure on healthcare in the United States—$2.2 trillion, 16% of the gross domestic product in 2007, and growing at more than twice the rate of inflation—diet-related chronic diseases, diabetes, heart disease, stroke, cancer, obesity and asthma, *etc.*, account for about 75%. Emphasis has been on therapeutic and surgical treatments after disease development; prevention through food and diet has been under-utilized.

Research in food and agriculture has the potential to aid development of relatively low-cost, preventive solutions to these pressing healthcare issues. This *Food and Agricultural Research: Innovation to Transform Human Health* report provides justification and an action plan.

Research in food and agriculture, including nutrition and veterinary medicine, has an impressive record. Multiple seminal, innovative and transforming contributions have been made to the discovery, description, prevention and treatment of human disease including:

- Vaccines
- Antibiotics
- Biosourced Therapeutics
- Models
- Production Systems
- HIV
- Prion Diseases
- Small RNA Therapeutics
- Biopharma Therapeutics

Developments in biology, including molecular genetics, will provide the knowledge, tools, and opportunities to couple food and agriculture with new approaches to improving human health and containing costs.. These mainly preventive approaches include:

- Essential Nutrient
- Functional Foods
- Probiotics
- Toxin/Allergen Reduction
- Altering Diet
- Enhanced Flavor/Taste
- Nutrigenomics
- Food Safety
- Education/Communication

To expeditiously bring these benefits to human healthcare, we need a structure that integrates food and agricultural research as a full partner in the national health-research mission. Current national funding for research on food and agriculture must be expanded substantially to ensure timely delivery of preventive benefits. This investment is justifiable in terms of the cost savings that will result from disease prevention. A 10% cost reduction would save over $200 billion every year.

The new funding should be competitive and open to individuals and, in particular, to self-assembled groups possessing necessary skills, *e.g.* scientists, sociologists, economists, communicators/educators, marketers and regulators, from academe, government and industry. Examples of such structures exist. Each program will target specific objectives to improve health.

Introduction[1,2]

Preservation of human health is one of the most pressing social, economic, technical and political challenges of our time. $2.2 trillion—16% of the gross domestic product—were spent on US human healthcare in 2007. These costs are growing at an unsustainable rate of over twice that of inflation in the United States and Canada. Diet-related chronic diseases such as diabetes, heart disease, stroke, cancer, obesity and asthma account for about 75% of US expenditure[3]. Food and agricultural research must become full partners to provide the necessary knowledgebase and technology to aid development of proactive solutions to healthcare issues that are primarily preventive and relatively low cost rather than reactive therapeutic and surgical solutions that are costly in economic and quality-of-life terms.

Food and Agricultural Research: Innovation to Transform Human Health justifies greatly expanded investment in this area.

Food will continue to provide nutrition, but will also have a prominent role in the prevention of disease. This role for food and agricultural research is potentially huge, but is poorly recognized and underfunded. The objective of this white paper is to expand awareness and stimulate action so that human health will fully benefit from the projected major contributions from food and agriculture. The explosion in life-science knowledge and technology are creating novel opportunities for timely delivery of these benefits.

Major Seminal Contributions and Future Potential[4]

Research in food and agriculture, including nutrition and veterinary medicine, has an impressive record with many seminal contributions to the discovery, description, prevention and treatment of disease. Examples of transformative, innovative contributions, and future potentials, include:

Vaccines

Vaccines are one of the most efficacious and economical methods of preventing disease and may also be used as therapy. Here, agricultural research was seminal. Cowpox provided the first human vaccine as cross-protection against small pox, which led to its eradication. In fact, the word vaccine, which was first used to describe the use of a cowpox-related virus, Vaccinia, to protect against smallpox, is derived from the Latin word for cow (*vacca*). The FDA recently approved the first human vaccine against bird flu as a contingency against future outbreaks. Experimental vaccines produced by plants have been shown to lead to human immunity. Plant-produced vaccines have shown therapeutic potential for treating cancer; within mere weeks, tobacco plants genetically engineered with individual human-lymphoma antigens produced vaccines that were immunogenic.

