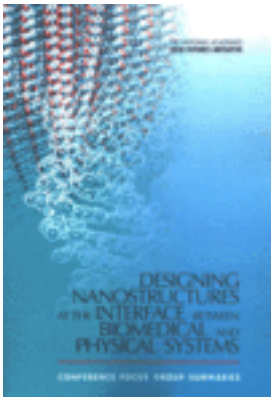

THE NATIONAL ACADEMIES
KECK FUTURES INITIATIVE

DESIGNING NANOSTRUCTURES AT THE INTERFACE BETWEEN BIOMEDICAL AND PHYSICAL SYSTEMS

CONFERENCE FOCUS GROUP SUMMARIES

Pre-Conference
Keck Center of the National Academies
Washington, D.C.
and
Arnold and Mabel Beckman Center of the National Academies
Irvine, California
September 18-19, 2004

Conference
Arnold and Mabel Beckman Center of the National Academies
Irvine, California
November 18-21, 2004

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The National Academies Keck *Futures Initiative*

The National Academies Keck *Futures Initiative* was launched in 2003 to stimulate new modes of scientific inquiry and break down the conceptual and institutional barriers to interdisciplinary research. The National Academies and the W.M. Keck Foundation believe that considerable scientific progress will be achieved by providing a counterbalance to the tendency to isolate research within academic fields. The *Futures Initiative* is designed to enable scientists from different disciplines to focus on new questions, upon which they can base entirely new research, and to encourage and reward outstanding communication between scientists as well as between the scientific enterprise and the public.

The *Futures Initiative* includes three main components:

Futures Conferences

The *Futures* Conferences bring together some of the nation's best and brightest researchers from academic, industrial, and government laboratories to explore and discover interdisciplinary connections in important areas of cutting-edge research. Each year, some 100 outstanding researchers are invited to discuss ideas related to a single cross-disciplinary theme. Participants gain not only a wider perspective but also, in many instances, new insights and techniques that might be applied in their own work. Addi-

tional pre- or post-conferences build on each theme to foster further communication of ideas.

Selection of each year's theme is based on assessments of where the intersection of science, engineering, and medical research has the greatest potential to spark discovery. The first conference explored *Signals, Decisions, and Meaning in Biology, Chemistry, Physics, and Engineering.* The 2004 conference focused on *Nanoscience and Nanotechnology: The Merger of Cell Biology and Physical Machines, A 21st Century Revolution.* Theme of the 2005 conference is *The Genomic Revolution: Implications for Science and Health.*

Futures Grants

The *Futures* Grants provide seed funding to *Futures* Conference participants, on a competitive basis, to enable them to pursue important new ideas and connections stimulated by the conferences. These grants fill a critical missing link between bold new ideas and major federal funding programs, which do not currently offer seed grants in new areas that are considered risky or exotic. These grants enable researchers to start developing a line of inquiry by supporting the recruitment of students and postdoctoral fellows, the purchase of equipment, and the acquisition of preliminary data—which in turn can position the researchers to compete for larger awards from other public and private sources.

National Academies Communication Awards

The Communication Awards are designed to recognize, promote, and encourage effective communication of science, engineering, and medicine within and beyond the scientific community. Each year the *Futures Initiative* honors and rewards individuals with three $20,000 prizes, presented to individuals who have advanced the public's understanding and appreciation of science, engineering, and medicine. Awards are given in three categories: book author; newspaper, magazine, or online journalist; and TV/radio correspondent or producer. The winners are honored during the *Futures* Conference.

In addition, during the first 18 months of the Keck *Futures Initiative*, the Academies undertook **a study on facilitating interdisciplinary research**. The study examined the current scope of interdisciplinary efforts and provided recommendations as to how such research can be facilitated

by funding organizations and academic institutions. *Facilitating Interdisciplinary Research* (2004) is available from the National Academies Press (www.nap.edu).

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Preface

At the National Academies Keck *Futures Initiative* Designing Nanostructures at the Interface between Biomedical and Physical Systems conference, participants were divided into interdisciplinary focus groups. The groups spent eight hours over two days exploring diverse challenges at the interface between physical science, biomedical science, engineering, and technology.

The focus groups were *not* expected to solve the particular problems posed to the group, but rather to come up with a consensus method of attack and a thoughtful list of what we know and don't know how to do, and what's needed to get there. The composition of the groups was intentionally diverse, to encourage the generation of new approaches by combining a range of different types of contributions. The groups included researchers from science, engineering, and medicine, as well as representatives from private and public funding agencies, universities, businesses, journals, and the science media. Researchers represented a wide range of experience—from postdoc to well-established in their careers—from a variety of disciplines that included chemistry, biology, physics, engineering, bioinformatics, medicine, toxicology, and applied anthropology.

The conference committee identified five objectives for the focus groups:

- To approach nanoscience/technology and biomedicine from the perspective of specific problems having potentially revolutionary impact, rather than from the perspective of extensions of existing technology
- To allow a group of people with a broad range of backgrounds to pool their insights and creativity to work on a shared problem
- To identify ideas and insights, common to a number of working groups, and to identify important fundamental problems in nanoscience/technology with the potential for very large impact on biomedicine
- To identify the best (by whatever metrics seem to fit) big problems in biology and biomedicine, to which nanoscience/technology might be applied, and to identify gaps in knowledge that limit progress in the solution of these problems
- To allow individuals to make connections with one another in small working groups

The groups needed to address the challenge of communicating and working together from a diversity of expertise and perspectives, as they attempted to solve a complicated, interdisciplinary problem in a relatively short time. Each group decided on its own structure and approach to tackle the problem. Some groups decided to refine or redefine their problems, based on their experience.

Each group presented two brief reports to the whole conference: (1) an interim report on Saturday to debrief on how things are going, along with any special requests (such as an expert in DNA sequencing to talk with the group); and (2) a final briefing on Sunday where each group:

- Provided a concise statement of the problem
- Outlined a structure for its solution
- Identified the most important gaps in science and technology and recommended research areas needed to attack the problem
- Indicated the benefits to society if the problem could be solved

Based on the group interaction and the final briefings, graduate science writing students in each group wrote the following summaries, which were reviewed by the group members. These summaries describe the problem, approach taken, group dynamics, the process the group followed to achieve its results, and benefits to society of the problem solution.

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Conference Summary

THE NATIONAL ACADEMIES KECK *FUTURES INITIATIVE* STIMULATES ADVANCES IN NANOSCIENCE THROUGH INTERDISCIPLINARY RESEARCH

By Kiryn Haslinger

On a bus from the John Wayne Airport in Orange County to the Newport Beach hotel where I was staying, the driver asked the gentleman in the front seat, "Are you here for the nano-conference." I, and several others seated near me, perked up, since we all were indeed there for just that reason. "Nano? What's that?" replied the man, who evidently was not one of the 155 researchers, policy makers, and writers who were invited for a four-day conference to discuss the latest advances in nanoscience and brainstorm about the most pressing big problems to which nanotechnology could be applied. "I don't really know," said the bus driver, "but I think it's really, really small."

Later that night at the kick-off reception, some of the best scientists, engineers, and medical researchers in the U.S. couldn't put it any more eloquently. The buzzing prefix that has taken the scientific world by storm refers to the size of structures, which are about a billionth of a meter: small objects with big potential. As objects shrink down to the scale of atoms and molecules, they are subject to the laws of quantum mechanics and do not behave according to the physics that governs the objects we encounter in

our macro-sized consciousness. Though quantum mechanics is celebrating a centennial this year (Einstein's paper describing a quantum mechanical phenomenon, the photoelectric effect, was published in 1905) humans still do not fully understand the laws that govern the world's most basic constituents. But harnessing the power of the nanoscale could mean more efficient electronics, significantly faster computers, effective environmentally friendly energy sources, and a possible revolution in the field of medicine.

These goals inspired the National Academies Keck *Futures Initiative* to host a conference on *Designing Nanostructures at the Interface of Biomedical and Physical Systems*. Launched in 2003, the National Academies Keck *Futures Initiative* (NAKFI) seeks to stimulate new modes of scientific inquiry and break down the conceptual and institutional barriers to interdisciplinary research. NAKFI is supported by a 15-year, $40 million grant from the W.M. Keck Foundation. Underlying the initiative is the conviction that interdisciplinary research and clear scientific communication are the cornerstones of modern scientific achievement. The *Futures Initiative* includes three primary components: seeding interdisciplinary research with competitive grants in emerging fields, rewarding first-rate scientific communication, and sponsoring conferences for a select group of the nation's brightest researchers. The conferences are intended to bring talented scientists, engineers, and medical researchers from diverse backgrounds together, to discuss a single topic, and determine the big questions that will define the great discoveries of the future.

Articulating questions is an accurate description of the format of this year's NAKFI conference. Indeed, throughout the four-day *Designing Nanostructures* conference, researchers continually struggled to state the problems that exist in attacking the exciting but ill-defined field of nanoscience. Richard Foster, a member of the W.M. Keck Foundation's board, kicked off the meeting in an introductory speech about the challenges of discovery by asserting this very idea. "The questions, at this stage, are more important than the answers," he said.

The conference's planning committee decided early on to develop an inquiry-based meeting centered on focus groups. Over the next few months, the organizers identified ten questions for the groups to address. Given this format, the committee also decided to hold a "pre-conference," in which seven researchers presented broad overviews geared toward an interdisciplinary audience—*The Future of Medicine*, *Optical Nanoimaging*, and *Nanotechnology Ethics*, to name a few. These tutorials were designed to help bridge the language gaps between disciplines and provide the focus groups

with common ground on which to explore their questions. At the *Designing Nanostructure* Pre-conference, on September 18-19, 2004, some 130 individuals from academia, industry, national labs, research foundations, government agencies, and the media gathered to prepare for the larger November meeting at the Arnold and Mabel Beckman Center of the National Academies in Irvine, California.

The conference, held November 18-21, 2004, was marked by a unique and innovative format. Instead of having several researchers communicate their work in formal detailed presentations, two scientists continued the set of broad tutorials begun at the pre-conference. Conference attendees were then divided into ten focus groups, each of which spent a total of eight hours exploring diverse challenges at the interface between physical science, biomedical science, engineering, and technology, interspersed with several hours of informal networking and in-depth technical poster presentations.

Cherry Murray, the conference's chair and Deputy Director for Science and Technology at the Lawrence Livermore National Laboratory, stressed the importance of the tutorials. Unlike most scientific meetings, where speakers can assume the collective understanding of particular fundamentals of their fields, interdisciplinary research requires a greater level of orientation and translation. Researchers must orient their collaborators to the basic principles in their fields, and articulate the open, exciting questions in their areas of research. They must also communicate clearly, demystifying the language of their disciplines and minimizing jargon.

Much of today's research requires expertise in more than one field, which is very difficult for a single person to master. Interdisciplinary research seeks to combine the skill sets of various researchers so that science can move forward through the creative collective efforts of collaborators. Highlighting NAKFI's mission, the opening session of the conference featured the release of the National Academies report on *Facilitating Interdisciplinary Research* commissioned by the Keck Foundation as part of the *Futures Initiative*. The report examines the current state of scientific research and support in the U.S., with a particular focus on how future generations of scientists should be trained. Covering all levels of scientific education, the report recommends ways for students and researchers to seek out interdisciplinary experiences and broaden their expertise by learning about other research fields. It encourages academic institutions to remove barriers to interdisciplinary research by developing joint programs and collaborating with industry and government organizations. Two of the major barriers to

interdisciplinary research are funding and the tenure process. How should collaborative groups share funding for a joint project? Will young researchers in academia risk their careers by taking the time to learn about other fields and work on interdisciplinary problems that cross the boundaries of traditional academic departments, in which decisions about promotion and tenure are made? The report suggests ways that the structures and goals of funding agencies and academic institutions could be revised to mitigate these challenges and encourage scientists to tackle the world's biggest scientific problems collaboratively.

In the spirit of the report's recommendations, NAKFI conference focus groups were dispatched to their first of several brainstorming sessions to discuss major challenges at the crossroads between nanotechnology and biomedical and physical systems. The membership of each focus group was intentionally diverse, in order to apply a broad range of skills to each problem. The groups included researchers from science, engineering, and medicine, as well as representatives from private and public funding agencies, universities, businesses, and the science media. Researchers represented a wide range of experience—from postdoctoral fellows to well-established career scientists—from a variety of disciplines that included chemistry, biology, physics, engineering, bioinformatics, medicine, toxicology, and applied anthropology. The group members were expected to pool their insights and creativity to provide a concise statement of their problem, outline a structure for its solution, identify the most important gaps in science and technology, and make recommendations about how to bridge those gaps. They were also charged with considering the potential benefits to society and ethical risks that solving the problem might present.

The focus groups were not expected to solve their problems, but several of them learned through the process that a concise, elegant statement of a problem leads naturally to an innovative solution. After a total of eight hours of group discussion, three groups thought they had developed potentially patentable ideas, and the conference organizers were challenged to develop mechanisms by which groups could publicly announce their solutions without losing their intellectual property protection.

The NAKFI conference was a proof in principle that when great minds come together, to focus on specific problems, they can accomplish amazing feats. At focus group report-outs on the last day of the conference, each group presented its problem and findings. As the appointed group members spoke, the prevailing feeling was a sense that anything is possible. A hand-held environmental DNA detector can be built for quick and easy

self-diagnosis of disease, or to determine the concentration of toxins in the air. A bio-battery, which would safely fuel implantation devices helping the blind to see, can be engineered to modulate output. Individualized medicine may be realized in the form of synthetic biofactories that can be engineered to monitor an individual's organs and produce enzymes that are dangerously lacking. You just have to ask the right questions. In a room full of people who don't speak the same scientific language, you must ask those questions very carefully, defining each and every term. The traditional hypothesis-driven scientific method is changing to reflect the method employed by the NAKFI conference focus groups.

Traditional disciplinary research also had a prominent role at the conference. Between focus group meetings, conference participants presented poster sessions of the current research being conducted in their labs. These sessions provided an opportunity for scientists to network and learn about advances in research from other scientists in one-on-one conversations.

Another major component of the *Futures Initiative* is the National Academies award for communicating science. Each year, three $20,000 Communication Awards are presented—one each for a book author; a newspaper, magazine, or online journalist; and TV/radio correspondent or producer—to recognize excellence in reporting and communicating science, engineering, and medicine to the public. Without talented writers and broadcasters, who bring details of the exciting potential of science and technology to nonscientists, the public's only exposure to what's happening in the lab may be through sensationalist science fiction novels and movies. To properly educate policy makers, businesspeople, and young future scientists, and to present a realistic platform on which to discuss the real ethical issues surrounding research, science communicators must carefully construct articles, books, and broadcasts that are scientifically accurate and, at the same time, accessible and interesting to those not trained in science. Matt Ridley was awarded a 2004 Communication Award for his book, *The Agile Gene: How Nature Turns on Nurture*, an insightful synthesis of how modern genetics has illuminated the age-old nature-nurture debate. Robert Lee Hotz was honored with an award for his gripping narrative on the space shuttle Columbia accident, "Butterfly on a Bullet." And Sue Norton and David Clark were honored for presenting the importance of engineering in scientific exploration in their stunning film, "Science of the Deep: Mid-Water Mysteries," broadcast on *The Science Channel*. In addition, as part of NAKFI's commitment to science communication, ten graduate student science writers were invited to attend the conference. Each writer

joined a focus group and was responsible for writing a report of the group's work.

