HEALTHCARE

ADVANCED TECHNOLOGIES FOR PROTEOMICS, DATA INTEGRATION AND ANALYSIS, AND BIOMANUFACTURING FOR PERSONALIZED MEDICINE

Technology Innovation Program
National Institute of Standards and Technology
Gaithersburg, MD 20899

The Technology Innovation Program (TIP)[1] at the National Institute of Standards and Technology (NIST) was established for the purpose of assisting U.S. businesses and institutions of higher education or other organizations, such as national laboratories and nonprofit research institutions, to support, promote, and accelerate innovation in the United States through high-risk, high-reward research in areas of critical national need. Areas of critical national need are those areas that justify government attention because the magnitude of the problem is large and societal challenges that can be overcome with technology are not being sufficiently addressed.

TIP seeks to support accelerating high-risk, transformative research targeted to address key societal challenges. Funding selections will be merit-based, and may be provided to industry (small or medium sized businesses), universities, and consortia. The primary mechanism for this support is cost-shared cooperative agreements awarded on the basis of merit competitions.

AN AREA OF CRITICAL NATIONAL NEED

The proposed topic *"Advanced Technologies for Proteomics, Data Integration and Analysis and Biomanufacturing for Personalized Medicine"* is within the critical national need area of *Healthcare*. The topic was selected from a larger set of challenges in healthcare where transformative research could be expected to have large societal impact. The input regarding potential challenges in healthcare was obtained from government agencies and advisory bodies (such as the National Research Council, the National Academy of Sciences, and the Science and Technology Policy Institute), industry and nonprofit organizations, leading researchers from academic institutions and others.

Real-time, non-invasive technologies for evaluating and measuring proteomics in live tissues (e.g., *ex vivo* cultured tissues) and living systems (e.g., model organisms such as *C. elegans*, animal models, and human subjects) is a critical need for understanding how proteins are synthesized and how they function and interact in a live tissue environment. It is also important that this research be done in a cost-effective way. This transformative research will enable development of new biomarkers and next generation diagnostics and therapeutics. Most of the current proteomics research focuses on analysis of proteins in single cells and in extracts of cells and tissues. The multi-cell, multi-layer, functional environment in tissues and living systems makes real-time live tissue proteomics research a significant challenge. Novel tools and technologies are needed to detect protein synthesis and multiple protein interactions in their natural

environment which may involve novel path-breaking techniques or novel integration of existing techniques for developing stronger molecular probes and more sensitive imaging systems.

Although several data resources, such as genomic, epigenomic, proteomic and toxicogenomic databases, are being developed using Federal and non-Federal funds, novel data integration and analysis tools are needed to more accurately analyze and integrate the biological data from diverse databases and integrate it with patient history (or histories) and record (or records) while protecting patient privacy. This research may support or enable the development of safe and cost-effective personalized treatment strategies.

The future of personalized medicine also requires a change in the biomanufacturing paradigm including small production batches running in parallel or in a campaign fashion, use of smaller disposable bioreactors rather than traditional large fermentation tanks, automated closed production process, novel membrane adsorption strategies in place of traditional chromatography and short-term stability studies in place of long-term stability studies. New non-invasive sensing and monitoring technologies and product analysis techniques are needed for safe and cost-effective manufacturing of personalized biopharmaceuticals.

Clearly, high-risk high-reward transformational research and technological innovations are required to overcome these challenges within the critical national need area of *Healthcare*. Additionally, without the ability to develop cost-effective personalized diagnostics and treatments, the U.S. may lose these technological innovations to overseas competition. This white paper outlines an opportunity to conduct high-risk high-reward research for developing integrated platform technologies (enabling multi-use technologies) in three key topic areas within the critical national need area of *Healthcare*: 1) real-time, non-invasive proteomics in live tissues and systems; 2) analysis and integration of biological data from disparate databases with patient-specific data; and 3) cost-effective manufacturing of personalized biopharmaceuticals. The technological solutions to these need areas have the potential for a large societal impact on safe and cost-effective medical diagnostics and treatments as well as on other application areas beyond healthcare and personalized medicine such as biofuels, biodefense and agriculture.

