FOODS FOR HEALTH

A NEW INITIATIVE

Committee Report
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Preface

The University of California, Davis is internationally recognized as a world leader in life sciences research, particularly in areas related to food production, nutrition, toxicology and health. Individual departments are widely recognized for their specific expertise. Given its mission, UC Davis is identifying areas of research and service to maximize our collective impact on society and provide direct benefit to the citizens of our state and nation.

This report describes a new campus initiative entitled "Foods for Health". The research, outreach and teaching programs encompassed by the Foods for Health initiative will build on campus strengths by cutting across departments, schools and colleges to create synergies not achievable without this initiative. Faculty from the School of Veterinary Medicine, the School of Medicine, the School of Engineering, the Division of Biological Sciences, the College of Agricultural and Environmental Sciences, the College of Letters and Science and the USDA Western Human Nutrition Research Center (WHNRC) will be key players. Aspects of the initiative will appeal broadly to chemists and biologists regardless of college affiliation. Economic, legal and social issues will provide opportunities for input from other parts of the campus community. Given the high interest among faculty and potential for exciting scientific discoveries in the area of foods and health, we envision that this initiative will become a signature piece for UC Davis.

Introduction

There has been a recent paradigm shift in how food and diet are viewed with respect to human health and well being. The Food and Nutrition Board of the Institute of Medicine (IOM), working in cooperation with scientists from Canada, recently developed Dietary Reference Intakes (DRIs) for the essential nutrients. In marked contrast to the previous Recommended Dietary Allowances (RDAs), which were focussed on preventing primary nutritional deficiencies in entire population groups, the new DRIs define nutrient targets for the "individual". In addition to placing the emphasis on individuals instead of populations, the new DRI values were developed to identify the amounts of essential nutrients that an individual needs to consume to reduce their risk for chronic disease. This new emphasis on the role of "essential" nutrients in promoting human health and well-being is evidenced by the recent proliferation of nutritional genomics research programs and centers. Nutritional genomics view food as more than a source of calories but rather as a complex mixture of dietary components whose impact on health is shaped by human genetic variation. This new view of food for health presents a number of challenges. For example, for several nutrients, the new DRI values are set at levels that cannot be easily met from non-fortified foods. What are the quantitative nutritional requirements needed to produce optimal metabolism and health, particularly for the macronutrients? How can nutrient intake be optimized for each individual, given the genetic diversity and complexity of common dietary chemicals? How can we assess the changing nutritional needs of an individual from birth through death, given the available

molecular and genomic technologies? How do we ensure that dietary recommendations, particular those based on knowledge of genotype, is used in a socially responsible manner?

In parallel with the IOM's reports on essential nutrients, the DRI parent committee recognized that there are non-essential nutrients in the diet that can significantly reduce the risks for chronic diseases. Expert panels are being developed to identify these nutrients and define the amounts of these nutrients that individuals need to consume to achieve health benefits. The recent surge of interest in phytochemicals illustrates the growing awareness of the potential health benefits associated with consuming these compounds. Importantly, the phytochemical profile and content in foods can be markedly influenced by agricultural practices, as well as by post-harvest processing. The opportunity exists to develop and deliver food products that contain precise mixtures of nutrients tailored to needs of the individual or subpopulation. As a consequence of this potential, health care providers and public health policy makers are increasingly looking to diet as a means to decrease the incidence of many chronic and age-related diseases. Part of this interest in dietary solutions is occurring as a consequence of the rising cost of conventional medical treatment and drugs. Part of this interest reflects an increasing awareness that dietary intervention can prevent, delay, and treat many common diseases and enhance the quality and length of life. At the national and international level, the line between food and medicine is becoming increasingly blurred.

The Foods for Health Initiative aims to develop a comprehensive program at UC Davis that considers all aspects of food from the farm to the table to the ultimate health of the individual. The overall goal of the initiative is captured, in a simplistic fashion, in Figure 1. By improving the nutrient profile of certain plants and animals, we should be able to build the knowledge base and innovative technologies needed to transform California agriculture and the food production/processing industries. As depicted in Figure 2, there are multiple ways in which the nutrient profile of a food can be altered. Research conducted under the initiative will employ these approaches as well as explore new technologies and research strategies. It is the development and implementation of these new technologies and strategies that will be critical to the initiatives success. In other words, we will seek to make large, rather than incremental, changes in the way foods are produced, processed and used to promote health.

The initiative will also serve as a launching point for the development of new undergraduate and graduate curriculum.

Figure 1

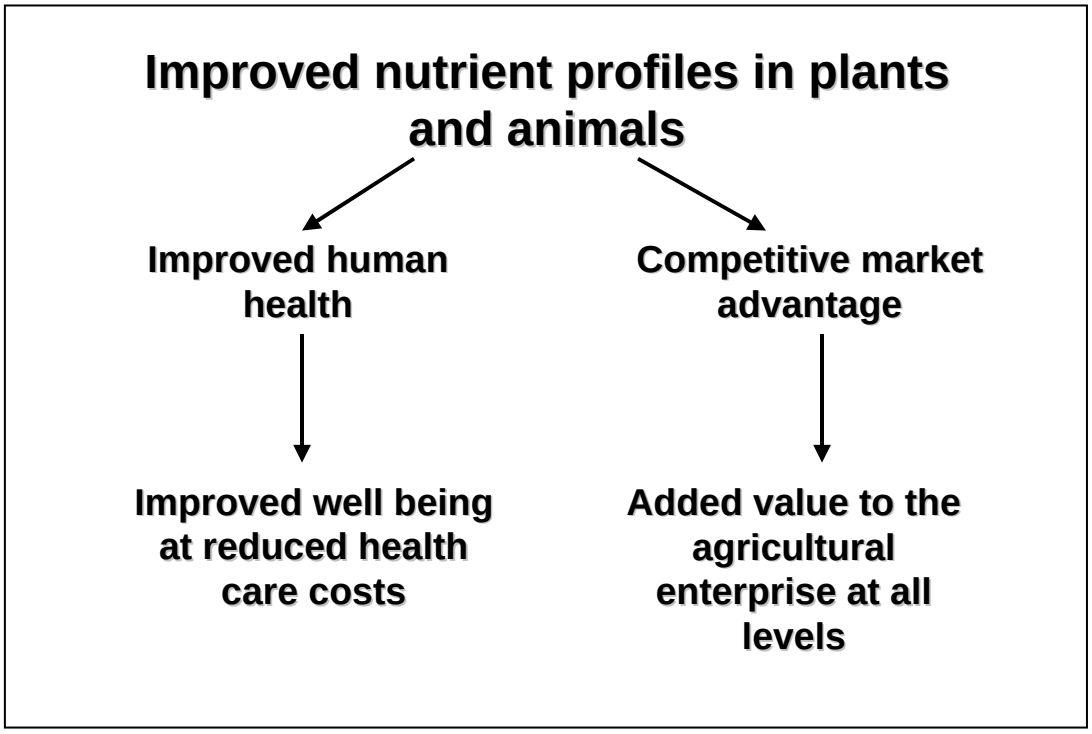
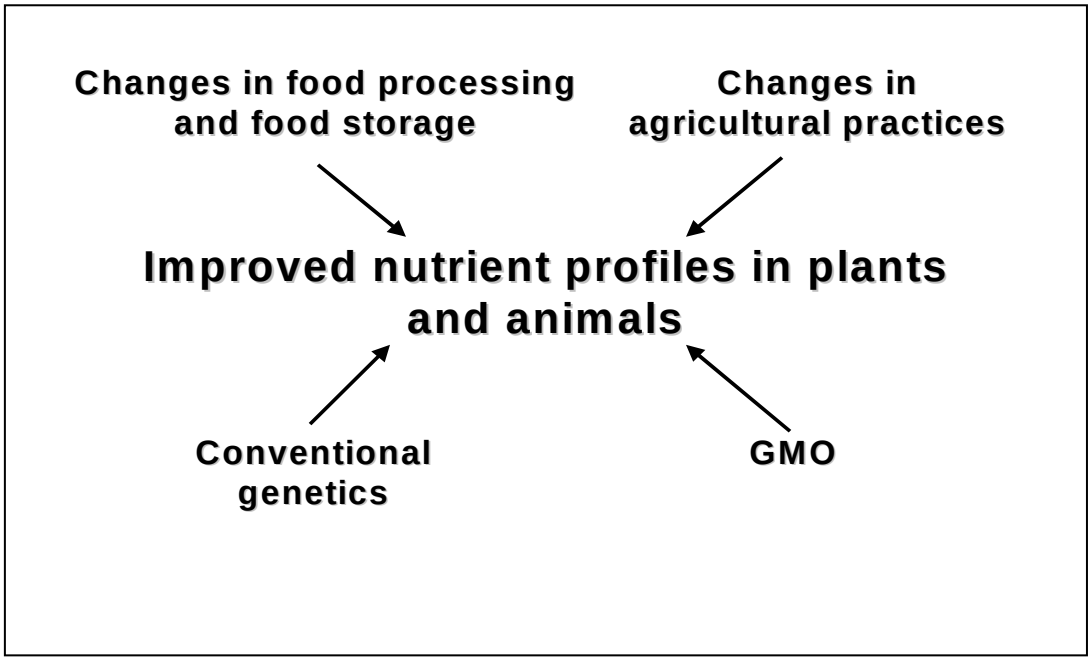