The NAKFI ideal of enhancing communication among researchers, funding agencies, universities, and the public while stimulating interdisciplinary research at the frontiers of science was realized through the creative teamwork of the *Designing Nanostructures* meeting participants. Nanoscience and its application to biomedicine are at the cutting edge of research, and the partnerships formed at the conference are likely to have a significant impact on future research applying nanotechnology to biomedical problems.

On December 29, 1959, at the annual meeting of the American Physical Society, the great physicist Richard Feynman conceived of manipulating materials on the atomic scale. Though he did not use the word "nanoscience," he generated excitement in the idea that controlling particles to advance technology and enhance human existence would one day be possible. "In the year 2000, when they look back at this age," Feynman predicted, "they will wonder why it was not until the year 1960 that anybody began seriously to move in this direction." After 100 years of quantum mechanics and 45 years of nanoscience, researchers are making great leaps forward in harnessing the potential of nanotechnology. The Keck *Futures Initiative* conference was an important step forward in the progress of this exciting field.

A Micro System to Isolate, Sequence, and Identify DNA from a Small, Low-Concentration Sample

FOCUS GROUP DESCRIPTION

Background

There is a constant demand to sense and analyze biological agents and components for purposes such as collection of genomic data, diagnosis of diseases, controlling of production processes, detection of the crime site, inspection and monitoring of environmental contamination, and warning for bioterror attacks. The most common bio agents range from DNA to proteins to viruses. Biosensing requirements are short response time, accurate and reliable reading, low equipment and operation costs, compact system size, low power consumption, etc. However, one of the most critical problems in biosensing is the sample quality. Many samples are too low in agent concentration and too small in volume. For example, many modern genomic and molecular biology assays involve selective amplification of specific regions of interest to extremely high concentration levels, followed by extraction and purification of the amplified products. Although there are several popular multiplication and isolation methods, such as PCR, in general, the reactions are slow and the equipment is cumbersome and costly.

The Problem

It is desirable to have a nano or microsystem that can effectively multiply and isolate bio agents in a picoliter, low-concentration sample at a high

rate with a simple operation procedure. It is further desirable that the sensing or analysis function is integrated into the nano or micro system so that the complete result is immediately available after the multiplication and isolation procedure. The following are some examples that need to be addressed:

- Methods that can multiply the picoliter-volume DNA concentration by several orders of magnitude
- Nano or micro-devices that can multiply the picoliter-volume DNA concentration by several orders of magnitude
- Nano or micro-sensors that can monitor the DNA concentration change in a picoliter volume
- Nano or micro-devices that can recover low concentration DNAs from a picoliter volume solution
- Nano or micro-devices that can separate different DNAs in a picoliter volume solution
- Nano or micro-devices that can identify different DNAs in a picoliter volume solution
- Nano or microsystems that can simultaneously multiply, isolate, and identify DNAs in a picoliter volume solution

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FOCUS GROUP SUMMARY

Summary written by:

Susan Brown, Graduate Student, Science Communication Program, University of California, Santa Cruz

Focus group members:

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Summary

Genomic information is expanding on an unprecedented scale. Pathogens, new organisms, and diseases are being identified on the basis of genetic sequences.

If genomic information could be harvested quickly and inexpensively, it could be applied widely in beneficial, practical applications.

If inexpensive, fast, and ubiquitous, the technology could be used to identify specific strains of illness-causing pathogens. In a clinic, for example, treatment could be immediately tailored to the infection. If cheap and robust, detectors could be placed in public places or carried into battlefields where they could identify harmful pathogens quickly enough to prevent widespread infection.

Imagining a way to realize this potential became the focus for our group. We wanted to design a device that would take an unprocessed biological sample—from the air, soil, a patient, a crime scene, ancient bone—and, within a single device, process, detect, and identify the genetic material found in the sample. To make the technology widely adoptable, we also aimed for a solution cheap enough to be disposable and as easy to use as a home pregnancy test.

By the end of the first session, our goal became "the unambiguous identification of any unknown DNA and/or RNA within minutes from a native sample at low cost."

Currently, samples can be screened for known pathogens or genetic sequences in a matter of hours to days. The costs remain high, particularly for sequencing, at hundreds of dollars per sample, with initial capital investment for equipment in the tens of thousands.

Circling in on a solution

Over the course of four sessions, we proposed a solution that combines current state-of-the-art technologies to achieve the goal.

Defining a solution was an iterative process, but the outline of what could be achieved was developed early. From there, we identified the bottlenecks in the process to determine how the goals could be accomplished more quickly and at lower cost.

Early in the process the group divided the problem into four basic steps:

- separate nucleic acids from the sample
- sequence or detect the nucleic acids
- process the sequence information
- report the outcome

Separating nucleic acids from a gunky sample

Extracting genetic information quickly and cheaply from unpurified sample with no preprocessing using a single device challenged the group. It requires the ability to handle gunky samples, such as mucus or soil. The device would also have to separate all the other cellular components from nucleic acids.

Early in our discussion, we decided against amplifying the DNA be-

cause the required primers and thermocycling would greatly increase cost and time. New technologies that promise to sequence individual molecules of nucleic acid are on the horizon.

We considered a wide variety of solutions, such as binding nucleic acids to magnetic beads and sucking them out of solution, or using a microfluidics array in which posts deflect and slow larger molecules in a sort of nanoscale pachinko machine to fractionate cellular components by size.

In the end, we decided to minimize fluids and instead use multi-layer thin films with enzymes and other reagents impregnated in each layer to initially separate nucleic acids from other components of the sample. The sample would pass through a filter under pressure to remove macromolecules, and then through a film impregnated with enzymes, such as lysozyme, to open the cells.

The final film would contain chaotropic salts, just before the sample passed through to a binding matrix material, such as a glass fiber mat. In the presence of chaotropic salts, DNA binds to glass fibers. Other cellular components would then be eluted using a valved microfluidics device to pump ethanol through to rinse waste into a separate chamber, followed by water or a buffer solution to elute the DNA from the binding material.

The DNA could be fragmented for faster parallel sequencing by passing it rapidly through narrow microchannels to sheer it into randomly sized pieces. The original sequence would be recovered by assembling the sequences of overlapping fragments.

Rapidly sequencing small amounts of unknown DNA

This is a hot field with both private industry and government agencies, such as DARPA and NIH, investing millions in its solution. We assumed rapid development of each of these sequencing options would lead to several fast and inexpensive options. To expand on the group's expertise, we imported several visitors, including Andrew Ellington, to share specialized knowledge in various areas.

We focused on two similar approaches based on the sequencing of overlapping fragments of DNA.

One option would be to sequence fragments of DNA that are immobilized on a solid surface. Biochemical reactions would be used to read the bases in each individual molecule. For example, DNA polymerase or exo-

nuclease could be engineered to generate an optical signal as each base is added or deleted.

The sequence information could be recorded for all the DNA fragments simultaneously using a sensitive charge coupled device (CCD) to detect the optical signals. The polymerase and exonuclease reactions are fast, about 10,000 bases per minute. The challenge will be to design a detection system that can operate at the speed of the reaction.

Alternatively, the DNA could be passed through nanochannels and the sequences detected electrochemically. An array of nanochannels could be used to increase efficiency.

Finally, resequencing chips that hybridize DNA are currently available. But the chips require known sequences, and processing takes hours to days. The processing time is likely to fall with incremental improvements in the technology. Resequencing chips will be most useful for focused applications that discriminate between several known options, such as different strains of influenza virus.

Identifying sequences

For focused applications, in which sequences would be compared to a known and limited set, a lexicon could be stored on a chip. In that case, sequencing and identification could occur in the same step.

In the more ambitious case, in which the sample is completely unknown, the sequences may need to be compared to a database, such as GenBank, using a remote device. This last part would likely be a small reusable radio-frequency or Wi-Fi handheld instrument in the field, a desktop computer connected to the Internet in a clinic or laboratory, or a satellite communication device in a remote place.

Reporting signals

The end users will need to know what to do once the sequence is identified. For home-test applications the message needs to be simple and clear. Group members envisioned tissues that, when you blow your nose into them, revealed a message based on your illness, such as "go to the emergency room," "call your doctor," or "have chicken soup." The same device that analyzed a nasal swab could pop out a pill tailored to the particular strain of pathogen, for example.

Sensors deployed in public places could be programmed to deliver simi-

lar messages warning people not to enter an area if intentional release of a pathogen is detected.

Gaps between current science and technology and realizing this vision

Current sequencing methods are not sensitive enough to allow rapid and reliable sequencing of single molecules of DNA. If more sensitive detection systems are developed, such as the ones we have proposed here, the high cost of DNA amplification by PCR could be eliminated. Highly parallel sequencing of single DNA molecules is the key to achieving our goal.

Success will require other technological advances as well. For example, the multi-layer films suggested for the first step have excellent permeability and filtering properties, but still need to be optimized to work in the robust, field-based kits the group has proposed.

Finally, despite rapid advances, the database of gene sequences remains incomplete. It is also inaccurate, containing wrong and sometimes mislabeled sequences. More information about sequences and better retrieval schemes will allow the system to find answers in an imperfect database.

Potential benefits and dangers to society

Information More ubiquitous sequencing would help to clean up the genetic databases. If widespread sensing of DNA sequences reveals something novel, the sequence could be submitted to a temporary database. If confirmed, for example by additional sensing, it could be added to the database. Errors in sequences could also be corrected if a mechanism for comparing the differences detected in the field were incorporated. Linking development of this new technology to mechanisms for checking, correcting, and updating the database could rapidly accelerate the acquisition of new genetic information.

Health The greatest potential benefit would be a vast improvement in human health and safety. Early detection of infectious agents could lead to an end to epidemics, even an end to infectious disease. Rapid and accurate diagnosis, especially in a home-based kit, would minimize the impact of minor illness for the individual, but also for society in fewer lost workdays and a reduced burden on the health care system.

Deployment of sensors in public places or gatherings that might be

vulnerable to biological attack could lead to early detection and save lives.

These benefits may come at a cost. Identifying pathogens is of no use if treatments are not available. The greater good to society will come only if most people with infectious disease comply with treatment. Would we force people to comply? A conflict between society and individual rights may arise.

Finally, fast and inexpensive sequencing will lead to the sequencing of individuals' genomes. Patients' own cells will be included in any biological samples, thereby making this likely. Good will come of that if drug treatments can be tailored to their individual genetic makeup—relieving patients of treatments with harmful side effects that are unlikely to work and more rapidly identifying those most likely to do good.

But genetic information about individuals could lead to discrimination in employment or lack of access to medical insurance. Genetic information could be psychologically harmful to individuals if there is nothing they can do about their condition. And doctors who withhold information from their patients for that reason may be vulnerable to liability suits.

If scientists keep these concerns in mind as they develop this new technology, safeguards can be put into place as it is implemented. Doing so will go a long way toward reassuring the public and preventing the kind of opposition that might obstruct the introduction of a potentially widely beneficial new approach.

Build a Synthetic Self-Replicator

FOCUS GROUP DESCRIPTION

Background

Long a fascination of science fiction writers and space exploration visionaries, nanomachines that can replicate themselves are already here: we have an existence proof on Earth in complex living systems, such as one-celled (and even more complex many-celled) organisms. Other "bio-nanomachines"—viruses—are able to reproduce themselves through the use of cell machinery external to themselves. Creating synthetic self-replicators would greatly scale up production of nanomachines from the atomic and molecular scale to the macroworld, as the process of self-replication allows for exponential growth. Your task is to propose a scientific plan for the design and creation of a simplified synthetic self-replicating nanomachine, using a replication method either completely self-contained, as in a cell, or requiring the use of external machinery, such as by a virus.

The Problem

All cells on earth appear to be built according to the same molecular plan, using evolved molecular self-replication:

- Ribosomes are molecular assemblers working from stored information.
- DNA is the information storage medium, directing the assembly of other parts.
- DNA polymerase duplicates the information storage medium.
- Thousands of enzymes convert available raw materials to building blocks required for the assembler and duplicator.
- The cell provides the following required infrastructure:
  - —The lipid cell membrane serves to define the body of the cell.
  - —The membrane signaling and transport proteins serve to allow for communication, energy, and raw material transport to and from the external environment.
  - —Complex machinery exists to allow for reproduction by binary fission.
  - —Various enzymes exist for regulation and error correction of cell processes.

1. Current estimates (Ref 1) of the minimal number of DNA genes needed to create a living organism modeled after the modern cell machinery above are in the range of 250-350; however, this design is limited by the process of evolution. Can we design a more efficient and simpler self-replicator? For example, it is believed (Ref 2) that primordial life was based on RNA, and there are attempts to create RNA ribozymes in the lab (Refs 1, 2) as well as a major advance in understanding of ancient RNA processes that still exist in modern organisms (Ref 3). Another possibility would be to create stable alternatives to DNA and RNA, such as synthetic short peptide chains that can be more robust (Ref 1) for information storage and control. Yet another possibility is to create self-replicating DNA objects using synthetic DNA structures as engineering materials akin to viruses, requiring access to external machinery for replication (Ref 4).

2. Current cell machinery is limited to water environments and thus a limited temperature range, in which thermal statistical motion and a diffusion-to-capture paradigm occurs for most functional tasks. Larger and more specialized tasks are carried out by machine-phase assemblies. Could we design self-replicators that evolve and grow in environments without water?

3. DNA, RNA, and most proteins have limited lifetimes in cells due

to degradation by nucleases and denaturization (Ref 5). Is it possible to create more robust and longer lived replicators? What are the trade-offs?

4. The measured mutation rate in bacterial cells is 1 nucleotide in 10^9 nucleotide polymerization events. What level and kinds of transcription and replication error rate and error correction processes are needed to sustain self-replicating nanomachines? (Ref 6) Although transcription errors can be fatal, some types of transcription errors, along with gene duplication and complex gene networks, can help an organism evolve in a changing environment (Ref 7).

5. Self-replicating nanomachines would have many positive uses for society, but their possible existence in the near future also raises many concerns of "gray goo" either inadvertently or purposefully being unleashed on the environment with unforeseen possible grave consequences. What kind of ethical controls should be put in place over their creation and use?