MAGNITUDE OF PROBLEM:

Affordable and effective healthcare is fundamental to the nation's quality of life and important for future growth. Yet, escalating healthcare costs are a huge problem. The healthcare spending per capita in the U.S. is high and rising: $6,096 in 2004[2], $7,026 in 2006[3] and up to $7,900 in 2007[4]. As a proportion of gross domestic product (GDP), public healthcare spending in the United States (U.S.) is larger than in most other large Western countries.[5] Currently, the U.S. is already spending over $2 trillion annually on healthcare in the U.S. [6] The November 2007 report, *"The Long-Term Outlook for Healthcare Spending,"* by the Congressional Budget Office projects that without any changes in Federal law, total spending on healthcare will rise from 16 percent of the GDP in 2007 to 25 percent in 2025 and the Federal spending on Medicare and Medicaid will rise from 4 percent of GDP to 7 percent over the same period.[7] The 2007 data show that the U.S. spends 31 percent of its total healthcare budget on hospital care, 21 percent on physician and clinical services, and 10 percent on retail prescription drugs.

The U.S. also spends 7 percent of its total healthcare budget or $155.7 billion per year on administrative costs associated with the current third party payer insurance system.[8] Moreover, the 2008 report by the Commonwealth Fund stated, "in an era of medical care and advances, national investment in research regarding clinical and cost-effectiveness - what works well for which patients and when - has failed to keep pace to inform healthcare decisions,"[9] indicating the need for a personalized approach to safer and more effective healthcare.

Promise and Challenges of Personalized Medicine:

One way that "personalized medicine" is defined is, "a form of medicine that uses information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease."[10] Such information could be used to characterize the disease, select between different medications and or tailor their dosage, provide a specific therapy for an individual's disease, or initiate a preventive measure that is particularly suited to that patient at the time of administration.

Given the significant advances made and abundance of data generated through the pioneering Human Genome Project led by the National Institutes of Health (NIH) and the Department of Energy (DOE), and other programs such as "Tools for DNA Diagnostics" focused program funded by the former Advanced Technology Program at NIST, the field of personalized medicine is attempting to unlock the vast implications of genetic variability within the human organism to significantly alter approaches to new drug development, diagnostics and treatment regimens in the 21st century and beyond. Although the advances in understanding genetic variability have raised high hopes for a new era in the prevention and treatment of disease, the research has not yet satisfactorily translated into safe and effective personalized diagnostics and therapeutics.

Moreover, physicians typically do not have the detailed analyses of clinical study information needed to select optimal drug treatments and dosages on the basis of a patient's unique genetics, physiology, and metabolic processes which can result in a certain amount of trial and error to evaluating treatment approaches. Furthermore, currently approved drugs work only in a fraction of the population; as a consequence, dollars are spent on drugs that do not work for everyone. For example, a 2001 report suggested that on average, a marketed drug works for only 50 percent of the people who take it.[11] Additionally, a significant number of patients suffers from side effects from prescribed medicine. The September 2009 National Academy of Sciences report titled, *A New Biology for the 21st Century: Ensuring the United States Leads the Coming Biology Revolution,* further emphasized the need to apply a new biology approach to allow monitoring of each individual's health and treat any malfunction in a manner that is tailored to that individual.[12]

The pharmaceutical companies typically do not have tools and technologies to identify patients who will likely respond to a specific drug without experiencing adverse effects. Many times, a drug seems to work well in clinical trials with limited adverse effects but either additional or an increase in adverse effects are seen when the drug is approved for marketing. Between 1995 and 2005, about 34 drugs were withdrawn from the market[13] (and some of the adverse effects of withdrawn drugs may be related to individual genetic makeup). Many promising drugs never get approved because they cannot demonstrate efficacy in a large number of patients leading to many costly and

failed trials. It is estimated that the drug candidates entering Phase III clinical trials fail 50percent of the time.