Figure 2



Specifically, the program will:

- identify nutrients and diets that promote health, prevent metabolic diseases and reduce the risk for chronic diseases;
- develop new agricultural and food processing principles and technologies that enhance the quality of foods and increase the concentrations of desirable nutrients in target foods;
- Investigate diet/genome interactions and the role of common human genetic variation in the assimilation, metabolism and storage of dietary chemicals.
- identify agricultural practices that improve the value of crops, thereby enhancing the value produced by California's agricultural industry;
- develop a greater knowledge base that will provide consumers with food choices identified/designed to improve their health and thus encourage consumer interest in healthier diets and food products;
- identify components in plants and animals that contribute to the development and progression of certain diseases when consumed in excess;
- identify innovative means to decrease the concentration and bioactivity of these negative components in target foods;
- establish the means to evaluate the long term public health impacts of consuming different diets and food products;
- analyze "ex-ante" consumer reaction to potential (or actual) new agricultural products and determine the expected demand for such products.

As a result of the initiative, the campus will be exceptionally well poised to obtain significant new extramural funding in the area of Food and Health, an area that we expect to grow more rapidly in the future. The principal beneficiaries of the fruits of this initiative will be the campus, the state and the nation. The Foods for Health initiative will provide a model of multidisciplinary and integrated research to improve human health locally and globally. The initiative will also provide the intellectual leadership needed to guide California agricultural and food through into the 21st century.

Beyond Human Health

Although this inititiative lays the groundwork for improving foods for human health, the same principles that are driving the new DRIs for humans will undoubtedly also drive the development of new dietary recommendations for herd and companion animals. We envision that the Foods for Health Initiative will also contribute to the identification of improved foods and animal diets. Diets based on a knowledge of nutritional status, nutritional requirement and genotype, will result in greater feed efficiencies and yield in farm animals, and companion animals that are healthier and live longer.

Background

Why is this new initiative needed? Food is an essential input and is simultaneously one of life's great delights. Food nourishes, comforts, protects and provides pleasure. Modern science and technology have provided unparalleled value to

consumers through the creation of many safe, tasty and nutritious foods. The creation of these foods has been driven by the development of scientific knowledge at all levels of the agricultural enterprise -- from genetic improvements in production agriculture to mathematical control of food processing systems, and from molecular understanding of food safety to statistical precision in the evaluation of consumer sensation. One of science's great achievements of the 20th century was building the quantitative knowledge of the nutritional requirements for humans and animals and practically eliminating primary nutrient deficiencies in the developed world.

The successes in health that have been achieved by defining the essential nutrients are occurring at an opportune moment. Despite past success by researchers in identifying essential nutrients, consumers are being faced with a new set of challenges. At a time when the opportunities to produce a wide variety of foods to improve health would seem unprecedented, increasing numbers of individuals are choosing diets that increase their risk for metabolic imbalances and disease. Complicating matters further, some diet-related diseases may be, in part, the result of successes in improving quality and cost by the agriculture and the food sciences. For example, contributing factors in the increase in obesity includes the low cost of food and the development of tastier foods. The resulting paradox is that the more we develop inexpensive, tasty foods (reasonable goals), the more we encourage overeating and development of certain chronic diseases. Consumers and public health policy makers are increasingly viewing their foods and the agricultural enterprise as a negative, destructive influence on their overall lives. As a result, the value system of agricultural products and foods is deteriorating. It is vital that we act to restore public confidence in food and its benefit to human health. This goal can only be accomplished by building new scientific knowledge that can be provided to empower individuals to make better choices from a wider variety of superior foods that improve all aspects of their quality of life. Such health solutions that include greater value in foods will invigorate the California agricultural enterprise.

A revolution in biological knowledge is following on the heels of the global initiative to sequence the human genome and the application of massive computing power to study the genomes of living organisms. Such knowledge promises to drive a better understanding of the interrelationship of agriculture, diet, foods and health, the molecular basis of food, flavor and texture, why we find foods delicious, and how we can enhance our experience with food. We seek knowledge that will not only define in molecular detail which foods are safe, but help us to develop foods that make consumers healthier than they would have been had they not eaten the specific foods. Knowledge of biological structures and functions will allow us to improve the engineering processes of formulating foods, and it will provide a greater understanding of biomaterials leading to new types of foods and new benefits to health within traditional foods.

Foundations of the Foods for Health Initiative

To achieve a new direction for research and innovation in foods, to empower individuals to greater personal freedom for choosing their foods and achieving superior

personal health, the UC Davis Foods for Health Initiative will establish three thematic axes as underlying platforms. These are:

- ***Individualize*** metabolic, nutritional and behavioural knowledge, for quantitative assessment, interpretation and intervention.
- ***Integrate*** all aspects of food's values including health, safety, quality, delight, convenience, economy, efficiency and sustainability. By improving these values infuse greater return to the entire agricultural food chain.
- ***Inform***: the world to share in this new knowledge.

-***individualize*** This axis will put in place the knowledge, tools and models to dramatically change the way humans control their health, moving from a model of nutrition based on avoiding deficiencies in the population, to an individual and health promotion model, based on individual assessment of metabolism and nutritional status. Driven by the tools of functional genomics, proteomics and metabolomics, this axis will develop the genetic and metabolic knowledge that is needed to link diet to physiological and biochemical phenotype, develop quantitative assessment technologies, acquire and annotate databases of individual metabolites from humans and animals, and establish the clinical and animal models to demonstrate the principles of modern health. The assets are already in place to make this a reality. These include: the nation's leading agricultural college, which has clear pre-eminence in food production, food science and nutrition, partnered with one of the nation's leading medical schools that addresses family health and disease prevention, the world's leading veterinary school, and the USDA Western Human Nutrition Research Center (WHNRC). Existing infrastructural support includes the School of Medicine's Clinical Nutrition Research Unit, the College of Agricultural and Environmental Sciences' Ragle Facility.