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FOCUS GROUP SUMMARY

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Summary

Focus Group 2 met to discuss how scientists might develop synthetic self-replicators, devices that can make copies of themselves. These devices could have many valuable applications. Substances made of microscopic self-replicators could heal themselves by producing replacements for damaged parts. For example, molecular scale self-replicators could combine to form self-maintaining paint or spacecraft skins that can repair damage caused by space debris. In addition to replacing damaged parts, self-replicators can scale up production exponentially, as each new product is at the same time a new factory for more products. This could be a solution for accurately and inexpensively producing useful quantities of novel nanoscale materials.

While technological applications have caught the attention of many, including science fiction writers, researchers are also excited about potential non-technological payoffs for research into self-replicators. Building

our own self-replicators could give us insight into the origins and mechanisms of existing self-replicators, ranging from bacteria to balboa trees, all of life, in fact, including ourselves.

Life serves as proof that self-replication is in fact possible. Other, nonliving self-replicators also exist. Because a range of self-replicators exist in the world, the members of the focus group had to first define the parameters for designing a model self-replicating system.

The group discussed several types of existing self-replicators. First, several examples of simple replicators were named. Fire, in the right environment, produces more fire. Crystal seeding leads to more crystal. Autocatalytic reactions produce chemicals that in turn increase the reaction. For example, if hit with a source of energy, like gamma rays, formaldehyde makes glycoaldehyde. Once glycoaldehyde is present, it can couple with formaldehyde and break it apart, making two glycoaldehyde molecules where there had been one. These in turn can convert more formaldehyde to glycoaldehyde. As long as formaldehyde is available, this reaction causes more of itself to occur.

Viruses fall into another category of self-replicators. They are more complex than fire, but to make copies of themselves they have to depend upon the machinery inside biological cells. One of the things that make viruses interesting is that, like life, they carry instructions for copying themselves. They inject either DNA or RNA into a cell, where cellular machinery follows the directions and produces more viruses.

The last category of self-replicators the group considered was biological cells. In part because many in the group hoped to use the pursuit of a synthetic self-replicator to throw light on the origins of life, the group decided to specify a self-replicator much like a cell. Like fire and crystals, its self-replicator would make copies of itself. Like viruses, it would contain instructions for self-replication. It would be like a cell in many ways. First, unlike viruses, the replicator would include the machinery for carrying out the instructions. Also, it would take simple environmental materials, as cells use amino acids, and create something more complex, such as a cell's proteins. The group wanted to make clear it was not looking for a self-replicator that made copies of itself by, for example, breaking off parts of a more complex material in the environment.

In addition to these basic requirements, the group hoped its self-replicator would have other things in common with a cell. The instructions in a cell can be changed, and as a result the cell can produce different kinds of products and perform various functions. Muscle cells can contract. Nerve

cells can process and send signals. Likewise, an ideal synthetic self-replicator would be programmable so that it could serve multiple functions.

The group decided its self-replicator could be different than a cell in one important way: it would not necessarily have to have a physical barrier like the cell's membrane. The group's self-replicator still would need to be distinct from its environment, if only to confirm that it is indeed making a copy of itself. Rather than using a physical barrier, however, this distinction could be made by defining the parts or functions of the self-replicator.

By agreeing not to include a requirement for a cell membrane-like physical boundary, the group significantly reduced the complexity of the design task. At the same time, the group increased the requirement for researchers to control the environment for the self-replicator. In a cell, the membrane, including its embedded proteins, control what comes into the cell. By doing this it creates a special environment within the cell that allows the reactions necessary for the cell to function and eventually copy itself. For the group's self-replicator, the researchers in effect take the place of the membrane, carefully preparing and maintaining the environment. They would keep out things that might damage the machine, and they would include an energy source and all the required raw materials. The need for this specified environment makes it much less likely that this self-replicator could survive and reproduce outside of the lab.

In summary, the group defined as its goal a self-replicator that:

- produces a copy of itself
- carries information for replication
- is distinct from its environment
- uses raw materials that are simpler than the final product
- ideally would be programmable and multifunctional

The group's defined goal will not be easy to accomplish. As a first step, however, the group outlined a research direction building on current work with RNA. David Bartel of the Massachusetts Institute of Technology has developed an RNA-based RNA polymerase, that is, a form of RNA that can copy RNA. If this polymerase could make a copy of its own RNA sequence, it would be a self-replicator.

For this to happen, key obstacles need to be overcome. For one thing, so far the polymerase is slow and as a result cannot copy long strands of RNA such as itself. Another main problem is the fact that once the RNA is

copied and folds into a non-linear structure, like a helix, its parts are no longer available to be copied again. What is needed is another enzyme, a helicase, that will unfold the structure so it can be copied.

In spite of these obstacles, working with RNA seems promising because, in addition to possibly fulfilling the group's basic requirements, it might even lead to a device that can be programmed to perform a variety of functions. Nucleic acids have been used for a variety of surprising things. Researchers have made DNA that folds into an octahedron, opens and closes like a pair of tweezers, or walks on a substrate much as the protein molecular motor kinesin walks along microtubules. They have also used RNA for a variety of catalytic roles. Even more functions may be found if the so-called RNA world hypothesis is correct. According to Nobel Prize for Chemistry winner Sidney Altman, in the primitive earth RNA both stored genetic information and performed, "the full range of catalytic roles necessary in a very primitive self-replicating system." If scientists are able to synthesize an RNA-based self-replicator, it may confirm this hypothesis and give us a better understanding of how life could have begun and evolved.

The proposed self-replicator might work something like this: RNA polymerase would be added to a solution containing all the raw materials it needs, including fuel in the form of rNTP. The helicase would unfold some of them, making them available for copying by other, still folded, molecules of RNA polymerase. These copies would fold into new RNA polymerase molecules. These could be fed other strands of RNA that code for RNA-based structures like tweezers and catalysts, or more polymerase.

After offering the RNA example, the group went on to suggest that non-biological heteropolymers might be used to make self-replicating machines that could survive within extreme environments like space, where the vacuum, cold, and radiation would keep biological self-replicators from functioning or even maintaining integrity. Such non-biological self-replicators would depend upon a supply of raw materials that do not occur naturally, suggesting that they would not be able to replicate outside of a carefully prepared environment. While the theoretical advantages of non-biological heteropolymers make them desirable, the group noted that building them would present an array of new obstacles.

Public concerns about self-replicators have been heightened by books like Michael Crichton's *Prey*. Although the replicators proposed by the group would likely have trouble surviving outside of narrow environments,

the group proposed that attempts to make self-replicators should be accompanied by critical assessments of safety issues, including consideration of ways to recognize and respond to unforeseen problems. These assessments from the beginning should include discussions between scientists and nonscientists with the goal of self-regulation.

Build a System That will Detect Disease In Vivo and Report Back Results

FOCUS GROUP DESCRIPTION

Background

Human disease is currently assessed by several methods: blood tests, physiological monitoring (blood pressure, heart rate), imaging (MRI, Ultrasound), or laboratory analysis of tissue samples obtained by biopsy. However, disease processes occur at the molecular level inside cells and tissues distributed throughout the body and unfold at the 10 nm to 10 micron length scale. Examples include neuron dysfunction in Alzheimer's, unregulated cell proliferation in cancer, or atherosclerosis in blood vessels. The body has natural surveillance mechanisms, such as immune cells, which continuously circulate through the blood, lymph, and tissues and detect foreign invaders; however, technological analogs that could survey the body 'from the inside' to detect disease early are not available. To be useful, such a device or system would need to interface with physicians and patients to provide data that can be acted upon. In the lay press, this idea is often discussed in the context of the 1966 science fiction film, the Fantastic Voyage, where a surgical team was miniaturized and injected into the circulation of a dying man.

The Problem

• Consider how diseased tissue would be recognized. One way is to use the circulation to survey all the blood vessels of the body. There is emerging evidence that vessels of diseased tissues have distinct characteristics from others. What other ways might be worth considering? Keep in mind burgeoning efforts to identify molecular markers using genomic/proteomic technologies for many disease processes.

• Consider how detection of diseased tissue would be reported to the physician. One way is to transmit a signal with radio waves. Another is to image using signals that penetrate tissues (i.e., near infrared light). Another is to collect a sample that has a 'record' of what was encountered in the body. What other ways might be worth considering?

• Consider how such a device might help treat disease. One way is to deliver a drug. Another is to destroy tissue with heat. Another is to alter the diseased tissue via gene delivery. What other ways might be worth considering? How would one monitor the progress/success of such a therapy?

• Design a device that combines all these desired features: (1) recognize disease tissue, (2) report back to physician, (3) treat disease, and (4) monitor therapy. What are the tradeoffs that one must consider? How might chemistry/engineering/biology at the micro- and nanoscale help address these limitations?

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FOCUS GROUP SUMMARY

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Summary

Remember the 1966 Science Fiction movie Fantastic Voyage where the protagonists travel inside the body to remove a blood clot? Thirty-nine years later, Focus Group 3 did not quite suggest sending people inside the body to detect disease. Instead, the group suggested sending nanoparticles. The particles would bind to certain disease specific target molecules in the blood stream, on cell surfaces or even inside cells. They would "recognize" which molecules they encountered because their surfaces would be specifically and irreversibly changed by binding to a specific target molecule. The particles could then be collected and analyzed after excretion in the urine so doctors could check what's wrong inside the body. While the initial concept was straightforward, several details needed to be clarified.

One question is how to introduce the particles into the blood stream. Various methods of introducing the nanoparticles into the body were discussed: taking a pill, inhalation, or entry through the skin via a patch or injection. In addition, the particles would have to be less than 5 nm in diameter so they can be excreted through the kidney. The material of which they are made has to be both biocompatible and inert. The group considered gold and diamond, both of which are already approved by the FDA for use inside the human body, good candidates.

The next challenge was to make sure the particles would not be rejected by the immune system. Here the water-soluble polymer Poly (Ethylene Glycol), or PEG, could be used because it has been shown not to be recognized by the immune system. The particles would then have to specifically detect certain molecules that indicate disease states. Initially, the

group considered particles that detect specific disease targets and then send a signal to a monitoring device outside the body.

This solution, however, could be very costly; so the group decided to solve the problem without a monitoring device. For example, an additional PEG or related cross-linked hydrogel layer could be placed on the outside of the particle. The particle would shed this layer once it binds a specific target molecule. One possible mechanism is to place ligand-receptor pairs in the outer layer. Binding of a target molecule would replace the ligand in the outer layer and cause it to fall off.

Alternatively, certain molecules in the outer layer could be cleaved by a target molecule. One example is metalloproteases found in atherosclerotic plaques that can cleave proteins. Such a cleavage would cause the nanoparticle to shed its outer hydrogel layer after it encountered metalloproteases.

Whatever the shedding mechanism, the loss of the outer layer would give the nanoparticles a memory as to which molecules they encountered in the body. The presence of particles collected in the urine without the outer layer would then indicate to a physician that the particles bound to their specific target.

One of the great advantages of such a nano-approach is that one could place a "nanotrailmix" of particles specific for hundreds—if not thousands—of different molecular targets in the body at the same time. The term "trailmix" applies because different particles would have different outside layers depending on their molecular targets, similar to "peanuts that have different kinds of salt on them," as one group member put it. It appears that the group came up with the term nanotrailmix for the first time, illustrating the innovative nature of the focus group discussions.

However, the trailmix-approach poses a problem: How do you know which particle missing its outer layer encountered which target molecule? To find out, particles with different specificities could be "bar-coded" to make them identifiable. One way to do this is to place oligonucleotides—or short DNA molecules—in the inner PEG layer left behind. The oligos could then be used to hybridize to their counterparts on a DNA microarray chip. Alternatively, one could use a RAMAN active substance for the inner PEG layer. Different substances could emit different wavelengths after excitation with laser light, and this could serve as a particle ID.

So which targets could such a system detect? The group decided to approach the problem in three stages of developing the technology, with

the most accessible targets addressed first, in Stage 1. Stage 1 targets are molecules accessible from the bloodstream where the nanotrailmix is circulating anyway, such as Prostate Specific Antigen, a protein expressed in the prostate thought to indicate the presence of cancerous cells. Other possible targets are metalloproteases in atherosclerotic plaques, although these may be too unspecific, because they are elevated in the vessels of inflammatory lesions and cancers, and probably other diseases as well, one group member said. However, that group member added, inflammation, cancer and premalignant lesions are recognizable from more specific vascular changes. For example, tumor blood vessels express molecular markers that can even be specific for a given type of cancer.

Stage 2 would be to detect targets outside the peripheral blood system, in the intercellular space. As long as the nanoparticles are smaller than 50 nm, they could leave the cardiovascular system through pores. Possible targets are cancer cells expressing altered receptors or, in the brain, amyloid plaques in Alzheimer's patients.

The most difficult region for the particles to reach is the inside of cells—Stage 3—to detect, for example, such cancer-specific molecule variants as mutated p53. To enter cells, a nanoparticle could contain a molecule in the outer layer that can induce uptake into the cell. Such molecules are already known; for example, a peptide from the TAT protein of the HIV virus can enter into cells and is capable of taking a payload, even a nanoparticle, with it.

One major target that can be monitored by a nanotrailmix approach in all three stages of development is infectious agents such as viruses, bacteria or parasites, some of which can be present in the bloodstream as well as on cell surfaces or inside cells. A nanotrailmix has the "nanoadvantage" of early and rapid identification of such infectious agents, whereas the conventional approach involves growing cultures before the infectious agents can be identified. This advantage comes to play at all three stages. For example, while current blood tests can already measure molecules in the blood without any nanoparticles, a nanotrailmix would enable doctors to measure a large number of possible targets at the same time. "A nanotrailmix approach gives you the ability of massive parallelism," said one member of the group.

It is unclear, however, where in the body the particles encounter their target molecules once they are in the urine. Imaging could be used to specifically look for the location of these target molecules, perhaps even using nanoparticles coupled to contrast agents and then localized inside the body.

Many more hurdles and gaps in knowledge remain to be overcome. One is that there is little known about the biocompatibility of nanoparticles. The strategy for the particles to exit cells is unclear as well. It may also be difficult to amplify the signal coming from the oligonucleotide barcodes. One way to label them is fluorescent molecules, but with only a few fluorescent molecules per nanoparticle, the signal may be too weak. Another concern is the potential environmental impact of the particles.

The group also discussed the potential societal impact of the nanotrailmix approach. One group member pointed out that continuous monitoring with nanoparticles could make people overly concerned about their health. "Maybe you are going to have some serious hypochondriacs," that group member noted. The problem could be avoided if hospitals analyze the particles and alert patients only if they find something. Another problem is that every single particle type might require separate FDA approval. "Maybe your grandchildren will see this technology," a group member said.

Group members agreed that the societal impact of the nanotrailmix technology would be positive in that it would be easily deployable to developing countries, and it would enable the collection of new research data for epidemiological studies. However, there was concern about privacy issues, with the collection of so much data, and about possible false negative or positive results. The exact cost of care using the nanotrailmix technology is unknown, but some in the group said it might cost less to determine the kind of cancer a patient has than such current invasive approaches as surgery.