Biopharmaceuticals is one of the fastest growing categories of healthcare costs. One of the reasons for the high cost of these products is high manufacturing cost and a long period of product development. Currently, the cost of biopharmaceutical development is about $1.2 billion/drug, and the development can take 8-15 years.[14] Current manufacturing processes are quite variable, and the cost of failed batches is a significant part of the manufacturing cost. A recent report indicated that on average a biopharmaceutical production facility experiences batch failure once every 40.4 weeks, or 9.4 months, and contamination was noted to be one of the primary causes of batch failure.[15]

The manufacturing of biopharmaceuticals is complex and costly, and is based on a large-scale process involving batching and frequent sampling to monitor the quality and safety of the production system. Personalized medicine requires multiple smaller size volumes of patient-specific biopharmaceuticals and thus needs a change in the biomanufacturing paradigm. More effective manufacturing processes with on-line monitoring and analytical strategies are needed for developing a cost-effective biomanufacturing process for safe and effective and affordable personalized diagnostics and therapeutics.

During a June 1, 2007 congressional hearing on the Food and Drug Administration (FDA)'s Critical Path Initiative,[16] the FDA Commissioner Dr. Andrew C. Von Eschenbach commented, "Despite the unprecedented increase in funding for biomedical research, both in the private sector and through Federal funding through the National Institutes of Health, this increased research has not translated into many new medical products being available in the medical marketplace."

Significant progress has been made with the investment of Federal agencies such as NIH and the National Science Foundation (NSF) in genomics, proteomics and related topics. However, many challenges still remain for developing an understanding of complex biological systems in wellness and disease states. For example, we still need to fully understand what specific genetic or proteomic information leads to disease mechanisms and how to prevent and treat diseases with that information. Understanding the connection between genetic and proteomic variations and disease states could provide earlier and more accurate diagnosis and targeted treatment. Such understanding will require significant additional investment in innovative high-risk high-reward technological advances to understand real-time protein function and interactions in living tissues and systems in order to develop cost-effective diagnostic tools and therapies for personalized healthcare. Moreover, the wellness and disease states result from a complex interaction between an individual's genetic makeup and the influence of environmental factors such as diet, exercise, exposure to toxins, and drug intake. Understanding the influence of these factors is also needed. Current approaches have typically focused on studying a few factors at a time. With the investment from NIH, databases such as genomic, epigenomic, toxicogenomic and proteomic databases are being developed and the technologies are being developed to measure the data on environmental toxins, dietary intake, and physical activity of individuals. However, to recommend preventive measures and safe and effective treatment for an individual, integrated data analysis of multiple factors will be required to link personal molecular biology to the environmental triggers. Such analysis will necessitate combining

disparate databases such as genomic, epigenomic, toxicogenomic and proteomic databases and linking the data to patient-specific data such as nutrition, diet, exercise, and environmental exposure such as exposure to cigarette smoke or asbestos.

The promise of personalized medicine, if fully realized, has the potential to significantly impact the nation's healthcare. However, significant challenges exist to the development of safe and effective personalized diagnostics and therapeutic approaches. Specifically, the challenges associated with understanding protein interactions in live tissue environment, data integration and analysis and manufacturing of biopharmaceuticals, if not addressed in a timely manner, could exacerbate the spiraling cost of healthcare as well as related losses in productivity, quality of life and U.S. competitiveness. TIP funded research could potentially lead to patient-specific diagnostics and therapeutic approaches with reduced undesirable side effects of treatments and hence unnecessary hospitalization, and doctor visits. The biomanufacturing innovations could reduce the cost of manufacturing and the costs of drugs for patients. Thus TIP funding has the potential to impact healthcare costs across the enterprise (i.e., hospital care, physician and clinical services, retail prescription drugs, and administrative cost of third party insurance).

MAPPING TO NATIONAL OBJECTIVES:

The TIP emphasis on platform technologies for advanced proteomics for linking genomic changes to wellness or disease states, data integration and analysis, as well as for biopharmaceutical manufacturing as societal challenges for healthcare for moving forward personalized medicine maps well to the national objectives, Administration guidance, and NIST's core competencies.

The Administration has clearly identified the need to enhance healthcare quality while reducing healthcare cost as a critical need. In his inaugural address, the President commented, "We … will wield technology's wonders to raise healthcare's quality and lower its cost." The Administration's primary goal is to improve America's competitiveness and employ science, technology and innovation to solve our nation's most pressing problems, which is also the primary focus of TIP. The Administration is also interested in advancing the biomedical research field by supporting investments in this field and improving coordination within government and the healthcare enterprise through unique partnerships.[17] Moreover, the FY 2011 R&D priority memorandum from the Office of Science and Technology Policy (OSTP) highlights the need to invest in biomedical science and information technology strategies to help Americans live longer, healthier lives while reducing healthcare costs.[18] In September 2008, the President's Council of Advisors on Science and Technology (PCAST) released, *Priorities for Personalized Medicine*, an objective look at the field that maps the barriers preventing its widespread adoption.[19] In this report, the PCAST recommended that, "In order to develop technology and tools that will allow for the advancement of personalized medicine, the Federal government should develop a strategic, long-term plan that coordinates public and private sector efforts to advance research and development relevant to personalized medicine."