-***integrate*** This axis will promote research in the principles needed to integrate food functions across the entire campus initiative. While there is an increasing tendency to view some foods as medicine, foods carry values quite different from those for pharmaceuticals. Pharmaceuticals are typical of 'or' value carriers: you take this drug 'or' that drug. Foods instead carry values in aggregate. Foods must be simultaneously safe, delicious, stable, affordable and nutritious. Thus, increased healthful benefits will similarly be added one after another, ingredients good for muscles can add to ingredients good for bone, can add to ingredients for brain. The first generation of healthful-value added foods sought to out-compete traditional foods with a single health attribute attempting to carry all of the value of the new food. This approach did not succeed. Individuals are unlikely to choose a strawberry with a slightly higher added health value if it is not as delicious as the original product. The UC Davis Foods for Health Initiative will go beyond simply adding healthful ingredients to foods. Rather the initiative is aimed at pioneering a new generation of integrated foods in which each traditional value is equal to, or superior to, its predecessor. This strategy requires a level of collaboration and coordination that is now possible with the emerging fields of informatics. UC Davis is positioned to be a leader in this bioinformatics platform with the existing strategic organization within the CAES. Organizations such as CIFAR and the Robert Mondavi

Institute could become campus windows to the principles of integrating all food values from the farm to the family table, delivering delicious, fresh and safe commodities, as well as a scientific understanding of individual foods or food components and the whole diet.

-inform The Foods for Health Initiative will build a new platform of knowledge management for these scientific principles of food. One goal of the initiative will be to create a publicly accessible electronic bioinformatic environment that allows rapid access and exposure to scientific breakthroughs, networked across the campus and around the state. The values of food have traditionally been powered by individual choice. Free choice is only possible from an informed, knowledgeable consumer base. Examples abound that show value in agriculture comes from a knowledgeable consumer that takes advantage of personal choice. Wine, cheese, organic foods, and even designer fashions, recover value to the agricultural enterprise via consumers who know what they prefer. Individual knowledge and choice in wine or cheese can be learned by tasting. Individual variation and preference for optimal metabolism require both personal measurement and access to biological knowledge. The initiative proposed for UC Davis could never be applied to its logical consumer if the knowledge we are building is not accessible to the individual. In axis 1 and 2, we will develop the tools of assessment and the biological knowledge. In axis 3, we will provide worldwide access by pioneering, designing, and becoming, the nation's leader in a new generation of bioinformatic tools to provide unprecedented knowledge of personal health and the biological, agricultural and food science necessary to deliver it as personal choice.

Individualizing Health

Genomics, enabled by bioinformatics, is in the process of revolutionizing our understanding of biology. The medical sciences, especially those devoted to understanding and intervening in disease are profiting already from this understanding. Scientists have strived for the last century to deduce the mechanistic basis of the relationship between diet and health by understanding the interaction of nutrients with metabolic pathways. The tools to extend this approach to understanding integrative metabolism in each human will be based on genomics, proteomics, metabolomics and bioinformatics and underlying biochemical and chemical principals. *Genomics* provides the blueprint. *Proteomics* provides the structures and catalytic activities that are needed for organisms to maintain function and homeostatic metabolism within an active dynamic environment. *Metabolomics* provides a quantitative measure of the actual functioning of any particular organism as reflected by its overall metabolism. Expertise in *genomics, proteomics and metabolomics* is necessary to understand and predict overall individual health from basic nutrient actions to the interactions between food microorganisms and the human intestinal system, including the gut and immunocompetent cells, and the mechanisms underlying the interactions of the microbial community in the intestinal tract.

A potential deficiency in the current scientific toolbox is the lack of metabolomic technologies required to provide real time individual assessment of health as metabolic

status. A goal of the Foods for Health Initiative is to guide collaborative research to expand metabolic nutrition in three dimensions--assessment, mechanism, and human variation. Human metabolic health must be quantitatively assessable at the level of each individual, the mechanisms linking diet and metabolism need to be established, the basis of individual variations in the response of metabolism to diet need to be discovered and finally, all three of these dimensions of knowledge need to be catalogued as quantitative databases in electronically accessible form. It is expected that through the proposed initiative, UC Davis will become the world leader in building, applying, and validating these tools and databases to foods for individual health.

Integrating all Food Values

The integration of foods for health will be applied throughout agriculture, but most immediately in food processing and optimizing the quantitative parameters of traditional and advanced unit operations. Food commodities are traditionally processed first to achieve storage stability and safety with considerable excess of energy applied to ensure a large margin for error. This margin of error is necessary due to our inexact knowledge of the composition and structural complexity of biological materials, the natural variability of living organisms as food process input streams and the response of these materials to processing parameters. UCD's initiative will integrate across the CAES to assemble the considerable knowledge of biological organisms from bacteria and viruses, to plants and animals, to identify and optimize food process design across all cost-sensitive inputs, including non-renewable energy costs to provide a new level of food safety and quality.

Given the campus' strength in phytochemical research, an early goal of the Foods for Health Initiative is to identify ways to enhance the collaborative efforts of the college aimed at the identification and characterization of putative health promoting phytochemicals. One step toward this goal would be the development of a facility for analysis of phytochemicals. Additional details concerning this concept are discussed in a later section.

Food safety and security is becoming more of a concern for consumers and the food industry. There are new opportunities to ensure the inactivation or inhibition of undesired microbes, to understand the ecology of food-borne microbial populations, and to translate population-based toxicological, pathological and tolerance evaluation of foods and food compounds into individual delivery of safe food. Foods Genomics era tools will allow for a new definition of safe food to the consumer, e.g. foods will not just be safe, but foods will make the consumer safer. As an example, the lactic acid bacteria program on campus, under David Mills, is rapidly emerging as a model for how genomics era technologies are building knowledge that will change the value system of food commodities.

The future for food processing is not in simply processing for greater safety, but in merging biological knowledge of living organisms with the biomaterial knowledge necessary to convert them to foods. Traditional food processing relies on the aggressive

input of energy to restructure the constituents (biomaterials) of living organisms into simpler miniaturized forms of stable, relatively uniform foods systems. During processing of raw commodities, the inherent biological properties of the living systems are lost to the final food product in the need to ensure the elimination of any and all potentially hazardous constituent molecules (toxins, protease inhibitors, etc.). Modern research is providing a detailed description of the structural and functional properties of biological macromolecules. Such knowledge is the cornerstone of functional genomics, proteomics and metabolomics. The UC Davis campus has an opportunity to translate this knowledge into an equally accurate knowledge of the biomaterial properties of each of the constituents present in a complex mixture. It is envisioned that it will soon be possible to use the inherent structural properties of natural food commodities to bio-guide processing to self-assemble new foods with a minimum of external energy while retaining a maximum of the values of foods including nutrition, safety, delight, cost, and stability. This is a research area in which our campus should excel.