Some group members indicated that there is a long way to go before the technology discussed becomes realized. "This is really hard, and that's fine; it's not going to happen over night," commented one group member. "We need to be very careful what we promise."

The challenge is to incorporate sufficient specificity and functionality into the particles, but still conform to the size requirements, one group member said, adding that the functional layers will likely make the particle larger than 5 nm. "That's not to say it can never be done, but these are the kinds of challenges that you are going to have to figure out," the group member noted, adding that one could use self-destructive polymers so particles bigger than 5 nm would eventually go away; or one could use composite particles that fall apart at some point. It was also suggested to keep the particles circulating so they could be bigger than 5 nm. After encoun-

tering their targets, the particles could change color or become fluorescent while in circulation, so as to be detectable by optical methods, for example, through the skin or eye.

However big the challenges are, many in the group said that simply discussing such issues in the focus group gave them novel insights from other disciplines. "It was intriguing and enthralling to brainstorm with people of such diverse backgrounds," one group member said. "The networking through brainstorming was a very effective mechanism."

Build a Cell-Chip Interface to Sense Response to Drug Leads and Toxins

FOCUS GROUP DESCRIPTION

Background

The responses of biological systems to drugs or toxins are typically measured at supracellular levels, ranging from tissue cultures to whole organisms. Some measurements have become possible at the level of single cells by the use of fluorescent indicators (e.g., fluorescent protein indicators of gene expression, calcium concentration, or receptor binding and internalization). A number of assay systems of these kinds has been commercialized (Ref 1). The further development of cellular scale detection, and the development of models of cellular scale responses, would contribute greatly to the discovery of new pharmaceuticals and protective agents.

The Problem

Some issues relating to the development of cellular scale detection methods and models include the following:

- Some biopolymers are present in small numbers in the cell, so that noise due to small sample sizes should be considered (Ref 2).
- Electronic detection of bioactive molecules by nanoscale systems, such as carbon nanotubes, is currently being explored (Ref 3). A useful on-

line lecture by G. Gruener is available at http://cyclotron.aps.org/weblectures/biology2004/20040201-umwlcd0001-002/real/index.htm.

- Optical nanosensors for use in single cells are also currently being explored (Ref 4).
- What other ideas might be worth considering? Inverted receptors, with normal cytoplasmic readout side available outside the cell for signal transduction? Functionalized viral capsids or other structures that might be endocytosed?

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FOCUS GROUP SUMMARY

Summary written by:

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Focus group members:

- Barbara Baird, Nanobiotechnology Center Director, Nanobiotechnology Center, Cornell University
- Nathan Baker, Assistant Professor, Department of Biochemistry and Molecular Biophysics, Washington University, St. Louis
- Mark Banaszak Holl, Professsor, Department of Chemistry, University of Michigan
- Andrew Barron, Charles W. Duncan, Jr., Welch Chair of Chemistry, Department of Chemistry, Rice University
- Brian P. Helmke, Assistant Professor, Department of Biomedical Engineering, University of Virginia

- Shana Kelley, Assistant Professor, Department of Chemistry, Boston College
- William King, Assistant Professor, Department of Mechanical Engineering, Georgia Institute of Technology
- Dan Luo, Assistant Professor, Department of Biological and Environmental Engineering, Cornell University
- Scott Martindale, M.A. Candidate, Print Journalism, Annenberg School for Communication, University of Southern California
- Anatoli Melechko, Doctor, Molecular-Scale Engineering and Nanoscale Technologies Group, Oak Ridge National Laboratory
- Adrienne Minerick, Assistant Professor, Dave C. Swalm School of Chemical Engineering, Mississippi State University
- Paul Nealey, Professor, Department of Chemical and Biological Engineering, University of Wisconsin
- Michael Sailor, Professor, Department of Chemistry and Biochemistry, University of California, San Diego
- Edward (Ted) Sargent, Associate Professor, Department of Electrical and Computer Engineering, University of Toronto
- Philip Szuromi, Supervisory Senior Editor, Science Magazine
- Todd Thorsen, Assistant Professor, Department of Mechanical Engineering, Massachusetts Institute of Technology
- Victor Ugaz, Assistant Professor, Department of Chemical Engineering, Texas A&M University
- Markus Zahn, Thomas and Gerd Perkins Professor of Electrical Engineering, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology

Summary

Imagine being able to take measurements on a single cell, to get accurate readouts that overcome the immense challenges of low signal outputs and interference, with a precision and an effectiveness that allows for early detection of disease and readily gauges the effectiveness of new drug therapies.

In three days of intensive roundtable discussions, an 18-member focus group discussed how to turn that vision into a reality.

With expertise in all of the applied sciences, from cell biology to electrical engineering to biophysics, the group pooled its knowledge and labo-

ratory experience to brainstorm, debate, and mull over a macroscopic answer to a very microscopic problem.

"What if we made it our goal to come up with a laboratory technique that penetrated every biology lab in the country?" asked William King, an assistant professor of mechanical engineering at the Georgia Institute of Technology.

The concept of extracting information from cells is not new. For decades, electrophysiologists have prodded and poked at cells, extracting limited amounts of data on physiological cell states and processes. But the focus group felt that the envelope could be pushed further, that a "nanoprobe" could be created to garner virtually unlimited data from a single cell.

The first task: defining the problem. Because the assignment as presented was intentionally vague, group members had their own interpretations and preconceived notions about how to tackle it. The group drifted into lengthy discussions of existing technologies and how such technologies could fit into a master plan for this project. Microarray technology, which essentially places a human on a chip, was initially viewed as key to building a cell-chip interface, as were standard techniques for measuring protein concentrations and other physiological states inside a cell.

Eventually, the question came back to nanotechnology and how it could be used to find a new solution to an old problem. What more could nanotechnology offer that existing technologies did not already offer?

The group continued to dissect the assignment, next questioning the value and practicality of taking measurements on a single cell. Would interrogating individual cells be possible? Could it be done *in vivo*? Would it be more useful to focus first on an *in vitro* model? Given federal laws governing scientific research on human beings, the group realized that an *in vitro* model would be a more practical approach, at least initially.

But even working with cells in a laboratory comes with its own set of problems, as group members pointed out. The finicky nature of human cells, along with the challenge of artificially inducing sickness or disease, led some to question the necessity of using human cells at all.

"If we can build up an artificial cell, then we won't have any problems delivering nanoprobes," said Dan Luo, an assistant professor of biological and environmental engineering at Cornell University.

Edward Sargent, an associate professor of electrical and computer engineering at the University of Toronto, liked the idea, pointing out that one

could remove the contents of a cell, then add organelles back one at a time for greater control over an experiment.

But Barbara Baird, director at Cornell University's Nanobiotechnology Center, pointed out that artificial cells are very different from real cells. "I don't think anyone would believe an artificial cell would be a good model," Baird said.

As group members continued to brainstorm and debate, the focus of the discussion gradually began to shift to the next major task: conceptualizing the nanoprobe and its potential—and potential limitations.

Group members agreed that the nanoprobe should act like a camera, taking "snapshots" of the cell at given points in time. Yet what would the nanoprobe measure and report back?

Because the goal of the probe was to detect disease, the group realized that they would first need to know disease expression profiles—that is, the proteins expressed in diseased cells. But scientists do not know expression profiles of all diseases, especially at the intracellular level. Compounding the problem, as some group members pointed out, would be the challenge of designing a probe specific enough to detect only the expression profiles of interest.

Others pointed to the difficulties of interpreting the profiles, and that was assuming such data could be obtained in the first place. The group agreed that a baseline must first be established to gauge changes to a cell in response to single or multiple challenges. However, given cell-to-cell variability, the group acknowledged the enormous challenge of developing accurate baseline readings for a single cell.

Also brought up was the question of scale—that is, how big the nanoprobe would be. The group agreed that the nanoprobe should package the maximum number of parameters into a minimum amount of space. However, figuring out how many parameters could fit into a single probe was not something group members could resolve until they knew what the parameters were going to be.

Then there was the practical question of what the probe would be made of. Would it be encapsulated? If so, how? Resolving these manufacturing questions, the group realized, was not feasible in the time allotted.

Some group members, for the sake of discussion, suggested 10 nanometers as the theoretical diameter of the nanoprobe and asked the group whether a cell could take it up. Their colleagues had the answer: with an average diameter of 10 micrometers, a cell easily could take up a 10-nanometer probe.

With this discussion came the question of whether the probe should enter the cell like a submarine or take all of its readings from the outer surface of the cell membrane. Some group members also asked whether it would be necessary to get the probe back out. Everyone agreed that keeping the probe outside the cell would be easier and pose less of a problem, but the group also realized that far more data could be gathered if the probe also entered the cell.

The answer, then, at least from a theoretical basis, was simple—the probe would almost certainly have to enter the cell. But would it be just one probe? The group discussed the possibility of a number of different probes, some inside the cell and others outside. These probes, supplemented by other cell-targeted techniques, such as dielectric constant spectroscopy, stretching, and compressing, were all viewed as potentially useful in extracting the maximum amount of data from a single cell.

The next logical concern was whether the nanoprobe might have perturbations on normal cellular processes and affect the readouts. A nanoprobe measuring 10 nanometers in diameter would only take up about a billionth of the volume of the average mammalian cell, but because cells have no free space inside, group members pointed out that any volume added to the cytoplasm could have detrimental effects. However, others pointed to the inevitability of invasiveness and advised against dwelling on it.

Also discussed was a viable method of signal detection, given the small size of the nanoprobe and its consequently small signals. Group members pointed out the pros and cons of chemical, electrical, magnetic, and fluorescent signals. They debated using different combinations of these signals and discussed how best to amplify the signals.

Some suggested that detecting tiny signals would be accomplished most effectively by using fluorescent dyes instead of using such instruments as mechanotransducers and magnetic detectors. Others pointed to the efficacy of indicators that track everything from DNA methylation states and gene mutation to cell cycle checkpoints and viscosity.

Throughout the focus group discussions, each issue discussed seemed to raise an entirely different set of questions and challenges. During the first day of talks, group members realized that, because of the size of the group, the discussion was unfocused and not everyone was on the same page or necessarily putting priorities and objectives in the same place. But the group devised an effective solution: each member prioritized his or her

goals for the discussion by writing on a sticky note the biggest problem or objective of building the cell-chip interface.

The sticky notes were placed on a whiteboard and grouped into categories. Several members saw the delivery of the nanoprobes as the key issue to resolve. Others saw signal detection as the biggest hurdle. Still others saw resolution, readout, and controlling the cell's activity as key issues to discuss. Once these priorities had been established, more focused discussions were possible.

By the end of the conference, group members proudly reported that they had developed an outline for interrogating an individual cell using nanotechnology. The theoretical protocol was as follows:

- Position a cell over the nanoprobes.
- Use mechanical force to impale the cell on a microfluidic array.
- Create a cellular activity profile using nanoprobes that act as mechanical and chemical sensors.
- Compare the activity profiles of healthy and diseased cells, to identify diseased states of individual cells.

While the focus group did not generate a detailed plan of attack—which was not the goal of the conference—group members learned how their colleagues tackle scientific problems and how to pool knowledge and talents to conduct interdisciplinary research. Perhaps equally important, the group learned to have fun at the same time.

"We decided to build a cell torture device instead," said Todd Thorsen of the Massachusetts Institute of Technology, who presented the group's findings to conference attendees.

Sequence a Single Molecule of Protein

FOCUS GROUP DESCRIPTION

Background

The study of protein structure and function is central to understanding living systems. However, the diversity and complexity of proteins render even the simplest characterizations challenging. The most basic level, determining the primary structure, involves sequencing the polypeptide chain. Even state-of-the-art commercial sequencing techniques require picomolar samples, equivalent to micrograms of protein or ~10^{13} molecules. In contrast to this scale, laboratory experiments at the forefront of the field can access and manipulate single proteins with various physical techniques. These experiments have already shed light on structure and dynamics. Beyond simple sequencing, the higher-order structure of proteins—linked to understanding the folding process—remains elusive in the general case.

The Problem

As typical methods for determining sequence and structure of proteins require large quantities of the molecule, these studies are often delayed until the requisite quantities are synthesized or purified. In the case of high-resolution crystallography, additional effort is required to crystallize sufficient quantities of the protein. Given the appearance of groundbreaking

single-protein studies with new tools, will it soon be possible to sequence a single molecule of protein? Consider a combination of existing techniques or newer techniques which need to be developed; for example:

- Modifications of common amino acid sequencing techniques (filtration, cleavage, etc.)
- Mass spectrometry
- Optical tweezers
- Cantilever-based force measurements
- Nanopores/microfluidics
- Scanning probe methods
- Crystallography
- Electron holography

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FOCUS GROUP SUMMARY

Summary written by:

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Focus group members:

- David Auston, President, Kavli Foundation
- Mark Hersam, Assistant Professor, Department of Materials Science and Engineering, Northwestern University
- Abraham Lee, Professor, Department of Biomedical Engineering, University of California, Irvine
- Luke Lee, Professor, Department of Bioengineering, University of California, Berkeley

- Randolph Lewis, Professor, Department of Molecular Biology, University of Wyoming
- Hari Manoharan, Assistant Professor, Department of Physics, Stanford University
- Maureen McDonough, Graduate Student, Science Writing Program, Massachusetts Institute of Technology
- Thomas Perkins, Associate JILA Fellow, JILA, National Institute of Standards and Technology and The University of Colorado at Boulder
- Jon Pratt, Manufacturing Metrology Division, National Institute of Standards and Technology
- Alan Russell, Director, McGowan Institute for Regenerative Medicine, University of Pittsburgh
- David Tennenhouse, Vice President, Corporate Technology Group, Intel Corporation

Summary

The protein sequencing group considered themselves lucky. With a clearly defined problem in hand, several members came to the first session with ideas about what the solution should look like. Jotted down on hotel letterhead the night before, it was clear that several of these eleven men wanted their solution on the fast track to the final presentation. The thought of finishing early and taking off to Disneyland was considered, but was taken off the table when everyone began to realize that not everyone had the same answer to the problem.

The group's problem was to figure out how to sequence a single protein molecule. The sequencing techniques currently used by researchers require a large and highly concentrated sample of a protein. However, many proteins exist naturally in extremely small quantities: an individual cell may only have one or two copies of specific hormones and transcription factors. The ability to sequence these proteins would help in determining their structure; and, by combining sequence and structure information, large amounts of a specific protein could be produced and used in therapies. Such techniques could also be used diagnostically by identifying specific proteins associated with conditions or diseases.

There was little debate about the focus group's goal or its importance, but deciding what was the best line of attack proved challenging. There were many strong personalities; as a result, no one person was able to force his vision upon his colleagues. Some group members were in favor of "visu-

alization" and believed that if a protein could be linearized and attached to a solid surface without any contamination then the sequence could be read using an atomic force microscope. Other members were in favor of the "flow channel" method in which a protein would be linearized and passed though a channel that would detect the sequence via nano-array. Someone else continued to stress the importance of using information available from the sequence of the human genome, by checking the determined amino acid sequence against known DNA sequences.

