Critical National Need Idea Title:

Label-Free Robust Inexpensive Devices for Personalized Medicine and Diagnostics

"The convergence of scientific opportunity and public health need represented by personalized medicine warrants significant public and private sector action to realize the development of a promising class of new medical products"

"Priorities for Personalized Medicine", President's Council of Advisors on Science and Technology Report, 2008

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SUMMARY

The current economic crisis has limited the public and private funding of technological innovation that will be required to make personalized medicine a reality within the next decade. This document describes a critical need for additional government funding for the development of highly advanced, label-free, user-friendly, multiplexed, inexpensive medical diagnostic devices for use in personalized medicine. This paper outlines administration guidance, reviews existing market players, and provides an example of a promising label-free detection technology for personalized medicine diagnostics that will benefit from government funding in addition to yielding benefits in other areas of unmet medical, environmental, agricultural or military needs.

LINK TO ADMINISTRATION GUIDANCE AND JUSTIFICATION FOR GOVERNMENT ATTENTION

Recently, the President's Council of Advisors on Science and Technology (PCAST) unveiled a proposal to study personalized medicine (PM) and clearly affirmed the importance of PM to the national interests of the USA [1]. PCAST defined personalized medicine as "*the practice of tailoring medical treatments for patients based upon their individual responses to specific drugs*".

PCAST recognized the tremendous value of PM for potentially dramatic reductions in health care costs and increasing the quality of life while emphasizing significant challenges remaining in introducing PM in everyday medical practice. Among challenges cited were the lack of *cost-effective tests and diagnostic instruments*, potential for "*regulatory delays* with complex tests/therapies", and "*disincentive for innovation* for increasingly smaller markets".

On a technical level, broad implementation of many aspects of PM will require the introduction of a new class of inexpensive diagnostic instruments that do not require time-consuming sample preparation. Ideally, such instruments could be operated in a doctor's office by unsophisticated personnel. Currently, a number of devices are in development but a significant investment will be required to bring these promising new technologies to the market.

On the implementation and funding level, challenges such as the anticipated regulatory delays and disincentive for investments in niche, high risk markets diminishes the likelihood that a small business will be able to secure adequate venture capital that will be required to advance novel technologies. Indeed, as documented in [2], advancing PM will require a complex interaction between governmental, academic, and industrial organizations, which is impossible to achieve under just public sector financing, especially in the current economic climate.

Nature of the Problem

Rather simplistically, when determining the impact of a particular drug treatment in a given patient, it is possible to gather biological data on a molecular level by evaluating the concentration and interactions of specific biomolecules in the patient's body (RNAs, DNA, proteins, etc) in addition to quantifying trace amounts of the drug molecules. The high levels of sensitivity that are required for such measurements are commonly achieved by directly tethering one of the interacting molecules with a fluorescent, enzymatic or radioactive marker. Light or radiation emitted by such labels can then be detected with well-established methods.

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While techniques and instrumentation that rely on labeling are progressively becoming more common place in research institutions, they will likely be prohibitively impractical for use in the clinic for the following reasons:

- Significant amounts of time will be required for sample preparation
- High cost of reagents and instruments will limit use
- Complicated operating protocols will require sophisticated users/operators

A second fundamental problem with the direct labeling of a biomolecules is the risk of assay artifacts due to heterogeneous conjugation that may result in an inherently nonquantitative measurement. Additionally, researchers have demonstrated that the presence of a fluorescent label can have detrimental effects on the affinity of an antigen-antibody interaction which is the basis for many of the biosensors currently in development.

The widespread application of PM will require multiparameter biomolecule detection technologies that are more sensitive, simple to operate, and less expensive than what are currently state of the art. Several novel small footprint label-free affinity sensors are in various stages of development and have the potential to close this gap and facilitate clinical diagnosis and improved disease management. Advancements in label-free sensing technologies will also allow for broader applications in the areas of protein-protein interaction studies, infectious disease detection, biowarfare pathogen detection, protein-drug interactions, vaccine development, food safety, detection of chemical pollutants and the like.