There are vivid examples in which highly specific biological properties of the original living organism are a key to the processing strategy and ultimately the organoleptic attractiveness of final food products. The renneting of bovine milk to induce the natural aggregation of milk caseins leading to the gelation events of cheese manufacture is such a process. The final product takes advantage of the self-assembly properties of milk casein micelles that are colloidally stabilized in milk by kappa caseins, but destabilized when rennin cleaves their solubilizing glycomacropeptide. Another example is leavened bread in which both composite processing and biological restructuring are the basis of breads' basic structure, texture and nutrition. In this case, wheat seeds are ground to disassemble the majority of their biological structures through mechanical energy, but then the biological processes of yeast fermentation achieve simultaneously the enzymatic elimination of phytic acid during dough incubation, and the biochemical production of carbon dioxide gas as leavening within a mechanically reworked protein gel structure. In each of these examples, bread and cheese, taking advantage of the biological properties of the living organisms led to substantial value both organoleptically and with greater safety and nutritional value. Furthermore, the inherent variation in biological organisms that do not allow the standardization of simpler food processing objectives is not a disadvantage to these foods, but rather a benefit leading to distinctly flavored and textured cheeses and breads. Cheeses, breads, wines and yogurts provide proof of what is possible when the biological processes of catalysis, self-assembly and restructurization are exploited in food processing. The biological knowledge that is emerging with functional genomics, proteomics and metabolomics is providing the knowledge necessary to readdress food processing using biomolecular activities rather than simply composite biomaterial properties. The Foods for Health Initiative will spearhead an evolution of food and products processes. By integrating the above tools and knowledge, process design engineers can then work in a coordinated fashion with plant bioengineers to produce crops that are not simply enriched in a single valuable component, but instead are redesigned to increase the myriad value of foods for enhancing an individual's quality of life.

Informing the Citizen

The explosion of data and their management as information and knowledge has been enabled by the even more rapid evolution of computing power. However, in order to gain full access to these powerful tools, it is paramount to resolve the challenge of unifying complex and dissimilar data into usable information and knowledge. The need to combine observations from numerous sources and domains into first, seamless searchable databases, and then building information into knowledge can only be addressed by a major University commitment to the bioinformatics of foods for health.

Advances in data collection, storage, and distribution technologies have outpaced techniques to assist the analysis, and interpretation of this information. This need will be addressed within the Foods for Health Initiative. High technology information management systems are starting to play a fundamental role for the experts who are working on their development, even though they are, however, almost invisible for most potential users. The Foods for Health Initiative will provide an opportunity to apply these appropriate information management systems to their most important challenge, and integrate all of the value parameters of food into a revitalization of the agricultural enterprise.

Economics in the Foods for Health Initiative

The Foods for Health Initiative will contain an economics component. Producers and consumers respond to economic incentives and such incentives will be important determinants of the ultimate success of the Foods for Health Initiative. Research on Foods for Health has been carried out at several universities during the last decade. Following an initial period of excitement, the initiatives have lagged. Diminished expectations and enthusiasm have resulted because it has been difficult to produce results that have clear and tangible value.

Research results must be used on a significant scale if they are to have social value. To be utilized, research results must be converted into products that consumers believe are beneficial and that they want to purchase. Firms must find it profitable to produce and market the products. Thus, economics is an important tool in helping to evaluate foods for health research in the short and longer term. Ex ante analysis should not be used as a hard and fast criterion, but rather as a part of an approach where scientists systematically explore information to determine the types of research that appear most promising.

Individual research projects, if well defined in terms of the expected inputs and results can be evaluated using benefit-cost methodology. Such evaluations are useful by providing a structure to the research approach, as well as for indicating whether the research is likely to produce outputs whose value significantly exceeds the cost of the research. Carrying out a benefit-cost analysis requires identifying the important inputs in the research process, their cost and the time at which each input is used, and the principal results, their value (e.g., the profit that can be generated from a product multiplied by the

number of products that can be sold), and when that value can be realized. The ultimate profitability of research usually depends on a fairly small number of key parameters. Identification of these parameters and the analysis of how changes in their magnitudes affects the expected profitability of the overall research enterprise is useful for identifying aspects of the research process that should be monitored and continually reevaluated to ensure that a process remains attractive.

In most universities, research projects are not subjected to explicit economic analysis. Researchers typically develop proposals and submit them to granting agencies. Granting agencies evaluate research for its promise and, in most cases, the social attractiveness of different research projects is subjectively subsumed in funding decisions. That is doubtlessly the best approach in the case of the Foods for Health Initiative as well. However, by having economists maintain an ongoing dialogue with biological scientists who are seeking to create new Foods for Health, the economists, in cooperation with the biological scientists, can develop models that explore the potential effects of different goals.

For example, if one goal of a Foods for Health Initiative is to develop fruits and vegetables, or processed food products, that have positive effects on health and longevity, the question is how much effect these products might have (per unit of serving), how long they must be consumed to have a significant effect, and whether their health effects can be combined with sensory aspects that make the product more sufficiently desirable than other (less healthy) alternatives to make the whole enterprise profitable? Economists may not be able to study a specific product, as it may be some years before a tangible product is produced. However, economists can explore the general theme to better characterize its nature and the important aspects of research.

For example, imagine that a research program determines that a particular nutritional compound is beneficial to consumers. The natural question is then to ask: what will happen to the average consumer if he/she consumes a specific amount of the compound (in whatever form desired, e.g., a 4-ounce serving three times a week) over 60 years, beginning at age 1? Will the average individual suffer significantly less chronic illness of a specific type? If so, what is the value of the reduced "suffering" to the average consumer? Will the average individual live longer than the average person that has not consumed the product (or some smaller amount of the product?)? If so, what is the value of the higher life expectancy?

Of course, to the extent that the effect of compounds can be related to specific genetic characteristics of individual consumers, the effects of the product become much more specific. Since it is known that risk is usually an important factor affecting willingness to pay for an attribute, consumers should be willing to pay more for a product that is more certain to help them rather than for one whose effect is highly uncertain. The question again is, how much more are they willing to pay? Valuing specific outputs is usually done in one of two ways: by induction from what individuals are observed to pay for other products with similar effects, or by asking individuals what they would pay for

such products were they to exist. Obtaining information on the above type of questions will be used to help prioritize research projects across the Food for Health Initiative.

Strategic Plan for the Foods for Health Initiative

Metabolomics

Metabolomics is key to the Foods for Health Initiative. This part of the initiative recognizes that scientific discovery is driven by the quality of questions and the tools to answer them. Thus, success in metabolomics will come when metabolomics tools are placed into the hands of scientists with the best problems to solve. The goal of a centralized facility will be achieved gradually, first building the databanks housed together with the central processing units that provide the bioinformatics tools needed to coordinate the multiple databases generated around the campus. As the university resources expand, more and more of the technologies necessary to manage high throughput, data systems (e.g. metabolite analyses) will be co-localized in a central facility for metabolomics and bioinformatics.