The differences in opinion regarding the ideal solution led to a tendency for individuals to interject with statements or questions that would pull the discussion toward the idea in which they were most interested. Even with this tug-of-war, most of the group's discussions were very productive and focused on specific aspects of the problem. Eventually an agreement was reached to focus on the solution that was showcased in the group's final presentation. It was not a coincidence that this solution involved input from most of the group.

The first decision to be made was whether the protein should remain intact, throughout the sequencing process, or if each amino acid should be systematically cleaved and detected. One of the benefits of keeping the sequence intact is that a single protein molecule could be sequenced many times. The group members in favor of visualization and the flow channel solutions cited repeatability as a huge benefit to their approaches. However, it was estimated that the visualization technique would take a trained technician an entire day to sequence a single protein, and a more efficient method was desired. The flow channel solution was also ruled out because most of the group was convinced that the forces exerted on the linearized protein as it passed though the channel would break it apart. So the group was forced to deal with the fact that the protein would need to be chopped up. There would be only one opportunity to read the sequence and then "game over."

The group decided that the chopping reactions currently used in sequencing could be used in single molecule sequencing as well. Using specific chemical reactions, individual amino acids could be cleaved from the amine end of the protein one at a time. In the first step of the group's design, the protein would be bound to the sample chamber at the carboxyl terminus. There was concern about losing the single protein molecule in this step, so it was suggested that a fluorescent probe could bind to the protein. Once detected, the stepwise reaction would cleave off a single amino acid to be identified.

The free amino acid would then be washed down into the first detection chamber. Here the amino acid would be temporarily bound to a silver substrate, and a laser would be used to generate a surface enhanced Raman spectra. SERS detection provides some information about the structure of a molecule, and may be able to determine the specific amino acid, but at a minimum could be used to ensure that an amino acid was released during the cleaving reaction, which only goes to 99.8 percent completion.

The amino acid would then be washed down into the second detection chamber called the riboswitch chamber. A riboswitch is a sequence of RNA that cuts itself in half when a specific molecule binds to it. Two naturally occurring riboswitches have been discovered that are tripped by gylcine and lycine, respectively; and the group suspected that switches specific to the remaining 18 amino acids could be engineered. The riboswitches that are specific to each of the 20 amino acids would be attached along a wall of this detection chamber. Like balloons on strings, attached to each variety of riboswitch would be a specific colored quantum-dot. Also called Qdots, these semiconductor nanocrystels light up in a variety of colors.

All of the lycine switches, for example, could be red; and all of the glycine switches could be green. When the amino acid enters the chamber it would bind to its specific riboswitch, which would then cleave itself; and a specific colored Qdot would be released. A sensor would detect the color, and the amino acid could be identified and then compared to the Raman spectra results. The amino acid and the Qdot are then washed out of the chamber and another amino acid could be cleaved in the sample chamber. The determined sequence would then be compared to known sequences in a database.

As creative and colorful as this idea is, the group identified several places where the mechanism could break down. One concern that deeply bothered the group was how to ensure that the amino acid did not get stuck to a wall on its way through the detection chamber. It was suggested that a solution with a high salt concentration could be used to wash off a stuck amino acid, but that could raise stability problems with the surface/riboswitch/Qdot complexes.

Research challenges were identified at each of the steps in the group's solution. The sample chamber needs to be scaled down to a single molecule. The SERS detection chamber needs an optimized surface substrate, and Raman signature spectra for each of the 20 amino acids need to be determined. The riboswitch chamber needs switches and quantum dots

specific to all 20 amino acids and a way to attach the switches to the chamber wall and the dots to the switches.

The second solution presented was the rejection of the central dogma. More dramatic and perhaps less practical of a solution, some members of the group hope to achieve "reverse translation." The argument presented was that though an enzyme that could achieve reverse translation has not been identified, it may exist somewhere in nature. After all, no one believed that reverse transcription was possible until it was discovered that nature had found a way. Even if the enzyme could not be found in nature right now, perhaps it could be created in a laboratory. In order to work, the enzyme would need to be able to use tRNA to identify each amino acid in order and ligate the RNA codons to generate the mRNA.

Another solution involved the riboswitch model. If DNA could be released instead of a quantum dot, then each piece of DNA representing an amino acid could be ligated to the previous piece, creating a sequence of DNA that corresponded to the amino acid sequence. The standard procedures for DNA sequencing could then be used and, in effect, reverse translation achieved.

What made this focus group unique was the specificity of the problem. Because there was no real debate about what the problem was, there was time to address several possible solutions and their individual challenges. The design and the discussions were about details. And though they did not get a chance to go to Disneyland, I think everyone was happy with the focus group's findings.

Build a Glucose Sensor to Circulate (Implant) In Vivo in Humans and Regulate Insulin

FOCUS GROUP DESCRIPTION

Background

The continuous monitoring and maintenance of near normal blood glucose levels could save diabetic patients from serious complications. The development of reliable long-term functional implantable biosensors for continuous glucose monitoring has become of interest in the development of optimum treatment of diabetics.

The Problem

- Development of novel biocompatible implantable materials that can be processed using micro and nano processing techniques for fabricating glucose sensors
- Development of novel micro and nano fabrication techniques to fabricate implantable devices as glucose sensors
- Development of novel surface modification techniques for biomolecule immobilization to improve biocompatibility and functionality of implantable glucose sensors
- Development of novel methods with high specificity and reliability for rapid and continuous detection of glucose level in vivo

• Development of novel techniques to couple smart insulin delivery systems to implantable nano or micro glucose sensors

Initial References

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FOCUS GROUP SUMMARY

Summary written by:

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Focus group members:

• Ananth Annapragada, Associate Professor, Department of Bioinformatics, University of Texas Health Science Center at Houston
• Andres Garcia, Associate Professor, Department of Mechanical Engineering, Georgia Institute of Technology
• Eleni Kousvelari, Acting Director, Center for Biotechnology & Innovation, National Institute of Dental and Craniofacial Research
• Greg Lanza, Assistant Professor of Medicine, Department of Medicine and Biomedical Engineering, Adjunct Assistant Professor of Biomedical Engineering, Washington University Medical Center
• Peter Ma, Associate Professor, School of Dentistry, University of Michigan
• G. Ramanath, Associate Professor, Department of Materials Science and Engineering, Rensselaer Polytechnic Institute
• Robert Raphael, Law Assistant Professor, Department of Bioengineering, Rice University
• Dave Roessner, Evaluation Consultant, The National Academies Keck *Futures Initiative*
• Judith Stein, Chief Technologist-Emerging Technologies, Department of Polymer and Specialty Materials, GE Global Research

- John V. Stone, Applied Anthropologist, Institute for Food and Agricultural Standards, Michigan State University
- Jonathan Stroud, Graduate Student, Science Writing Program, University of Southern California

Summary

Focus Group 6 at the 2nd Annual National Academies Keck *Futures Initiative* Conference was initially charged with "Building a glucose sensor to circulate (implant) in vivo in humans and regulate insulin."

Instead, they determined and ranked the most viable options for glucose sensing and insulin delivery in the near future, using the scientific, social, and ethical implications of those treatments as a framework for consideration. They then presented their results to the general assembly of the *Futures Initiatives* conference.

The group was 1 of 10 such focus groups at the conference. The purpose of these focus groups was twofold: first, to facilitate future interdisciplinary research by developing ties between scientists from diverse fields of interest; and second, to solve potentially revolutionary problems using nano- or microtechnology and a wealth of expertise.

They did this by introducing individuals from diverse science-related backgrounds and giving them a challenging nano- or microscience-related problem, which they then attempted to solve over the five focus group sessions.

The idea was novel and admittedly untested, said Dave Roessner, an evaluation consultant for the National Academies Keck *Futures Initiative*. "It's an experiment," he said. "I'm fascinated with watching the process."

Over the course of the four-day conference, the group met for eight hours over four sessions.

The Group 6 members first introduced themselves one by one, summarizing their diverse areas of expertise, which ranged from applied anthropology to tissue engineering.

The members included Ananth Annapragada, an associate professor at the University of Texas Health Science Center at Houston; Andres Garcia, an associate professor at the Georgia Institute of Technology; Eleni Kousvelari, the acting director of the National Institute of Dental and Craniofacial Research; Greg Lanza, an assistant professor of medicine and adjunct assistant professor of biomedical engineering at Washington University Medical Center; Peter Ma, an associate professor at the University of

Michigan; G. Ramanath, an associate professor at Rensselaer Polytechnic Institute; Robert Raphael, an assistant professor at Rice University; Judith Stein, the chief technologist for emerging technologies at GE Global Research; John V. Stone, an applied anthropologist at Michigan State University; and Roessner.

Initially, the group appointed Annapragada the leader, and then asked Lanza, a member of the conference planning committee, to explain the types of diabetes, current treatments and problems facing physicians.

"Diabetes is a complicated disease fundamentally associated with a lack of insulin, the hormone that helps regulate blood sugar," he said.

"Diabetes mellitus has two distinct varieties: diabetes type I is an autoimmune disease found in younger patients, while diabetes type II occurs as a result of obesity and hypertension and normally develops in older patients," he said.

In type II, the body's cells build up a resistance to insulin, and the pancreas' islet cells, which secrete the hormone, must work harder, producing more insulin to assist in the uptake of glucose by the cells.

Complications arising from diabetes involve blindness, renal disease, neuropathy, cardiovascular problems, stroke, and heart attack. "Hypervascularization in the eye can also lead to blindness," he said. Furthermore, hypoglycemia leads to the metabolism of fatty acids into ketones, which results in acidic blood.

"Obviously there are a lot of issues that can still be resolved, especially with type II diabetes," Garcia said. "The potential threats are enormous."

Diabetes can be treated by exercise and diet control, but often more action is required. Currently, managing diabetes normally involves sensing the levels of glucose in vivo by drawing a small amount of blood through the skin, normally with a small needle, or a "finger-stick."

"Then, once reliable and regular sensing occurs, an adequate level of insulin must be injected into the patient's blood stream," Lanza said.

There are many different types of insulin on the market, including short- and long-lasting versions. However, in almost all cases, the insulin must be injected intramuscularly multiple times a day.

After Lanza finished explaining diabetes, its treatments, and its complications, the group decided to abandon the original focus of building a circulating glucose sensor.

Many group members did not have the background to develop a novel micro- or nanotechnology approach to address the problem, according to group members.

"Instead, we chose a different path," Roessner said.

The group decided to focus on current technologies and experimental approaches to the problem and to use their interdisciplinary expertise to attempt to gauge which technology has the highest chance of success. The group also highlighted the major barriers to more effective insulin regulation. Key to the discussions was that the group framed their process around the potential social and ethical considerations, rather than incorporating such considerations at the end of the process.

"(Some of) these systems have been around for decades," Annapragada said. "We turned them around and looked at it from a consumer's point of view."

What emerged was a list of different techniques currently being used to address the problem.

The most common means, according to Lanza, is a regular fingerstick coupled with intramuscular insulin injections. But the pain, regular injections, and the chance of human error make this treatment option imperfect.

Some patients wear an external, programmable insulin-pump that doses them before meals, but users must still routinely monitor their glucose levels. In addition, the pumps, which often contain an implanted needle for insulin delivery, can become infected.

Nancy Moteiro-Riviere, a professor who had worked with glucose-sensing technology, described a glucose-sensing watch she helped develop at North Carolina State University.

She said the "GlucoWatch" used reverse-iontophoresis to pull glucose out of the skin transcutaneously. In addition, the watch stored the information and even told time.

The group then looked at an SMSI implantable sensor. The sensor, which is currently undergoing clinical trials, uses radio frequencies to broadcast glucose information to a receiver worn outside the body, has a 6 to 12 month shelf life, and is the size of a small, thin pill.

Lanza also described an ingestible gastrointestinal mucosal patch that adheres to the GI and loads the blood with insulin, as well as an aerosol form of insulin that is inhaled.

He discussed experimental stem cell implants and islet cell implants, and explained that currently, insulin-producing islet cell implants are only viable for 60 days on average.

"Control is the problem," Lanza said. "The goal is to try to keep the

glycemic control as tight as possible." Otherwise, he said, people quickly become hypoglycemic, growing faint and syncopated.

The group decided that monitoring glucose levels was the first step to solving the problem.

They decided to focus on an ideal glucose-sensing device, and asked each member to brainstorm their own solution to the glucose-sensing problems. The group then reconvened and members presented their ideas.

Roessner suggested a tiny implantable sensor capable of transmitting reliable glucose data to receptors outside the body, not unlike the SMSI glucose sensor, only smaller, more reliable, and with a longer device lifetime.

Kousvelari proposed an intra-dental implant residing in a false tooth, an idea Stone seconded and expanded on. "You could include a port to pump insulin in," he said.

Then Garcia suggested a contact lens that has the ability to fluoresce in response to the concentration of glucose.

Ma proposed a gum with the ability to sense glucose levels in saliva; he also suggested a tissue-engineered cell-based system.

Next, Annapragada suggested inhaled particles that contained a compound that would break down and release insulin when the concentration of glucose in the lungs (a symptom of diabetes) rose.

Raphael had two ideas: First, a liposome that contained a glucose-binding protein and an MLCS channel, which would respond to mechanical stresses and then, when the glucose bound to the liposome, would release insulin; and second, non-invasive optical imaging that would send lasers through the skin and detect the level of glucose.

Ramanath put forward an earring or tattoo receiver with a chip made from conducting polymers, and that used frequency to monitor glucose levels through sweat, body heat, and intravenous fluids.

Lanza's idea was an external skin patch that could sense glucose through the skin.

Group members then voted for their first and second favored approach to the problem. Once the votes were tallied, the group picked the three with the most votes, deeming them the most viable.

An implantable micro- or nanosensor was the most popular solution, followed by tissue engineering implants and an external glucose sensor.

Then the group drafted a list of criteria which they believe a sensing apparatus would need to meet to be ideal. The group then prioritized attributes that were necessary to ensure that the objectives would be met.

The list of attributes included sensitive and reliable output, real-time output, an interrogation capability, device lifetime, device size, the expected inflammatory or immune response, convenience of implantability, recoverability, power source, cost-effectiveness, programmability, and the measure of fail-safe assurance.

These factors were all given a rating: either easiest to overcome, moderate to overcome, or hardest to overcome. The group then constructed a color-coded chart that helped visualize the differences between the three distinct approaches.

The group discussed the social and ethical implications of each approach, weighing the pros and cons of each. The group decided the general public would be far more receptive to an external glucose sensor, making it a much more marketable approach. They then presented their results to the conference.

When asked how they felt about the focus group sessions, some members felt the level of expertise was lacking, but said that the broad set of backgrounds helped the group consider a wide range of implications.

"We voted on limited expertise, but it almost doesn't matter," Roessner said. "The interchange and exchange that went on was superb."

