Cancer Nanotechnology Symposium
Nanotechnology Platforms for Molecular Medicine

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Introduction

If the Nation is to meet the goal of eliminating suffering and death from cancer, clinicians will need new ways to detect, treat and prevent cancer and metastases. One expectation of the field is that this era of post-genomic science, with its emphasis on genomic and proteomic analysis and systems biology, will generate unprecedented advances in knowledge, fostering paradigm-changing diagnostics, therapeutics and preventatives. At the same time, nanotechnology is rapidly making a mark among a small but growing group of cancer researchers funded by the National Cancer Institute (NCI) as a disruptive set of tools capable of leveraging scientific advances into a new generation of targeted clinical agents.

As a key component of NCI's new five-year initiative, the Alliance for Nanotechnology in Cancer, the NCI desires to boost the number of multidisciplinary teams of cancer and nanotechnology researchers who are interested in working together to develop new methods for diagnosing, treating and preventing cancer. To help catalyze the formation of such multidisciplinary teams, the NCI is holding a series of symposia aimed at bringing together experts in nanotechnology and cancer research, both basic and clinical, for roundtable discussions among one another regarding possible common ground for applying nanotechnology to cancer-related research and development projects.

On February 22, 2005 the NCI convened the seventh of these regional symposia in close collaboration with the Lombardi Comprehensive Cancer Center, Georgetown University, the University of Virginia, University of Maryland, Howard University, and Virginia Tech. This symposium, held on the Georgetown University campus in Washington, DC, brought together scientists and clinicians with a wide range of expertise from multiple

research institutions and cancer clinics across the Mid-Atlantic region for a series of technical presentations on the intersection between cancer and nanotechnology. These presentations were designed with two ideas in mind: to give nanotechnologists and cancer researchers an idea of the state of the art in each other's disciplines, and to generate ideas for collaborations between the two groups.

PLENARY SESSION

The meeting opened with welcoming remarks by Dr. Richard Pestell, Director of the Lombardi Comprehensive Cancer Center, and Dr. Anna Barker, NCI Deputy Director for Advanced Technologies and Strategic Partnerships. Dr. Pestell noted that this symposium was the first time both cancer and nanotechnology researchers from across the Mid-Atlantic region came together. He offered that this meeting represented an exciting prospect to catalyze research in this area. Dr. Barker then gave some of the rationale for NCI's long-standing commitment to nanotechnology and to training cancer researchers who are versed in the science and methodology of nanotechnology. She commented on the fact that nanotechnology was already being used in clinical oncology and that over the next five years nanotechnology will have an enormous impact on both cancer research and clinical oncology. She then asked those attending the symposium to listen carefully to the scientific presentations with the idea of forming new problem-solving teams that can leverage the combined expertise in cancer and nanotechnology represented at the symposium.

Cancer Plenary Session

Ronald DePinho, M.D., Director of the Center for Applied Cancer Science at the Dana-Farber Cancer Institute and Professor of Medicine and Genetics at Harvard Medical School, started the symposium with a review that he titled "Cancer 101." The main assumption made today, he began, is that since cancer is a genetic disease it should be possible to catalog all of the inherited and acquired mutations that characterize cancer, to understand fully the functional consequences of these alterations, and implement a strategy to treat and prevent these consequences. The paradigm for the future of cancer, then, should be to develop the technology necessary to perform a comprehensive non-invasive genotyping that would identify, at the least, individuals who are at risk of developing cancer, and optimally, cells that are at risk of becoming malignant. It would then be possible to intervene early in the cancer process and ultimately prevent disease from developing.

We now know the core features of the cancer cell. Aberrant growth control leads to enhanced cell survival, followed by abnormal differentiation, which in turn leads to unlimited replicative potential, the development of host-tumor symbiosis, and finally, tumor formation. Normal cells move to hyperplasia, to benign tumor, to *in situ* cancer, to advanced primary cancer that is locally invasive, and finally to metastatic cancer. This evolution can take a very long time to develop, particularly during the early stages. The greatest opportunity that exists, then, is in early diagnosis – if you can detect cancer before it becomes metastatic, you get a 10-fold better outcome, largely because the tumor load is lower. Our thinking about the processes involved in the development of cancer is dominated by the genetic paradigm, since it is mutations in oncogenes and tumor

suppressor genes that trigger these key events. The sources of the mutations are many: replication errors, loss of chromosome maintenance, DNA repair deficiencies, checkpoint deficiencies, “endogenous” mutagens caused by intracellular generation of reactive oxygen, for example, and environmental mutagens, including irradiation, tobacco smoke, and aflatoxins.