> **Medicine will eventually be transformed from an instinctive art of alleviating symptoms to a science of personalized health care…. The role of government is to create a platform that allows all the elements a personalized health care industry needs to flourish.**
>
> ***[3]*** *ALEX AZAR, Former Deputy Secretary of Health and Human Services*

Outcomes of Success

- Development of a new class of inexpensive instruments that assist in the early accurate diagnosis and personalized treatment of cancer, autoimmune, cardiovascular, infectious, and other inflammatory diseases and metabolic disorders such as diabetes or Alzheimer's.
- Tremendous cost-savings resulting from early diagnostics and improved treatment of such diseases
- Advancements in science, medicine, and technology originating from adoption of the new class of diagnostic devices in research labs and industrial settings
- "Spill-over" of technological advances to other areas of science and technology

Evidence of Commitment

A number of small and large companies and academic organizations are focusing their research and development efforts in the area of label-free diagnostics. The first widely adopted label-free commercial instrument was introduced by Biacore almost a dozen years ago. Biacore (now a division of General Electric) currently offers several instruments that range in price from $200K to $700K and BiOptix Diagnostics Inc, 2009

require expensive consumables (~$400 per test cartridge), a large footprint, and extensive operator training.

Several smaller companies are currently offering and/or developing new, small and inexpensive label-free biodetectors. Among these companies are Axela, ForteBio, Maven Technologies, and BiOptix Diagnostics. In academia, notable investigators in the field of label-free biosensors include Dr. Robert Corn (Professor, University of California at Irvine) , Dr. David Myszka (University of Utah, Director, Center for Biomolecular Interaction Analysis), and Dr Rosina Georgiadis (Associate Professor, Physical and Analytical Chemistry of Interfaces, Boston University). If a solicitation related to advancing the development of label-free inexpensive diagnostic devices is issued, is likely that these companies and academic groups will submit proposals.

While several label-free biodetectors are already on the market, the costs of these commercially available instruments are prohibitively expensive, thus making widespread adoption of the technology for PM unrealistic. Additional drawbacks for using these available devices for personalized diagnostics is the lack of sensitivity, limited multiplexing capabilities, and difficulty of use in a clinical setting. NIST funding, if provided, will widen the playing field and allow other potential players to advance their promising approaches and ideas, thus increasing the likelihood of a success in the pursuit of rapid, inexpensive diagnostic tool for diagnosis and disease management.

ESSENTIALS FOR TIP FUNDING

As a company built on the idea of bringing an inexpensive label-free diagnostic device to the market, BiOptix performed extensive market research and attempted to secure funding from almost a dozen well-known national venture capital groups. The feedback we received was that while our technology was impressive, it was viewed too risky because it would require FDA approval and many years before the investors would see a return on their investment. It is likely that other companies with devices similar to ours have suffered the same financial setbacks given the slow growth of this particular industry.

TIP funding would enable parties involved in exploring additional avenues of research with an expedited time line. This will open additional market opportunities in parallel and benefit the economy significantly earlier than via organic growth and serial market expansion, and prime the company for future venture capital support and commercialization funding.

Given the abovementioned points, we strongly believe that NIST funding is critical for advancing the state-of-the art technology in the area of real-time, label-free biodetection and bringing small, inexpensive, sensitive diagnostic instruments rapidly to the market.

ASPECTS OF SCIENCE AND TECHNOLOGY INVOLVED

As mentioned previously, a number of companies are currently developing promising technologies suitable for use in label-free, inexpensive, diagnostic devices. Moreover, in such a broad area as PM, it is likely that different areas of diagnostics will be served by different market players. It is not the objective of this white paper to review or prioritize these technologies. Instead, this document aims to emphasize the need for government intervention and enhanced funding in the area of developing inexpensive diagnostic devices regardless of a particular technology, company, or academic organization involved.

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Despite the fact that there exist several competitive technologies for fast label-free detection, most of them fall under the definition of *affinity sensors* and share the following attributes:

- Detection of biomolecular interaction involves immobilizing one molecule on a surface and bringing the sample in contact with the surface
- If molecular interaction occurs, micro properties of the surface layer change, as target molecules are now attached to the capture molecules immobilized on the surface
- Changes in the surface properties are detected by various optical techniques

Given the described commonality of most label-free detection technologies, a solicitation aiming at stimulating this area should include provisions for the following:

- Development of new surface chemistries for immobilization of the capture molecules
- Optimization of the surface properties of the sensing elements
- Additional assay development
- Development of advanced optical detection methods and optical elements

Clearly it would be impossible to discuss every "label-free, multiplexing, ultrasensitive" diagnostic instrument that is currently available. Therefore, we have included one example of a novel label-free detection technology and prototype diagnostic instrument that is under development by BiOptix Diagnostics Inc. Additional discussion provides an overview of the fundamentals of Surface Plasmon Resonance enhanced Common Path Interferometry in addition to the hurdles that we face in bringing this instrument to commercialization.