Group members said that, while they did not believe the group developed any novel ideas, they thought the interdisciplinary nature of the discussion was enriching and significant. "We spent a lot of time debating the social and ethical implications of this technology," Annapragada said.

Stone agreed. "I don't know how useful what we came up with will be," he said. "But it was an interesting process."

An In Vivo Nanofactory: The Medicine of the Future

FOCUS GROUP DESCRIPTION

Background

Science fiction writers have conjured up bacterial colonies as future large-scale factories of engineered nanomaterials or nanomachines, which could then be assembled or self-assemble into macroscale objects useful to society. The convergence of nanotechnology with biotechnology has the potential to enable engineered biological processes to catalyze, 'grow,' and assemble complex engineered objects (Ref. 1). One step forward in this future vision is to use engineered biological (bio-mimetic) processes to create a desired step in such an assembly process, such as to create a nano chemical factory to synthesize three amino acids in a row, to synthesize a drug, or to perform a function such as closing a shutter or generating voltage across particular nanocontacts.

Science has made progress along these lines: cells are remarkably efficient at catalyzing a wide range of chemical reactions (Ref 2), such as fermentation, respiration, and photosynthesis, using a variety of electron donors and acceptors. Recently, researchers have been able to program cells in rudimentary ways to perform tasks not evolved in nature (Ref 3). For several years, researchers have been able to couple natural biomachines with engineered materials to create a hybrid nanomachine (for one example, see Ref 4). In addition, researchers have been able to; use RNA reactions inher-

ent to biomineralization pathways to catalyze mineralization reactions *in-vitro* (Ref. 5), use DNA or viruses to assemble nanocrystalline arrays (Ref. 6), and use biological pathways to create new engineered materials (Ref. 7). Researchers are also beginning to harness nature's self-assembly processes (Ref. 8).

The Problem

Your task is to create a scientific plan for using biological or biomimetic mechanisms to create one or more steps in a bio-nanoscale assembly process that could be scaled up to synthesize useful products in volume.

- First, the group should decide what the ultimate product is, such as, for example:
  - —Create an engineered method of effective remediation of contaminated ground water, where the nanoproduct can learn what the dangerous contaminants are, grow the machinery to neutralize them, and then afterwards disassemble into environmentally friendly materials;
  - —Create an engineered method for creation of 'smart' clothes that will sense the environment and automatically adjust their breathability, UV blocking ability, water repellency, toughness, cooling and heating or germicidal abilities; or,
  - —Feel free to create your own grand challenge.
- Next, pick one or several limiting steps in the manufacture of such a product and come up with a scientific plan to potentially accomplish them, including what scientific knowledge or engineering prowess we currently lack, and thus would need to learn in order to accomplish this task. For example, in choice a) or b) above, how would one go about creating swimming devices or fibers that 'sense' the environment around them? What should be sensed? Once the environment is measured, what mechanisms, including feedback and control, would be relevant to react to that information? How does one deal with stochastic processes on the nanoscale?
- Finally, use the group's ingenuity to propose a plan for the manufacture in large volume of your product or sub-product, using biomimetic principles. As always, the group should discuss the ethical considerations in the manufacture of your products. How would one perform the manufacture as safely as possible? What controls should be put in place?

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FOCUS GROUP SUMMARY

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Summary

Tiny solutions for big problems

When great minds in modern science convene to identify and solve the big problems facing the world, it is impossible for them to disregard flaws in human health. Disease comes in many forms, but consistently confers pain and suffering on individuals. Some of the greatest challenges in science and engineering today involve understanding diseases at a fundamental level and developing innovative solutions for battling them.

This grand challenge was the inspiration for a group of 13 researchers—biologists, chemists, physicists, and engineers; the best in their respective fields—to propose the construction of a biological *nanofactory* that could be broadly applied to prevent or remedy diseases ranging from mental retardation to prostate cancer.

The nanofactory was a solution to a problem posed to these researchers

at the Second Annual National Academies Keck *Futures Initiative* Conference, "Designing Nanostructures at the Interface between Biomedical and Physical Systems." Charged with "building a factory to synthesize products," utilizing biological systems as starting materials, the group pooled their broad and varied areas of expertise to design a prototype for an artificial *pseudo-cell* that will have the ability to manufacture and deliver a biological product to an appropriate region of the body to correct an existing biological condition. Such a nanofactory would be therapeutic in a number of diseases including diabetes, thyroid disorder, and cancer.

A nano-"mobile defense force"

Before delving into the specific aspects of disease chemistry, the group used their engineering prowess to describe a prototype for their powerful nanofactory, a weapons factory a billion times smaller than a single bullet, that could single-handedly wage war against human disease.

A sketch of the nanofactory highlights six basic components. These key features are comparable to those required in a more conventional factory.

Just as pharmaceutical or car manufacturers must carefully select their location site to market their product to consumers, the nanofactory must have a mechanism for targeting the region for which it will manufacture its products. A delivery sensor—manifested as a cell-specific antibody or another recognition molecule—can be chemically attracted to the body tissue that would benefit from the factory's product.

A second, and somewhat self-evident, requirement of the factory is its walls. A car company will construct a building that will be suitable for the conditions necessary for its purpose; and the nanofactory, likewise, needs a compartment that can contain its inner workings. It must thus be like a human cell, which is compartmentalized inside a vesicle. The pseudo-cell's walls can be built out of a variety of materials that will suit its purpose of containing the inner workings without being rejected by the body. Both a lipid bi-layer and a polymer structure would serve to sequester the chemical assembly line. while allowing the flow of water through its pores to survive the strict osmotic regulations that the human body requires.

Next, there must be a front door, or input gate for the raw materials—chemical precursors, cofactors, and energy molecules—to flow in. In the most sophisticated incarnation of the nanofacotry, the door will be locked and will only open when the product the factory creates is needed in the

body. The key to opening the door will be a sensor that will detect chemical levels near the factory site.

Once the door is open, reactants, cofactors, and energy molecules can flow into the factory where they will move through an assembly line of enzymes each with a specific job to modify the raw materials into the desired product. The enzymatic assembly would be specific to the metabolic pathways necessary to produce the output of each nanofactory.

After the product is created it must exit the factory to be distributed where it is needed. An output gate can also be regulated with a key that will detect the presence of product inside the cell and open only when there is material to exit.

Finally, there must be damage control. What if the factory malfunctions or the patient reacts badly to its insertion? As it cannot be withdrawn, it must have a self-destruct mechanism that could be initiated by an external electric or magnetic field—something like an MRI—that would trigger the factory walls to decompose so that its inner workings could diffuse safely through the body.

A model for moderating PKU

The features described here must undergo significant engineering analysis to determine the best solutions to remedy or prevent a particular disease. A simple prototype can be built to provide an important proof-of-principle that the strategy will work.

A prototype nanofactory can be built to contain phenylalanine hydroxylase (PAH), the naturally occurring enzyme that is absent in sufferers of phenylketonuria (PKU) who experience severe mental retardation because the phenylalanine they consume in their diet cannot be properly converted to tyrosine. This disorder results from a common genetic mutation that affects 1 in 10,000 individuals. There is no cure; and the only remedy is a simple dietary measure that urges individuals genetically predisposed to PKU to avoid eating foods high in phenylalanine or its precursors, such as diet soda due to the product aspartame.

An anti-PKU nanofactory would include only one enzyme, PAH, in a simple assembly line that would convert phenylalanine, entering through the input gate, into tyrosine, which would exit through the output gate and diffuse through the patient's blood, remedying the natural deficiency. The factory could be dissolved in a solution and administered through injection. It would be targeted to the liver, where PAH is normally produced, via

chemical receptors. Intelligent design may mitigate the need for such receptors. Since all mid-size objects put into the body tend to congregate in the liver, an appropriately sized nanofactory—about 100 nanometers in diameter—will be drawn to the right place without any sensors. The tyrosine product would exit into the patient's blood stream, preventing a profound irreversible mental disease.

This pared down factory, proposed by the group, may require input and output sensors to serve as door-keys, but a molecular understanding of the nature of the disorder must be mastered for their design. While this gap in knowledge is not a general scientific failure, it was, unfortunately, not available within the expertise in the group. It points to a larger gap, though, for the expansion of this technology for other diseases: the metabolic pathways and basic biochemistry of the problem must be understood before a factory can be built to fill in for the body's malfunction.

Miniaturized pharmaceuticals

The design for the nanofactory laid out by the group can be modified for the production of hormones like thyroxine to manage thyroid disorder; growth factors, such as tumor necrosis factor-α (TNFα), to specifically target and kill cancerous tumors; and insulin precursors that could be produced and self regulated to relieve diabetes sufferers of daily injections. Nanofactories could also be used to withdraw unwanted materials from a biological environment—toxic chemicals resulting from a drug overdose or excess LDLs (low density lipoproteins), famous for their link to heart disease**.** Each of these conditions would require a complex multi-enzyme assembly line to produce the biomedically useful product.

The nanofactory blueprints developed by the group have the potential to revolutionize individualized medicine. Instead of taking daily doses of drugs, which are mostly excreted before they are absorbed and can cause nasty side effects, injections of medicinal nanofactories have the potential to offer selective, regulated, time-sensitive therapy to produce and deliver the medicine your body needs exactly when and where your body needs it.

While the factory blueprints can be drawn up without much further effort, as the biochemistry and engineering knowledge already exists, there are some gaps that must be bridged before the nanofactories can be mobilized to treat disease. The most difficult challenges to overcome will be disease specific, as the construction of the nanofactory will vary based on its desired function. Designing a vesicle to safely contain particular enzymes

will, of course, vary with the nature of those enzymes. The size and durability of the cell may also change, depending on its ultimate desired lifetime. A PKU sufferer, for instance, would require injections throughout his life, so a very stable pseudo-cell would maximize the factory's lifetime so that the patient would need to receive an injection only, say, once a month.

Unknown unknowns

Science fiction writers have conjured up images of nanomachines that can self-assemble into macroscale objects with powerful functions. Even on the nanoscale, a self-sustained and self-regulated factory inserted into a human body could potentially wreak biomedical havoc instead of providing therapeutic assistance to its host. Is such a concern menacing enough to impede research into their construction?

On the other hand, therapeutic nanofactories could be considered to be "politically correct" stem-cells, as they can be created to provide distinct therapy to various parts of the body selectively, without dealing with the matter of using discarded embryos. In addition, while the mechanism of stem cells is not yet well understood, the nanofactories present an intelligent alternative because they will be able to regulate and correct metabolic processes in a planned and organized way.

There are, as always, ethical concerns that must be considered along side the scientific details of the new technology. Overall, if further development of the in vivo nanofactory is approached with biochemical acumen and levelheaded caution, the gaps that exist in the current scientific wisdom can and should be resolved. The in vivo nanofactory holds a world of promise in treating a range of human diseases.

Postscript:

To further explore this topic, a focus group member recommends the following publication:

Noireaux, V. and Libchaber, A., *A vesicle bioreactor as a step toward an artificial cell assembly*, PNAS, December 21, 2004, vol. 101, no. 51, 17669-17674. (Published online before print December 10, 2004).

Improve Hydrogen Production by Genetic Methods: Design a Better Nanomachine

FOCUS GROUP DESCRIPTION

Background

In our increasingly mobile but always-connected society, there is a need for better small energy storage and conversion devices to provide a remote power source exactly where it is needed and only when needed, for example in cell phones, remote sensors, or in-body implants such as pacemakers, medical sensing, or drug dispersal devices. As our planet's fossil fuel supply diminishes and our concern for global warming, pollution, and other environmental costs of our current energy supply system increases, it is essential that we develop cleaner, more environmentally benign power sources as well. Ref 1 provides an overview of challenges in energy technology that could be addressed by nanotechnology. Miniature biofuel cells could be a means of converting stored bioenergy to power, or alternatively of harnessing hydrogen gas from inexpensive, readily available materials such as sea water for a source of fuel when needed.

Unicellular microorganisms are remarkably efficient at catalyzing a wide range of chemical reactions (Ref 2), such as fermentation, respiration, and photosynthesis, using a variety of electron donors and acceptors. Recently, researchers have been able to program cells in rudimentary ways to perform tasks not evolved in nature (Refs 3, 4).

Several types of algae and bacteria can produce hydrogen by photosyn-

thesis or fermentation. Photobiological technology holds great promise; however, as oxygen is also produced, the technology needs to overcome the limitation of oxygen sensitivity of the hydrogen-evolving enzyme systems. Screening for naturally occurring organisms, which are more tolerant to oxygen, as well as creating new genetic forms of the organisms that can sustain hydrogen production in the presence of oxygen is currently being performed (from Ref 5).

Biofuel cells have been reported (see Ref 6) achieving several hundred nanowatts of power, in which tethered biological enzymes at two electrodes first strip a hydrogen ion off glucose and then combine the H+ with oxygen to create both power and water.

Nanotechnology is currently revolutionizing small battery technology—see for example Ref 7.

The Problem

Given the information provided above (and any other research you choose to conduct) your task is to provide a scientific plan to create a programmed microorganism or a collection of nanobiomachines that uses water or oxygen as an input and creates a local source of hydrogen gas for use as a fuel. Decide on your specific goal, keeping in mind the following questions:

- What will be the power or hydrogen gas generation requirements needed for powering a PDA or a pacemaker 5-10 years from now? (Ref. 8)
- What are the environmental, safety, temperature, longevity, antifouling, or other engineering requirements needed?
- How efficient can this process be? Are there fundamental limits? If so, what are they?
- What are the overall fuel cycle costs of such a proposed technology?
- How would this technology compare (cost, size, efficiency, safety, environmental impact, temperature range, ease of use, robustness, and reliability) to competing technologies, such as nano fuel cells or nanobatteries?

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FOCUS GROUP SUMMARY

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Summary

Tiny solutions for big problems

Focus Group 8 proposed a novel, two-part approach to improving biological hydrogen production for local, off-grid energy generation. The overall goal was to use clean, renewable, and biodegradable resources and methods to reduce dependence on hydrocarbon fuels at a scale useful to small, remote villages.

The general idea was to develop first "a better bug" to convert solar energy to harvestable hydrogen gas. The proposed approach draws on contributions from Mother Nature's protozoans, bacteria and photosynthetic algae, assisted by high-tech methods from the biological, chemical, genetic, and pharmaceutical sciences. The improved, more robust organisms would then be put to work on-site within a nearly closed system aimed not only at hydrogen production, but also optimal utilization and recycling of by-products and end-products.

The social process that generated this proposal over the course of 7 1/2 hours together was a rather nonlinear, synergistic one. It entailed periods of whirlwind group discussion—with topics ranging from bovine flatulence to melting igloos—punctuated by occasional retreat for individual or small-group research and reflection. It began with groping for problem definition on Friday. It culminated Saturday with a surprising emergence of the final proposal—a "weird hybrid" incorporating many "crazy" and initially disconnected ideas from the preceding far-ranging conversations.