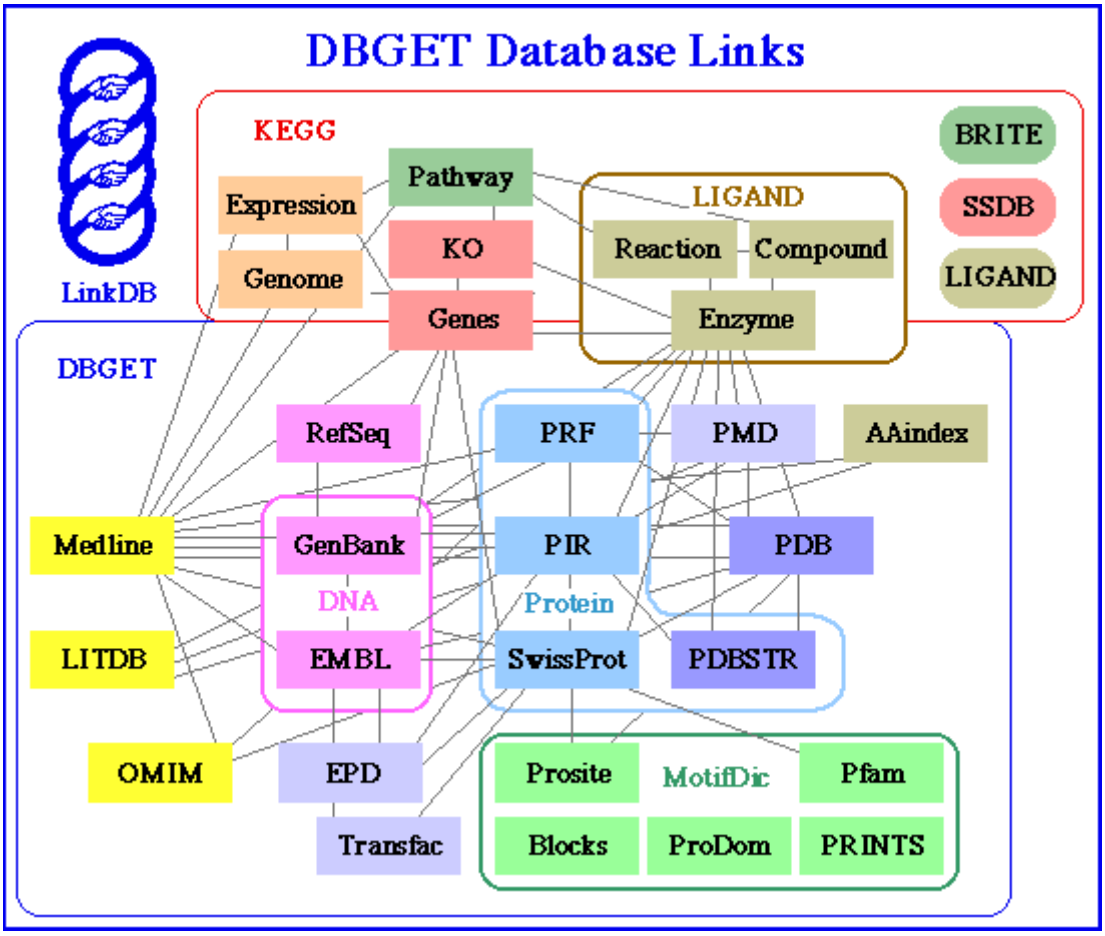
The basic strategy of the metabolomics core is to recruit the core metabolite laboratories on campus to provide a "first of its kind" demonstration of functional metabolomics. This campus-wide program would evolve into an ongoing working model of how metabolomics can be used as the knowledge base of metabolic regulation, leading eventually to the use of metabolomic assessment as part of an individuals' routine health care. It is envisioned that the Schools of Medicine and Veterinary Medicine, the WHNRC, the College of Biological Sciences and the CAES will play important roles in this component of the Initiative. Academic laboratories together with their full spectrum of biological models will be critical for developing the knowledge of how pathways are regulated in microorganisms, plants, animals and humans. The routine assessment of personal metabolites will become a self-supporting industry separate from academic research. Academic research in conjunction with clinical research programs (both human and animal) and managed health care will define and provide regulatory consensus on how excursions from normal metabolite concentrations could and should be adjusted, i.e. via drugs, diet and or other interventions. Of course analytical chemistry is at the core of the technology needed to deliver the analytical data upon which metabolomic information is based. Chemists and engineers within and associated with the college are needed to make cheaper, faster, better methods of analysis to support this science.

1. Establish the Metabolomic Database Platforms

To date no individual site nor institution has taken the responsibility of establishing the full spectrum of metabolites in key fluids, tissues and cells in humans animals or plants, even though various organizations publish complete metabolic pathways i.e. KEGG (Figure 3). It is not possible to begin a metabolomic program until the basic metabolites are identified and assembled in an accessible database platform. As one of the world's largest bioscience universities, working to define itself in the

bioinformatic information era, this is a logical goal for the campus. The existing major databases of biology (Figure 3) illustrate the state of the art of modern informatics in accessing biologically structured databases, and also points to the glaring omission of metabolite databases at the present time.

Figure 3 KEGG's database linking system together with the major biological databases that are immediately queried from this site.



2. Designate and Capture the Key First Generation Metabolomes

UC Davis can take the initiative in defining priority organisms and phenotypes for which underlying metabolic data will be most informative and thus most likely lead to successful applications. The campus will become synonymous with these choices as it moves to become a major metabolomic center, and therefore it is necessary to define these targets well. It is important at this point to declare that the Foods for Health Initiative is not a disease-based initiative. The goal is not to define the metabolic regulations associated with known pathologic, toxic or genetic diseases, but rather to establish metabolic dysregulation within a normal, non-diseased population. It is well established that a normal population includes those phenotypes whose differences in

metabolism will eventually lead to deleterious outcomes. An important step in this process will be to identify the key health issues in humans. Which animal species, and which health problems, will serve as the guiding example of successful management of chronic degeneration, or breed specific health problems? In plants, which metabolic pathway understanding will lead to important improvements in growth efficiency, pest resistance, and commodity value or bioremediation management? In bacteria, what phenotypes are associated with biological, or processing outcomes, and of compelling value?

3. Consolidate, Consensus Models for Identifying the Mechanisms Underlying Metabolic Variation of Biological Importance from Goal 2.

The broad application of metabolomic principles will be most successful with the application of well-defined biological models in which the tools of metabolomics have been established and validated. The remarkable utility of E. coli, S. cereviseae, C. elegans and M. musculus and their respective genomes have led to the rapid emergence of functional genomics. The consensus establishment of these models will similarly move metabolomic analysis forward by shared comparisons and validation. Functional metabolomics will then proceed rapidly along research lines in which comparisons to functional genomics are possible to allow multiple investigators to compare results and detailed molecular analyses. These models would include a resource of specific gene knock-outs, knock-downs, and knock-ins as the means to test specific hypotheses for metabolic regulation. The strength of the campus in murine biology, the strengths of the School of Medicine and the UCD Veterinary School, its association with Animal Science of CA&ES and the programs of the Division of Biological Sciences are critical for these approaches.

4. Coordinate the Functional Annotation of the Key Metabolomes.

The assignment of function to each of the respective metabolites in terms of the pathways that are involved in their formation and elimination, and how each metabolite varies in the population as a function of health will take considerable effort. A major step in this direction is simply placing the metabolomes in an internet-accessible site combined with standardized format informatics support that is analogous to SwissProt. The annotation of the respective metabolomes in the future will include not only the metabolic reactions that produce and eliminate each of the various metabolites but the coordination of multiple pathways that combine to influence the quantities of fluxes of each metabolite. A Metabolomics Center at UCD will be an ideal setting to coordinate with the Genome Center to cross-annotate the metabolomes and genomes. A significant strength of the Davis campus could be the development of a unique dimension to metabolite annotation, and external regulation. Assignments of function will eventually include the interaction of environment with metabolites including nutrients, drugs, toxins, stressors and other exogenous variables that interact with the metabolic targets, and delivery systems.