"If label-free techniques are required at all cost, then combining SPR with interferometry techniques offers the best route for competing with luminescence techniques for biomolecule sensing."[5]

From: R. Ince, R. Narayanswamy, "Analysis of the performance of interferometry, surface plasmon resonance and luminescence as biosensors and chemosensors," *Analytica Chimica Acta*, 569, 1-20, (2006).

Surface Plasmon Resonance enhanced Common Path Interferometry (SPR-CPI) is a potentially market-disruptive technology for biomolecule interaction analysis invented by the BiOptix team, including 2005 Physics Nobel Laureate Dr. John Hall.

Measuring refractive index changes at a surface by comparing phase shifts between two orthogonal polarizations contained in a single sensing laser beam enables a label-free microarray detection method that breaks new ground in terms of sensitivity, operational cost, performance, flexibility and durability. It is expected to serve many markets and make a significant impact for both commercial and governmental customers by providing previously unattainable levels of analysis sensitivity in a simpler, higher throughput microarray based analysis platform.

The SPR-CPI concept has sound theoretical justification and preliminary data has been obtained, but sufficient venture capital funding has not been secured because of perceived technical risk and extended commercialization time lines. In the case of BiOptix Diagnostics' biodetector, additional funding is needed in order to improve a number of aspects of the technology described below.

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Perhaps the most important task is to increase the number of sensing spots on the microarray sensing elements with consideration given to low instrument cost and ease and reliability of manufacturing. Currently the instrument uses 2x2 microarrays allowing for simultaneous detection of up to 3 targets with one reference channel. Our market research indicates that medium density arrays, with about 100 (10x10) sensing spots are needed in many areas of diagnostic and drug treatment optimization.

Potentially insurmountable problems can arise with precise optical alignment of two photo detectors in the instrument – one for each polarization – and the microarray sensing spots when using such medium density arrays. The BiOptix engineering team in collaboration with Dr. Glushchenko has identified a novel solution to this problem that allows utilization of a single detector, thus dramatically simplifying the alignment and guaranteeing manufacturability. This solution relies of modulating the laser beam with a very fast switching liquid crystal retarder (LCR). Such retarders could be built using ferroelectric nanoparticles (~10 nm).

This new liquid crystal technology will advance the development of unique optically transparent polymer/ liquid crystal composites, addressing the need for a fast switching of a large amount of phase retardation required for the fabrication of modern adaptive optical elements. This technology utilizes a combination of two recently discovered technologies: stressed liquid crystals and diluted colloids of inorganic ferroelectric nanoparticles (~10 nm) in nematic liquid crystals. The stressed liquid crystals comprise interconnected microdomains of a liquid crystal dispersed in a sheared polymer structure. The shearing deformation imposes a unidirectional orientation of the liquid crystal, providing some of the optical transparency in visible, and greatly reducing the switching time of the materials. The large local electric fields associated with ferroelectric nanoparticles drastically affect the liquid crystal order, which should provide even more optical transparency to the entire system.

The development tasks involved in introduction of such new nanoparticles-based liquid crystals include: 1) incorporation of ferroelectric nanoparticles into a high birefringence liquid crystal, 2) design and fabrication of stressed liquid crystals doped with ferroelectric particles, 3) demonstration and optimization of the main electro-optical properties of the new materials, 4) development of a theoretical model defining the interaction of ferroelectric particles with a liquid crystal material in polymer confining geometries, and 5) characterization of the materials' performance in a variety of optical devices and their relationship to the intrinsic properties of the materials used.

Figure 1. Working prototype of label-free, highly-sensitive, rapid biodetector developed by BiOptix Diagnostics Inc.

Expected New Outcomes and Capabilities

Once the above research goals are achieved, the potential for multi-faceted commercial success is high. SPR-CPI is intended to be deployed as a platform technology that is compatible with almost any application where biomolecular interactions are measured, including PM. The technology's key benefits are its multiplexed microarray capability with high sensitivity, low cost, small size, and robust design, which compared to other contemporary detection methods, will enable entry into many market segments that are currently poorly served.

The fields of science that will benefit from this multidisciplinary project include physics, optics, chemistry, and biochemistry, as well as industrial research, drug discovery, diagnostics.

Development of nanoparticle-based fast switching liquid crystal retarders needed for medium density label-free diagnostic microarray device will also have utility in a variety of commercial and military photonic systems including micro phase arrays, changeable focus lenses, phase retarders, and beam steering devices. The materials are enabling to other emerging industries dealing with adaptive optical technologies. In general, this part of the project addresses the needs of the optical industry, which is an important aspect of the US commercial economy and will play an increasing role in the US as well as world society.

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