Dr. DePinho then showed how the progression of human pancreatic cancer can be explained by a series of molecular events tied to well-characterized gene mutation. Though some of these genes are indeed known, there are many more chromosomal aberrations and mutations that we have yet to characterize, particularly those involved in the earliest stages of disease. Identifying these genes affords a great opportunity over the next two to three years.

Having said that cancer is a disease of genes, it is also important to remember that cancer is a disease of the organism, too. Tumors, explained Dr. DePinho, are complex organ systems that involve multiple cells and cell types, including immune cells, fibroblasts, endothelial cells, and perivascular cells. A good illustration of this principle comes from experiments in which fully initiated tumor cells are mixed with normal fibroblasts and no tumor grows. Only when the fibroblasts are activated, too, does a tumor develop. This multicellular involvement provides further opportunities for detecting the earliest stages of cancer. For example, recent work has identified stage-specific vascular and stromal markers for pancreatic islet tumor growth.

Turning back to the underlying genetics of cancer development, Dr. DePinho noted that a major checkpoint in the cell cycle is controlled by the retinoblastoma protein. When mutations trigger hyperphosphorylation of pRb, aberrant cell proliferation begins, which normally triggers apoptosis through a second protein, p53. Blocking p53 action, again through mutation, removes this second checkpoint, unleashing unlimited replication and cell survival. But normally, the cell would run into a third checkpoint: telomere loss, which would lead to massive recombination at the chromosome ends and crisis that leads to cell death. To progress to malignancy, then, cancer cells have to reactivate telomerase in order to preserve telomeres and survive this crisis stage. Understanding the events triggered at each of these stages, and identifying ancillary biomolecules involved at each stage, affords significant opportunities for developing diagnostics and strategies for intervening in these processes.

As illustrations, Dr. DePinho reviewed many of the signaling cascades involved in each of the stages of cancer development. The apoptosis cascade, for example, is where most drug resistance develops, so understanding this network better may provide new ways of avoiding resistance. Telomerase represents another checkpoint that presents opportunities. Cancer cells somehow navigate the two sides of telomere shortening to their advantage – on the one hand, shortening leads to chromosomal instability, which can produce the mutations that a cancer cell needs to survive, while on the other hand, too much shortening will trigger cell death. New mouse models of human telomere activity should enable researchers to better understand this conundrum and identify new diagnostic markers for telomere erosion.

Dr. DePinho then discussed the mouse models of human cancer consortium, a group of 20 NCI-funded groups that is creating and validating mouse models of many cancer types. This consortium is responsible for evaluating new technologies and methodologies that might prove useful in generating new mouse models, as well as for creating a repository for and database of mouse models of cancer. He noted some of the techniques used to create new mouse models and the role that mouse models can play in all stages of basic and clinical development research. He then closed his talk by mentioning briefly the recent discovery of cancer stem cells that may explain why tumor shrinkage does not always translate into a cure.

Nanotechnology Plenary Session

Samuel Stupp, Ph.D., Professor of Materials Science, Chemistry, and Medicine, and Director of the Institute for Bioengineering and Nanoscience in Advanced Medicine at Northwestern University, introduced the symposium attendees to some of the fundamental precepts of nanotechnology and provided an exciting overview of his laboratory's work developing multifunctional organic nanostructures. Nanotechnology, began Dr. Stupp, is creating a revolution across all of science that will impact broadly the development of new technologies. At its heart, nanotechnology is the bottom up design of *function* at the nanoscale, and the fruits of this design principle are represented by a wide range of nanostructures, including carbon nanotubes, fullerenes, molecular machines, quantum dots, and organic nanostructures with a variety of shapes, including rods and mushrooms.

Dr. Stupp commented that though organic nanostructures may not be as well known as their inorganic counterparts, they will ultimately have the biggest impact in medicine, starting over the next couple of years. Organic nanostructures are supramolecular assemblies of folded polymers. Creating such structures via bond-by-bond synthesis is impractical, so the best way of making them is to create smaller organic molecules that are programmed for self-assembly. For optimal function, these constituents are also programmed to biodegrade into non-toxic components once bioactivity is no longer needed. This bioactive-to-biodegradable concept is key if organic nanostructures are to play an important role in biomedicine.