5. Direct the Campus Animal Models and Clinical Patient Populations to the Task of Validating the Mechanisms and their Applications as Interventions.

Scientific consensus will need to be developed for the use of individual metabolic assessment as an approach to improved health and nutrition. Scientists assembled around evidence-based experimentation and clinical trials will only build such consensus. The University of California, Davis is the well positioned to carry out this assembly of consensus. Possibly an early application of this technology will be to clinical populations already under high stress. Metabolomic evaluation of patients with cardiovascular disease, on hemodialysis, or chemotherapy constitutes groups where careful metabolic analysis and nutritional intervention could have a dramatic impact on the quality of life.

Phytochemicals

Diets rich in plant foods have been associated with a reduced risk for certain chronic diseases in numerous epidemiological studies. As a consequence of the above, there has been a surge of interest in the characterization of the health benefits of specific phytochemicals and their metabolites.

Faculty expertise in phytochemical research is very strong on the Davis campus, so we are in a position to assume an international leadership role in this field. A major plank in the Foods for Health Initiative would assist in the coordination of campus research projects aimed at the development of improved food products for human health. As is depicted in Figure 4, the Center would facilitate a comprehensive view of the development of new foods, with attention given to the multiple variables involved including food safety, palatability processing, and economic viability. The proposed Center will link different research units throughout the campus, and it will aggressively work toward obtaining extramural Center grants in the areas of plant production, food processing, food safety, and diet and health, with an emphasis on phytochemicals. As is depicted in Figure 4, the Center grants will integrate research from multiple units on the campus. The goal of all of the Center grants would be to work toward the development of the model depicted in Figure 5, in which units, such as the Phytochemical Research Center, will coordinate programs of new healthy foods.

Figure 4

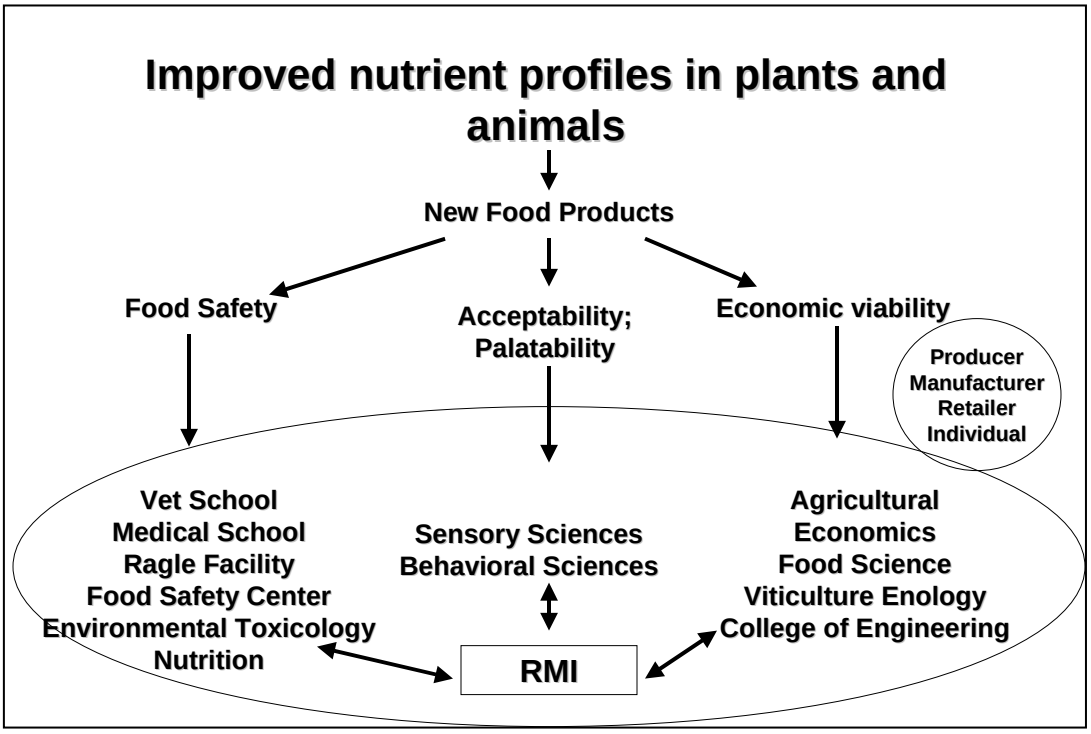
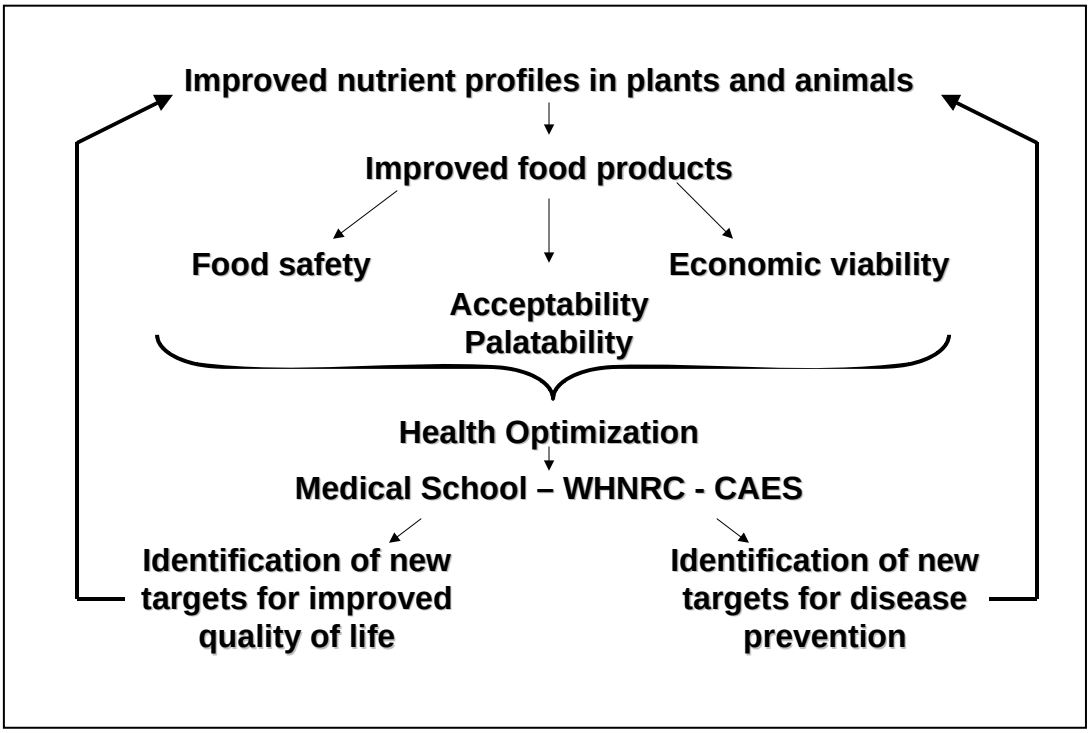


Figure 5



Phytochemical Analytical Core Support Unit

There is a significant strength within UC Davis in the area of Plant Biology, phytochemical analysis. This strength is found in multiple departments; including Food Science Nutrition, Pomology, Vegetable Crops, and Vitculture and Enology. While a reasonable amount of communication exists among investigators on the Davis campus who have interests in phytochemical analysis, the magnitude of this interaction could be significantly enhanced by the development of a common analytical core support unit. Importantly, it is envisioned that this support unit would not only facilitate the analysis of phytochemicals in raw and finished food products, but it would also provide assistance toward the measurement of phytochemical metabolites following their consumption as either purified products, or in complex foods. An additional function of the analytical core support unit would be to provide assistance in the design of experiments aimed at the evaluation of the biological effects of phytochemicals. The analytical core facility unit would also serve as a central site for the collection and storage of data concerning food phytochemicals. The establishment of the type of unit described above would significantly increase the UC Davis potential for obtaining extramural Center grants in the area of phytochemical research. Given the wide diversity and complexity of phytochemicals, the analytical core unit would need to identify a relatively short list of phytochemical families that would be the focus of attention in the unit.

