POLICY FORUM: BIOMEDICINE

The NASA-NCI Collaboration on Biomolecular Sensors

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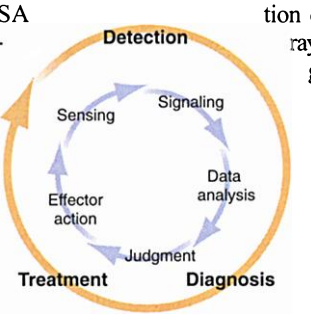
A collaboration between the National Aeronautics and Space Administration (NASA) and the National Cancer Institute (NCI) may seem like a joining of two very different disciplines. However, the NCI and NASA have recognized mutual objectives where partnering could significantly expedite technological advances critical for the success of their respective missions. The NCI's need is for technologies that can couple minimally invasive sensing and signaling of early molecular signs of cancer in patients and that will have the capability for controlled and monitored intervention. NASA's requirements are for monitoring and maintaining the spacecraft environment, remote sensing of life on distant planets, and for diagnosis and treatment of injury and emerging disease in astronauts during long-duration space missions. Development of these future sensors/systems will require advances in miniaturization, sensor development, signal amplification, data mining, and bioinformatics, as well as fundamental biology.

Toward this end, NASA and NCI proceeded from signing a Memorandum of Understanding (MOU) in April 2000 to developing a program to promote and support biomedical and technology research together. NASA and NCI sponsored a Collaborative Working Group on Biomolecular Systems and Technology (*1*) that was used to provide a framework for the program. NCI and NASA plan to invest $80 million over the next 4 years in this program. Thus, the Broad Agency Announcement released on 8 January 2001 was crafted to enable each agency to select and fund investigator-initiated proposals as grants or contracts (*2*). Although funding will originate with one or the other agency for a given investigator, the scientific portfolio so established will be considered as one, integrated program. The NASA and NCI program managers will work closely together to promote joint management, information sharing, and the success of the agency-specific and joint programs. Although NASA and NCI will continue to promote related research and technology innovation within our existing programs (such as NCI's Unconventional Innovations Program and NASA's Cellular and Molecular Biotechnology Program), this new venture will place emphasis on multidisciplinary collaboration in combination with committed expertise from the physical sciences or engineering, as well as an appropriate area of biomedical research. Collaborative management will include joint review of progress reports, joint development and attendance at principal investigator (PI) meetings including PIs from related programs, cost sharing of meetings, and joint site visits.



Biosensors. NASA and NCI target the development of biosensors that will function within the living body to link capabilities for (i) sensing the earliest molecular signatures of disease, (ii) generating a detectable signal that will relay the sensed profile, (iii) providing suitable data for analysis, (iv) supporting a decision-making process to establish next steps, and (v) effecting an action appropriate for the detected signature.

As stated in the announcement, "Proposals are expected to project innovation beyond the range of research traditionally supported through the NIH investigator-initiated research support process and existing NCI and NASA programs." The announcement represents our commitment to explore approaches that might be considered high-risk under traditional funding mechanisms.

New technologies, such as expression array profiling, have offered the possibility that the complete spectrum of macromolecules and processes can be analyzed simultaneously. Early indications suggest that analysis technologies working at a scale representing the entire complement of the genome will yield information about disease and biology that more accurately reflects the complex workings of cells and tissues than conventional technologies that target individual genes or gene products. To make dynamic measurements and analyses and to manipulate macromolecular processes in the living body will require creating tools that function unobtrusively in the nanoworld of the cell. Central to the development of such tools is the creation of biosensors that can link capabilities for recognizing macromolecular constituents of the cell, sensing the presence of defined signatures, generating an identifiable signal, serving as the platform to introduce an intervention, and monitoring the real-time impact of intervention on targeted molecular processes. Currently, our ability to use molecular markers to detect disease states is in its infancy. Ideally, biosensors will be used to monitor human physiology and to detect, diagnose, and treat cancer, pathology resulting from injury or illness, and radiation damage from galactic cosmic rays. New computational strategies and information technologies are being developed that could support creation of dynamic, responsive systems capable of monitoring macromolecular processes.

The program will support the development of components, as well as the integration of the components into a fully integrated, multifunctional platform. The biosensors will provide the basis for a continuous informative feedback loop that will monitor not only the presence and progress of the disease, but also the efficacy of the intervention and the ability to modify the intervention protocol in real time. The integration of new capabilities for sensing at nanoscales and dynamic information collection and analysis coupled to our rapidly expanding understanding of the molecular workings of cells make this a time of unique opportunity for promoting research toward our common goals.

NASA Goals and Requirements

As exploration missions leave Earth's orbit and head to Mars and beyond, evacuation to Earth and instant communications with ground personnel become impossibilities. Effective clinical care on long-duration missions will require advanced, accurate, on-board diagnostic equipment or systems capable of autonomous intervention. At the same time, NASA requires advanced information systems to handle data acquisition, processing, and evaluation to support essential on-board diagnostic and therapeutic functions. Continuous on-board health monitoring at a macro- and microcellular level will be essential for early detection of disease and radiation damage, as well as to evaluate countermeasure effectiveness.

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This will pose many fundamental problems. For example, when a human being, who is adapted to function within Earth's gravity field, experiences microgravity conditions, every system of the body studied to date undergoes changes as it adjusts to its new environment.