The basic idea, then, is to think of making these as self-assembling systems with multiple regions and functions, i.e., a central core that could embed in a membrane, then a cap that would be exposed to the environment, like a membrane bound receptor. The mushroom-shaped structures that Dr. Stupp and his colleagues have developed self-assemble into sheets, with a visible green surface (the caps) and a blue surface (the core stems). Other building blocks assemble into twisted nanostructures that are 10 nanometers in diameter and microns long, and double helices with defined handedness and whose pitch can be dialed in through the chemistry of the monomers.

One aspect of organic nanostructures that intrigues Dr. Stupp is the role they may be able to play in regenerative medicine. In his vision, organic nanostructures could eventually herald a day when it is possible to regenerate fully functional tissues and organs as a

means of repairing cardiac function, bone fractures, worn cartilage, and tumor-laden tissues. The idea is to use nanostructures to manage early cell behaviors, such as proliferation, migration, apoptosis, feeding, recruitment, angiogenesis, and differentiation. In his vision, self-assembled polymers, containing integrated biochemical signals, would create artificial matrices for regeneration.

Dr. Stupp then reviewed some of his laboratory's work, noting that he and his collaborators have created a toolbox of 200-300 different biodegradable monomers. As an example, he showed how amphiphilic peptide-like monomers will self-assemble with a change in charge into long fibers. As he explained it, the molecules will self-assemble in order to minimize exposure to water of the hydrophobic portion of the monomer and maximize exposure of the hydrophilic portion. The resulting fibers, which cells readily import across the cell membrane, are some 6-8 nanometers in diameter and microns in length. Depending on the starting monomers, these fibers can be used to repair spinal cord injuries, fractures, and stroke-related damage.

As far as using these self-assembling nanostructures as a platform for developing cancer therapeutics, Dr. Stupp noted that the hydrophobic core of these structures can be packed with drug molecules, while the surfaces can be tailored to either acts as cell recognition agents themselves or as linkage sites for more traditional targeting molecules, such as integrins, receptor ligands, and monoclonal antibodies. These polymers can also be designed to release multiple growth or inhibition signals in a time-controlled manner, and Dr. Stupp believes it is only a matter of time before his group will be able to incorporate other types of signaling and reporter functions into these polymers. He ended his talk by noting that these organic nanostructures do not elicit an immune response, unless tailored to do so. The lack of immunogenicity may result from the fact that these structures degrade directly to amino acids and amino acid analogues and not into immunogenic protein or peptide fragments.

Cancer Focus Session

Nanodelivery Systems: Expanding the Therapeutic Potential

Esther Chang, Ph.D., Professor of Oncology and Otolaryngology at Georgetown University Medical School, began her talk by noting two approaches to sensitize tumors to radiotherapy and chemotherapy. The first approach involves using tumor suppressor gene therapy to restore apoptotic pathway function, an important cell cycle checkpoint. The second approach is to down-regulate oncogene expression using antisense oligonucleotides or small interfering RNA (siRNA) therapy in order to perturb cell growth signaling pathways. While both approaches are promising, they have been plagued by an inability to reliably and efficiently deliver nucleic acids into tumor cells.

Nanoscale cationic liposomes have been Dr. Chang's choice for overcoming this delivery issue, and she reviewed her laboratory's progress working with these constructs. She began by reminding the audience that liposomes can be modified for targeting, something her group has been doing using folate and anti-human transferrin receptor single-chain antibody fragment. Numerous experiments using transferrin-targeted liposomes with several different reporter genes and therapeutic genes demonstrated that targeting is quite

specific for both primary and metastatic tumor cells expressing the target. Experiments with the LacZ reporter gene showed that transfection efficiency of targeted cells is high, and that the reporter genes are not expressed in normal tissue, except for a small amount in phagocytic macrophages. And in a welcome surprise, the expressing reporter gene even found previously undetected small metastatic lesions in mice. Nucleic acid payloads were successfully delivered to bone and brain, too.