Antibiotics

Agricultural research also provided the seminal advance for microbially-produced antibiotic therapy. Fleming discovered penicillin and showed that it was produced by a fungus commonly used in cheese making. However, it was not useful as a therapy until agricultural scientists selected fungal strains with higher productivity, and developed the fermentation system to produce clinically useful quantities for use in World War II. Other antibiotics are products of agricultural research.

Biosourced Therapeutics

Botanicals have been the source of over 25% of human therapeutic drugs. Aspirin for pain (and now cardiac-disease prevention) was originally isolated from willow bark; taxol for treating certain cancers was derived from the yew tree; the blood thinner coumadin was extracted from moldy sweet clover; and artemisinin from wormwood is a new cure for malaria, replacing quinine derived from cinchona bark. Therapeutics derived from animal sources include porcine insulin used to treat diabetes.

Chicken Dog, Pig & Plant Models

Chicken, dog, pig and, more recently, plant models have been useful in understanding and treating human diseases. Gene therapy to overcome retina-related blindness in dogs was a model for recent initial success in similar treatment of human blindness. Newborn pigs were used to understand how rotaviruses cause diarrhea and to develop oral vaccines against these devastating pathogens. Research using the model plant arabidopsis yielded discoveries with potential human-health benefits in the areas of, for example, inflammation and tumor suppression, macular degeneration, and arthritis.

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[1] The National Agricultural Biotechnology Council has already produced reports relating to food, agriculture and human health. Most relevant is NABC Report 14, *Integrating Agriculture, Medicine and Food for Future Health* (2002); others are NABC Report 2, *Agricultural Biotechnology: Food Safety and Nutritional Quality for the Consumer* (1990) and NABC Report 17, *Agricultural Biotechnology: Beyond Food and Energy to Health and the Environment* (2005).

[2] The proposal is relevant to the United States and Canada. Public agricultural research institutions in both countries are members of NABC.

[3] Centers for Disease Control and Prevention (2004). Chronic Disease Overview.

[4] Links to additional information are available at NABC's webpage http://nabc.cals.cornell.edu/.

Production Systems

Chicken eggs are broadly used in human vaccine production partly because, while they support growth of mammalian pathogens, the product carries no risk of disease from the presence of avian pathogens. Agricultural research has led to the use of baculoviruses that infect insects as production systems for therapeutics and vaccines, *e.g.* HPV[5] vaccine. These baculoviruses, grown using insect-cell lines, were initially developed to control insect infestations of crop plants.

HIV

Investigations of retroviruses in cats and chickens provided fundamental knowledge that jump-started understanding of HIV infection in the early 1980s.

Prion Diseases

Pioneering research on prion diseases like scrapie in sheep and mad-cow disease (bovine spongiform encephalopathy, BSE) in cattle provided the basis for understanding Creutzfeldt-Jakob disease (CJD) in humans.

Small-RNA Therapeutics & Diagnostics

Small RNAs control gene expression. Agricultural scientists made this seminal discovery by showing that they protect plants from viral infection. They are expected to have major impacts on cancer diagnosis and treatment, and treatments of cardiovascular and muscular diseases, diabetes, viral diseases, *etc*. A recent scientific article, "MicroRNAs make big impression in disease after disease,"[6] captures the potential. A 2006 Nobel Prize was awarded for this area of research.

Biopharma Therapeutics & Xenotransplants

Agricultural and veterinary-medicine research produced the first transgenic plants and animals. Both transgenic plants and animals are being used, mainly experimentally, to biomanufacture therapeutics and vaccines—"biopharma"—making it possible to rapidly scale up production of molecules that would otherwise be scarce or produced only by extraction from human tissues or blood. Absolute containment will be key so as to segregate pharma plants and animals from their food/feed counterparts. The Food and Drug Administration recently approved a plant-produced vaccine for animals and a human antithrombin produced in goat milk for humans with genetic deficiency. Bioengineered pigs may be a source of organs, such as livers, for xenotransplantation into humans.

[5] Human papilloma virus.

[6] Couzin, J. (2008) Science 319 1782–1784.