In the FY 2009 priority memorandum,[20] OSTP identified a critical need for research to understand complex biological systems. The proposed TIP research emphasis on personalized medicine technologies for real-time, non-invasive proteomics in live tissues

and systems has the potential to generate knowledge to more fully understand complex biological systems.

In March 2007, the Department of Health and Human Services (DHHS), announced policies, investments and next steps for the DHHS Personalized Healthcare Initiative as a top priority. This initiative focuses on R&D in genomic and molecular medicine, adoption and networking of health information technology, accelerated development and use of evidence based care, and privacy and clinical decision support tools. In contrast, the proposed TIP emphasis is on platform tools and technologies for live tissue proteomics and data integration and analysis to complement the DHHS effort in evidence based care and clinical decision support tools.

In a 2009 address on the state of personalized medicine,[21] Dr. Francis Collins, formerly the director of the National Human Genome Research Institute (NHGRI) at NIH, commented, "*If we are serious about predictive medicine, and using personalized genomics to inform that we are not going to change the genome,… it's the environment we are going to want to change."* The milestones Dr. Collins expects to be achieved by 2015 are "*complete genomic sequencing for $1000 or under"* and identification of *"many more risks for heritable diseases and a growing number of targeted therapeutics."* The emphasis of the proposed TIP research on platform technologies for data integration and analysis could accelerate further understanding of gene/environment interactions in human populations.

In 2004, FDA published a document titled *Challenges and Opportunities on the Critical Path to New Medical Products*[22] to provide FDA's analysis of the pipeline problem relating to the recent slowdown in innovative safe and effective medical therapies reaching patients. FDA's analysis indicated that the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic research. The new science is not used to guide the technology development and downstream translational research in the same way that it is accelerating the discovery process. New tools are needed to get better answers about how the safety and effectiveness of new products can be demonstrated in faster timeframe with more reliability and lower cost. For example, a better biomanufacturing tool kit is needed to provide the infrastructure necessary for translating laboratory prototypes into commercial products. Specifically, novel process analytical technologies are needed for cost-effective scale-ups of biopharmaceuticals. The proposed TIP research emphasis on cost-effective biomanufacturing technologies has the potential to yield affordable personalized diagnostics and therapeutics.

Mapping to NIST:

The identified critical national need area of *Healthcare* contains several technical challenges associated with advanced proteomics, data integration and analysis and biopharmaceutical manufacturing for personalized medicine that map well to the NIST mission and complement the current and future NIST research. Measurements and standards for personalized medicine has been a priority of NIST research. In 2007, the NIST external advisory board, the Visiting Committee on Advanced Technology (VCAT) also recognized the importance of 21st Century Diagnostic Medicine or personalized medicine and recommended it as a priority for NIST.[23] The 2007 NIST U.S. Measurements and Standards (USMS) report[24] recommended technological innovations

for sensor-based proteomics, advanced DNA analysis, imaging technologies, and systems for lower cost diagnostics. The proposed TIP emphasis could accelerate technological innovations in sensor-based proteomics, imaging technologies and systems for low-cost diagnostics, key need areas that were identified in the 2007 USMS report.

In October 2008, NIST held a symposium on 21st Century Biosciences Innovation in collaboration with the University of Maryland, Baltimore County (UMBC).[25] The goal of the symposium was to get input from the stakeholders on challenges and measurement, science, standards and technology barriers to innovation for 21st century biosciences. Some of the key technological needs identified during the symposium include: 1) technologies to measure and track properties of cancer cells within a population of normal cells; 2) technologies capable of acting like global positioning system for intracellular components for conducting 3-dimensional biology research; 3) non-invasive measurements on systems such as embryo development; 4) better tools for measuring quiescent cells; and 5) biomanufacturing technologies for more effective upstream and downstream processing with associated measurements. The proposed TIP research emphasis on advanced platform tools and technologies for non-invasive proteomics in live tissues and systems, and on cost-effective biopharmaceutical manufacturing maps well to the technology need areas identified by the October 2008 NIST symposium. Moreover, the proposed TIP research emphasis on platform technologies for non-invasive proteomics will avoid sampling, a topic that stimulated significant discussion raising issues, such as sample integrity and sample-to-sample variability, during the October 2008 NIST symposium.