Once Dr. Chang's group had developed and tested this delivery system, the laboratory began focusing on developing new adjunct therapeutics that would sensitize malignant cells to molecular or conventional therapeutics. The goal, she explained, is to improve the efficacy of the main therapeutic while reducing side effects, resistance, and recurrence. Their first choice was to deliver the gene coding for p53, a gene that is inactivated in a majority of cancers and is a major target of drug resistance. Experiments in animal model of prostate cancer showed that restoring wild-type p53 function did, in fact, produce tumor regression when the animal was also treated with radiation therapy. Moreover, tumor growth remained suppressed for at least 18 months after therapy had stopped. Similar results were seen when p53 was delivered along with conventional chemotherapy in a mouse model of metastatic melanoma. Based on these results, Dr. Chang and her colleagues expect to begin clinical trials imminently in patients with advanced solid tumors. In response to a question, Dr. Chang also noted that nucleic acid bearing cationic liposomes are stable for over three years.

Dr. Chang then briefly discussed early results of experiments using cationic liposomes to deliver fluorescently labeled siRNA in a mouse model of human pancreatic cancer. Fluorescence imaging showed that siRNA was successfully delivered to both the primary tumor and metastatic lesions in the liver. Dr. Chang also showed images obtained using targeted cationic liposomes to deliver the MRI contrast agent Magnevist® to tumors. The images showed a clear increase in contrast when Magnevist was delivered using the targeted liposome compared to free agent.

Proteomic Studies of Changes in the Plasma Membrane and Nucleus in Resistance to Cancer Therapy

Catherine Fenselau, Ph.D., Professor of Chemistry and Biochemistry at the University of Maryland in College Park, began her talk by noting that proteomics is a field that would benefit greatly from partnership with nanotechnology. Characterizing the human proteome, she said, is a more difficult challenge than sequencing the human genome, and nanotechnology will be needed to overcome many of the analytical and data acquisition problems associate with this challenge. She noted that there are somewhere on the order of 100,000 proteins in the human proteome, occurring over a large dynamic range and with large range of chemical properties. Where nanotechnology can help most is in the development of technology that will enable reproducible fractionation of protein mixtures, enrichment of minor components, and parallel quantitative comparisons of differential expression.

Turning to her research, Dr. Fenselau said that her goal is to integrate proteomic studies of sub-cellular organelles in order to obtain a drug resistance profile. She explained that protein changes characterize drug resistance, and thus a global differential analysis of proteins in drug resistant and non-resistant cells would be useful for individualized medicine efforts. So far, her group has been developing methods for separating membranes from different organelles and then analyzing the proteins in those membrane fractions. This effort has led to the identification of some 540 proteins. Extending this work further, Dr. Fenselau and her collaborators have used metabolic isotope labeling to compare relative protein abundance between drug resistant and drug susceptible tumor cells grown in culture. These experiments have identified reproducing differences between the resistant and susceptible cells, including the occurrence of at least 15 proteins that are differentially expressed in the drug resistant cells.

Pentameric Nanoparticles Function as a Highly Efficient Vaccine Platform
Richard Schlegel, M.D., Ph.D., Professor of Pathology at Georgetown University Medical School, spoke about his group's efforts at developing cancer vaccines using nanoparticles as the active vaccine component. He noted that greater than 99 percent of all cervical cancer is caused by infection with one of 4-5 different pathogenic papilloma viruses (HPV), and that HPV infection is prevalent worldwide. HPVs have also been implicated in oral, anal, and epidermal carcinomas.

Recounting his group's initial collaborative efforts, Dr. Schlegel noted that their first generation vaccine was developed using virus-like particles (VLPs) that forms spontaneously from one of the proteins in HPV. That VLP-based vaccine, created 10 years ago, produced 100% effect in protecting against viral challenge and tumor formation. That technology has since been licensed to one of the large pharmaceutical companies, which is conducting clinical trials in humans. A preliminary report published in 2004 shows the promise of this approach. The one drawback is that this vaccine is difficult and expensive to produce, and it needs to be refrigerated, which would be problematic for distributing the vaccine in the less developed world.