Other Landmark Contributions

Agriculture and veterinary medicine[7] have been pioneers in innovations relating to disease. Examples include the discovery of the first mammalian virus, the agent of foot and mouth disease. Rous sarcoma was the first cancer shown to be caused by a virus. Marek's disease of chickens was the first cancer treated with a vaccine. HPV[5] vaccine is now being broadly administered to women to reduce risk of cervical cancer. The first attenuated bacterium administered as a vaccine was for chicken cholera. Antibody-producing B-immune cells were discovered in bursa of chickens. Insect-transmitted diseases such as Texas fever contributed to the discovery that mosquitoes transmit malaria and yellow fever. Agricultural research developed DDT to stop transmission of insect-borne diseases. Male-sterile insects led to the eradication of the screwworm and its contamination of wounds, a technology that has been used throughout the world. The emergence of the SARS coronavirus from an animal host and its pandemic spread in 2003, and recent concerns with bird flu and swine flu, illustrate the connection between diseases circulating in mammalian and avian populations and the potential problems they create by moving to humans.

Agricultural research related to human health has been recognized with over fifteen Nobel prizes, many relevant to human health. For example in the 1960s, the structure of transfer RNAs was elucidated, providing one of the keys of the gene-to-protein sequence in living organisms; to recognize this historic event, the US Department of Agriculture recently renamed the laboratory where the work was done the Robert W. Holley Center for Agriculture and Health.

Most of the above examples benefit human health through disease treatment, while some, such as vaccines, are also preventive. The following examples are mainly preventive. Some, such as essential vitamins, amino acids, fatty acids and micronutrients, have a history of preventive benefits, but most of the others will require further research to realize such potential.

Essential Vitamins, Amino Acids, Fatty Acids & Micronutrients

Many earlier contributions of agricultural research were related to the discovery of essential vitamins, amino acids, minerals and fatty acids. For example, rickets was an important disease until the discovery that insufficient vitamin D is causal. Elucidation of this linkage, and the discovery in the 1920s that inclusion of irradiated milk in the diet could prevent the disease, resulted from agricultural

[7] National Research Council (2005) Critical Needs for Research in Veterinary Science. Washington, DC: The National Academies Press.

research. Today, increasing the intake of vitamin D is being evaluated for prevention/treatment of certain cancers and cardiovascular disease. The role of omega-3 fatty acids, derived from fish, flax and nut foods, is being recognized in neural and cardiovascular health and in child development. Research is in progress to modify the fatty acid composition of plant lipids in order to improve the healthfulness of their oils, *e.g.* making soybean oil more like canola or olive oil. Plant proteins often do not have a distribution of amino acids that is optimal for the human diet. Corn, with insufficient lysine, and soybean with too few sulfur-containing amino acids, are being modified to improve dietary balance. Vitamin A and its precursor β-carotene are necessary for normal vision. In some developing countries where rice is a major part of the diet, children become blind because of vitamin-A deficiency. Genetically improved generations of Golden Rice are being developed to contain enough β-carotene to prevent millions of cases of blindness. The HarvestPlus Cassava Alliance, with Gates Foundation and other support, seeks to increase the β-carotene and iron and zinc contents (biofortification) of this major food crop for tropical America and Africa. Foods containing vitamins and other bioactives at levels much greater than minimal nutritional requirements are *Functional Foods*, which are expected to prevent or slow chronic disease development as nutrient levels have protected against acute nutritional diseases.

Functional Foods

Vitamins and other phytochemicals are suggested to have functions in disease prevention beyond their value as nutrients. Examples are antioxidants, phenolic acids and polyphenols (anthocyanins, proanthocyanidins, flavonones, isoflavones, resveratrol—associated with red wine—and ellagic acid). Lycopene, glucosinolates and allyl sulphides have been reported to have beneficial protective and/or therapeutic effects on a variety of diseases. Evidence for the effectiveness of these compounds is based mostly on cell and animal studies. Human clinical data are needed to establish efficacy, such as has been generated for the cholesterol-reducing effects of β-glucans in oats and barley.

Probiotics

Probiotics are microbes that promote health. Genome sequences of gut-flora bacteria are providing understanding of the molecular bases of health-promoting benefits. Dietary priobiotics are being marketed on the basis of promotion and maintenance of human health, *e.g.* as yoghurts with clinically proven gastrointestinal benefits.