In 2009, NIST sponsored another symposium to discuss the *Future of Manufacturing Study* conducted by SRI International and to develop technology roadmaps on how NIST can support the manufacturing sector in 2020. [26] The presentations by SRI International highlighted several biopharmaceutical manufacturing challenges including: 1) process analytical technologies that can analyze the health of a production system and quality of the product in real-time, allowing efficient production; 2) efficient detection of harmful agents or other contaminants in real time; and 3) cost-effective production systems that can efficiently manufacture high quality product (e.g., bacteria, CHO cells). The proposed TIP emphasis on cost-effective manufacturing technologies for personalized biopharmaceuticals maps well to the biomanufacturing needs identified during the 2009 NIST/SRI International symposium.

NIST laboratory research:

Ongoing Research:
The March 2009 NIST document, *Measurement Challenges to Innovation in the Biosciences: Critical Roles for NIST*,"[27] and the May 2009 document, *Measurement Science, Standards and technology to Support Innovation in Healthcare*, [28] highlighted a total 2008 NIST biosciences investment of $41.3 million, of which, 34 percent ($21.5 million), has been invested in healthcare in the measurement and standards areas of diagnostics, drugs and pharmaceuticals, non-drug therapeutics (e.g. brachytherapy), and non-diagnostic medical devices. Additionally about $1.4 million has been invested in non-medical biomanufacturing measurement and standards. The NIST laboratories have also collaborated with FDA in the FDA Critical Path Initiatives related to the development of instrument calibration standards to encourage of process analytical

technology. The TIP emphasis on platform technologies for real-time non-invasive proteomics in live tissues and systems, data integration and analysis and biopharmaceutical manufacturing complements the current NIST laboratory research in measurement and standards for diagnostics, drugs and pharmaceuticals and biomanufacturing.

Proposed Research:
The proposed NIST investment in the May 2009 NIST document, *Measurement Science, Standards and Technology to Support Innovation in Healthcare*, highlights several future areas of NIST research in measurement and standards to enable personalized medicine and advanced diagnostics. The NIST 3-Year plan[29] includes a proposed investment of $10 million in measurements of biomolecules. The proposed TIP research emphasis on platform technologies for real-time non-invasive proteomics in live tissues and systems, data integration and analysis and biopharmaceutical manufacturing complements the proposed NIST laboratory research in measurement and standards topic areas such as biomolecule measurements in cells and blood, characterization of manufactured proteins and process validation and computational tools for image analysis, bioinformatics and network. The proposed TIP research could moreover accelerate the development of personalized diagnostics and therapeutics making affordable personalized medicine a reality.

MEETING A TIMELY NEED NOT MET BY OTHERS:

Although significant Federal investment has been made in healthcare and personalized medicine, currently several gaps exist. As indicated by the mission statements on the websites, the NSF is primarily focused on basic research in all fields of fundamental science and engineering, except for medical sciences, and NIH is primarily focused on fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to extend healthy life and reduce the burden of illness and disability. These agencies do not specifically focus on the development of high-risk high-reward platform technologies, a topic area that maps well to the mission of TIP and the overall mission of NIST. A gap analysis of current Federal investment in research on proteomics, data integration and analysis and biomanufacturing indicates that significant Federal efforts have been directed to developing physicochemical techniques (e.g. mass spectrometry, two-dimensional gel electrophoresis) for characterization of proteins in cells and extracts of cells and tissues, and identifying diagnostics based on genetic markers and biomarkers in cells, cell extracts and in serum and blood samples. However, investment is needed in developing cost-effective tools and technologies that would allow real-time non-invasive measurement of proteins and protein/protein interactions in tissues, organs and living systems. Moreover, as highlighted in the 2006 FDA Critical Path Opportunities list, the 2008 NIST symposium on 21st Century Biosciences Innovation, and the 2009 SRI International study, research gaps exist in developing a cost-effective biopharmaceutical manufacturing process. This is especially important for manufacturing of safe and effective and affordable personalized medicines using a real-time bioreactor monitoring.