To improve upon this first attempt, Dr. Schlegel and his colleagues produced mutations in the HPV protein that enable this protein to form a pentameric nanostructure, rather than the full spherical structure that forms from the native protein. This pentameric structure, some 10-12 nanometers in diameter, is easily and inexpensively produced, and can be made into a stable powder that is easily reconstituted before use. Tests conducted so far have shown that even small amounts of this vaccine provide total protection in dogs against HPV infection and tumor development. Based on these results, Dr. Schlegel has begun work with three other research groups to design and develop pentameric nanoparticles for both prophylactic and therapeutic use against cervical cancer, as well as other viruses and tumor antigens.

Federal Initiatives in Nanotechnology

New Frontiers for Nanotechnology in 2005: Cancer Research in the Context of the National Nanotechnology Initiative

Mihail Roco, Ph.D., Senior Advisor for Nanotechnology at the National Science Foundation, briefly reviewed progress in nanotechnology over the past four years, noting that this progress has brought us to a place where the National Nanotechnology Initiative (NNI) need to reprioritize its efforts in 2005. He commented that the advent of nanotechnology is important because it is a historical event in our understanding, control and transformation of natural, living, and human made systems. He predicted that our ability to systematically control matter on the nanoscale will lead to a revolution in technology and industry in four phases. The first phase has produced passive nanostructures, such as coatings, nanoparticles, and nanoscale polymers and ceramics that have novel and useful properties. The second phase, which we are just entering, will result in the production and use of active nanostructures such as amplifiers, targeted multifunctional drugs, and adaptive structures. The third phase, which will come about around 2010, will produce systems of nanosystems and the fourth phase, which we will reach between 2015 and 2020, will produce molecular nanosystems.

Dr. Roco then noted that there are 22 agencies involved in funding nanotechnology and conducting nanotechnology research. Nanotechnology has become pervasive in government, and in society in each year since 2000, not only has funding grown, but more has been spent than was requested. In reviewing the accomplishments of this effort, he highlighted the development of fundamental knowledge for controlling matter at the nanoscale and the creation of an interdisciplinary nanotechnology community. He discussed that U.S. investment in nanotechnology accounts for approximately 25 percent of global government investments, but that the U.S. has accounted for approximately 50 percent of highly cited papers, 60 percent of U.S. patents, and 70 percent of nanotechnology startups. The nation now has over 35 new large nanotechnology research centers, networks, and user facilities. Ten percent of NNI funding has been earmarked for studies on environmental, health, and safety concerns.

The second NNI strategic plan, which will guide Federal funding from 2006-2010, has four main goals:

1. **Maintain a world-class research and development program** aimed at realizing the full potential of nanotechnology. *(Support R&D for active nanostructures and nanosystems.)*
2. **Facilitate transfer of the new technologies** into products for commercial and public benefit. *(Increase funding for technological innovation and multidisciplinary R&D platforms.)*
3. **Develop educational resources, a skilled workforce, and the supporting infrastructure and tools** needed to advance nanotechnology. *(Access to research facilities and educational opportunities in nanoscale science and engineering for half of the undergraduate and graduate students by 2010.)*
4. **Support responsible development of nanotechnology** thru societal, environmental and health implications R&D, and interaction with the public. *(Address sustainability and life cycle of products.)*

National Cancer Institute Funding Opportunities
Gregory Downing, D.O., Ph.D., Director of the NCI's Office of Technology and Industrial Relations, reviewed some of the details of the NCI's new Alliance for Nanotechnology in Cancer. He identified the six key focus areas – molecular imaging and detection, *in vivo* imaging, reporters of efficacy, multifunctional therapeutics, prevention and control, and research enablers – and identified the four major programs of the Alliance:

1. Centers of Cancer Nanotechnology Excellence – NCI expects to fund 5-6 centers, using a U54 mechanism, that integrate platforms and expertise in a team-based, multidisciplinary approach. The goal of these centers is to accelerate the time cycle over which a researcher moves from the laboratory to the comprehensive cancer centers and SPOREs. Funding will total $90.8 million over 5 years. Proposal receipt date is March 25, 2005.
2. Multidisciplinary research teams – Teams focus on training programs for senior fellows and postdoctoral fellows and interagency collaborations. About 30 awards, totaling $15.5 million, will be made over 3 years. Proposal receipt date is March 25, 2005.
3. Nanotechnology platforms for cancer research – Programs, established through an RO1 mechanism to focus on the six key areas, will create platforms that are aimed at deployment for clinical applications in cancer research.
4. Nanotechnology Characterization Laboratory – NCL's mission is to help standardize and characterize nanoparticles for use in cancer research and clinical development efforts. The NCL will also develop and conduct an assay cascade for preclinical use and serve as a nexus for multidisciplinary research, development, and clinical applications. The NCL will work closely with other government agencies to leverage resources and expertise.