Elimination/Reduction of Food-Borne Toxins

Plants contain toxins, their natural protectants against mammalian and pest predation. Some such toxins are highly poisonous to humans, *e.g.* ricin in castor beans. Crops bioengineered for pest resistance have reduced levels of mold-produced aflatoxins. Some toxic compounds may cause chronic disease if consumed over long periods. Canadian researchers genetically modified oilseed rape, a mainly industrial crop, so as to reduce erucic acid and glucosinolates and produce canola, a major new food-oil source with desirable fatty acid composition. Elimination of plant toxins should make our foods more healthful, by reducing the diseases they cause.

Elimination/Reduction of Allergens

Many of our major foods—soybean, wheat, peanut, milk, eggs, shellfish, *etc*.—contain potent allergens that are intolerable or even lethal for some humans. Susceptibility to these allergens is due to a combination of genetics, age, history and, potentially, the gut microbiota. Some of these foods, *e.g.* rice, wheat, soybean and peanut, are being genetically modified to eliminate/reduce their allergens.

Altering Diet

Altering the diet will mean inclusion of more healthful foods. Ideally, these foods will be similar to traditional counterparts, and, in some cases, will be enhanced in desirable flavors and tastes. Current technology enables modification of food composition, increasing desirable and decreasing undesirable components. Examples of modified foods already in the marketplace include milk that is reduced in fat content (2%, 1% and skim) and free of lactose for consumers who are lactose intolerant. Recent elimination of trans fatty acids in processed foods has improved their healthfulness. Wheat products reduced in gluten content may lower the incidence of celiac-disease symptoms. Organically produced food is another example; a small but growing number of consumers perceive increased healthfulness based on altered production methods and are willing to seek out and pay a premium for food that meets the organic standard. Although organic foods have not been proven scientifically to be more healthful, the broad expansion of organic food sections in grocery stores suggests ready acceptance of foods differentiated by verifiable changes in composition and clinical evidence of contributions to improved health. Some of these foods will be directed to niche markets of individuals based on their genetics. An encouraging 2008 survey[8] found that 67% of Americans have made changes to improve their diet; however, achieving broad improvement in the healthfulness of the national diet will need major initiatives in communication and education.

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8 International Food Information Council (IFIC) (2008) 2008 Food & Health Survey: Consumer Attitudes Toward Food, Nutrition & Health. Washington, DC: IFIC.

Enhancement of Flavor & Taste

The food pyramid was developed to guide consumers in selecting foods with cumulative beneficial effects, *e.g.* those with less sugar and fat, and more fruits and vegetables. Considering the increasing rates of obesity, diabetes and other chronic diseases, less-healthy foods are winning the acceptance race versus more healthy foods. A major factor in this unfavourable situation is the dominant role of taste—less-healthy foods often have preferred taste. Taste and price have the greatest impacts on food-purchase decisions[8].

Improving taste and flavor should enhance acceptance and consumption of healthy foods. Different individuals detect flavors differently, based on their genes. For example, about 20% of the population do not like the taste of broccoli, which is recognized to provide human-health benefits. Human taste buds detect at least five tastes: sweet, salty, bitter, sour and umami (savory). Researchers are using receptors for the various tastes to develop GRAS[9] compounds, as alternatives or enhancers, to reduce intake of sugar, fat, salt, *etc*. These molecular approaches should provide powerful redirection of food selection with the potential to increase the consumption of healthier foods with protective benefits.

Genetic Modification

Many of the benefits described above will require genetic modification of the food source. Some will require "traditional" breeding as has been done over the years to most of our plant, animal and microbial food sources. For example, the conversion of rapeseed to canola used traditional plant breeding at the organismal level to produce the desired genetic modification. On the other hand, molecular genetic techniques were used to engineer microbial production of highly pure—98%—chymosin for manufacture of hard cheeses. The bioengineered product, FDA-approved in the early 1990s, has largely replaced crude chymosin (rennin, only 2% pure) obtained from calf stomachs. Crop plants, such as soybean and corn, genetically engineered with improved agronomic traits, are being commercialized in most of the world except Europe. Most of the soybean grown worldwide is bioengineered. For many of the projected health benefits, food crops and possibly animals will need to be modified using molecular genetics as well as traditional methods. Research investment is needed to develop the scientific base to evaluate these products and, in due course, to assure domestic and export markets that they are safe for consumption. These products must be as safe as their non-engineered parents; in addition, they will provide health benefits beyond those of their parents.