The establishment of the phytochemical unit is designed to provide a model for subsequent cores of expertise as the foods for health initiative proceeds. Thus, the university's Food for Health Initiative will stimulate programs in areas of growing expertise in beneficial food grade bacteria (probiotics), milk-derived bioactivities, fibers and oligosaccharides.

Human Health Assessment Core Unit

The phytochemical analytical core support unit will provide guidance to investigators with respect to the analysis of phytochemicals. This unit will also help coordinate, and provide information on the basic chemistry of phytochemicals identified by the campus as top priority nutrients for investigation. A Human Health Assessment Core Unit will be established as a complement to the Analytical Core. As is depicted in Figures 4 and 5, as an essential step in the development of new Foods for Health is the evaluation of the acceptability of these foods. With respect to palatability, and cultural behavioral bias', the Human Health Assessment Core Unit will help investigators identify potential strengths and weaknesses in the products they are working on with respect to their potential future acceptance by the public. This core facility will also provide a means through which products could be tested for palatability and other hedonic properties.

A second function of the Human Health Assessment Core Unit will be to provide guidance to investigators with respect to the approaches to evaluate the potential health benefits of diets, foods and food ingredients and the need to establish simultaneously

safety and potential deleterious side effects. Toward this end the Health Assessment Unit will provide direction on how investigators can evaluate the bioavailability, and bioactivity, of target polyphenols. It is anticipated that by working with faculty and staff associated with resources such as the Ragle Facility and the WHNRC, investigators will be able to design and execute studies aimed at the evaluation of the new food products. It is anticipated that faculty in the School of Medicine will become significantly involved with the Foods for Health Initiative, and that clinical trials evaluating select foods will be conducted in collaboration with the Medical School.

UCD Community Health Surveillance Program, (Sacramento Nutrition Application Program; SNAP)

The Foods for Health Initiative will be significantly enhanced due to UCD's community health program. To some extent, this program will be similar to the famous Framingham Study. However, in our case, and to our advantage, we will enroll subjects in the Sacramento-Davis metropolitan area, the most diverse metropolitan area in the country. It is anticipated that they will be followed over the course of years-decades and enrolment is likely to be dominated by subjects who already participate in the UC Davis Health System. However, this Program will not be inclusive of persons enrolled in the UC Davis Health System. By using this large database in a population study, the health benefits and economic impact of foods and nutrition to the population can be observed in a longitudinal fashion. There are a number of advantages related to locating the UC Davis Community Health Program in the Sacramento-Davis metropolitan area including a combined population of over 1.5 million people, the aforementioned most diverse metropolitan area in the country, and the only significant research institution in the area, which means there would be little or no competition for enrolling subjects. This large population will be the ideal foundation on which the other components for the Foods for Health Initiative can garner baseline and longitudinal data including analytic and phenotypic assays and testing the economic impact of foods over the course of decades.

UCD Individualized Medicine Program, (Sacramento Nutrition Intervention Program; SNIP)

It is clear that individualized medicine is the "Wave of the future," however, before beginning such a venture, it is imperative that the appropriate infrastructure and networks are in place. It is envisioned that individuals participating in the UC Davis Health System will enroll in the "UC Davis Individualized Medicine Program." Investigators will be able to use state-of-the-art electronic medical records to gather information about individuals in the Program, after they have given consent and all privacy issues are addressed. That individual will then be entered into a cohort of other individuals in the Program to be established at UC Davis.

The Program will include extensive testing and phenotyping of these individuals to determine that particular individual's risk of disease or risk of having recurrent disease response to nutritional programs and treatments, etc. For example, an individual person's postprandial response to a given meal will help to stratify risk and guide dietary and pharmacological therapies for antherosclerotic cardiovascular disease. Thus, this

program, in collaboration with the healthy foods production, analytic/phenotyping and economic impact cores, will seek to define appropriate foods for the individual given their pre-existing genetic and lifestyle make-up.

Food Safety Core Support Unit

An essential step in the production of new foods is the evaluation of their safety. This of course includes development of new methods for the quantitative evaluation of pesticides, mycotoxins, and pathogens in food. The Food Safety Core Support Unit will provide guidance to investigators with respect to the different approaches that can be used to evaluate potential toxicity of the compounds and food, under study. The support unit will provide information on how compounds can be screened in a sequential manner, using a combination of in vitro assays, whole animal studies and human clinical trials. The Food Safety Core Support Unit will provide investigators with information on the type of data that they will need to be in compliance with FDA regulations concerning nutrition health claims.

Economic Core Support Unit

The Economics Core Support Unit will provide investigators an opportunity to have their projects evaluated at their onset with respect to the long-term economic viability and value of the end product they are aiming to provide. This unit will be available to provide advice on the potential costs associated with; the implementation of changes in agricultural practices and food processing; the production of the new food products; the projected costs of the new food product relative to foods already available in the market; the size of the market that may be available to the product; and the potential for economic return to producers at the different stages of production. This unit will also work to further the development of strong links between the campus and private industry.

Academic and Outreach Programs

Undergraduate Education

A "Foods for Health" minor would be attractive to students in a wide variety of majors. It is proposed that students who chose Foods for Health as a minor would need to take 12 units of upper division courses that would complement their major. As an example of the above, students whose major is Nutritional Science might take additional courses in Food Science (i.e. FST 103; FST 150; FST 140) that would add to their understanding of Food Chemistry and Food Processing; students in Food Science might take additional courses in Nutrition such as Nutrition 114, Nutrition 116AB, or Nutrition 112, courses that address nutrient-disease interactions and nutrition policy issues. Students in both majors might also consider taking additional courses in environmental toxicology or agricultural economics that focus on Food Toxicology, or the economics of health care, and the potential role of diet in reducing health care costs. Students in majors such as Environmental Toxicology, Agricultural Economics, and Pomology would be

directed to a set of courses that emphasize principles of Food Science, and of diet and health.

The key goal of the minor program would be to provide students from diverse majors an integrated picture of agriculture, diet and health. The expectation would be that students graduating with this minor would have a basic understanding of food from crop, to plate, consumption through metabolism. A capstone course for students in this minor would be a three-unit upper division honors level course that would discuss food and health from perspectives of public policy and ethics, economic realities, and evidence-based medicine with a focus on the potential role of diet in reducing the onset and progression of chronic disease.

Graduate Education

A four course series (2 units each) will be developed in the area of Foods for Health. The four courses will be focused on: a) public policy topics ranging from the ongoing GMO debate regarding their potential impact on public health to the evolving role of foods as medicine; b) metabolomics (topics ranging from the principles of metabolism to bioinformatics); c) diet and chronic disease (topics ranging from the role of diet in the prevention of disease, to diet-genome interactions); and d) economics (topics ranging from the social cost of health care to the need for enhanced value and competitiveness of American agricultural products). It is anticipated that graduate students seeking an emphasis in Foods for Health would take at least three of the above two unit courses, and they would do six units of graduate research (299 or 230) in a laboratory or facility outside of their primary graduate group. The training received through the minor should provide individuals with a broad, integrated understanding of the multiple dimensions to the design, production, testing, and economics of novel food products aimed at the optimization of health.