Nanotechnology Focus Session
Magnetic Nanotubes for Drug Delivery
Sangbok Lee, Ph.D., Assistant Professor of Chemistry and Biochemistry at University of Maryland in College Park, spoke about his work developing magnetic nanotubes and put forth some ideas and concepts on how these could be used in clinical applications. Color-coded nanotubes, for example, could be used for bio-imaging, and conducting polymer nanotubes could be used to develop ultrafast electronics. Other potential applications include chemical separations and triggered drug delivery and release.

Dr. Lee then discussed how his group has been using the well-defined pores in membranes for producing nanostructures such as nanowires and nanotubes. An advantage of this method is that the nanostructures produced have distinct inner and outer surfaces, each with its own set of useful chemical properties. The inner spaces, for example, can be filled with drug molecules, while the outer surface can be functionalized with targeting molecules. *In vitro* experiments have shown that magnetic nanotubes can be functionalized to provide sustained release of a model drug. Magnetic field-assisted immunobinding may be useful in increasing the sensitivity of chip-based assays.

Nanowire-Based Devices
Paola Barbara, Ph.D., Assistant Professor of Physics at Georgetown University, spoke about her research developing carbon nanotubes into wires and transistors that might be useful as chemical and biological sensors. Carbon nanotubes, she explained, are essentially small wires, 1-3 nanometers in diameter. These nanotubes can be single walls of graphite or multiple concentric walls, and they are mechanically strong and electrically conductive, which has made them useful as tips for atomic force microscopes.

Carbon nanotubes can behave as metals or semiconductors, depending on how they are built. Semi-conducting nanotubes are useful as transistors because applying a voltage across the nanotube converts it from a conducting to non-conducting state. Since the behavior of the nanotube depends on its composition and functionalization, it is a relatively straightforward idea to use such transistors as sensitive molecular sensors. To illustrate this idea, Dr. Barbara noted that a nitric oxide sensor made of carbon nanotubes operated at room temperature, experienced a big conductance change when exposed to low levels of nitric oxide, responded in as little as two seconds, but unfortunately, had a recovery time of about 12 hours after each measurement. Changing the composition of the nanotubes reduced the recovery time to an hour.

Nanoscale Self-Assembled Organic Films on Optical Fibers for Use as Biosensors
James Heflin, Ph.D., Associate Professor of Physics at the Virginia Polytechnic Institute and State University (Virginia Tech), discussed his laboratory's work developing nanoscale films that could find use in biosensor applications. These films are created layer by layer, allowing for the very careful control of the final structure and composition of these films. In one example, polyanions and polycations were deposited in a bilayer whose thickness and composition could be controlled by varying pH and salt concentrations.

The goal in creating these films is to use them as coatings for glass fiber optics in order to produce optical sensors. Experiments so far have shown that such films can be derivatized to include antibodies and other binding reagents on the film surface. Upon binding of film-bound antibody to its substrate, the optical properties of the film change. Indeed, using a commercially available antibody against a fragment of capsase-3, an enzyme involved in apoptosis, Dr. Heflin and his group are hoping to create an apoptosis sensor that might find use in assessing drug efficacy. His group has just begun this project in collaboration with Dr. Chang's group at Georgetown University.

Multidisciplinary Team-Building Session
Center for Nanoscopic Materials Design
Robert Hull, D.Phil., Professor of Engineering at the University of Virginia, discussed some of the novel methods his group is developing for creating templates on which to grow new nanoscale materials. This effort is currently focused on inorganic materials, but this goal is to extend this to a wide variety of organic and inorganic materials and to

develop techniques that will provide flexibility in determining surface chemistry, structure, and crystallography at length scales of 10s of nanometers.

Using equipment available at the University of Virginia's Center for Nanoscopic Materials Design, Dr. Hull's group has exploring real-time nanoscale lithographic patterning. The advantages of this technique are that it permits rapid prototyping of new designs because it is a direct process and does not require photoresists or masks. High resolution is another plus, as is the wide range of chemistries and materials available for use, and the relatively low cost of creating devices. The major disadvantage is that the technique is too slow to enable serial production of multiple devices. A complementary approach is to use microcontact printing, which uses molds made from an initial device to achieve high throughput.