SOCIETAL CHALLENGES:

Societal challenges are defined as problems or issues confronted by society that when not addressed could negatively affect the overall function and quality of life of the nation,

and as such justify government attention. The societal challenges that TIP is proposing to address are: 1) understanding real-time protein interactions noninvasively in complex biological systems which will enable real-time non invasive tracking of cells and cellular molecules in living tissues and systems; 2) integrated analysis of multiple factors allowing linking of personal molecular biology to the environmental triggers (such analysis will necessitate combining data from disparate databases such as genomic, epigenomic, toxicogenomic and proteomic databases and linking the data to patient specific data such as nutrition, diet and exercise); and 3) cost-effective manufacturing of diagnostic and therapeutic products for personalized medicine. Delays in addressing these challenges could negatively impact the safety and economic security of the nation. The specifics of each challenge are discussed below:

1) *Issues with Understanding Proteins and Protein Interactions in Live Tissue Environments and Hence Fully Understanding Complex Biological Systems:*

The key to how an individual's response to therapeutics differs from the response of others is in the genetic variability that creates the differences between people and their susceptibility to diseases as well as their responses to drug treatment. Typically, variability lies in 0.1 percent of the three billion bases of DNA that vary from person to person. The past and present U.S. genomics research and initiatives led by NIH such as the NIH $1,000 Genome Initiative and Epigenomics Initiative have resulted in an abundance of data. Our ability to measure and sequence genes and genomes may allow us to obtain full sequence data for a few thousand dollars within next few years. We can currently measure gene expression on a large scale using DNA microarray technology pioneered by other Federal programs such as the former NIST Advanced Technology Program's "Tools for DNA Diagnostics Program." [30] However, major challenges still remain to fully understand complex biological systems in wellness and disease states. For example, we still need to discover what specific genetic information leads to disease mechanisms and how to prevent and treat diseases with that information. Understanding the connection between genetic and proteomic variations and disease states could provide earlier and more accurate diagnosis and targeted treatment. Such understanding will require significant additional investment in research and technology to elucidate the molecular underpinnings of disease and the development of diagnostic tools and therapies for personalized healthcare. The Institute of Systems Biology[31] has identified key challenges and needs for tools for obtaining digitized information on cellular contents as evidenced by the statement on the Institute's website:

> *A requirement of systems biology is that to specify systems, millions of measurements must be made … These measurements must identify, quantify, and characterize component variations (e.g. mRNA splicing or protein processing or modification, localize, measure turnover rates…)… development of measurement tools … will lead to the digitalization of biology … obtain content of single cells. We must also develop powerful and sensitive molecular imaging techniques to characterize molecular behavior in vivo …*

Among the analyses of cellular components, the analysis of proteins is much more complex than DNA or RNA due to distinct physicochemical properties of each protein and wide dynamic range of protein expression. Moreover, each protein can express different post-translational modifications that further add to the complexity. Two

current technologies that are widely used in proteomics research are 2-dimensional gel electrophoresis that is quantitative and accurate but may not be sensitive and mass spectroscopy which is sensitive and accurate but may not be quantitative. Although extensive efforts have been spent on studying proteins, so far only a few thousand proteins, of potentially several thousands of predicted protein targets have been assigned functionality. Thus, many more potential protein targets may be missing from the drug discovery and development arena. In living tissues or systems, cells are dynamic and changing and responding to cues from other cells and their environment. However, most of the current knowledge of cells comes from single cell analysis and analysis of cell and tissue extracts. Real-time evaluation of proteins, with their attributes such as correct folding, post-translation modifications, subcellular localization, and interaction with other proteins in live cell systems and tissues is a challenge using current technologies. The September 2009 National Academies of Sciences report, *A New Biology for the 21st Century*, [32] highlighted the need for technologies to analyze the cell's complicated internal protein complexes as they are forming, working and disassembling. Furthermore, as indicated by one speaker at the U.S. Human Proteome (HUPO) meeting in San Diego CA, February 22-25, 2009, current proteomics technologies are expensive and not affordable for many researchers studying proteins. Thus, novel cost-effective proteomics technologies are needed to allow all the researchers including biologists and clinicians to study and understand proteins and protein interactions in the wellness and disease states in humans.