Outreach and Public Service

One component of the outreach and public service plan contained within the Foods for Health Initiative will be to establish a series of short courses and workshops. It is envisioned that the Foods for Health program, in conjunction with the RMI, CIFAR, and UC Cooperative Extension, will conduct short courses/workshops dedicated to building the knowledge of food and health of professionals in food production, food process design, industrial and institutional recipe development, and the culinary arts, applied to populations with defined nutritionally-related health problems. Consumers and professional chefs are increasingly faced with the problems of diet-restrictions and larger proportions of consumers are unable to choose normal foods and diets due to increasing constraints on their health. Responding to this need to match overall nutritional quality within restricted diets, the RMI will equip the next generation of food professionals to provide higher value food and dining options. Foods must match traditional preferences for structure, texture, taste and flavor while addressing the diet constraints that new health issues demand. Food professionals will need to obtain a greater understanding of nutrition, modern health issues, food labeling and the role of specific food ingredients in

food qualities, health and nutrition. The goals of the short courses/workshops will be to provide the academic training needed for the state and nation's professionals in the food and agricultural sector, to produce a continuously growing network of these professionals and to increase the visibility and influence of the University's Foods for Health program around the nation.

The instructors of the short courses will be drawn from the University of California, Davis and its extensive network of collaborating scientists, professionals and institutions. Courses could be hosted by the Robert Mondavi Institute in collaboration with partnering organizations, such as the Culinary Institute of America.

Depending on its reception, the described outreach program could evolve into a self-sustaining certificate program.

Competing Centers

The Foods for Health Initiative program at UC Davis can take advantage of the ongoing scientific and development programs around the world, particularly in Europe and Japan. A description of some of the larger established centers is given in Table 1. Few centers offer all that the UC Davis campus could. Some have capabilities and collaborators that UC Davis might partner with to form a multi-university center that includes disciplines not well represented at UC Davis. Although there is an equally long list of centers that focus on public health communications, including the Mayo Clinic, Harvard School of Public and Tufts, these were not included since that is an isolated function of a center. Some of these centers focus on government funding, and some on private funding, however none are exceptional at securing both. Centers that have a business element are best at securing broad private funding sources. The world wide research initiative in foods for health is taking various forms, but in every case the competitive position of domestic agriculture is a major theme of the research and its intended applications. The Davis Foods for Health Initiative similarly should seek to specifically enhance the health and quality of life of Californians, and the value and competitiveness of California agriculture.

The European union has established an aggressive scientific program on foods for health over the past 5 years. The successes of these initiatives have led, for example, to the inclusion of a major commitment to Foods for Health in the 6th framework program in which 600 million euros is dedicated to supporting scientific research in food quality and safety over the next 4 years. The major focus areas of the EU's initiative are to explore the epidemiology of diet-related health outcomes, the mechanisms relating diet to health, the analysis of commodities and traceability of foodstuffs through the agricultural chain, and the development of safer, more efficient, and environmentally friendly agriculture and food processing. In addition to European-wide initiatives, various national programs are investigating diet and health from the genomics of foods and consumers to the role of diet in the composition and health impact of the bacterial microflora. In all programs in European food research, there is a strong emphasis on networking with

national and international food industries to carry the research quickly forward into product innovation and health improvement.

The first organized regulatory framework for health value added foods was implemented in Japan with their FOSHU program. This regulatory framework stimulated a claim-based marketing atmosphere in the Japanese food industry joining the food industry and the academic community together to provide foods with claims: Foods for Special Diets; Foods for Pregnant or Breast-feeding Women; Foods for Infants; Foods for Aging Persons; Foods for Specified Health Use (FOSHU), which are foods that may improve specific health conditions. The result of this regulatory framework is a decidedly focused research environment in Japan in which industry and academia have studied foods and food ingredients from concept to product quickly and cost-effectively. To date over 250 foods have demonstrated health benefits using defined human clinical trials, and these foods have been granted FOSHU status. As a result, the Japanese scientific research environment is focused on human clinical demonstration of efficacy, rather than on extensive mechanistic research or altering food commodities.

Administration

The Foods for Health Initiative that is described in this proposal will involve multiple departments and colleges. Given the above, for the Initiative to be successful, the administrative leadership of the program needs to reflect the multiple components of the campus that we outlined in the proposal. It is proposed that a Director, Co-Director and Executive Advisory Committee be appointed to oversee and execute the Initiative. To firmly establish the broad college scope of the Initiative, it is suggested that Dean Van Alfen consider the appointment of an Associate Dean as the first Director of the Foods for Health Initiative. The Executive Committee should be composed of members drawn from the core facility support groups. The Executive Advisory Committee in consultation with the Dean should choose the Co-Director. It is recommended that the Co-Director receive 25% release time in order to ensure that they have adequate time to focus on the development and implementation of the Initiative.

Location/Space

The identification of space needs for the initiative is dependent on the portions of the outlined initiative that are adopted, as well as on the emendations to the initiative that will occur during its review. At present, it is suggested that consideration be given to the identification of one central administrative office for the Foods for Health Initiative. The Director, Co-Director and Executive Advisory Committee would use this office as needed. It would serve as the central point source for information concerning the Initiative. Given that a major goal of the Initiative will be to bring new extramural resources, including Center grants, to the campus, it is anticipated that the office will need to be supported by a 50% time administrative assistant.

With respect to laboratory space, while not essential to the initiative's success, the time with which success is achieved would be shortened by the identification of space

that could be dedicated to metabolomic and analytical core support units. The amount and location of the space needed for the above would be driven by a combination of the expectations of the facilities for the initiative, the establishment of appropriate recharge systems, and the amount of initial investment in equipment the campus is willing to make.

Costs

Administration: 25% release time for the Co-Director. 50% of an Administrative Assistant. $10,000 (year est.) for office supplies associated with the direction and implementation of the initiative.

Faculty

The cumulative strength of the faculty of UC Davis with respect to the type of programs described in this initiative are truly impressive. However, gaps exist in three key areas: Bioinformatics, metabolomics (particularly with respect to intermediary metabolism) and epidemiology. Future faculty recruitments in these areas would strengthen the campus position in the area of Foods for Health. However, the launch of this initiative should not be delayed until their recruitment.

Core Facilities

To a significant extent, the funding of the core facilities should be accomplished through a recharge system. However, initial start up funds will be needed toward the purchase of some instrumentation. Specific identification of the needed instrumentation and the associated costs will be done following agreement on the size and scope of the core facilities. However, as a guide it is estimated that for the metabolomic phenotyping infrastructure, year one expenses would be on the order of $100,000 (split equally between personnel and equipment); year two would be on the order of $400,000 (majority of funds to be used towards the purchase of a LC-MS/MSC TOF/TOF); and year three would be on the order of $1,000,000 (majority of the funds to be used towards the purchase of a dedicated 600 MTZ NMR with cryoprobe). In addition, start up, and maintenance, funds for supplies and equipment support will be needed for the core facilities. A modest amount of support past year one should also be available to ensure that investigators who do not have extramural funding during the initial phase of their work have an opportunity to use the core facilities to obtain the preliminary data/information they need to prepare competitive extramural grants.