Other equipment at the Center has enabled Dr. Hull and his collaborators to explore the use of anodic etching and electrochemical nanomachining for making biologically useful devices. Using these techniques and others, Dr. Hull's team has been creating nanopatterned surfaces to specify focal adhesion locations and build protein array assemblies. In one example, the researchers used selectins to create adhesion-rolling points, enabling them to measure leukocyte rolling. He closed his remarks by noting that only by bringing together experts in nanofabrication, chemistry, and biology, is it possible to move ahead rapidly in this inherently multidisciplinary field.

National Nanotechnology Infrastructure Network

Gary Harris, Ph.D., P.E., Professor of Electrical Engineering and Director of the Nanoscale Science and Engineering Facility at Howard University, then discussed some of the specifics of the National Nanotechnology Infrastructure Network (NNIN), a 13-institution network available to the nanotechnology community. The NNIN is different than most NSF programs because it is aimed at developing the infrastructure needed to do nanotechnology, not for specific projects. Each center charges minimal user fees and provides a trained core of individuals to help users rapidly explore a given research project. The key, he explained, is to enable rapid advances in nanotechnology through open access to facilities with over $150 million in equipment across the network. He noted, too, that the time from application to start of project is typically less than two weeks. For the years 2004-2005, there will be an expected 3000 unique users over the network, from all sectors and across a wide variety of applications.

As an example of the type of project that the network enables, Dr. Harris discussed a project involving the development of a retinal prosthesis that can convert light into an electrical pulse. Such prosthesis might be useful in treating the two major diseases of the retina: retinitis pigmentosa (RP) and age-related macular degeneration. Efforts to create such a prosthesis using standard silicon-based nanocircuitry have not succeeded because the optical properties of silicon do not match those of the eye. Instead of silicon, Dr. Harris's group has used gallium arsenide and gallium indium arsenide materials, and has so far managed to create a chip that responds in a manner similar to that of the eye.

Efforts are now aimed at developing biocompatible coatings to make this device biocompatible.

Dr. Harris closed his talk by noting that nanotechnology is going to require somewhere between 800,000 – 1 million trained people at all training levels by 2010. To help drum up interest in nanotechnology, Howard University and the NNIN are developing the NanoExpress, a traveling laboratory that will visit high schools and colleges across the nation.

From Concept to Platform

In the final talk of the symposium, Robert Menzi, M.A., Chief Operating Officer of Protiveris, discussed some of challenging work needed to develop a commercial technology platform. In this case, Protiveris is attempting to develop microcantilevers into a broadly applicable diagnostics platform that can serve as a foundation for the multitude of proteins and gene products coming from the research lab. Such cantilevers translate binding into an optical signal, which can form the basis of biosensors that detect specific biomolecular interactions in real time at very high sensitivity. Mr. Menzi showed examples of using microcantilevers to study DNA base pair interactions, to detect prostate specific antigen (PSA), and to isolate individual molecules from complex molecular mixtures.

Mr. Menzi noted that the development efforts at his company are not pushing the boundaries of science, but rather the boundaries of engineering. The challenge is to deliver arrays of microcantilevers in various lengths and thicknesses that push the limits of standard fabrication techniques. Currently, his company's production array has 16 cantilevers per chip, but work is underway to increase this density by a factor of four. The problem then is to develop a multiplexed laser and detector system capable of measuring cantilever deflections on the nanometer scale. Solving this problem took the efforts of a large system of investigators at multiple institutions who worked with Protiveris engineers.

During the discussions following the presentations, all of the members of the Multidisciplinary Team-Building Panel noted the power of Federal efforts to create teams of researchers who can bring their expertise to bear on nanotechnology problems. Mr. Menzi predicted that such efforts will also catalyze company formation, which he expects to accelerate greatly in the coming years. Dr. Harris noted that there are still cultural obstacles that inhibit team building, and that getting involved with one of the national facilities, including the Nanotechnology Characterization Laboratory, can help break down those barriers. In closing Dr. Hull noted that if the NCI Alliance for Nanotechnology in Cancer can achieve even half of what it has laid out in the timeframe, that effort alone will have accomplished a total validation of the NNI.