High-risk high-reward research is needed for developing technological platforms for real-time non-invasive protein detection in living tissues and living systems. Specifically, transformational technological advancements are needed to develop an integrated approach involving stronger molecular probes that can be detectable in living tissues or systems by external imaging modalities and imaging technologies that are sensitive enough to detect signals from labeled proteins in tissues. Novel sensitive platform technologies are needed to non-invasively evaluate interactions of multiple proteins in important cellular pathways such as the apoptosis pathway, sinuclein pathway, or proteolytic pathway, each of which may be critical in understanding several disease states. This research would enable understanding of protein signatures in wellness and disease states and subsequently the development of personalized diagnostics and therapeutics. The research in addition may allow tracking of cells in the body and identifying cells that deviate from their normal behavior. For example, identifying cells in tissues that are in their precancerous state or tumor cells that are ready to migrate to a new site in the body is critical for developing effective personalized treatments. The research could also enable detection of viruses in the host and further the development of biodefense agents and as well as vaccines and therapeutics for plant and animal diseases.

2) *Issues with Data Analysis and Integration for Development of Personalized Treatment Strategies:*

Wellness and disease states result from a complex interaction between an individual's genetic makeup and the influence of environmental factors such as diet, exercise, exposure to toxins, and drug intake. Current approaches have been typically focused on studying a few factors at a time. With the Federal investments, data resources such as genomic and proteomic databases are being developed and technologies are being developed to measure environmental toxins, dietary intake,

and physical activity of individuals. However to recommend preventive measures and safe and effective treatments, an integrated analysis of different data sets will be required. Such analysis will necessitate combining data from disparate databases such as genomic, epigenomic, toxicogenomic and proteomic databases, and linking it to patient specific data such as nutrition, diet and exercise. The Institute of Systems Biology[33] has identified key challenges and needs for data analysis tools for accurately integrating and analyzing biological data as indicated by the following statements on the Institute's website:

> *Systems biology research suffers from having... too much data… The volumes of data generated… present two challenges 1) Data space is finite, hypotheses must be carefully formulated to search data space 2) Most large datasets are replete with technical and biological noise, or various types of systematic errors… The integration of global datasets from different laboratories may represent serious challenges …*

Specific challenges in combining data across different platforms include use of different procedures and time periods for collection, organization and storage of data which may require data normalization and statistical adjustments for multiple sample testing. Moreover, important information necessary to decipher data semantics, such as context, may be missing. For example a query may identify relevant datasets labeled with the term metastasis. However, metastatic processes could be different among different tissues and may require tissue information to avoid errors in dataset selection. Lack of such information could lead to errors in data integration and pose challenges in developing a rule-based computational procedure. [34] [35] The current toolbox does not include algorithms and computational tools necessary to accurately analyze data from multiple molecular biological databases, each of which may have biological data errors, while integrating those data with patient-specific data and protecting patient privacy. There is a need for high-risk high-reward research for developing information technology platforms that could potentially enable integration and analysis of disparate data sets not only for personalized medicine but for other application areas such as food safety and biodefense.

3) *Issues with Cost-effective Manufacturing of Biopharmaceuticals for Personalized Medicine:*

Personalized medicine requires a change in the biomanufacturing paradigm including small production batches running in parallel or in a campaign fashion, use of disposable bioreactors rather than fermentation tanks and automated closed production process, membrane adsorption strategies in place of the traditional chromatography techniques and short-term stability studies in place of long-term stability studies. Although some progress has been made in remote sensing technologies for bioreactor monitoring, investment appears to be lacking in key enabling technologies for an automated high-throughput and cost-effective biomanufacturing process for simultaneously producing multiple safe and effective patient specific biopharmaceuticals. Such technologies will require an on-line monitoring of multiple bioreactors for safety, quality and consistency of production runs without introducing cross contaminations. Moreover, research efforts appear to be lacking in developing cell-free production systems that could replace live cell and bacterial production systems, developing self correcting production systems, and developing tools for rapid on-line detection of contaminants (foreign DNA, proteins,