"I'm astounded," said one group member in the immediate wake of the final session. "I called my wife and said, 'I just saw an amazing two days.'"

What's the problem?

Initially charged with designing and growing "a bacterial or cellular factory to perform electrolysis of seawater to create hydrogen gas," Focus Group 8 devoted Friday's initial 1-hour session to surveying the group's range of expertise and defining the exact problem to be tackled.

On board were representatives from biochemistry, biophysics, chemistry, economics, electrical engineering, entrepreneurial enterprise, environmental chemistry/engineering, nanotechnology, physical chemistry, and physics. (Longed for by weekend's end were biologists of various stripes.)

"What's the problem?" became the morning's mantra as the group struggled to define which pieces of the hydrogen-production maze to address. To help frame the conversation, the group considered scales ranging from cityscape (100s kW/day) to microscales appropriate for space applications or human implantation (αW/day).

A variety of hydrogen-producing approaches were tossed up, ranging from the "pure biology" of hydrogen-producing green algae to the photoelectrochemistry of titania (titanium dioxide) semi-conducting nanoparticles. One "crazy, intriguing proposal" was to assemble a collection of hydrogen-producing enzymes, like biological "spare parts," to crank away within a tiny liposome pouch.

The group mused that significant contributions might come ultimately from developing a systems approach to hydrogen production and by-product utilization, rather than focusing on any single part of the production process.

By lunchtime and session's end, the group had decided to work on the problem of: *local production of hydrogen gas on a moderate scale (on the order of 10 kW) based on a non-hydrocarbon source*. A backyard in Somalia or remote Texas might be typical deployment sites.

Crazy thoughts and cow parts

Having narrowed the focus to moderate-scale hydrogen production—means yet to-be-determined—Focus Group 8 re-convened Friday afternoon to identify current bottlenecks that might yield to innovative approaches. Envisioning eventual depletion of hydrocarbon fuel resources, the group focused on methods driven ultimately by sunlight.

The pros and cons of a variety of approaches were considered in a 10-way, Ping-Pong-style group discussion with frequent contributions from

the World Wide Web. "Purely biological systems are self-replicating." Good. "But, accumulated waste products eventually shut down the system." Not so good. "But, wastewater treatment plants manage to keep such systems going." Good. "But, biological 'spare parts' don't have to be kept alive." Even better. "But, biological parts in isolation don't tend to function for very long." Not so good.

Occasional long silences and contributions prefaced by, "Here's a crazy thought," were characteristic of the afternoon's conversation.

The bottleneck issue of oxygen toxicity cropped up repeatedly. Hydrogenase, the enzyme responsible for biological hydrogen production, is inactivated by oxygen—which is typically co-generated during the hydrogen production process. It is the Achilles' heel of biologically based hydrogen-generation methods.

By afternoon's end, two persistent notions had earned summary diagrams on the whiteboard. One included the novel use of hydrogenosomes, organelles found in some anaerobic protists and fungi. The other was larger in scale, laying out in concept a complete, nearly closed system powered by sun and wind energy, and generating usable hydrogen, oxygen, and fresh water. It incorporated the novel use of reusable cobalt salen to capture the problematic oxygen. One participant likened this approach to "dissembling a cow and selling every part."

At day's end, the group disbanded with lingering questions about many practical issues, such as component stability, production capacity, and system efficiency.

Design Principles of Living Systems

FOCUS GROUP DESCRIPTION

Background

Human functions are the most complicated systems. It is probably the greatest scientific and engineering challenge to duplicate some or all the basic human functions on a chip. The success of this work can be of tremendous societal and economic rewards. While the basic functions of a human organ are generally understood, the feasibility of fabricating nano or micro devices on a chip that supply the same biological, chemical, and electrical activities as those of a human organ has only been explored recently. Some of these examples include artificial noses, tongues, ears, retina, skin, etc. There are many more human functions that can be duplicated on a chip. Furthermore, with advancement of the nanoscience and engineering, the integration of several human functions on a chip seems to be feasible. In principle, a human chip can be prepared based on the same or completely different scientific principles from the biological reactions in the actual human organ. The following are examples of the human on a chip concept.

The Problem

- Identify basic human functions in the nanoscale.

- Build a nano digestion system that converts organic materials into energy.
- Build a nano breath system that converts O_2 to CO_2 and, in the meanwhile, releases energy.
- Build a nano viewing system that detects images and transfers them into digital data.
- Build a nano smelling system that can simultaneous identify different chemicals in a low concentration, low volume gas sample.
- Build a nano listening system that can record and identify acoustic signals over a wide range of frequency.
- Build a nano sensing system that can simultaneously detect minor changes of temperature, pressure, humidity, and other environmental factors.
- Build a nano electromechanical or optomechanical system that can move with the input of light, sound, temperature, etc.
- Build a chip that contains more than one of the above functions.

Initial Reference

1. Freedman, David, *The Silicon Guinea Pig. Technology Review*, June 2004. 107:62-69.

FOCUS GROUP SUMMARY

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- Mercedes Talley, Program Director, W. M. Keck Foundation

Summary

The task was to determine how to build a "human on a chip." The problem was that no one really knew what that meant.

Among the 17 experts gathered, amidst backgrounds ranging from materials science to vascular biology, everyone had a slightly different speculation about the intention behind the phrase.

Was it a charge to build a microfluidic system that would give quasi-human responses to drugs—a kind of biomolecular crash-test dummy intended to speed up the expensive early trial phases of drug discovery? Was it some borg-inspired desire to have human processes take place on some injectable piece of plastic—an artificial oxygen filter for asbestos-torn lungs, or emergency islet cells for diabetics? Maybe a trash digester for the colon.

It could be a call to put human sensory systems on a chip. Artificial eyes, ears, nose, tongue, and skin combined together to make the ultimate

pseudo human probe. Then again, it's our mind that's *really* what makes us human, isn't it? Maybe this should be some sort of preliminary mock neural network.

For all I knew, "human on a chip" suggested a recipe for soylent green guacamole.

After a day's discussion, the issue came down to realizing that this was, after all, a nanotechnology conference. The secret of the group's purpose was buried in the implicit fact that, at some point, nanotechnology and the workings of human cellular biology are going to have to merge in a complex and meaningful way. And, scientists today aren't exactly sure how these two technologies are going to interface.

This uncertainty arises because nanotechnology works on a scale where many biological functions at the cellular and sub-cellular level are controlled by weak, non covalent interactions, such as electrostatic, van der Waals forces, hydrogen bonds, and metal coordination chemistry. When you push molecules together, you change their chemical activities. And when you change their activities, you change their physical conformation; it's just occurring on a very, very small scale. While researchers can make pretty good guesses at how fairly simple and uniform nanostructures behave at this level, the complex mosaics of the human body, like the hierarchical assemblies of proteins that make up our cells and tissues, are still outside current understanding.

So, the group devised a way to set up a scheme that would enable a very fundamental meeting between nanotechnology and the human body, while at the same time allowing researchers to find out more about those biological complexities that they don't understand. They reworked their group's title into "Design Principles of Living Systems," at the cell level, and designed a device called a multiplexed dynamic force spectroscopy array.

Inside a human cell, the workings of a single protein—how the long chain of peptides kinks or untangles in order to hide or expose active links—isn't solely dictated by regulatory enzymes or chemical triggers in the environment. The protein is also being tugged, stretched, and scrunched by the surrounding intracellular and extracellular matrix that gives cells their shape. These physical forces radically skew how a protein reacts to chemical and enzymatic cues, and cell function results from this form of interplay between mechanics and chemistry.

The basic schematic of the array looks a bit like an underwater clothesline. The protein to be studied is strung like a tangled cable between two,

20-nm-thick. These can be Carbon, Nickel, Platinum, or Polypyrrole/Gold composite nanowires. Using subtle electric pulses or weak magnetic fields, those two nanowires can be sheared outward, creating a tug-of-war stress on the protein, or pulled inward, bunching the protein up.

Researchers could then use an imaging technique, such as fluorescence resonance energy transfer (FRET) or fluorescence recovery after photobleaching (FRAP), to observe how this protein responds to different enzymatic and chemical cues while under this stress. For more advanced studies, more proteins could be added to the same nanowires or to nearby sets of nanowires to see how the proteins react.

Donald Ingber of Harvard Medical School, who was chosen to act as spokesperson for the group, suggested that a good first object of study would be fibronectin, a relatively well-understood glycoprotein responsible for binding cell membranes to the extracellular matrix that holds multiple cells together. From there, more complex proteins could be observed.

Eventually computer models could be designed around these observations, allowing researchers to more accurately model reactions that cells would have to different stimuli. Being able to individually scrutinize proteins in a mechanically relevant context would also help drug developers pin down what enzymatic and protein pathways are really being affected by potential medical treatments.

The array could also become a finely tuned biosensor. Proteins could be engineered to open different active binding sites under different shear forces, so that modulating the forces would cause the proteins to react if certain molecules targeted to those sights (possibly chemical weapons or illegal drugs) were present in the surrounding solution.

The plan for the array, however, is far from realistic at this point. The optical methods of observing the individual chemical events and protein structure aren't sensitive enough to observe individual changes in proteins as they happen. Not to mention that there is no method accurate enough to place individual proteins between the wires and reliably attach the ends.

"On top of the technical problems, there is the simple fact that this is also the exact type of research that is not going to get funded through your typical channels," Ingber said. It's too rooted in "maybes" and too far removed from application. But, it might be a good idea to keep in mind for ten years from now . . . if anyone asks you to design a human on a chip.

Grow a Biological In Vitro Power Source on a Chip

FOCUS GROUP DESCRIPTION

Background

There is much interest in finding alternative and renewable energy processes. Significant gains have been made in approaches, such as photovoltaic, wind, and solar/thermal, but the costs of these units can still be considerable; and some require rather sophisticated manufacturing infrastructure. A biologically driven energy source is an appealing alternative, especially one that could convert waste into energy.

The Problem

Consider the design of a power source that is biological in nature and provides an energy output that can be utilized reasonably in an industrial setting (i.e., electricity, hydrogen). This system does not have to be suitable for in vivo use, nor does it have to rival the absolute efficiency of conventional systems; but it should have the potential of improving the current costs to produce clean energy. For comparison, a current, commercially available, solar panel of $1.27m^2$ can generate 167 watts with irradiation of $1kW/m^2$ (~13 percent efficiency) and costs about $600 to purchase.

As one example of biological power sources, photosynthesis is used by plants to convert water and carbon dioxide into ATP and carbohydrates.

This cycle can be interrupted to produce hydrogen. Other microorganisms (bacteria, algae) can also be used to produce hydrogen, in a similar cycle. Unfortunately, most of these are self-limiting reactions, where the organisms are inhibited by the reaction byproducts. It may be possible to modify the enzymes, or the sensitivity of the organisms to the reaction byproducts, to improve the efficiency of these processes, but other technical approaches (i.e., the use of membrane reactors, scavengers, etc.) have also been attempted at the macro scale. Micro and nano scale systems offer many advantages for the design of continuously operating systems for biological energy conversion.

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FOCUS GROUP SUMMARY

Summary written by:

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Focus group members:

- Clemens Burda, Assistant Professor, Department of Chemistry, Case Western Reserve University
- Jennifer Cha, Research Staff Member, Department of Advanced Organic Materials, IBM Almaden Research Center
- Andrew Ellington, Professor, Department of Chemistry and Biochemistry, University of Texas at Austin
- Mark Humayan, Professor, School of Medicine, University of Southern California

- Eric Jakobsson, Professor, University of Illinois at Urbana-Champaign
- David LaVan, Assistant Professor, Department of Mechanical Engineering, Yale University
- Jessica Marshall, Graduate Student, Science Communication Program, University of California, Santa Cruz
- Vijaykrishnan Narayanan, Associate Professor, Department of Computer Science and Engineering, Pennsylvania State University
- Richard J. Schwartz, Co-Director, Purdue University/Birck Nanotechnology Center
- Ali Shakouri, Associate Professor, Department of Electrical Engineering, University of California, Santa Cruz
- Peter Wolynes, Principal Investigator, Department of Chemistry and Biochemistry, University of California, San Diego
- Lynne Zucker, Professor, Department of Sociology, University of California, Los Angeles

Summary

A handful of engineers, a pair of biologists, a couple of chemists, and a sociologist walk into a conference room. They've been told to solve a problem. One of the biologists says to the others, effectively, "This problem is stupid." Debate ensues and, in the end, two probably patentable ideas emerge, one posed by the dissenter.

The punch line of the story isn't laughable, but there is a punch line, nonetheless: diverse and intelligent minds stuck in a room together can do a lot in 8 hours.

This focus group was tasked with the problem titled, "Grow a biological in vitro power source on a chip," which implied to some group members a small-scale application, perhaps powering an implantable medical device.

But below the title, the problem description explained the goal as a technology that "should have the potential of improving the current costs to produce clean energy." This description implied to other group members that the aim was to devise a large-scale alternative energy source—replacing photovoltaics, for example—based on biology.

The researchers' first job, then, was defining the problem. They brainstormed broadly and discussed both approaches, initially responding

to the skepticism offered by one group member that a small biological power cell was a "fundamentally non-doable, non-worthwhile problem."

After initial brainstorming, the group began, somewhat inadvertently, by designing a system that achieved the latter goal of a large-scale biological power source. But by the end of the four 2-hour sessions, the group had design ideas for both applications.

In brainstorming and defining the problem, the researchers discussed power requirements for various devices and applications, and considered the unique attributes of biology and the nanoscale in energy conversion. In particular, group members considered the efficiency of photosynthesis—nature's way of converting renewable, light energy into energy for growth. Photosynthesis is about 35 percent efficient at harvesting light energy (at certain wavelengths), but only about 1 percent efficient at converting that energy into glucose. By comparison, a modern photovoltaic panel is about 15 percent efficient. The group discussed possible applications that could accommodate the mediocre efficiency of photosynthesis.

The group also discussed unusual examples of energy generation in nature, including the electric eel, capable of producing a single 600-volt shock each hour. They discussed microbiological approaches to energy conversion, noting the disadvantage that microorganisms are evolved to use harvested solar or chemical energy for growth, not for surplus power generation. This makes such systems inefficient at external power generation, and can cause devices to foul as organisms multiply and form biofilms.

By the end of the first session, the group had discussed both ideas and sketched the architecture of a plan for a large-scale biological power source. The goal of creating a small, implantable, biological power source initially seemed intractable, because calculations suggested supplying enough power to run anything for a useful period of time was unlikely to be possible. Later, the realization that some devices have very low power requirements opened the door for discussion of this as a feasible approach.

The second session included a more detailed mapping of a solution to the large-scale power generation problem, making use of the expertise of several of the group members. With the initial concept—posed by the group's initial skeptic—on the table, each researcher contributed to the solution. Leaving the initial debate behind, the group grew enthusiastic as ideas came together.