Nutrigenomics

Developments in biology and genomics will provide the opportunity to couple agriculture, food and nutrition with new approaches to improving human health (nutrigenomics[10]). A few individual human genomes have already been sequenced and major efforts are being focused on developing low-cost genomic sequencing for individuals. The information generated by these approaches will provide the bases for clinical trials that can link individual genotypes to outcomes, in contrast to the current "one size fits all" approach. In addition to genomics, an expanded use of other "omics," such as metabolomics, will provide more precise diagnostic and treatment directions. These innovations will lead to a greater ability to design prevention-and-treatment interventions that depend on implementing diet and life-style changes, initially at the group level and, in time, may be individualized.

Food Safety

Food safety, essential to human health, will be further improved by continued innovation. Microbial contamination of fruit and vegetable produce and animal and poultry products is the major cause of food poisoning. Improved diagnostics and traceability will reduce microbial-contamination problems. Irradiation is another option to minimize food-borne illnesses. Production practices, such as routine use of antibiotics in poultry and animal production, are being discontinued so as to diminish development of antibiotic resistance in microbes infecting humans, and to prolong efficacy of antibiotics. Animal vaccines were recently introduced to reduce shedding of toxic microbes during meat processing. Rapid-readout online tests of poultry, animal and vegetable products should identify unsafe foods before they enter the distribution chain. In addition, country-of-origin labelling will facilitate traceability.

Communication & Education

Disseminating the message of the necessity to eat more healthfully will need massive and continuous efforts in our educational institutions, but also aimed at adults. The potential benefits are compelling: improved longevity and quality of life, reduced chronic-disease rates and containment of national healthcare expenditures. Major reduction in smoking over the past 50 years provides a good analogy. Newsletters dealing with human nutrition are available from university and advocacy organizations—one of which has about a million subscribers[11]—documenting the interest in diet and health. A rating system using stars to identify the nutritional value of supermarket foods has been introduced and should facilitate consumer selection of healthy food.

[9] Generally regarded as safe.

[10] The National Academies Food and Nutrition Board (2007) Nutrigenomics and Beyond: Informing the Future—Workshop Summary. Washington DC: The National Academies Press.

[11] *Nutrition Action Newsletter*, published by the Center for Science in the Public Interest.

Action Plan

The following action plan is proposed for expeditious delivery of the benefits outlined above, to reduce the cost of healthcare and improve the quality of life.

- Research in food and agriculture, including nutrition and veterinary medicine, must become a full partner in the national mission to improve health. Our academic and government structures separate food and agriculture and human health. Colleges of agriculture and life sciences function separately from colleges of medicine and public health; the US Department of Agriculture is separate from the Department of Health and Human Services; governmental appropriations for agriculture are separate from those for human health. The proposed *One Health Initiative* is an encouraging step, seeking to unite veterinary and human medicine. Expansion is needed to unite food and agricultural research with health in both academe and government.
- Public funding for food and agricultural research, including nutrition and veterinary medicine, requires a log step increase, not redirection of existing funding, to provide the knowledge and technology for the disease-prevention opportunities outlined. The National Institute of Food and Agriculture (NIFA) initiative could be a canopy. The new USDA Agriculture and Food Research Initiative (AFRI) is a positive step; however, a much larger funding commitment is needed.
- Funding should be competitive and open to individuals, to generate new knowledge, and, in particular, to self-assembled groups from food, agriculture and health focussed on specific targets and possessing the necessary breadth of skills, *e.g.* scientists, economists, sociologists, clinicians, marketers, regulators and communicators/educators from academe, government and industry. Examples exist of such integrated programs in food, agriculture and human health[12]. Inclusion of academe, government and industry seeks to capture outstanding talent independent of sector location and, in the case of industry, couples the technology to its ultimate delivery.
- The targeted programs may include functional foods, probiotics, reduction/elimination of food-borne toxins, reduction/elimination of allergens, diet alteration, flavor and taste enhancement, nutrigenomics, food safety, communication/education, and others to be identified.
- An initial long-term commitment (*e.g.* 5 years) will be needed to attract the innovative individuals needed to assure the desired outcomes in these challenging programs.