protein aggregates, endotoxin) in production runs. Furthermore, technologies are not available for rapidly predicting immunogenicity of biopharmaceuticals during production runs and tools for on-line monitoring of the specificity of biopharmaceuticals such as antibodies. Unfortunately, current biopharmaceutical manufacturing processes for cell-scaffold products do not allow for accurate on-line, real-time, non-destructive analysis of product for safety and quality. Technological innovations requiring high-risk, high-reward transformational research are needed to overcome these challenges. The TIP investment in high-risk high-reward research to enable platform tools and technologies in these areas could accelerate the development of a safe and cost-effective biomanufacturing process for personalized diagnostics and biotherapeutics. The tools and techniques developed could also enable cost-effective manufacturing of other biologically derived products such as biofuels, biodetergents, and agricultural products.

SUMMARY:

The societal challenges proposed to be addressed within the critical national need area of *Healthcare* reflect areas of investment where existing efforts are disparate and Federal government leadership is necessary to accelerate advancements. Private funding is not available due to technical and business risks associated with this effort. Investment in personalized medicine represents an opportunity for TIP to have broad impact that crosses many industry sectors - existing and new. As indicated by the stakeholders in public meetings and in white papers submitted to TIP, the Small Business Innovation Research (SBIR) funds are insufficient to accelerate research on high-risk high-reward technology platforms. No agency is funding significant amounts in development of advanced platform tools and technologies for the three areas: 1) non-invasively monitoring proteins in living tissues and systems in real time, 2) data integration and analysis, and 3) more effective biopharmaceutical manufacturing for personalized medicine. Addressing these societal challenges will impact healthcare by lowering primary treatment costs, pharmaceutical development costs, clinical trial effectiveness and costs, diagnostic efficiency, and biopharmaceutical manufacturing as well as enable cost-effective manufacturing of biofuels, plastics and agricultural products.

A TIP program in advanced technology platforms for these three areas supporting personalized medicine would result in cost-effective solutions that could lead to : 1) earlier disease detection; 2) optimal therapy selection; 3) fewer adverse drug reactions; 4) better patient compliance with therapy; 5) new and better targets for pharmaceutical and biotechnology drug development; 6) faster, less expensive, and more efficient drug trials; 7) the ability to use a wider range of drugs; 8) fewer withdrawals of marketed drugs; and 9) reductions in overall healthcare cost.

In addition the research could impact: 1) imaging individual metastasizing cells before the cell develops into secondary tumors, saving the lives of those who die each year of metastatic cancer; 2) monitoring of military personnel in the field in foreign countries, in real time at the single molecule level to prevent exposure of biological weapons before clinical symptoms develop; 3) additional drug discoveries based on newly discovered targets; and 4) preventing many diseases (e.g. viral, cardiovascular, oncologic, autoimmune, or epigenetic) through earlier disease detection.

The TIP investment in non-invasive sensing and analysis technologies for proteomics and biopharmaceutical manufacturing may lead to non-invasive point-of-care diagnostics that avoid sampling and the associated issues with sample integrity and stability, and sample-to-sample variability.

The TIP research emphasis also complements the R&D investment by other Federal agencies such as the National Cancer Institute (NCI)'s Clinical Proteomic Technologies for Cancer Initiative (CPCT), and the National Heart Lung and Blood Institute's (NHLBI) Innovative Proteomics Centers Initiative and the Production Assistance for Cellular Therapies (PACT) Program, the National Institute of Biomedical Imaging and Bioengineering's Biomedical Technology Resource Center Program and the NIST research in measurement science and standards in personalized medicine.

Potential participants, including small and medium size companies, universities, national laboratories and other organizations, have indicated interest in the challenge areas and have capabilities and relevant experience to conduct high-risk high-reward research in: 1) tools for non-invasive, real-time live tissue and systems proteomics; 2) data analysis and integration tool development; and 3) tools for safe and cost-effective biomanufacturing process. TIP has received a number of healthcare-related white papers that indicate that technologies for advanced proteomics, monitoring of cells in live tissues, data integration and analysis, and biomanufacturing are societal challenges of high priority within the critical national need area of *Healthcare*.

REFERENCES

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