The group's proposal circumvents the low efficiency of natural photosynthesis by converting light directly into electricity, eliminating a carbohydrate intermediate. The approach includes a strategy for expanding the

spectrum of absorbable light beyond the normal (narrow) range allowed by photosynthesis.

One of the group members said of the proposed approach, "I think it stands scrutiny as an idea."

Returning to the room the second day, the group discussed the small-scale power generation device. Their approach mimics power generation by the electric eel, which has long fascinated scientists. Looking for information online, the group found Volta's 18th century drawings of the eel's electric organ and descriptions of surprising early experiments.

As the sixth hour in the room approached, the group allowed itself to joke about Star-Trek-like possibilities, including implantable eels, noting that if body piercing could take off, so could eel implants.

In the final session, late Saturday afternoon, conference keynote speaker Dr. Mark Humayan, of the University of Southern California, joined the group before his evening talk on the implantation and testing of an artificial retina in patients who had lost their vision. He brought medical expertise to the group, and his knowledge of power requirements for medical implants—which are much lower than the group thought—allowed the group to identify a feasible application for their small-scale power-generating device and to elaborate on its design. Again, enthusiasm grew as the group approached a solution, and the broad expertise of the researchers was impressive to see as they contributed to the solution.

Throughout the discussions, the group remained focused on quantitatively evaluating the feasibility of their ideas: back-of-the-envelope calculations flew fast and furious. The researchers recalled values from memory for biological and physical parameters—power requirements, dimensions, absorption spectra, process efficiencies—and fluently manipulated these numbers to estimate the limits of possible approaches and the requirements of possible applications.

Both environmental and health benefits exist for society by the development of these ideas. A biological power source would offer a clean and renewable energy source, avoiding fossil fuel consumption and the need for toxic materials used in photovoltaics and batteries. A small, implantable biological power source would be biocompatible and alleviate concerns about implantation safety and disposal of today's batteries, which contain metals and other highly toxic components; modern implanted batteries must be carefully encased before implantation.

Although the ideas generated by the group may seem fantastic, the

researchers' commitment to assessing a minimum of feasibility was a key aspect of the discussion.

Indeed, one of the biologists summed up the session with his own punch line, satisfied that the group met at least one standard in their proposals:

"I don't think we've violated any laws of thermodynamics."

That's a good start.

Appendix

The National Academies Keck *Futures Initiative* Designing Nanostructures Pre-Conference

Videoconference between the Keck Center of the National Academies (Washington, DC) and the Arnold and Mabel Beckman Center of the National Academies (Irvine, CA)

September 18 - 19, 2004
Final Agenda

Keck Center Auditorium (Washington, DC)	**Beckman Center (Irvine, CA)**
Friday, September 17 (EDT)	***Friday, September 17 (PDT)***
	7:30-10:30pm Hospitality Suite / Jazz Hyatt Newporter, rooms 319 & 321
Saturday, September 18 (EDT)	***Saturday, September 18 (PDT)***
	7:45am Bus pick-up from the Hyatt Newporter to the Beckman Center
11:00 - 12:30 Lunch w/ Speaker	8 - 9:30 Breakfast w/ Speaker

Welcome
Cherry Murray (DC)
Chair, National Academies Keck *Futures Initiative* Nano Steering and Planning Committees
Physical Sciences Research Senior Vice President
Bell Labs, Lucent Technologies

Nanotechnology Ethics
Peter A. Singer, MD, MPH, FRCPC (DC)
Sun Life Financial Chair in Bioethics, Director of the Joint Centre for Bioethics
University of Toronto

12:30 - 2:30pm Sessions 1 & 2*	9:30 - 11:30 Session 1 & 2*

Future of Medicine – Session 1
Judith L. Swain, M.D. (Irvine)
Chair, Department of Medicine
Arthur L. Bloomfield Professor of Medicine
Stanford University School of Medicine

Nanoscale Materials: Some Progress, Some Problems, and Some Promise – Session 2
Mark A. Ratner (DC)
Morrison Professor of Chemistry
Northwestern University

2:30 - 3:00 Break	11:30 - 12:00 Break

*** Each session is 1 hour – 40 minutes for the presentation, 20 minutes for Q&A. Speakers will be distributed between Keck and Beckman Centers. The location the speaker will be live is given in parentheses after each name. All sessions and speakers, except the Funding & Administration of Interdisciplinary Research panels, will be videoconferenced to the other location.**

Keck Center Auditorium (Washington, DC)		**Beckman Center (Irvine, CA)**	
Saturday, September 18 (EDT)		***Saturday, September 18 (PDT)***	
3:00 - 5:00pm	Sessions 3 & 4*	12:00 - 2:00pm	Sessions 3 & 4*

Overview of Biological Machines – Session 3
David S. Goodsell (Irvine)
Associate Professor, Department of Molecular Biology
The Scripps Research Institute

Optical Nano-Imaging – Session 4
Shuming Nie (DC)
Director of Cancer Nanotechnology, Winship Cancer Institute
Associate Professor of Biomedical Engineering, Chemistry, Hematology, and Oncology
Emory University and Georgia Institute of Technology

5:00 - 7:00	Dinner w/ Speaker	2:00 - 4:00	Lunch w/ Speaker

Communicating Science
Joe Palca (DC)
Correspondent
National Public Radio

7:30 - 11:00	Hospitality Suite at Hotel Monaco – Room 443 (Informal discussions, snacks)	4:00 - 6:00	Panel: Funding and Administration of Interdisciplinary Research

Moderator:
Andy McCammon, J.E. Professor of Theoretical Chemistry, University of California, San Diego

Panelists:
Dave Eaglesham, Chemistry and Materials Science Chief Technologist, Lawrence Livermore National Lab
Samuel I. Stupp, Board of Trustees Professor of Materials Science, Chemistry and Medicine, and Director, Institute for Bioengineering and Nanoscience in Advanced Medicine, Northwestern University
Mercedes Talley, Program Director, W.M. Keck Foundation

6:00	Bus pick-up from Beckman Center to the Hyatt Newporter
7:00 - 11:00	Hospitality Suite at Hyatt Newporter – Garden 2 & 3 (Informal discussions, buffet)

*** Each session is 1 hour – 40 minutes for the presentation, 20 minutes for Q&A. Speakers will be distributed between Keck and Beckman Centers. The location the speaker will be live is given in parentheses after each name. All sessions and speakers, except the Funding & Administration of Interdisciplinary Research panels, will be videoconferenced to the other location.**

Keck Center Auditorium (Washington, DC)		**Beckman Center (Irvine, CA)**	
Sunday, September 19 (EDT)		***Sunday, September 19 (PDT)***	
8:00 - 9:00am	Breakfast		
9:00 - 10:30	Panel: Funding and Administration of Interdisciplinary Research Moderator: Cherry Murray, Physical Sciences Research Senior Vice President, Bell Labs, Lucent Technologies Panelists: Eric Jakobsson, Director, Center for Bioinformatics and Computational Biology, NIH/NIGMS Aravinda Kini, Program Manager, Office of Basic Energy Sciences, Department of Energy Conrad Masterson, Jr., Nanotech Foundation of Texas Celia Merzbacher, National Science and Technology Council, Office of Science and Technology Policy, Executive Office of the President Fraser Stoddart, Director, California NanoSystems Inst.		
		6:45am	Bus pickup from the Hyatt Newporter to Beckman Center
10:30 - 11:00	Break	7:00 - 8:00	Breakfast
11:00 - 2:00	Sessions 5 & 6 & 7*	8:00 - 11:00	Sessions 5 & 6 & 7*

Future of Tissue Engineering – Session 5
Samuel I. Stupp (Irvine)
Board of Trustees Professor of Materials Science, Chemistry and Medicine
Director, Institute for Bioengineering and Nanoscience in Advanced Medicine
Northwestern University

Clinical Nano-Imaging – Session 6
Samuel A. Wickline, M.D. (DC)
Professor of Medicine, Biomedical Engineering, Physics, Cell Biology and Physiology
Washington University School of Medicine

Future of Nano-Devices – Session 7
Evelyn L. Hu (Irvine)
Professor, Department of Electrical and Computer Engineering
Director, California NanoSystems Institute
University of California – Santa Barbara

2:00pm	Lunch / Leave for airports	11:00	Lunch
		11:00 & 12:15	Buses depart for Hyatt Newporter and John Wayne Airport

*** Each session is 1 hour – 40 minutes for the presentation, 20 minutes for Q&A. Speakers will be distributed between Keck and Beckman Centers. The location the speaker will be live is given in parentheses after each name. All sessions and speakers, except the Funding & Administration of Interdisciplinary Research panels, will be videoconferenced to the other location.**

The 2nd Annual National Academies Keck *Futures Initiative* Conference

Designing Nanostructures at the Interface between Biomedical and Physical Systems
Arnold and Mabel Beckman Center, Irvine, California
November 18–21, 2004

AGENDA

Thursday, November 18 (Hyatt Newporter)

5:30 p.m.	Registration opens (Plaza Arbor)
6:00 – 7:00 p.m.	Buffet Dinner (Plaza Arbor/Plaza 1 & 2)
7:00 – 9:00 p.m.	Tutorial Plenary Sessions (Plaza 1 & 2)

Theory and Error Correction
Peter Wolynes, Professor
Department of Chemistry and Biochemistry
University of California at San Diego

Overview of Cell Biology
Thomas D. Pollard, Eugene Higgins Professor
Department of Molecular, Cellular, and Developmental Biology
Yale University

9:00 – 11:00 p.m.	Informal Discussions/Reception (Plaza Arbor)

Friday, November 19 (Arnold and Mabel Beckman Center of the National Academies)

7:15 and 7:45 a.m.	Bus pick-up from the Hyatt Newporter to the Beckman Center
7:30 a.m.	Breakfast (Dining Room)
8:30 – 9:00 a.m.	*Welcome and Opening Remarks* (Auditorium) Wm. A. Wulf, President, National Academy of Engineering Richard N. Foster, Board Member, W.M. Keck Foundation Cherry Murray, Chair, Nano Steering Committee
9:00 – 10:00 a.m.	Facilitating Interdisciplinary Research Report Release (Auditorium)
10:00 – 10:30 a.m.	Task to Focus Groups (Auditorium)
10:30 – 11:00 a.m.	Break (Atrium)
11:00 – 12:30 p.m.	Focus Groups (Breakout Rooms)

1.	Multiply RNA/DNA.	(Laguna – 2nd floor)
2.	Synthetic self-replicator.	(Emerald Bay – 2nd floor)
3.	Detect disease in vivo.	(Balboa – 1st floor)
4.	Cell-chip interface.	(Newport – 1st floor)
5.	Sequence protein molecule.	(Irvine Cove – 2nd floor)
6.	Glucose sensor.	(Crystal Cove – 1st floor)
7.	Biological factory.	(Back Bay – 2nd floor)
8.	Electrolysis of sea water.	(Lido – 2nd floor)
9.	Human on a chip.	(Board Room – 1st floor)
10.	In vitro power source.	(Harbour – 2nd floor)

12:30 – 2:00 p.m.	Lunch Buffet/Networking (Dining Room)
2:00 – 4:00 p.m.	Poster Session I (first group of posters) / Networking (3:00 – 4:00 p.m.—Refreshments in Dining Room and Palm Court 2)
4:00 – 6:00 p.m.	Focus Groups (Breakout Rooms)
6:00 – 7:00 p.m.	Reception/Networking
7:00 – 9:00 p.m.	Dinner and Communication Awards Presentation (Atrium)
9:00 p.m.	Buses depart Beckman Center for Hyatt Newporter
9:30 – 11:00 p.m.	Informal Discussions/Hospitality Room Hyatt Newporter—Garden 3

Saturday, November 20 (Beckman Center)

7:15 and 7:45 a.m.	Bus pick-up from the Hyatt Newporter to the Beckman Center
7:30 a.m.	Breakfast (Dining Room)
8:00 – 10:30 a.m.	Focus Groups (Breakout Rooms) (Break refreshments will be available at 10:00 a.m. in Huntington Room, Palm Court 2 and Bay View 2)
10:30 – 12:00 p.m.	Focus Group Report-Outs (Each group gives an 8 minute debrief) (Auditorium)
12:00 – 2:00 p.m.	Lunch Buffet/Networking (Dining Room)

2:00 – 4:00 p.m.	Poster Session II (second group of posters)/ Networking (3:00 – 4:00 p.m.—Refreshments in Dining Room and Palm Court 2)
4:00 – 6:00 p.m.	Focus Groups (Breakout Rooms)
6:00 – 7:00 p.m.	Reception/Networking
7:00 – 9:00 p.m.	Dinner and Speaker (Atrium) Mark S. Humayun, MD Professor of Ophthalmology, Biomedical Engineering and Cell and Neurobiology, University of Southern California Associate Director of Research, Doheny Retina Institute
9:00 p.m.	Buses depart Beckman Center for Hyatt Newporter
9:30 – 11:00 p.m.	Informal Discussions /Hospitality Room Hyatt Newporter—Garden 1

Sunday, November 21 (Beckman Center)

7:15 and 7:45 a.m.	Bus pick-up from the Hyatt Newporter to the Beckman Center
7:30 a.m.	Breakfast (Dining Room)
8:30 – 10:15 a.m.	Focus Group Report-Outs (Auditorium) (15 minutes per group)
10:15 – 10:45 a.m.	Break (Atrium)
10:45 – 12:00 p.m.	Focus Group Report-Outs—continued (Auditorium)

12:00 – 1:00 p.m. Lunch

12:00 and 1:00 p.m. Buses depart for Hyatt Newporter and John Wayne Airport

Designing Nanostructures at the Interface between Biomedical and Physical Systems
Arnold and Mabel Beckman Center, Irvine, California
November 18–21, 2004

FOCUS GROUP TOPICS

1. Build a nano or micro system that can effectively multiply and isolate RNA or DNA in a picoliter-volume, low-concentration sample solution.

2. Build a synthetic self-replicator.

3. Build a system that will detect disease in vivo and report back results.

4. Build a cell-chip interface to sense response to drug leads and toxins.

5. Sequence a single molecule of protein.

6. Build a glucose sensor to circulate (implant) in vivo in humans and regulate insulin.

7. Use biological systems to build a factory to synthesize products.

8. Design and grow a bacterial or cellular factory to perform electrolysis of sea water to create hydrogen gas.

9. Build a human on a chip.

10. Grow a biological in vitro power source on a microchip.

Participants*

The National Academies Keck *Futures Initiative*
Designing Nanostructures at the Interface between Biomedical and Physical Systems

Pre-Conference

Videoconference between the Keck Center of the National Academies (Washington, DC) and the Arnold and Mabel Beckman Center of the National Academies (Irvine, CA)
September 18–19, 2004

Conference
Arnold and Mabel Beckman Center of the National Academies (Irvine, CA)
November 18–21, 2004

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*Most, but not all, attended both the Pre-Conference and Conference.

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