In conclusion, food and agricultural research has an outstanding record of contributions to human health, many seminal, and this action plan should expand the established record and, in addition, provide important low-cost prevention of diet-based chronic diseases.

[12] Integrated food, agriculture and human health programs include the North Carolina Research Campus, the Linus Pauling Institute at Oregon State University, the functional foods component of the Agricultural Bioproducts Innovation Program at Agriculture and Agri-Food Canada, and the USDA's Human Research Centers, one of which is at a college of medicine.

National Agricultural Biotechnology Council

Boyce Thompson Institute
David Stern
President

Clemson University
Susan F. Barefoot
Chief Operating Officer
Clemson University Experiment Station
Associate Dean, Food Safety and Nutrition

Cornell University
Margaret E. Smith
Associate Director,
Agricultural Experiment Station

Kansas State University
James E. Minton
Interim Director
for Research and Technology Transfer

Louisiana State University
John S. Russin
Associate Vice-Chancellor and Associate Director,
Louisiana Agricultural Experiment Station

Michigan State University
Steven G. Pueppke
Director, Michigan Agricultural Experiment Station
Assistant Vice-President for Research and Graduate Studies

Mississippi State University
Shane C. Burgess
Director
MSU Life Sciences and Biotechnology Institute
Co-Director, MSU Institute for Digital Biology

North Carolina State University
Kenneth R. Swartzel
Coordinator
Bioprocessing Programs, College of Agriculture
and Life Sciences

Ohio State University
Steven A. Slack
Associate Vice President
for Agricultural Administration

Oklahoma State University
Clarence E. Watson
Associate Director
Agricultural Experiment Station

Oregon State University
Lawrence R. Curtis
Associate Dean
College of Agricultural Sciences

Purdue University
Sonny Ramaswamy
Associate Dean and Director
Agricultural Research Programs

South Dakota State University
John Kirby
Associate Dean and Director
Agricultural Experiment Station

The Pennsylvania State University
Bruce A. McPheron
Associate Dean for Research,
College of Agricultural Sciences
Director of the Agricultural Experiment Station

Texas A&M University
William F. McCutchen
Associate Director,
Texas AgriLife Research

Member Institutions and Council Representation*

University of Arizona
Colin Kaltenbach
Vice Dean and Director,
Arizona Agricultural Experiment Station

University Of Arkansas
Mark J. Cochran
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University of California-Davis
Neal Van Alfen
Dean
College of Agricultural and Environmental Sciences

University of Florida
Mark R. McLellan
Dean for Research and Director
Florida Agricultural Experiment Station

University of Georgia
Robert N. Shulstad
Associate Dean for Research ,
College of Agricultural and Environmental Sciences

University of Guelph
Robert Gordon
Dean,
Ontario Agricultural College

University of Idaho
Gregory A. Bohach
Director
Idaho Agricultural Experiment Station
Associate Dean
College of Agricultural and Life Science

University of Illinois at Urbana-Champaign
Jozef L. Kokini
Associate Dean of Research,
Director, Illinois Agricultural Experiment Station

University of Kentucky
Nancy M. Cox
Associate Dean for Research
College of Agriculture

University of Missouri at Columbia
Marc J. Linit
Associate Dean for Research and Extension
College of Agriculture, Food and Natural Resources

University of Minnesota
F. Abel Ponce de Leon
Senior Associate Dean for Research
and Graduate Programs,
College of Food, Agricultural
and Natural Resource Sciences

University of Nebraska-Lincoln
Gary L. Cunningham
Dean
Agricultural Research Division

University of Saskatchewan
Graham J. Scoles
Associate Dean (Research)
College of Agriculture and Bioresources

University of Wisconsin-Madison
Molly Jahn
Dean and Director
College of Agriculture and Life Sciences

Washington State University
Ralph P. Cavalieri, Associate Dean
College of Agricultural, Human,
and Natural Resource Sciences
Director, Agricultural Research Center

* This document was not signed by the NABC member from the USDA

National Agricultural Biotechnology Council
B 15 Boyce Thompson Institute
Tower Road
Ithaca, NY 14853
607-254-4856   Fax-254-8680
http://nabc.cals.cornell.edu/   nabc@cornell.edu

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