Medical care in low Earth orbit is based on immediate access to a trained health evaluator on board the space vehicle, medical experts available by telemedicine procedures, diagnostics and therapeutics similar to those in most physicians offices, regular health monitoring during and after long-duration missions, and the ability to return an ill astronaut to a tertiary-care medical facility within several hours after a decision is made that such intensive therapy is warranted. In contrast, medical care for missions beyond Earth orbit must allow on-board, regular health-care monitoring; diagnostic equipment designed to meet spacecraft mass, volume, and power limitations; larger and diversified therapeutics availability; and the facilities of a tertiary-care hospital, including health-care providers.

Another priority is the development of biological and biomimetic autonomous spacecraft systems. Biomimetic systems bring a unique set of characteristics to any system (*3*, *4*): They can be adaptive, anticipatory, collaborative, curious, guided, self-modeling, and self-repairing. These systems will provide spacecraft and equipment with the ability to perform ultrareliable high-level functions, including some limited decision-making, with minimal human intervention.

A critical element in the exploration of our solar system, and one of NASA's primary strategic objectives, is the search for life. The ability to detect life outside of our own planet will rely, in part, on remote sensing of molecular signatures and processes that signal biological activity. In order to find signals of life, we need technologies that distinguish cellular processes and signals at molecular levels, imaging and signal-acquisition techniques to detect faint signatures of life, and information systems to handle the data acquisition and processing, as well as hypothesis generation and testing. The ability to detect and to identify life forms will rest on our thorough understanding of biological processes and signatures on our own planet.

NCI Goals and Requirements

Currently, the diagnosis of cancer usually follows detection of a mass that is palpable or resolvable by anatomic imaging, frequently many years after the earliest stages of cancer development. It is based on gross changes in size and shape of tissues and cells, rather than fundamental changes in the molecular processes that underlie development of disease, resulting in inadequate discrimination of the many types of cancer. Specificity and effectiveness of treatments could be dramatically improved if they were directed toward critical changes in molecular processes that result in the cancer phenotype. Beyond this, earlier detection of fundamental changes associated with cancer development, coupled with interventions targeted at critical molecular processes, could enable a new era focused on prevention.

The NCI is currently investing in a future where cancers are prevented, detected, diagnosed, and treated on the basis of the fundamental changes in molecular profiles and pathways of the specific disease. Current programs are attempting to define the expressed gene products of the human genome, identify mutations and polymorphisms in genes critical to the development of cancer, discover sentinel biomarkers of the early presence of disease, and establish informative diagnostic classification systems. Among these are the Cancer Genome Anatomy Project, the Early Detection Research Network, and the Director's Challenge. In addition, programs are aimed at discovering and exploiting molecular targets for cancer prevention and treatment.

To capture the full value of these discoveries will require technologies that enable specific identification of early-stage cancer and precancer in minimal numbers of living cells. Such systems might be introduced by minimally disruptive means including, but not limited to, ingestion, inhalation, single or limited numbers of injections, or implantation. It is intended, however, to exclude support for the development of analysis tools that require conventional biopsy for acquisition of specimens. This in turn necessitates minimally invasive technologies and biosensors, to scan or monitor the body for the earliest signatures of emerging disease. Future technologies must also support the seamless interface between detection, diagnosis, intervention, and monitoring of intervention success.

The NASA-NCI Collaboration

The NASA-NCI Fundamental Technologies for the Development of Biomolecular Sensors program will support successful academic, government, and industrial applicants in a limited set of key areas critical for the long-term goal of developing biomolecular sensors for long-duration space flight and cancer detection, diagnosis, and treatment. Proposed areas for research include the following:

1. Molecular recognition chemistries, materials, chemical composites, nanoparticles, nanostructures, agents, and devices suitable for in vivo use that have some or all of the following characteristics:
   - show enhanced specificity
   - demonstrate enhanced sensitivity
   - cross the cell membrane in vivo
   - can access deep tissues in vivo
   - are bioavailable and biocompatible
   - enable coincident detection of multiple parameters
   - have methods for rapid generation of recognition agents for newly defined targets
   - can serve as a platform for recognition, signaling, and intervention delivery.

2. Strategies for in vivo signal generation and amplification, in particular, those that can generate a detectable signal in deep tissues, signal amplification schemes that are biocompatible in vivo, and new materials or chemistries that enable such approaches.

3. Dynamic signal acquisition systems suitable for noninvasive, dynamic signal acquisition from deep tissues and systems of reduced scale suitable for long-term human space missions.

4. Tools for feature definition, extraction, and processing, including computational and mathematical approaches to distinguish and extract signals, approaches to dynamic feature extraction to enable dynamic decision-making, and demonstrations of the power of such computational tools on existing data sets.

5. Approaches and multifunctional technology platforms to create an interface between in vivo detection and targeted intervention, including nanostructures and/or devices and novel materials and composites that support linked recognition and signal generation (detection) and manipulation of molecular processes (intervention), as well as approaches to converting recognition and/or detection into intervention.

The goal, a challenging one, is to create new technology platforms that will change medical care on Earth and in space. To this end, NASA and NCI invite scientists, technologists, and engineers from all disciplines to take part in this new initiative on biomolecular systems and help shape the future of medicine.

References and Notes

1. A. Lawler, *Science* **288**, 415 (2000).
2. For further information visit http://rcb.nci.nih.gov/appl/rfp/17016/Table%20of%20Contents.htm.
3. Nanofabrication and biosystems: H. C. Hoch, L. W. Jelinski, H. G. Craighead, Eds., *Integrating Materials Science, Engineering, and Biology* (Cambridge Univ. Press, New York, 1996).
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